Supplementation of N-3 LCPUFA to the Diet of Children Older Than 2 Years: A Commentary by the ESPGHAN Committee on Nutrition

ESPGHAN Committee on Nutrition: [*3]*Carlo Agostoni,* [†]*Christian Braegger,* [‡]*Tamás Decsi,* [§]*Sanja Kolacek,* [||]*Walter Mihatsch,* [¶]*Luis A. Moreno,* [#]*John Puntis,* [**1]*Raanan Shamir,* [††]*Hania Szajewska,* [‡‡2]*Dominique Turck, and* [§§]*Johannes van Goudoever*

ABSTRACT

The aim of this commentary is to review data on the effect of supplementation of paediatric patients ages 2 years or older with n-3 long-chain polyunsaturated fatty acids (LCPUFA). Some evidence for a positive effect on functional outcome in children with attention-deficit/hyperactivity disorder (ADHD) was found; however, benefit was seen in only about half of the randomised controlled trials (RCT), and studies varied widely not only in dose and form of supplementation but also in the functional outcome parameter tested. The committee concludes that there are insufficient data to recommend n-3 LCPUFA supplementation in the treatment of children with ADHD, but further research on n-3 LCPUFA supplementation in ADHD may be worthwhile. The committee was unable to find evidence of a favourable effect of n-3 LCPUFA supplementation on cognitive function in children. Although no benefit of n-3 LCPUFA supplementation was seen for major clinical outcome parameters in children with cystic fibrosis, a potentially beneficial shift towards less-inflammatory eicosanoid profiles seen in 2 studies provides grounds for further investigation; it is possible that earlier and longer supplementation periods may be needed to demonstrate clinical effect. For children with phenylketonuria, the limited data available suggest that supplementation of n-3 LCPUFA to the diet is both feasible and safe, but offers only transient benefit in visual function. For children with bronchial asthma there are insufficient data to suggest that LCPUFA supplementation has a beneficial effect. The committee advises paediatricians that most health claims about supplementation of n-3 LCPUFA in various diseases in children and adolescents are not supported by convincing scientific data.

Key Words: attention-deficit/hyperactivity disorder, commentary, cystic fibrosis, n-3 long-chain polyunsaturated fatty acids, phenylketonuria

(*JPGN* 2011;53: 2–10)

Long-chain polyunsaturated fatty acids (LCPUFA) are important constituents of membrane lipids. For incorporation into membrane lipids of the human organism, LCPUFA should be either synthesized from the parent essential fatty acids, linoleic acid (C18:2n-6, LA) and alpha-linolenic acid (C18:3n-3, ALA), or taken up as preformed nutrients in the diet. The major n-3 LCPUFA are eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA). Fatty fish and various other seafoods are excellent dietary sources of both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (1).

The optimal intake of DHA and EPA remains controversial not only in infants but also in children. In 2002, the Institute of Medicine concluded that insufficient data were available to set a dietary recommended intake (DRI) or an adequate intake (AI) for EPA or DHA (2). Substantial new data led the Technical Committee on Dietary Lipids of the International Life Sciences Institute of North America to conclude in 2009 that there was a clear, inverse relation between EPA and DHA intake and risk of fatal (and possibly nonfatal) coronary heart disease in adults. This evidence supports a nutritionally achievable DRI for EPA and DHA between 250 and 500 mg/day. The Committee also stated that because of low conversion from dietary ALA, protective tissue levels of EPA and DHA can be achieved only through direct consumption of these fatty acids and that there is no evidence that intakes of EPA and DHA in the recommended range are harmful (3). The European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies (NDA) delivered a scientific opinion on dietary reference values for fat, including polyunsaturated fatty acids in 2009 (4). Taking into account that available data are insufficient to derive a DRI, the panel proposed setting an AI of 250 mg for EPA and DHA for adults based on considerations of cardiovascular health. The Panel proposed an AI of 100 mg DHA for infants older than 6 months of age and young children younger than 24 months. The available evidence did not permit definition of an age-specific AI for EPA and DHA for children ages 2 to 18 years. However, dietary advice for children should be consistent with advice for the adult population (ie, 1 to 2 fatty fish meals per week or ~250 mg/day of EPA and DHA).

Received February 11, 2011; accepted February 13, 2011.

From the *Department of Maternal and Pediatric Sciences, University of Milan, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, the †University Children's Hospital, Zurich, Switzerland, the ‡Department of Paediatrics, University of Pecs, Hungary, the §University Children's Hospital Zagreb, Croatia, the ||Department of Paediatrics, Deaconry Hospital, Schwaebisch Hall, Germany, the ¶Escuela Universitaria de Ciencias de la Salud, Universidad de Zaragoza, Spain, the #Leeds General Infirmary, UK, the **Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel-Aviv University, Israel, the ††The Medical University of Warsaw, Poland, the ‡‡Jeanne de Flandre Children's Hospital, Lille University Faculty of Medicine, France, and the §§Pediatrics, VU University Medical Center Amsterdam and Pediatrics, Emma Children's Hospital-AMC Amsterdam, The Netherlands.

Address correspondence and reprint requests to Dr Tamás Decsi, Department of Paediatrics, University of Pécs, József A. u. 7, H-7623 Pécs, Hungary (e-mail: tamas.decsi@aok.pte.hu).

[1]Committee Chair; [2]Committee Secretary; [3]Guest.

The authors report no conflicts of interest other than those reported on the ESPGHAN Web site.

DOI: 10.1097/MPG.0b013e318216f009

In adults, the daily dietary intake of n-3 LCPUFA is usually limited to 100 to 200 mg; that is, it was found to be around 110 mg/day in women and 170 mg/day in men in the United States (5). Dietary intakes of EPA and DHA were reported to be around 80 mg/day in both Australian children ages 12 to 15 years (6) and Belgian children ages 2.5 to 6.5 years (7), whereas about 150 mg/day intakes were found in Canadian children ages 1.5 to 5 years (8). In a recent survey of a large cohort ($n > 800$) of Australian children ages 13 to 15 years, mean intakes of EPA and DHA were found to be around 40 and 100 mg/day, respectively (9).

Both recommendations for n-3 LCPUFA intake and data on the health benefits of n-3 LCPUFA are inconsistent. Regular consumption of fish and/or seafood has been associated with health benefits in the general population; moreover, enhanced n-3 LCPUFA intake has been suggested in the treatment of various diseases. Numerous clinical studies have addressed the effect of n-3 LCPUFA supplementation in restoring health and maintaining well-being. The results of these studies have been summarised in reviews including several recent *Cochrane Database Systematic Reviews* addressing the potential role of n-3 LCPUFA adjuvant therapy in bipolar disorder (10), cancer cachexia (11), Crohn disease (12), cystic fibrosis (CF) (13), diabetes mellitus (14), end-stage renal disease after kidney transplantation (15), intermittent claudication (16), multiple sclerosis (17), and ulcerative colitis (18).

Although many of the above-mentioned diseases may manifest during childhood, most of the available systematic reviews drew conclusions from data obtained exclusively in adults. The aim of this commentary was to review data on the effect of supplementing n-3 LCPUFA in the diet of paediatric patients, thus providing accessible information on this emerging topic to the paediatric community.

The present review discusses the role of n-3 LCPUFA supplements for paediatric patients ages 2 to 18 years. Data obtained in infants and very young children (who potentially receive preformed n-3 LCPUFA via breast-feeding) were excluded because this population should be discussed separately. For the role of n-3 LCPUFA in the diet at younger ages, we refer readers to recent Cochrane reviews on the diets of preterm (19) and full-term (20) infants, a consensus recommendation (21), and our recent comments on breast-feeding (22) and complementary feeding (23).

METHODS

The aim of this review was to assess the effect of supplementing n-3 LCPUFA in children on functional outcome in various diseases and on cognitive function. To be included in the review, a study needed to meet all of the following requirements: randomised controlled trial (RCT), in children and adolescents (2 to 18 years), and investigating n-3 LCPUFA supplementation.

To identify publications the following databases were searched, using both free text and MeSH terms where appropriate: PubMed, Cochrane Library Register of Controlled Trials CENTRAL and SCOPUS. The search terms were as follows:

1. ''fatty acids, omega-3'' [MeSH]
2. ''omega 3'' [tw] OR ''omega-3'' [tw] OR ''n-3 fatty acid'' [tw] OR ''n-3 fatty acid'' [tw]
3. ''n-3 PUFA'' [tw] OR ''n-3 PUFA'' [tw] OR ''n-3 PUFAs'' [tw] OR ''n3 PUFAs'' [tw] OR ''n-3 polyunsaturated'' [tw] OR ''n3 polyunsaturated'' [tw] OR ''n-3 polyunsaturated'' [tw] OR ''n-3 polyunsaturated'' [tw]
4. LC-PUFAs [tw] OR LC-PUFA [tw] OR LCPUFAs [tw] OR LCPUFA [tw] OR ''long-chain polyunsaturated'' [tw] OR ''long-chain polyunsaturated'' [tw]
5. ''DHAs'' [MeSH] OR ''DHA'' [tw] OR ''docosahexenoic acid'' [tw] OR ''docosahexanoic acid'' [tw] OR DHA [tw]
6. ''EPA'' [MeSH] OR ''EPA'' [tw] OR ''eicosapentanoic acid'' [tw] OR ''eicosapentenoic acid'' [tw] OR EPA [tw]
7. ''fish oils'' [MeSH] OR ''fish oils'' [tw] OR ''fish oil'' [tw]
8. OR/1-7
9. ''randomised controlled trial ''[Publication Type] OR ''randomised controlled trial'' [tw] OR ''randomised controlled trials'' [tw] OR RCT [tw] OR RCTs [tw] OR randomisation [tw] OR randomisation [tw] OR random [tw] OR randomised [tw] OR randomised [tw]
10. 8 AND 9

The search was closed on 15 July 2009; however, it was repeated in a reduced form (restricted to publications dating after the original closure) on 15 March 2010. The reference lists of all of the included studies and review articles were also screened to identify possible studies of interest.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

n-3 LCPUFA are involved in numerous neuronal processes including effects on membrane fluidity and regulation of gene expression. The basis of the role of n-3 LCPUFA in the development and behaviour of children has recently been reviewed in detail by Schuchardt et al (24). Our literature search identified 8 RCTs addressing the effect of n-3 LCPUFA supplementation in children with attention-deficit/hyperactivity disorder (ADHD), making ADHD the most extensively investigated condition within this field (Table 1).

The age range of the children investigated was between 6 and 13 years in the majority of the studies, with only Johnson et al (25) including children ages 8 to 18 years. The daily dose of DHA supplementation was between 100 and 500 mg, and the duration of intervention was limited to a few (usually 2 to 4) months. The supplements also frequently contained EPA, and in some studies, n-6 LCPUFA in addition. The form of LCPUFA supplementation also showed variability: Whereas fish oil capsules were used in the majority of the studies, natural foods enriched with n-3 LCPUFA (26) and specially tailored phospholipids enriched with DHA and EPA (27) were also tested. The efficacy of supplementation was documented by measuring biomarker(s) in only 4 of 8 studies. Usually, multiple tests based on evaluation by both parents and teachers were used to determine the efficacy of supplementation on functional outcome.

Overall, 3 studies reported no major effect of supplementation. In a study supplementing 345 mg DHA daily for 4 months and addressing the effect of intervention by the Test of Variables for Attention and Children's Colour Test, despite a 2-fold increase in plasma phospholipid DHA values, no difference in any functional outcome parameter was reported (28). In 2 studies supplementing LCPUFA in a crossover design to Canadian (29) and Swedish children (25), only a subgroup analysis of small cohorts (eg, 4 patients in each subgroup) showed a detectable effect of LCPUFA supplementation.

Five studies reported a significant effect of n-3 LCPUFA supplementation. Two similar studies investigating the effect of supplementing 480 mg DHA daily together with either 180 or 80 mg EPA for a duration of either 3 or 4 months (in the United Kingdom and in the United States, respectively) found significant improvements in Conner's Parent Rating Scales (30) and in conduct problems (rated by parents) and attention problems (rated by

TABLE 1. Details of RCTs addressing the question of n-3 LCPUFA supplementation in ADHD

Data source		Country, age range (y) no. participants (intervention and control)	Short description of intervention	Biomarker	Functional outcome	Main result in functional outcome
1.	Voigt et al (28)	USA, 6–12, 32 and 31	345 mg DHA daily for 4 mo	Plasma phospholipid fatty acids	1. Test of Variables of Attention, 2. Children's Colour Test	No difference
2.	Richardson and Puri (30)	UK, 8–12, 22 and 29	186 mg EPA, 480 mg DHA (864 mg LA, 96 mg GLA, 42 mg AA) daily for 12 wk	None	Conner's Parent Rating Scale	Significant improvement from baseline on 7 of 14 scales
3.	Stevens et al (31)	USA, 6–13, 25 and 22	80 mg EPA, 480 mg DHA (96 mg GLA, 40 mg AA) daily for 4 mo	Total plasma and erythrocyte fatty acids	4 different tests	Significant improvement on 2 of 16 parameters (conduct problems rated by parents, attention problems rated by teachers)
4.	Hirayama et al (26)	Japan, 6–12, 20 and 20	700 mg EPA, 3600 mg DHA weekly for 2 mo	None	7 different tests	Significant improvement in visual short-term memory and errors of commission in the control group compared to the intervention
5.	Sinn et al (32,33)	Australia, 7–12, 36 and 27	558 mg EPA, 174 mg DHA, 60 mg GLA daily for 15 wk	None	Conner's Parents and Teachers Rating Scale	Significant improvement in inattention and hyperactivity/ impulsivity in the parents scale only
6.	Vaisman et al (27)	Israel, 8–13, 29 + 28 and 26	155 mg EPA and 95 mg DHA daily either as phospholipid or triaclyglycerol	Plasma and erythrocyte fatty acids	Test of Variables of Attention	Significant increases in scores in both intervention groups
7.	Bélanger et al (29)	Canada, 7–12, 37 (crossover design)	20–25 mg EPA and 8.5–10.5 mg DHA daily for 16 wk	Fatty acid compositional data	3 different tests	Only subgroup of patients (4 in each group) showed improvement related to n-3 LCPUFA
8.	Johnson et al (25)	Sweden, 8–18, 75 (crossover design)	560 mg EPA and 170 mg DHA daily for 3 mo	None	1. Investigator-rated ADHD Rating Scale, 2. Clinical Global Impression Scale	Only subgroup of patients (26%) responded with more than 25% reduction in symptoms

AA = arachidonic acid (C20:4n-6); ADHD = attention-deficit/hyperactivity disorder; DHA = docosahexaenoic acid (C22:6n-3); EPA = eicosapentaenoic acid (C20:5n-3); GLA = gamma-linolenic acid (C18:3n-6); LA = linoleic acid (C18:2n-6); LCPUFA = long-chain polyunsaturated fatty acids; RCTs = randomised controlled trials.

teachers) (31). Similarly, significant medium to strong positive treatment effects were found in parents' ratings of core ADHD symptoms, inattention and hyperactivity/impulsivity on the Conners Parent Rating Scale in Australian children receiving n-3 LCPUFA supplementation either with or without additional micronutrients (32). In a further crossover design study reported by the same group (33), n-3 LCPUFA supplementation with or without multivitamins and minerals resulted in significant improvements compared to placebo in a test on the ability to switch and control attention. Vaisman et al (27) investigated in parallel the effect of supplementing 250 mg/day DHA and EPA either esterified to phosphatidylserine lipids or in the form of conventional fish oil preparation. They found a significant improvement in the results of the Test of Variables of Attention in both groups supplemented with n-3 LCPUFA, but not in the controls receiving oleic acid as placebo. In contrast, Hirayama et al (26) observed significant improvement in visual short-term memory and a significant decrease in the number of errors of commission in children receiving olive oil as placebo, but not in those receiving the average intake of 3600 mg DHA + 700 mg EPA weekly in the form of fermented soybean milk, bread rolls, and steamed bread enriched with n-3 LCPUFA. Although the difference between groups disappeared after careful exclusion of children with the suspicion of ADHD only, this study raised the possibility of the beneficial effect of oleic acid, but not of DHA and EPA supplementation on functional outcome in ADHD.

DEVELOPMENT OF COGNITIVE FUNCTIONS

For the rationale of n-3 LCPUFA supplementation as a means to improve cognitive function in children, we refer again to the recent extensive review cited above (24). Five RCTs investigated the effect of n-3 LCPUFA supplementation on various cognitive functions (Table 2). Three studies compared n-3 LCPUFA with placebo (34–36), and in 2 studies n-3 LCPUFA supplementation was combined with either low or high intakes of other micronutrients (37,38).

Supplementation of 400 mg DHA daily for the duration of 4 months did not induce significant changes in the Leiter-R Test of Sustained Attention, the Peabody Picture Vocabulary Test, the Day-Night Stroop Test, and Conner's Kiddie Continuous Performance Test (34), although blood DHA concentrations significantly and positively correlated to scores on the Peabody Picture Vocabulary Test. In another study (36), supplementation of DHA in doses of 400 and 1000 mg daily for 56 days resulted in no consistent effect on various tests measuring cognitive and mood functions. In contrast, Dalton et al (35) used an experimental fish-flour bread spread providing about 80 mg EPA and 190 mg DHA daily and found significant intervention effects for the Hopkins Verbal Learning Test Recognition and Discrimination Indices as well as for the Spelling Test.

The NEMO Study Group (37) conducted two 2-by-2 factorial RCTs reported within the same paper. The authors concluded that supplementation of 22 mg EPA and 88 mg DHA for 6 days each week for a 12-month period did not influence general intelligence, verbal learning, and memory and visual attention. Muthayya et al (38) also carried out a 2-by-2 factorial RCT investigating the effect of the daily supplementation of 100 mg DHA for 12 months with either high- or low-dose micronutrient supplementation. They found no effect of DHA supplementation on a number of cognitive scores investigated after 6 and 12 months of intervention (38).

CYSTIC FIBROSIS

A potential role of n-3 LCPUFA supplementation in the treatment of CF has been inferred from both animal studies and human observations. Long-term DHA therapy resulted in significant amelioration of the severity of liver disease in a congenic murine model of CF (39). The availability of DHA was found to be significantly reduced in patients experiencing CF as compared to healthy controls, not only in a number of studies investigating blood lipids but also in mucosal and submucosal nasal-biopsy and rectal-biopsy specimens (40). Clinical outcome effects of supplementation of n-3 LCPUFA to children experiencing CF were investigated in 4 RCTs (Table 2).

No effect on the Shwachman-Brasfield score and pulmonary functions was seen in a study investigating the effect of supplementing about 50 mg EPA and 25 mg DHA in a crossover design with a 2-week-long treatment period only; however, a significant decrease in leukotriene B_4 concentrations was reported (41). Similarly, a further clinical study reported that supplementation of 200 mg DHA daily for a duration of 1 year did not influence 1 second forced expiratory volume and forced vital capacity (42). Similarly, Lloyd-Still et al (43) did not observe any detectable effect on lung function when supplementing 50 mg/kg/day DHA for 6 months.

Panchaud et al (44) investigated the effect of supplementing EPA and DHA in children in a weight-dependent manner (daily intake according to body weight: 200 mg EPA and 100 mg DHA <25 kg, 400 mg EPA and 200 mg DHA 26–50 kg, 600 mg EPA and 300 mg DHA >50 kg) for 6 months. The authors measured clinical parameters along with a series of cytokines and cytokine receptors. Although no influence on basic pulmonary function was seen, n-3 LCPUFA supplementation led to a significant decrease in the leukotriene B_4 to B_5 ratio, a finding suggestive of reduced pro-inflammatory eicosanoid production by neutrophils with enhanced n-3 LCPUFA supply (44).

PHENYLKETONURIA

Children with phenylketonuria (PKU) have a diet low in animal source foods that provides low amounts of DHA for plasma and erythrocyte lipids (45); consequently, normalisation of DHA status through supplementation of n-3 LCPUFA may offer clinical benefits. Two RCTs were conducted to elucidate the effects of LC-PUFA supplementations in children with PKU (Table 2).

In the first feasibility study, when children experiencing PKU received either commercially available fish oil capsules rich in EPA and DHA or blackcurrant capsules rich in essential fatty acids for 6 months, a significant increase in plasma DHA concentration and no adverse effects were seen in the fish oil group (46). In a double-blind, placebo-controlled trial (47), 20 children with PKU received supplementation either with a fat blend balanced in both n-3 and n-6 LCPUFA (providing about 8 mg EPA and 10 mg DHA per kg body weight per day) or placebo for 12 months. The patients also underwent neurophysiological assessment by means of visually evoked potentials evaluated at study entrance and 12 months later (48). By the end of the trial, the latency time in the P100 wave decreased significantly in children receiving the preparation with n-3 LCPUFA. When investigated 3 years after the end of the treatment, the P100 wave latency time values were similar in the 2 groups, and LCPUFA were found at the preintervention baseline level (49). Fish oil supplementation to patients with PKU resulted in improved visual evoked potentials (50) and motor skills (51) in 2 studies also including a few children younger than 2 years.

BRONCHIAL ASTHMA

Observational trials have reported that children who ate fish (52), particularly children who ate fresh, oily fish (>2% fat) (53),

TABLE 2. Diseases or functions for which >1 RCT addressed the question of n-3 LCPUFA supplementation in children

Data source	Country; age range (y); no. participants (intervention and control)	Short description of intervention	Biomarker	Functional outcome	Main result in functional outcome
Development of cognitive functions					
Osendarp et al (37)	Australia-Indonesia; 6–10 y; 96 and 102	22 mg/d EPA and 88 mg/d DHA	Plasma concentrations of selected fatty acids	Extensive batteries of cognitive tests	No difference
Dalton et al (35)	South Africa; 7–9 y; 91 and 92;	EPA: 329 vs 59, DHA: 475 vs 142 mg/100 g, experimental vs control diet	Plasma and red blood cell phospholipid composition	Hopkins Verbal Learning Test, Reading and Spelling Test	Significant intervention effects in Hopkins Verbal Learning Test Recognition and Discrimination as well as in Spelling Test
Ryan and Nelson (34)	US; 4 y; 85 and 90	400 mg/d DHA	Capillary whole blood fatty acids	4 different cognitive tests	No difference
Kennedy et al (36)	UK; around 11 y; 28 for low and 30 for high doses, 30 controls	400 mg/d or 1000 mg/d DHA	None	Internet Battery, Cognitive Drug Research Battery	''No consistent or interpretable effect''
Muthayya et al (38)	India; 6–10 y; 299 and 299	100 mg/d DHA with high or low micronutrient intakes	Red blood cell phospholipids	Extensive batteries of cognitive tests	No difference
Cystic fibrosis					
Kurlandsky et al (41)	USA; 6–16 y; 14 in crossover design	440 mg/d EPA and 240 mg/d DHA	Plasma and platelet phospholipids	Shwachman-Brasfield scores, forced expiratory volume and flow	No difference
Lloyd-Still et al (43)	USA; 8–20 y; 9 and 10	50 mg/kg/d DHA	Plasma, red blood cell, and rectal tissue fatty acid composition	Basic lung volume spirometric assessment	No difference
Panchaud et al (44)	Switzerland; mean 18 y; 17 in crossover design	390–1170 mg/d n-3 PUFA	Neutrophil membrane fatty acid composition	Lung function tests	No difference
Van Biervliet et al (42)	Belgium; mean 12 y; 8 and 8	200 mg/day DHA	Serum phospholipid fatty acids	Pulmonary function and number of infections	No difference
Phenylketonuria					
Agostoni et al (46)	Italy; 5–10 y; 10 and 11	90 mg/d EPA and 60 mg/d DHA for each 4 kg body weight	Plasma total lipids	None	Significant decrease in total cholesterol and triacylglycerol concentrations
Agostoni et al (48)	Italy; mean 13 and 14 y; 10 and 10	About 30 mg EPA and 40 mg DHA for each 4 kg body weight	Plasma and red blood cell lipids	Visual evoked potentials	Decrease in P100 wave latency
Bronchial asthma					
Hodge et al (53,54)	Australia; 8–12 y; 20 and 19	Dietary modification plus 720 mg/d EPA and 480 mg/d DHA	Plasma phospholipid fatty acids	Lung function, airway hyperresponsiveness and asthma severity	No difference
Nagakura et al (55)	Japan; mean 10 and 12 y; 15 and 14	EPA: 17.0–26.8 mg/kg/d, DHA: 7.3–11.5 mg/kg/d	EPA plasma concentration	Acetylcholine inhalation test and asthma scoring	Asthma symptom scores and responsiveness to acetylcholine decreased significantly in the intervention group only

DHA = docosahexaenoic acid (C22:6n-3); EPA = eicosapentaenoic acid (C20:5n-3); LCPUFA = long-chain polyunsaturated fatty acids; PUFA = polyunsaturated fatty acids; RCT = randomised controlled trials.

TABLE 3. Conditions for which only 1 RCT addressed the question of n-3 LCPUFA supplementation in children

Condition	Data source	Country; age range (y); no. participants (intervention and control)	Short description of intervention	Biomarker	Functional outcome	Main result in functional outcome
Autism	Amminger et al (57)	Austria; 5–17 y; 7 and 5	840 mg/d EPA and 700 mg/d DHA	None	Aberrant Behaviour Checklist	No difference
Crohn disease	Romano et al (58)	Italy; 5–16 y; 18 and 20	1200 mg/d EPA and 600 mg/d DHA	Red blood cell fatty acids	Relapse at 1 y	Significantly lower in the intervention group
Depression	Nemets et al (59)	Israel; 6–12 y; 10 and 10	400 mg/d EPA and 200 mg/d DHA	None	Children's Depression Rating Scale, Children's Depression Inventory, Clinical Global Impression	Significant effect of intervention in all 3 tests
Dysmenorrhea	Harel et al (60)	US; adolescents; 21 and 21	1080 mg/d EPA and 720 mg/d DHA	None	Cox Menstrual Symptom Scale	Significant reduction in symptom scale in the intervention group after 2 mo of treatment
Hyperlipidaemia	Engler et al (61,62,63)	US; 9–19 y; 10 in crossover design	1200 mg/d DHA	Plasma phospholipid fatty acids	Plasma lipid profiles, and endothelium-dependent flow-mediated dilation	Significant increase in HDL- and decrease in LDL-cholesterol, significant increase in flow-mediated dilation
Idiopathic dilated cardiomyopathy	Olgar et al (64)	Turkey; mean: 10 y; 18 and 13	800 mg/d EPA and 700 mg/d DHA	None	Cardiac functions	Significant increase of left ventricular ejection fraction, significant decrease in left ventricular internal diameter
Illness	Thienprasert et al (65)	Thailand; 9–12 y; 94 and 86	200 mg/d EPA and 1 000 mg/d DHA	Plasma phosphatidylcholine fatty acids	Episodes and duration of illnesses	Significantly fewer episodes and shorter durations of illness
Methylmalonic acidaemia	Aldámiz-Echevarria et al (66)	Spain; 9–16 y; 4 in crossover design	25 mg/kg/d DHA	Plasma total fatty acids	None	Significant decrease of plasma triacylglycerol concentration
Migraine	Harel et al (67)	US; mean: 15 y; 27 in crossover design	378 mg/d EPA and 249 mg/d DHA	None	7-point Likert scale	Significant reduction of symptoms in both the intervention and control groups, no difference between groups

DHA = docosahexaenoic acid (C22:6n-3); EPA = eicosapentaenoic acid (C20:5n-3); LCPUFA = long-chain polyunsaturated fatty acids; RCT = randomised controlled trials.

had a significantly reduced risk of bronchial asthma. Based on these observational studies, 2 RCTs evaluated the role of LCPUFA supplementation in the treatment of bronchial asthma (Table 2).

Children in the treatment group of an Australian study (54) received a diet rich in canola oil, capsules containing 180 mg EPA and 120 mg DHA, and were instructed to consume fish at least 1 meal per month, whereas children in the control group received a diet rich in sunflower oil, placebo capsules containing safflower, palm, and olive oils, and were instructed not to consume fish. At the end of the 6-month study period, the authors reported a significant increase in the mean plasma phospholipid n-3 LCPUFA concentrations, but no differences in any parameter of asthma severity.

In the second RCT (55), Japanese children received fish oil capsules containing 84 mg EPA and 36 mg DHA on the basis of the children's weight (6–12 capsules per day), or placebo. There was a significant increase in EPA serum concentrations only in the fish oil group (no information was given about DHA), with a significant decrease in both asthma scores and responsiveness to acetylcholine in the fish oil group, but not in the control group. These results suggest that in a controlled environment supplementation of LCPUFA may be beneficial for asthma severity.

These 2 studies were also identified in a recent meta-analysis that included both children and adults (56). The authors concluded that ''given the largely inconsistent picture within and across respiratory outcomes, it is impossible to determine whether or not omega-3 fatty acids are an efficacious adjuvant or monotherapy for children or adults.''

MISCELLANEOUS DISEASES

Table 3 summarises data on paediatric diseases and conditions in which only 1 RCT on n-3 LCPUFA supplementation was identified. Although some interesting results were generated, these studies are insufficient for making any recommendation, and are summarized here only as a basis for outlining further research priorities.

EVIDENCE SUMMARY AND RECOMMENDATIONS

The findings reported in this commentary suggest that the rationale for supplementing n-3 LCPUFA to children is mostly based on theoretical considerations, findings in animal studies, and clinical studies evaluating secondary parameters. There are few RCTs, most of which have great heterogeneity in study design and measured outcomes. Based on the limited evidence available, the Committee has reached the following conclusions:

1. There is some evidence for a potentially beneficial effect of n-3 LCPUFA supplementation on functional outcome in children with ADHD. However, because beneficial effects were seen only in about half of the RCTs, and the studies reporting positive effects varied widely in both the dose and form of supplementation and in the functional outcome parameter tested, available data are insufficient to allow recommendations of n-3 LCPUFA supplementation in the treatment of ADHD.
2. There is no evidence of a favourable effect of n-3 LCPUFA supplementation on cognitive function in children.
3. No beneficial effect of n-3 LCPUFA supplementation could be demonstrated on major clinical outcome parameters in children experiencing CF.
4. The limited data available suggest that supplementation of n-3 LCPUFA in children experiencing PKU is feasible and safe, but offers only transient benefits in visual function.
5. There are insufficient data to suggest that n-3 LCPUFA supplementation has a beneficial effect on bronchial asthma in children.
6. Paediatricians should be aware of the fact that most health claims regarding supplementation of n-3 LCPUFA in various diseases in children and adolescents are not supported by convincing scientific data.

FUTURE RESEARCH PRIORITIES

1. Further research on n-3 LCPUFA supplementation in ADHD may be promising. Agreement of researchers on dose and form of supplementation as well as on optimal tests for evaluating functional outcome is needed to achieve meaningful evidence on this topic.
2. The potentially beneficial shift towards reduced inflammatory eicosanoid profiles reported in 2 studies on n-3 LCPUFA supplementation in CF may provide a basis for further investigations in this field, and may suggest that earlier and longer supplementation periods are needed for achieving improved outcome.

REFERENCES

1. Kris-Etherton PM, Innis S. Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. *J Am Diet Assoc* 2007;107:1599–611.
2. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academy Press; 2002/2005.
3. Harris WS, Mozaffarian D, Lefevre M, et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr* 2009;139:804S–19S.
4. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA); Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. *EFSA J* 2010;8:1461.
5. Gebauer SK, Psota TL, Harris WS, et al. n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr* 2006;83(6 suppl):1526S–35S.
6. Meyer BJ, Mann NJ, Lewis JL, et al. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids* 2003;38:391–8.
7. Sioen I, Huybrechts I, Verbeke W, et al. n-6 and n-3 PUFA intakes in pre-school children in Flanders, Belgium. *Br J Nutr* 2007;98:819–25.
8. Innis SM, Vaghri Z, King DJ. n-6 docosapentaenoic acid is not a predictor of low docosahexaenoic acid status in Canadian preschool children. *Am J Clin Nutr* 2004;80:768–73.
9. O'Sullivan TA, Ambrosini G, Beilin LJ, et al. Dietary intake and food sources of fatty acids in Australian adolescents. *Nutrition* 2011;27:153–9.
10. Montgomery P, Richardson AJ. Omega-3 fatty acids for bipolar disorder. *Cochrane Database Syst Rev* 2008;2:CD005169.
11. Dewey A, Baughan C, Dean T, et al. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev* 2007;1:CD004597.
12. Turner D, Zlotkin SH, Shah PS, et al. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;2:CD006320.
13. McKarney C, Everard M, N'Diaye T. Omega-3 fatty acids (from fish oils) for cystic fibrosis. *Cochrane Database Syst Rev* 2007;4:CD002201.
14. Hartweg J, Perera R, Montori V, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008;1:CD003205.
15. Lim AK, Manley KJ, Roberts MA, et al. Fish oil for kidney transplant recipients. *Cochrane Database Syst Rev* 2007;2:CD005282.
16. Sommerfield T, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. *Cochrane Database Syst Rev* 2007;4:CD003833.

17. Farinotti M, Simi S, Di Pietrantonj C, et al. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev* 2007;1:CD004192.
18. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;3:CD006443.
19. Simmer K, Schulzke SM, Patole S. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev* 2008;1:CD000375.
20. Simmer K, Patole SK, Rao SC. Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev* 2008;1:CD000376.
21. Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med* 2008;36:5–14.
22. Agostoni C, Braegger C, Decsi T, et al. Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:112–25.
23. Agostoni C, Decsi T, Fewtrell M, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
24. Schuchardt JP, Huss M, Stauss-Grabo M, et al. Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr* 2010;169:149–64.
25. Johnson M, Ostlund S, Fransson G, et al. Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. *J Atten Disord* 2009;12: 394–401.
26. Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder—a placebo-controlled double-blind study. *Eur J Clin Nutr* 2004;58:467–73.
27. Vaisman N, Kaysar N, Zaruk-Adasha Y, et al. Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. *Am J Clin Nutr* 2008;87:1170–80.
28. Voigt RG, Llorente AM, Jensen CL, et al. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr* 2001; 139:189–96.
29. Bélanger SA, Vanasse M, Spahis S, et al. Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: a randomized, double-blind, placebo-controlled study. *Paediatr Child Health* 2009; 14:89–98.
30. Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:233–9.
31. Stevens L, Zhang W, Peck L, et al. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids* 2003;38:1007–21.
32. Sinn N, Bryan J. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *J Dev Behav Pediatr* 2007;28:82–91.
33. Sinn N, Bryan J, Wilson C. Cognitive effects of polyunsaturated fatty acids in children with attention deficit hyperactivity disorder symptoms: a randomised controlled trial. *Prostaglandins Leukot Essent Fatty Acids* 2008;78:311–26.
34. Ryan AS, Nelson EB. Assessing the effect of docosahexaenoic acid on cognitive functions in healthy, preschool children: a randomized, placebo-controlled, double-blind study. *Clin Pediatr (Phila)* 2008; 47:355–62.
35. Dalton A, Wolmarans P, Witthuhn RC, et al. A randomised controlled trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source. *Prostaglandins Leukot Essent Fatty Acids* 2009;80:143–9.
36. Kennedy DO, Jackson PA, Elliott JM, et al. Cognitive and mood effects of 8 weeks' supplementation with 400 mg or 1000 mg of the omega-3 essential fatty acid docosahexaenoic acid (DHA) in healthy children aged 10-12 years. *Nutr Neurosci* 2009;12:48–56.
37. Osendarp SJ, Baghurst KI, Bryan J, et al. Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia. *Am J Clin Nutr* 2007;86:1082–93.
38. Muthayya S, Eilander A, Transler C, et al. Effect of fortification with multiple micronutrients and n-3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study. *Am J Clin Nutr* 2009;89:1766–75.
39. Beharry S, Ackerley C, Corey M, et al. Long-term docosahexaenoic acid therapy in a congenic murine model of cystic fibrosis. *Am J Physiol Gastrointest Liver Physiol* 2007;292:G839–48.
40. Freedman SD, Blanco PG, Zaman MM, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. *N Engl J Med* 2004;350:560–9.
41. Kurlandsky LE, Bennink MR, Webb PM, et al. The absorption and effect of dietary supplementation with omega-3 fatty acids on serum leukotriene B4 in patients with cystic fibrosis. *Pediatr Pulmonol* 1994;18:211–7.
42. Van Biervliet S, Devos M, Delhaye T, et al. Oral DHA supplementation in DeltaF508 homozygous cystic fibrosis patients. *Prostaglandins Leukot Essent Fatty Acids* 2008;78:109–15.
43. Lloyd-Still JD, Powers CA, Hoffman DR, et al. Bioavailability and safety of a high dose of docosahexaenoic acid triacylglycerol of algal origin in cystic fibrosis patients: a randomized, controlled study. *Nutrition* 2006;22:36–46.
44. Panchaud A, Sauty A, Kernen Y, et al. Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: a randomized, crossover placebo-controlled trial. *Clin Nutr* 2006;25:418–27.
45. Galli C, Agostoni C, Mosconi C, et al. Reduced plasma C-20 and C-22 polyunsaturated fatty acids in children with phenylketonuria during dietary intervention. *J Pediatr* 1991;119:562–7.
46. Agostoni C, Riva E, Biasucci G, et al. The effects of n-3 and n-6 polyunsaturated fatty acids on plasma lipids and fatty acids of treated phenylketonuric children. *Prostaglandins Leukot Essent Fatty Acids* 1995;53:401–4.
47. Agostoni C, Scaglioni S, Convissuto M, et al. Biochemical effects of supplemented long-chain polyunsaturated fatty acids in hyperphenylalaninemia. *Prostaglandins Leukot Essent Fatty Acids* 2001;64: 111–5.
48. Agostoni C, Massetto N, Biasucci G, et al. Effects of long-chain polyunsaturated fatty acid supplementation on fatty acid status and visual function in treated children with hyperphenylalaninemia. *J Pediatr* 2000;137:504–9.
49. Agostoni C, Verduci E, Massetto N, et al. Long term effects of long chain polyunsaturated fats in hyperphenylalaninemic children. *Arch Dis Child* 2003;88:582–3.
50. Beblo S, Reinhardt H, Muntau AC, et al. Fish oil supplementation improves visual evoked potentials in children with phenylketonuria. *Neurology* 2001;57:1488–91.
51. Beblo S, Reinhardt H, Demmelmair H, et al. Effect of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria. *J Pediatr* 2007;150:479–84.
52. Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* 1992;5:921–9.
53. Hodge L, Salome CM, Peat JK, et al. Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996;164:137–40.
54. 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;11:361–5.
55. 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;16:861–5.
56. Reisman J, Schachter HM, Dales RE, et al. Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. *BMC Complement Altern Med* 2006;6:26.
57. Amminger GP, Berger GE, Schäfer MR, et al. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry* 2007;61:551–3.

58. Romano C, Cucchiara S, Barabino A, et al. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. *World J Gastroenterol* 2005;11: 7118–21.
59. Nemets H, Nemets B, Apter A, et al. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry* 2006;163:1098–100.
60. Harel Z, Biro FM, Kottenhahn RK, et al. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *Am J Obstet Gynecol* 1996;174:1335–8.
61. Engler MM, Engler MB, Malloy M, et al. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. *Int J Clin Pharmacol Ther* 2004;42: 672–9.
62. Engler MM, Engler MB, Arterburn LM, et al. Docosahexaenoic acid supplementation alters plasma phospholipid fatty acid composition in hyperlipidemic children: results from the Endothelial Assessment of Risk from Lipids in Youth (EARLY) study. *Nutr Res* 2004;24:721–9.
63. Engler MM, Engler MB, Malloy MJ, et al. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *Am J Cardiol* 2005;95:869–71.
64. Olgar S, Ertugrul T, Nisli K, et al. Fish oil supplementation improves left ventricular function in chidlren with idiopathic dilated cardiomyopathy. *Congest Heart Fail* 2007;13:308–12.
65. Thienprasert A, Samuhaseneetoo S, Popplestone K, et al. Fish oil n-3 polyunsaturated fatty acids selectively affect plasma cytokines and decrease illness in Thai schoolchildren: a randomized, double-blind, placebo-controlled intervention trial. *J Pediatr* 2009;154: 391–5.
66. Alamiz-Echevarria L, Sanjurjo P, Elorz J, et al. Effect of docosahexaenoic acid administration on plasma lipid profile and metabolic parameters of children with methylmalonic acidaemia. *J Inherit Metab Dis* 2006;29:58–63.
67. Harel Z, Gascon G, Riggs S, et al. Supplementation with omega-3 polyunsaturated fatty acids in the management of recurrent migraines in adolescents. *J Adolesc Health* 2002;31:154–61.