REVIEW ARTICLE

Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Malnourished Children: A Scoping Review

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ABSTRACT

Polyunsaturated fatty acids (PUFAs) intake may be beneficial in many aspects during the early phase of life. This scoping review aims to examine the beneficial outcomes and intakes of omega-3 and omega-6 PUFA among children. An electronic database search on academic journals published from 2017 to 2021 was conducted using Science Direct, PubMed, and Google Scholar. A total of 35 studies were identified and included in this scoping review. Majority of the findings found that PUFAs intake has a beneficial impact on the growth development, mental and cognitive health among children whether they are malnourished, sick or healthy individuals. Overall, this review may provide additional information on the benefits and recommended intake of supplementing PUFAs on children. More detailed research on this topic is needed to support these findings since it will contribute to the formation of the dietary intervention.
Malaysian Journal of Medicine and Health Sciences (2023) 19(6):285-296. doi:10.47836/mjmhs.19.6.38

Keywords: Polyunsaturated Fatty Acid, Omega -3 and -6 Fatty Acid, Children

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INTRODUCTION

Early childhood development, which lasts from birth until the age of eight, is crucial for cognitive, social, behavioural, emotional, and physical growth. A child's developing brain is extraordinarily plastic and adaptable during these years because billions of interconnected neuronal circuits are formed by the combination of genetics, environment, and experience. A stimulating environment, sufficient nutrition, and social interaction with attentive caretakers are necessary for the optimal brain development (1). Any delays in development during this early childhood stage will have long-term effects on a child's mental and physical health, behaviour and ability to learn. Apart from that, children are vulnerable to malnutrition, which is one of the contributing factors leading to poor health, negatively impacting their mental and physical development and learning capability in the future (2,3). The World Health Organisation (WHO) stated that 155 million children under the age of five are stunted, 52 million are wasted, and 38.3 million are categorized as overweight or obese, as per estimations (4,5). Undernutrition (wasting, stunting, and underweight), being overweight or obese, insufficient micronutrients, and the associated diet-related non-communicable illnesses are all examples of malnutrition.

Human requires polyunsaturated fatty acids (PUFAs), which can only be obtained from dietary intake. There are two types of PUFAs which is mainly omega-3 and omega-6 fatty acids. Both of these nutrients play an important role in the optimal growth, development and functioning of all organ systems especially the brain and central nervous system (6).

Omega 3 fatty acid (n-3 PUFAs) is a lipid consisting of aliphatic monocarboxylic acids which can be commonly found in food. There are three main n-3 PUFAs which are Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) derived from the marine sources commonly in fish and other seafood which demonstrated the most evidence of health advantages. Another omega-3 fatty acid is a non-marine n-3 LC-PUFA, alpha-linoleic acid (ALA) which is usually found in seed crops like canola, flaxseed and soybean (7). Consumption of n-3 LCPUFAs, particularly DHA and EPA, is thought

to be especially crucial for neuronal development and cognitive performance during early infancy due to the abundance of DHA inside the brain (8). LC-PUFAs including EPA, DHA and arachidonic acid (AA) is also involved in a variety of neurological functions, from membrane fluidity to gene expression control. As a result, n–3 LCPUFA intake may have a significant impact on the cognitive and emotional development in childhood and adolescence (9). In addition, LC-PUFAs have been shown to regulate immune cell activities and inflammatory processes. Thus, resulting in faster immune system maturation, enhanced intestinal wall integrity, and ability to fight infectious illnesses in children (10).

Omega-6 fatty acids (n-6 PUFAs) are PUFAs recognized by having a double bond in their chemical structure, with the position of six atoms away from the methyl group. The main dietary n-6 PUFAs are linoleic acid (LA) and arachidonic acid (AA). LA can be found in seeds, nut and plant oils such as sunflower seeds, pumpkin seeds, walnuts, and corn. This n-6 PUFAs serve as a precursor for producing eicosanoids and cytokines, involved in the regulation of inflammation, immune function and development of vascular system (11).

Fatty acid deficiency in children has been related to behaviour, learning, cognition problems and malnutrition. Learning and cognitive impairments among these children may due to complications with phospholipid synthesis (which makes up the brain cell membranes), glucose transportation and utilization, and neuron size reduction in the hippocampus, hypothalamus, and cerebral cortex (12). Thus, supplementing children with n-3 and n-6 fatty acids can help with neurodevelopmental problems like attention deficit hyperactivity disorder (ADHD) and developmental coordination disorder. Apart from that, malnutrition has been linked with PUFAs deficiency due to several factors including inflammation, infection, and poor anthropometry parameters (6). Therefore, the supplementation of PUFAs especially n-3 FAs may positively impact on the anthropometric parameters, body fat percentage and increases the appetite among malnourished children (13).

Given the importance of PUFAs among children whether they are healthy or sick, malnourished, autism and attention deficit hyperactive disorder (ADHD), this study examines the information regarding the beneficial outcomes and intakes of omega-3 and omega-6 FAs among these children throughout all the countries such as Hong Kong, Korea, Iran, Germany, Australia, etc.

METHODOLOGY

In this current research, a scoping review has been adopted to be applied in order to determine the beneficial outcome of omega-6 and omega-3 PUFA among children and its recommended intake. A methodological framework proposed by Arksey & Malley, 2005 (14) was conducted throughout this scoping review. This framework consists of five stages which were: (1) formulating the research question; (2) finding relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarising, and reporting the results. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) which was conducted using a flow diagram as shown in Figure 1 was used as a guideline in completing this scoping review to synthesize evidence and assess the scope of literature on the selected topic.

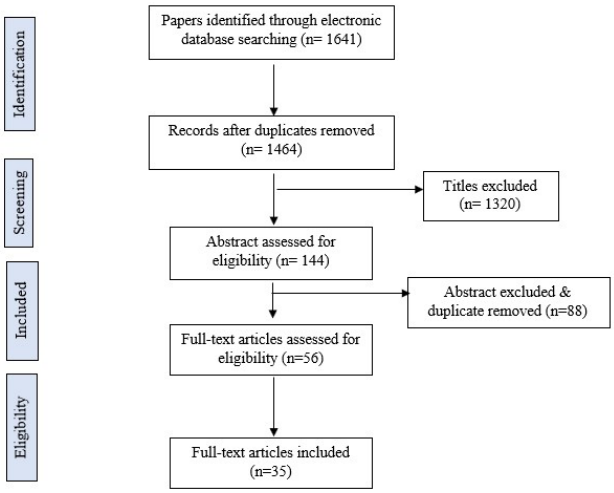

Figure 1: Flow chart of scoping review [based on framework by Arksey & Malley, 2005 (14)]

Identifying the research questions

The review questions were: (1) what are the beneficial outcomes of omega-6 and omega-3 PUFA on children? (2) what are the recommended intake of omega-6 and omega-3 PUFA on children?

Identifying relevant studies

The following databases were used to conduct an electronic search which are PubMed, Science Direct and Google Scholar. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) were also used as research resources. This search was limited to academic journals which has been published in English language from year 2017 to 2022. The study includes all sorts of studies, with the exception of systematic reviews and review papers. The researcher independently reviewed titles, abstracts and keywords for eligibility. Table I shows the key terms used during the article search.

Study selection

Upon careful consideration, studies were selected if they included information on: (1) participants' characteristics; (2) beneficial outcome of omega-6 and omega-3 fatty acids for children; and (3) recommended intake of omega-6 and omega-3 fatty acids.

Table I: Key search terms in scoping review

Key Search Terms
Benefit **OR** Health Impact **AND** Monounsaturated Fatty Acid **OR** linoleic acid **AND** malnourished child **OR** stunting child **OR** Failure To Thrive children
Beneficial **OR** Advantage **AND** Omega 3 Fatty Acid **OR** Docosahexaenoic acid **OR** Eicosapentaenoic acid **OR** alpha-Linolenic acid **AND** malnourished child **OR** Failure To Thrive children **OR** stunting child
Benefit **OR** Health Impact **AND** Polyunsaturated Fatty Acid **OR** Omega-3 Fatty Acid **OR** Omega-6 Fatty Acid **AND** malnourished child **OR** stunting child **OR** Failure To Thrive children
Benefit **OR** Effect **AND** essential fatty acids **OR** Polyunsaturated Fatty Acid **OR** Omega-3 Fatty Acid **OR** Omega-6 Fatty Acid **AND** malnourished child **OR** stunting child **OR** Failure To Thrive children
Intake **OR** recommed **AND** Polyunsaturated Fatty Acid **OR** Omega-3 Fatty Acid **OR** Omega-6 Fatty Acid **AND** Monounsaturated Fatty Acid **AND** child

Charting the data

Table II summarises the country(ies), author(s), year of publication, study type(s) and purpose(s), number and age of the participants, and findings regarding the beneficial outcome of omega-6 and omega-3 fatty acid on children and its recommended intake.

Collating, summarizing and reporting the results

Table II shows the results of review on the beneficial outcome of both omega-3 and omega-6 fatty acids on children followed by malnourished children. Then, it displayed the results regarding the beneficial outcome of omega-3 or omega-6 only on children followed by malnourished children.

RESULTS

During the search, a total of 1641 titles were identified with 144 abstracts being considered for inclusion. As shown in Figure 1, 35 studies were selected and included in this review. Majority of the research are Randomized Controlled Trials (29 studies, 83%), cross-sectional studies (5 studies, 14%) and observational non-randomized study (1 study, 3%). The sample size in the studies ranged from 20 to 2,565 participants, aged 6 months to 18 years old. This study summarises the beneficial outcome of omega-6 and omega-3 for children and their recommended intake as outlined in Table II. Twenty-four studies mentioned the intake or recommendation of PUFAs among the children which range between 150 to 2000 mg/day for omega-3 FAs and 60 to 280 mg/day for omega-6 FAs.

Beneficial outcomes of omega-6 and omega-3 fatty acid

Growth

Thirteen out of thirty-five studies discovered the beneficial impact of supplementing omega-6 or omega-3 FA towards children's growth whether they are healthy or malnourished children. The supplementation of omega-3 or omega-6 FA is associated with increased height or length and weight gain amongst children who are short stature or have normal health (10,15–21). In contrast, two studies reported no significant effects of PUFA supplementation on body weight (22,23). Furthermore, improvement in haemoglobin, nutrition, physical health and growth parameters such as body mass index (BMI) and body fat percentage was all related to the intake of PUFA (6,13). Olsen et al reported that PUFA status, particularly n-3LC-PUFAs, were associated with better development scores based on Malawi Development Assessment Tool (MDAT) z-scores among malnourished children with higher mid-upper arm circumference, more fat-free mass, better anthropometric measurement and iron status.

Mental and Cognitive Health

Fifteen studies found that the supplementation or intake of omega-6 or omega-3 FA may positively affect the mental and cognitive health of children. The role of PUFAs has been studied in various psychiatric disorder in children including depression, psychotic disorder, mood disorder, ADHD and Autism spectrum disorder (ASD). Several studies reported that supplementing omega-6 or omega-3 FA in children with ADHD may provide a beneficial effect such as improvement in the ADHD symptoms, inattention, social-emotional problems, cognitive function, aggressive and impulsive behaviour (25–28). However, there are some studies showed no significant advantages of these supplementations towards the symptoms of ADHD (28,29). Raine et al found that supplementing omega-3 among children with psychotic-like personalities may be beneficial in reducing their aggressiveness and antisocial behaviour. One study showed that treating the malnourished child with DHA high-oleic Ready-to-use therapeutic food (DHA-HO-RUTF) helps in improving cognitive development (31). Furthermore, intake of omega-6 or omega-3 FA is associated with better behaviour and social communication, improvement in cognitive functions, mental health, language development and performances of the children (9,32–36). Additionally, few studies reported no significant positive effects of omega-3 PUFA supplementation towards the self-regulation, executive and cognitive function which is related to the development of behavioural and cognitive process among pre-school children (37,38). Exploring the self-regulation and executive functioning among children may give insight for researcher regarding their academic performances, social behaviour and school engagement.

Visual and Neurological/Brain Development

Two studies reported that incorporating PUFA into one's diet in early life can give a positive impact on their neurological or brain development. Lepping and colleagues (2018) stated that "supplementing LCPUFAs throughout childhood may give long-term effects on brain structure, function, and neurochemical concentrations

Table II: Benefit of omega 3 and 6 fatty acid

No	Country	Study	Type and purpose of study	Participants characteristics	Intake/ supplement composition	Outcome
1	Mexico	Rivera-Pasquel et al., 2021	Randomized Double-Blind Clinical Trial • To assess the effect of PUFAs-fortified milk-based infant formula on lipid levels in Mexican infants 12 to 30 months old. • To evaluate anthropometry and micronutrient status of the infants	Subjects: 193 healthy infants aged 12-30 months old	-	• Infants consuming a milk-based formula containing PUFAs for four months significantly increased their percentage levels of DHA and alpha-linolenic acid compared with those who consumed Non-PUFAs-fortified formula. • Anthropometrical outcomes showed that infants in both groups slightly increased in length/height-for-age Z-score • Micronutrient composition within each group differed in that folate levels were significantly higher in infants from the PUFAs group as compared to their counterparts
2	Uganda	Jain et al., 2019	Cross-sectional study • To identify differences in FAs and growth based on HIV status in children between the ages of 6–10 years old in Kampala, Uganda	Subjects: 240 HIV-infected/uninfected children between 6 to 10 years old	-	• HIV positive children had significantly lower height-for-age-z-scores (HAZ) than uninfected children • Total omega-6 FAs were significantly associated with height-for-age-z-scores regardless of HIV status
3	United States	Lepping et al., 2018	Randomized Controlled Trial • To determine whether supplementation of long-chain polyunsaturated fatty acids (LCPUFA) during the first year of life influenced brain function, structure, and metabolism at 9 years of age	Subjects: 42 children (newborn up til age 9 years)	-	• LCPUFA supplementation during infancy has lasting effects on brain structure, function, and neurochemical concentrations in regions associated with attention (parietal) and inhibition [ACC], as well as neurochemicals associated with neuronal integrity [NAA] and brain cell signaling (mI)
4	Spain	Rodriguez-Hernandez et al., 2018	Observational Multicenter Nonrandomized Study • To assess the impact of omega-3 fatty acid supplementation among other nonpharmacological treatments on mental health and quality of life of children with behavioral disorders	Subjects: 942 children aged 6 to 12 years old with behavior-related problems		• Omega-3 fatty acid supplementation subgroup presented greater improvements in each category of SDQ, except for the emotion subscale. • Omega-3 fatty acid supplementation alone or in combination with other nonpharmacological treatments is effective in improving children's mental health
5	United States	Sheppard et al., 2017	Randomized Controlled Trial • To determine the feasibility of a full-scale trial of the effect of omega-3 and -6 fatty acid supplementation on ASD symptoms in children born preterm who were at increased risk for a diagnosis of ASD	Subjects: 31 children aged 18 to 38 months were randomized (receive an omega-3 and -6 supplement or a placebo for 3 months)	338 mg EPA, 225 mg DHA, 280 mg total omega-6 FA, 306 mg total omega-9 FA	• Efficacy of omega-3 and -6 fatty acid supplementation in improving aspects of early language development in children at risk for ASD, specifically gesture use
6	Canada	Devlin et al., 2017	Double Blind Randomized, Controlled Trial • To examine the effects of ARA and DHA supplementation in toddlers from 12 to 24 months of age compared to children following their usual diet on cognitive, language and visual-motor development, and biomarkers of ARA and DHA status.	Subjects: 133 healthy toddlers aged 12-14 months	200 mg/day DHA 200 mg/day ARA	• Increasing the ARA status in toddlers is associated with better neurodevelopment at age 24 months
7	Malawi	Stephenson et al., 2021	Triple-blind, randomized, controlled clinical feeding trial • Hypothesis of the study RUTF made with reduced amounts of linoleic acid, achieved using HO peanuts without added DHA (HO-RUTF) or with added DHA (DHA-HO- RUTF), improves cognition when compared with standard RUTF (S- RUTF)	Subjects: 2565 severe acute malnutrition children aged 6 to 59 months	-	• The use of DHA-HO-RUTF in the treatment of uncomplicated severe acute malnutrition resulted in an increased MDAT score, indicating a cognitive advantage 6 months after diet therapy was completed.
8	Cambodia	Sigh et al., 2020	Cross-sectional study • To measure fatty acid composition, particularly whole-blood PUFA content, in acutely malnourished children and identify associations with markers of nutritional and health status	Subjects: 174 children aged 0.5-18 years with acute malnutrition	-	• Wasting was not associated with any PUFA • Stunting and low height were consistently positively associated with total PUFA and positively with n-6 PUFA • Height was positively associated with n-3 long-chain PUFA (LCPUFA)
9	Northern Ghanaian	Adjepong et al., 2018	Cross-sectional Study • To determine the association between whole blood FAs and growth parameters in Northern Ghanaian children 2–6 years of age	Subjects: 307 children aged between 2 to 6 years (29.7% were stunted)	-	• Essential FA did not differ between stunted and non-stunted children and was not associated with HAZ or WAZ • In hemoglobin adjusted regression models, both HAZ and WAZ were positively associated with arachidonic acid, DGLA, DHA and ratio of DGLA/linoleic acid • Omega-6 FAs are critical in childhood linear growth

Table II: Benefit of omega 3 and 6 fatty acid (continued)

No	Country	Study	Type and purpose of study	Participants characteristics	Intake/ supplement composition	Outcome
10	West Africa	Yameogo et al., 2017	Cross-sectional study • To describe whole-blood PUFA levels in children with MAM and to identify correlates of PUFAs	Subjects: 1609 children with moderate acute malnutrition aged 6 to 23 months		• Children with MAM had low concentrations of whole-blood PUFAs, particularly n-3 PUFAs • Infection, inflammation, hemoglobin, anthropometry and diet were correlates of PUFAs concentrations in children with moderate acute malnutrition
11	Hong Kong	Raine et al., 2021	Randomized Controlled Trial • To examine whether omega-3 supplementation reduces antisocial behavior, and whether any treatment effects are a function of gender and psychopathy	Subjects: 324 schoolchildren aged between 8 and 18 years	840 mg omega 3 (300 mg of DHA, 300 mg of EPA, 180 mg of alpha-linolenic acid, and 60 mg of DPA)	• Findings suggest that omega-3 supplementation may be helpful in reducing childhood antisocial and aggressive behavior in females, and those with psychopathic-like personalities
12	Korea	Lee et al., 2021	Double-Blind, Randomized, Placebo-Controlled Trial • To investigate the efficacy of combined omega-3 and Korean red ginseng supplementation on ADHD symptoms and cognitive function in children with subthreshold ADHD	Subjects: 120 children aged between 6 and 12 years with subthreshold ADHD	500 mg of omega 3 (EPA, 294 mg; DHA, 206 mg)	• Significant effects on the scores of ADHD-RS, as well as several subscales of CBCL including ADHD and attention problem subscales were revealed • Combination of omega-3 and Korean red ginseng may have beneficial impact among children with subthreshold ADHD
13	Australia	Roach et al., 2021	Randomised, Double-Blind, Placebo-Controlled Trial • To investigate the effect of n-3 LCPUFA supplementation on self-regulation in preschool-aged children compared to a placebo supplementation. • To investigate the effect of n-3 LCPUFA supplementation on executive function, electroencephalography EEG measures and ADHD symptoms	Subjects: 78 children aged 3 to 5 years of age [n-3 LCPUFA treatment (n = 39) or placebo (n = 39) group]	1.6 g/day of EPA and DHA	• Significant modest positive Spearman correlations found between the HS-Omega-3 index® and both behavioural self-regulation and cognitive self-regulation • There were no improvements in SR or EF outcome variables for the n-3 LCPUFA group post intervention • No treatment effects were found in typically developing children
14	Iran	Doaei et al., 2021	Randomized Clinical Trial • To investigate the effect of omega-3 on social, verbal, and behavioral activities in ASD children	Subjects: 54 children aged 5 to 15 years with autism [case (n = 28) and control (n = 26) groups]	1000 mg/day Oemga-3 supplementation	• Findings found that omega-3 treatment improved autism characteristics including stereotyped behaviors and social communication
15	Denmark	Teisen et al., 2020	Randomized Controlled Trial • To investigate the effects of oily fish consumption on overall and domain-specific cognitive and socio-emotional scores and explore sex differences	Subjects: 199 Healthy 8-9 years old children	~300 g/week oily fish	• Oily fish dose dependently improves the cognitive function especially attention and cognitive flexibility, and reduces the socio-emotional problems
16	Taiwan	Chang et al., 2019	Double-blind, Randomised, Placebo-Controlled Trial (RCT) • To compare the effects of high-dose eicosapentaenoic acid (EPA, 1.2 g) and placebo on cognitive function (continuous performance test) youth (age 6–18-years-old) with ADHD • To examine the effects of baseline endogenous EPA levels on treatment response and the effects of EPA treatment on pufas levels	Subjects: 92 children aged 6 to 18 years old with ADHD	1.2 g/day EPA	• EPA treatment improves cognitive symptoms in ADHD youth, especially if they have a low baseline endogenous EPA level, while youth with high EPA levels may be negatively affected by this treatment
17	Denmark	Vuholm et al., 2019	Randomized Controlled Trial • To investigate whether intake ~300 g oily fish/wk affected diastolic blood pressure and serum triacylglycerol as well as other cardiometabolic markers in healthy danish 8- to 9-y-old children when compared with a similar intake of poultry as the control	Subjects: 197 children aged 8 to 9 years (received ~300 g/wk of oily fish or poultry (control))	~300 g/week oily fish	• Oily fish intake improved serum triacylglycerol and HDL cholesterol in a dose-dependent manner in 8 to 9 years old children, but had no effect on blood pressure, HRV, or glucose homeostasis
18	Spain	San Mauro Martin et al., 2019	Randomised Clinical Trial • To analyse changes in BIS-11c scores in children with ADHD after an 8-week intervention with the Mediterranean diet, omega-3 fatty acid supplementation, or Mediterranean diet plus omega-3 fatty acid supplementation, as compared to a control group	Subjects: 60 children aged 6 to 16 years with ADHD (1 control group and 3 intervention groups)	Recommendation: 2 omega-3 softgel supplements (550 mg/day EPA; 225 mg/day DHA)	• Omega-3 supplementation group showed a fairly significant decrease in the total BIS-11c indicating less impulsive behaviour.
19	Oman	Al-Ghannami et al., 2018	Randomised Open-Label Trial • To examine the effect of DHA enriched fish oil supplement and fish meal on cognitive and behavioural functioning manifested as ADHD in primary school students (9-10 years old) in Muscat, Oman.	Subjects: 132 healthy children aged 9 and 10 years (66 children receive fish oil; 66 children receive fish meal)	~100 g/weekday of fish (150-200 mg of DHA) 403 mg/day DHA fish oil capsule	• DHA levels increased by 72% and 64% in fish oil and fish meal group, respectively • The beneficial outcome of DHA in this study are cognitive and behavioural among health school children

Table II: Benefit of omega 3 and 6 fatty acid (continued)

No	Country	Study	Type and purpose of study	Participants characteristics	Intake/ supplement composition	Outcome
20	France	Cornu et al., 2018	Double-blind Placebo-Controlled Randomised Trial • To evaluate the efficacy of omega-3 fatty acids to improve ADHD symptoms in children with diagnosed ADHD	Subjects: 162 children aged 6–15 years with established diagnosis of ADHD	Recommendations: Children 6-8 years-336 mg EPA and 84 mg DHA Children 9-11 years-504 mg EPA and 126 mg DHA Children 12-15 years-672 mg EPA and 168 mg DHA	• Findings from this study does not show any beneficial effect of omega-3 supplement in children with mild ADHD symptoms • The total ADHD-RS-IV score reduction was greater in the placebo group than in the DHA–EPA group
21	Australia	Hansell et al., 2018	Randomized Controlled Trial • To examine the interactions between supplementation and TRAP with allergic disease and lung function outcomes at age 5 and 8 years	Subjects: 400 children aged 5 and 8 years	-	• Fish oil supplementation may protect against pro-allergic sensitisation effects of TRAP exposure • Supplementation also protected against the effect of traffic exposure on pre-bronchodilator FEV1/FVC ratio
22	Greece	Papamicheal et al., 2018	Randomised Controlled Trial • To investigate the efficacy of a Mediterranean diet supplemented with high omega-3 'fatty' fish intake in Greek asthmatic children	Subjects: 64 children (mean age 7.98 ± 2.24 years) with asthma	2 fatty fish meals per week (~150g of cooked fish)	• A Mediterranean diet supplemented with two fatty fish meals per week might be a potential strategy for reducing airway inflammation in childhood asthma
23	Sweden	Svensson et al., 2018	Double-blind randomized placebo-controlled trial • To evaluate the effect of 15 weeks' administration of 732 mg/day of omega-3 fatty acids (556 mg EPA, 176 mg DHA) on PA and relative body weight in children aged 7–9 years	Subjects: 423 children aged 7 to 9 years (204 were allocated to the omega-3 fatty acids group and 219 to the placebo group)	732 mg of omega-3 FA (556 mg EPA, 176 mg DHA) 60 mg of omega-6 FA (GLA)	• No significant effects of omega-3 fatty acids on PA or relative body weight were observed
24	Germany	Crippa et al., 2018	Randomized, Placebo-Controlled Clinical Trial • To investigate the efficacy of DHA dietary supplementation on behavior and cognition in school-aged, drug-naïve children with ADHD	Subjects: 50 children aged 7 to 14 years with ADHD	500 mg/day algal DHA	• 6 months treatment with supplemental DHA appears to have small positive effects on other behavioral and cognitive difficulties • DHA supplementation showed a significant, nonetheless quite small, effect on children's psychosocial functioning, emotional problems, and focused attention • 6-month DHA supplementation has no beneficial effect on the symptoms of ADHD in school-aged, drug-naïve children with an established diagnosis of ADHD
25	Germany	Demmelmair et al., 2018	Randomized Controlled Trial • To compare with a similar study design effects of salmon and meat intake on the outcomes of WPPSI-III tests and tests of fine motor skills in preschool kids in Germany	Subjects: 205 healthy children aged 4 to 6 years old	-	• Intake of farmed Atlantic salmon led to a greater increase of the raw scores of the picture concept and symbol search subtests, while in the six other subtests raw scores were not different between the groups • Modest positive association of salmon intake with the performance of preschool children in some subtests evaluating fluid intelligence but does not suggest an influence on global IQ development
26	Iran	Rahmani et al., 2018	Randomized, Placebo-Controlled, Double-Blind Trial • To test the hypothesis that vitamin D and omega-3 would decrease pediatric nocturnal enuresis compared to placebo	Subjects: 180 children aged 7 to 15 years old with nocturnal enuresis	1000 mg/day omega-3 gel capsule (180 mg EPA; 120 mg DHA)	• Findings from this study showed that supplementation with vitamin D and omega-3 could reduce the number of wet nights among 7-15-year-old children with nocturnal enuresis
27	Norway	Oyen et al., 2018	Randomized Controlled Trial • To investigate whether an increased intake of fatty fish compared to meat improves cognitive function in children 4–6 years old	Subjects: 218 children aged 4 to 6 years old (105 in the fish, and 113 in the meat group)	50-80 g fatty fish	• Fish group had a significant increase of red blood cell n-3 LC-PUFAs • There was no beneficial effect of fatty fish compared to meat on cognitive functioning in the preschool children. • When considering dietary compliance, we found a beneficial effect of fatty fish on cognitive scores.
28	Ethiopia	Argaw et al., 2018	Factorial Randomized Controlled Trial • To evaluate the independent and combined effects of fish oil (500 mg n–3 LC-PUFAs/day) supplementation to lactating mothers and their breastfed children, aged 6–24 months, on child morbidity, systemic inflammation, and growth in southwest Ethiopia.	Subjects: 360 mother-infant pairs with infants 6–12 months old	500 mg/day n–3 LC-PUFAs (169 mg DHA; 331 mg EPA)	• n–3 LC-PUFA supplementation given directly to children modestly increased relative weight gain
29	United States	Arnold et al., 2017	Randomized Controlled Trial • To examine fatty acid profiles, their response to omega-3 fatty acid supplementation, and associations with clinical status and treatment response in youth with mood disorders	Subjects: 95 children aged 7 to 14 years with depression	2 g/day Omega 3 supplementation (1.4 g/day EPA, 0.2 g/day DHA, and 0.27 g/day other Omega-3)	• 2 g/day of Omega-3 increases the EPA blood levels sevenfold and DHA levels by half • Body weight correlated inversely with increased EPA and DHA and positively with clinical mood response

Table II: Benefit of omega 3 and 6 fatty acid (continued)

No	Country	Study	Type and purpose of study	Participants characteristics	Intake/ supplement composition	Outcome
30	United States	Christian et al., 2017	Double-Blind Randomized-Controlled Trial • To examine the plasma PUFAs among 64 children and adolescents ages 7–14 years randomized to receive either ω-3 PUFA supplements or control capsules for 12 weeks	Subjects: 64 youth aged 7 to 14 years with diagnosis of mood disorder	2000 mg omega-3 supplements	• Results show strong linear relationships of both absolute body weight and BMI percentile with ω-3 PUFA accumulation in youth
31	Germany	Buchhorn, 2021	Randomized Controlled Trial • To proof the effect of an omega-3-fatty acid supplementation (245 days on average) on height and 24-hours HRV in 34 children with short stature of whom 17 children received an ongoing growth hormone treatment	Sucjects: 34 children with short stature Age of 6.6±4.4 years	1-2 g/day fish oil Recommendations: Children up to 8 years ~400 mg/day EPA and DHA. If able to swallow capsules ~800 mg/d EPA and DHA.	• During Omega-3-fatty acid supplementation together with growth hormone treatment the height percentile increases • Omega-3-fatty acid supplementation in children with short stature improves height and heart rate variability independently from an ongoing growth hormone treatment
32	Indonesia	Jutomo et al., 2020	Experimental randomized clinical trial design • To study the role of omega-3 fatty acid supplementation on anthropometric measures of toddlers with stunting, especially height	Subjects: 24 children aged 12 to 36 months (12 children: control group who received placebo; 12 children: treatment group who received omega-3 fatty acid supplementation for 2 months)	Body weight >10-20 kg given 500 mg of omega-3 fatty acids children weight of ≤10 kg given 350 mg of omega-3 fatty acids	• Supplementation of omega-3 fatty acids in children under five with stunting could significantly increase height
33	Saudi Arabia	Khan et al., 2019	Randomized Controlled Trial • To envisaged assessing the improvement in calorific intake correlating with growth parameters in children with sickle cell disease from Saudi Arabia by dietary supplementation with omega-3 fatty acids	Subjects: 86 children aged between 5 and 16 years old (24 children undertook the omega-3 supplementation for a period of 6 months)	Body weight < 25 kg given ~ 190 mg/day DHA Children weight > 25 kg given ~380 mg/day DHA	• Supplementation with the healthy fat omega-3 resulted in improved Hb percentage and highly improved growth parameters of BMI and body fat percent • Findings also found that the participants receiving supplementation of omega 3 FA has better appetite, and physical health
34	Germany	Bucchorn et al., 2017	Randomized Controlled Trial • To determine if supplementation of omega-3-fatty acids improves HRV in short stature and/or low birth weight children.	Subjects: 20 children (mean age of 7.4 ± 4.5 years) with short stature	1-2 g/day fish oil Recommendation: children up to age 8 years ~ 200 mg/day EPA and 40 mg/day DHA; If able to swallow capsules ~ 400 mg/day EPA and 120 mg/day DHA	• After supplementation of omega-3-fatty acids, the mean HRV significantly increased as indicated by nearly all time and frequency domain parameters • In children with short height due to intrauterine growth retardation, growth hormone deficiency, congenital abnormalities, and cardiac problems, our study found that omega-3 fatty acid supplementation improved HRV. • As a result, in order to improve their cardiovascular prognosis, we recommend omega-3 fatty acid supplementation for children with short stature who have a considerably lower 24 hour HRV.
35	Burkina Faso	Olsen et al., 2020	Cross-sectional study • To describe motor and language development of children with MAM and explore its nutrition and health-related correlates	Subjects: 1608 children with moderate acute malnutrition aged 6 to 23 months	-	• Children with higher mid-upper arm circumference, weight-for-height, height-for-age, fat-free mass, n-3 PUFAs, Hb, and iron status had better MDAT z-scores • PUFA status, especially n-3LC-PUFAs, were associated with better development scores.

Abbreviations: PUFAs, Polyunsaturated Fatty Acids; DHA, Docosahexaenoic Acid; HIV, Human immunodefeciency virus; HAZ, Height-for-age z-score; HRV, Heart Rate Variability; ACC, Anterior Cingulate Cortex; NAA, N-acetylaspartate; SDQ, Strengths and Difficulties Questionnaires, ASD, Autism Spectrum Disorders; EPA, Eico-sapentaenoic Acid; DHA, Docosahexaenoic Acid; ARA, Arachidonic Acid; HO, High-Oleic; RUTF, Ready-To-Use Therapeutic Food; MDAT, Malawi Developmental Assessment Tool; HAZ; Height-for-age z-score; WAZ, Weight-for-age z-score; DGLA, Dihomo-Gamma-Linolenic Acid, MAM, Moderate Acute Malnutrition; DHA, Docosahexaenoic Acid; EPA, Eico-sapentaenoic Acid; DPA, Docosapentaenoic acid; ADHD, Attention Deficit Hyperactivity Disorder; ADHD-RS, Attention-Deficit Hyperactivity Disorder Rating Scale; CBCL, Behavior Check List; HRV, Heart Rate Variability; SR, self-regulation; EF, executive functioning; ASD, Autism Spectrum Disorders; ADHD, Attention Deficit Hyperactivity Disorder; EPA, Eico-sapentaenoic Acid; HRV, Heart Rate Variability; HDL, High-density lipoprotein; BIS-11c, Barratt Impulsiveness Scale scores; ADHD-RS-IV, Attention-Deficit Hyperactivity Disorder Rating Scale version 4; TRAP, Traffic Related Air Pollution; FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; PA, Physical activity GLA, Gamma-Linolenic Acid; WPPSI-III, Wechsler preschool and primary scale of intelligence, 3rd edition; IQ, Intelligence quotient; BMI, Body Mass Index; HRV, Heart Rate Variability; Hb, Hemoglobin; BMI, Body Mass Index; DHA, Docosahexaenoic Acid; EPA, Eico-sapentaenoic Acid; HRV, Heart Rate Variability; MAM, Moderate Acute Malnutrition; MDAT, Malawi Developmental Assessment Tool

in areas associated with attention (parietal) and inhibition, as well as neurochemicals associated with neuronal integrity and brain cell signalling" (p.10) (39). In addition, another study found that elevating arachidonic acid levels in children is linked to improved neurodevelopment at 24 months of age 40.

Cardiovascular

Two studies reported the effectiveness of omega-6 or omega-3 FA intake on cardiovascular conditions. Vuholm and colleagues found that consumption of approximately 300 g oily fish per week has improved the serum triacylglycerol and high-density lipoprotein (HDL) cholesterol in children aged 8 to 9 years old. Another study discovered that it is recommended to supplement omega-3 FA to children with short stature as it may help in improving their cardiovascular prognosis by increasing the heart rate variability (HRV) (42).

Asthma

One study showed that high omega-3 FA supplementation may be beneficial for children with asthmatic problems (43).

Other disease

One study found that supplementation of omega-3 FA and vitamin D among children with nocturnal enuresis reduces the frequency of wet nights (44). Another study reported that the fish oil supplementation may help prevent the development of pro-allergic sensitization caused by traffic-related air pollution exposure (45).

DISCUSSION

Polyunsaturated fatty acids are essential in various aspects, including the growth and development in early years of life, preventing cardiovascular diseases, improving chronic inflammation and malnutrition status. Additionally, PUFAs plays a critical role in the development and function of the brain and neurological system, particularly throughout the childhood phase (46). However, some studies also show no beneficial effect after the supplementation of PUFA.

In this review, several studies showed the impact of PUFAs intake on child growth and the later life complications such as cardiovascular disease. Stunting and short stature were found to be consistently associated with total PUFA and n-6 PUFA (17). A double-blind, randomized clinical research study showed that children who received infant formula enhanced with micronutrients and PUFAs had better lipid profiles compared to children who only got micronutrient-fortified formula. Infants in both groups improved their length/height-for-age Z-score (16). Additionally, the findings was consistent with another study reporting that supplementing stunted children under age five with 350 – 500 mg of omega-3 fatty acid may help them grow taller (18). This shows that height was favourably related to supplementation or intake of PUFAs due to their by-products throughout the early development, which are essential for organogenesis, growth hormone synthesis, and general growth regulation via maintaining the structural integrity of cell membranes, and immune system function (47).

Apart from that, stunting has also been correlated to an increase risk of cardiovascular disease later in life (15,48). This may be due to its relation with higher systolic blood pressure, stiffening in blood vessels, and increased in levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol and insulin (48). The findings was consistent with another study conducted by Reiner Buchhorn reporting that supplementation of 1-2 grams of fish oil per day among short-statured children has improved the height and heart rate variability (HRV) (15). Improvement in the HRV may become an indicator of lesser cardiovascular morbidity and mortality in both children and adults (42).

This review found that the supplementation of PUFAs, especially omega-3 FAs among children with sickle cell disease (SCD) was expected to improve their nutrition and growth parameters which is important because these children are more likely to suffer from malnutrition, which results in stunted growth and increases the severity of anaemia . This can be proven by a study conducted among SCD children showing that the supplementation of omega-3 FAs for six months significantly improve their haemoglobin percentage, BMI and body fat percent (13). Apart from that, this findings was consistent with previous findings showing that supplementing SCD patients with necessary omega-3 fatty acids reduces anaemia, vaso-occlusive pain episodes, white blood cell count, and pro-thrombotic activity (49).

Furthermore, children supplemented with omega-3 FAs were related to their growth development. Argaw et al found that daily supplementation of 500 mg omega-3 LC-PUFAs on children enhanced their relative weight gain by a small amount and increased the mid-upper arm circumference (MUAC). This may be due to the potential effect of omega-3 LC-PUFAs in altering the child's immunological response towards viral threats and inflammation, which results in better growth and improvement in morbidity (10). In contrast, one study mentioned that administration of omega fatty acids as much as 732 mg/day for 15 weeks had no significant effects on physical activity or relative body weight (22). Besides poor growth, research has shown that adequate dietary intake of omega-3 long-chain polyunsaturated fatty acids is crucial for overall health and wellbeing, particularly in the development of the brain and cognitive (50).

Supplementing omega-3 FAs in children with behaviour-related problems such as ADHD, either alone or in combination with other nonpharmacological treatments, has been shown to improve mental health, cognitive and brain development of children (34). This may be related to the effectiveness of omega-3 FAs supplementation in improving ADHD symptoms and also the child's psychiatric symptoms such as depression, social problems and aggressive behaviour (25,27). However, the findings regarding the exact intake of omega-3 FAs supplementation among these children may vary according to previous studies which range between 500 to 775 mg per day. In contrast, omega-3 supplementation had no therapeutic effect in children with mild ADHD symptoms 29. This may be due to the ineffectiveness of DHA–EPA related to the inadequate pharmacological effect or the selection of children with mild ADHD who have little chance of improvement.

In addition, this review found some consistency in the findings supporting the relevance of n–3 LCPUFAs for optimum brain development and the need for children to eat fish or supplementation of oily fish in a dose-dependent manner due to its effectiveness in increasing cognitive performance, particularly attention and cognitive flexibility, and reduced the social-emotional issues (9,33). However, a study conducted by Øyen

et al (37) stated that there were no significant effects of providing fatty fish on cognitive performance as judged by the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI- III).

Furthermore, findings from a study conducted by Sheppard et al (35) suggested that both omega-3 and -6 supplementation may be beneficial for cognitive function especially in language development among children at risk for autism spectrum disease (ASD). ASD refers to a group of conditions related to neurodevelopmental diseases which are characterized by significantly decreased abilities in verbal and nonverbal communication, socialization and habitual behaviours (51). Therefore, the intake and supplementation of PUFAs are important for ASD children in improving their cognitive development.

In this review, it has been reported that children with allergies, including asthma, may benefit from the supplementation of PUFAs. This can be proven by a study showing that following a Mediterranean diet supplemented with two meals of 150 g cooked fatty fish twice a week could reduce airway inflammation in children with asthma (43). Fatty fish is high in EPA and DHA, which inhibit the activity of cyclooxygenase and lipoxygenase enzyme and reduce pro-inflammatory mediators like 2-series prostaglandins and 4-series leukotrienes (leukotriene E4, leukotriene B4), eosinophils, and tumour necrosis factor-a, which promote airway edema, mucus secretion, bronchial inflammation (52).

From this review, the recommended supplementation intake of omega-3 and omega-6 FA varies according to studies, country, age and body weight of the child. However, no studies mentioned the recommended intake of PUFA supplements among Malaysian children. As stated in the Malaysian RNI (53), citing the Food and Agriculture Organization's 2010 report, there is plausible evidence to recommend an optimal EPA + DHA intake range for chronic disease prevention which is adjusted according to age. For example, those aged 2 to 4 years, it is recommended to take 100 to 150 mg; 4 to 6 years take 150-200 mg and for those aged 6 to 10 years can take 200 to 300 mg. However, based on the current evidence, providing children aged 2 to 18 years with an age-specific quantitative estimate of necessary dietary intake for EPA + DHA is not possible. In addition, there is apparently insufficient data associating increased intake of DHA and/or EPA with better physical or mental development or specific functional advantages in children aged 2 to 18 years (53).

The Recommended Nutrient Intake (2017) (53) for the Malaysian population recommends that n-6 PUFA (LA) intakes are advised at 3 to 7% of Total Energy Intake (TEI), whereas n-3 PUFA intakes are recommended at 0.3-1.2 percent TEI. This range of n-3 FA intakes is recommended after taking into account the current n-3 content of typical Malaysian diets as well as the feasibility of increasing consumption without making significant dietary adjustments. The average Malaysian's n-3 fatty acid intake remains low. There are several ways to improve this problem which are eating more tofu, fishes and pulses such as beans, and dhal; using cooking oil that is a blend of palm olein with addition of n-3 rich vegetable oil such as canola and soybean; and including n-3 (ALA or EPA + DHA)-rich novel foods.

Finally, the limitation of this scoping review is that few studies on the beneficial outcome of omega-3 and omega-6 polyunsaturated fatty acids on children have been undertaken in Asian nations. As a result, future research should focus on the mechanism of the benefits and its recommended intake to address these issues. Apart from that, limited information regarding the influence of omega-3 and omega-6 FA ratio among children were discussed in this study. Previous study reported that lower omega-6/omega-3 ratio (4:1 or less) are more effective in lowering the risk of many chronic diseases such as cardiovascular, autoimmune disease, asthma, allergies and etc (54). Thus, further research should include the ratio of omega-3 and omega-6 due to their importance in health outcomes.

CONCLUSION

In conclusion, this scoping review of thirty-five studies reported various beneficial outcomes of omega 3 and omega-6 polyunsaturated fatty acids on children. The discrepancies in study results could be due to a variety of reasons, including differences in methodological approach and inter-study variability of biological parameters like participant age, gender and disease. However, majority of the studies showed the beneficial impact of PUFAs supplementation on the children's growth and brain development, mental and cognitive health, cardiovascular disease and allergies. Overall, this review may provide additional information on the importance of supplementing PUFAs for children's health. To support these findings, more comprehensive research regarding this topic is needed as it can help in further development of the dietary intervention.

ACKNOWLEDGEMENT

The authors would like to thank the Ministry of Higher Education Malaysia for funding this study (grant number: PRGS/1/2021/SKK07/UIAM/02/1).

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