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

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

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 trials (RCT); children ages 8 to 18 years; the daily dose of DHA supplemented was between 100 and 500 mg; and the duration of intervention was limited to a few (usually 2 to 4) months. The outcomes of these studies were measured in a number of ways: biomarker(s) were documented 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.

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

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 Letter-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 B4 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 25–50 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 B4 to B3 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 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>
<thead>
<tr>
<th>Data source</th>
<th>Country; age range (y); no. participants (intervention and control)</th>
<th>Short description of intervention</th>
<th>Biomarker</th>
<th>Functional outcome</th>
<th>Main result in functional outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of cognitive functions</td>
<td>Osendarp et al (37) Australia-Indonesia; 6–10 y; 96 and 102</td>
<td>22 mg/d EPA and 88 mg/d DHA</td>
<td>Plasma concentrations of selected fatty acids</td>
<td>Extensive batteries of cognitive tests</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
<td>Plasma and red blood cell phospholipid composition</td>
<td>Hopkins Verbal Learning Test, Reading and Spelling Test</td>
<td>Significant intervention effects in Hopkins Verbal Learning Test Recognition and Discrimination as well as in Spelling Test</td>
</tr>
<tr>
<td></td>
<td>Ryan and Nelson (34) US; 4 y; 85 and 90; 400 mg/d DHA</td>
<td></td>
<td>Capillary whole blood fatty acids</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kennedy et al (36) UK; around 11 y; 28 for low and 30 for high doses, 30 controls</td>
<td>400 mg/d or 1000 mg/d DHA</td>
<td></td>
<td>Internet Battery, Cognitive Drug Research Battery</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Mathayya et al (38) India; 6–10 y; 299 and 299</td>
<td>100 mg/d DHA with high or low micronutrient intakes</td>
<td>Red blood cell phospholipids</td>
<td>Extensive batteries of cognitive tests</td>
<td>No difference</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Kurlansky et al (41) USA; 6–16 y; 14 in crossover design</td>
<td>440 mg/d EPA and 240 mg/d DHA</td>
<td>Plasma and platelet phospholipids</td>
<td>Schwachman-Brasfield scores, forced expiratory volume and flow</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Lloyd-Stil et al (43) USA; 8–20 y; 9 and 10</td>
<td>50 mg/kg/d DHA</td>
<td>Plasma, red blood cell, and rectal tissue fatty acid composition</td>
<td>Basic lung volume spirometric assessment</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Panchaud et al (44) Switzerland; mean 18 y; 17 in crossover design</td>
<td>390 – 1170 mg/d n-3 PUFA</td>
<td>Neutrophil membrane fatty acid composition</td>
<td>Lung function tests</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Van Bierlaert et al (42) Belgium; mean 12 y; 8 and 8</td>
<td>200 mg/day DHA</td>
<td>Serum phospholipid fatty acids</td>
<td>Pulmonary function and number of infections</td>
<td>No difference</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Agostoni et al (46) Italy; 5–10 y; 10 and 11</td>
<td>90 mg/d EPA and 60 mg/d DHA for each 4 kg body weight</td>
<td>Plasma total lipids</td>
<td>None</td>
<td>Significant decrease in total cholesterol and triacylglycerol concentrations</td>
</tr>
<tr>
<td></td>
<td>Agostoni et al (48) Italy; mean 13 and 14 y; 10 and 10</td>
<td>About 30 mg EPA and 40 mg DHA for each 4 kg body weight</td>
<td>Plasma and red blood cell lipids</td>
<td>Visual evoked potentials</td>
<td>Decrease in P100 wave latency</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Hodge et al (53,54) Australia; 8–12 y; 20 and 19</td>
<td>Dietary modification plus 720 mg/d EPA and 480 mg/d DHA</td>
<td>Plasma phospholipid fatty acids</td>
<td>Lung function, airway hyperresponsiveness and asthma severity</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Nagakura et al (55) Japan; mean 10 and 12 y; 15 and 14</td>
<td>EPA: 17.0 – 26.8 mg/kg/d, DHA: 7.3 – 11.5 mg/kg/d</td>
<td>EPA plasma concentration</td>
<td>Acetylcholine inhalation test and asthma scoring</td>
<td>Asthma symptom scores and responsiveness to acetylcholine decreased significantly in the intervention group only</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Data source</th>
<th>Country; age range (y); no. participants (intervention and control)</th>
<th>Short description of intervention Biomarker</th>
<th>Functional outcome</th>
<th>Main result in functional outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>Amminger et al (57)</td>
<td>Austria; 5–17 y; 7 and 5</td>
<td>840 mg/d EPA and 700 mg/d DHA None</td>
<td>Aberrant Behaviour Checklist</td>
<td>No difference</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Romano et al (58)</td>
<td>Italy; 5–16 y; 18 and 20</td>
<td>1200 mg/d EPA and 600 mg/d DHA Red blood cell fatty acids</td>
<td>Relapse at 1 y</td>
<td>Significantly lower in the intervention group</td>
</tr>
<tr>
<td>Depression</td>
<td>Nemets et al (59)</td>
<td>Israel; 6–12 y; 10 and 10</td>
<td>400 mg/d EPA and 200 mg/d DHA None</td>
<td>Children’s Depression Rating Scale, Children’s Depression Inventory, Clinical Global Impression</td>
<td>Significant effect of intervention in all 3 tests</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>Harel et al (60)</td>
<td>US; adolescents; 21 and 21</td>
<td>1080 mg/d EPA and 720 mg/d DHA None</td>
<td>Cox Menstrual Symptom Scale</td>
<td>Significant reduction in symptom scale in the intervention group after 2 mo of treatment</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Engler et al (61,62,63)</td>
<td>US; 9–19 y; 10 in crossover design</td>
<td>1200 mg/d DHA Plasma phospholipid fatty acids</td>
<td>Plasma lipid profiles, and endothelium-dependent flow-mediated dilation</td>
<td>Significant increase in HDL- and decrease in LDL-cholesterol, significant increase in flow-mediated dilation</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>Olgar et al (64)</td>
<td>Turkey; mean: 10 y; 18 and 13</td>
<td>800 mg/d EPA and 700 mg/d DHA None</td>
<td>Cardiac functions</td>
<td>Significant increase of left ventricular ejection fraction, significant decrease in left ventricular internal diameter</td>
</tr>
<tr>
<td>Illness</td>
<td>Thienprasert et al (65)</td>
<td>Thailand; 9–12 y; 94 and 86</td>
<td>200 mg/d EPA and 1000 mg/d DHA Plasma phosphatidylcholine fatty acids</td>
<td>Episodes and duration of illnesses</td>
<td>Significantly fewer episodes and shorter durations of illness</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Aldimiz-Echevarria et al (66)</td>
<td>Spain; 9–16 y; 4 in crossover design</td>
<td>25 mg/kg/d DHA Plasma total fatty acids None</td>
<td></td>
<td>Significant decrease of plasma triacylglycerol concentration</td>
</tr>
<tr>
<td>Migraine</td>
<td>Harel et al (67)</td>
<td>US; mean: 15 y; 27 in crossover design</td>
<td>378 mg/d EPA and 249 mg/d DHA None</td>
<td>7-point Likert scale</td>
<td>Significant reduction of symptoms in both the intervention and control groups, no difference between groups</td>
</tr>
</tbody>
</table>

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


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