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Omega-3 fatty acids throughout childhood and adolescence

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Abstract

Omega-3 fatty acids (FA), particularly eicosapentaenoic and docosahexaenoic acids, play a vital role throughout life. These essential molecules are integral to cell membranes and serve as precursors to various bioactive metabolites that can contribute to the prevention of numerous chronic non-communicable diseases. Since our bodies cannot produce omega-3 FA efficiently, these nutrients must primarily be obtained through diet, with seafood being a major source. After birth, newborns receive omega-3 FA through breast milk. Suitable omega-3 FA intake during pregnancy and breastfeeding, often through fish oil supplementation, ensures normal growth and development and reduces the incidence of allergies in infants. Inadequate omega-3 FA intake in children and adolescents is connected to asthma and skin diseases, as well as various neurological and psychiatric disorders. Conversely, higher omega-3 FA consumption improves cognitive function and bone health, and it is linked to better control of depressive and manic symptoms in adolescents with bipolar disorder. Given their extensive health benefits, ensuring adequate omega-3 FA intake through diet or supplementation is crucial for these population groups throughout life.

Keywords: *omega-3 FA; eicosapentaenoic acid; docosahexaenoic acids; dietary intake; children; adolescents; brain; inflammation.*

INTRODUCTION

Optimal childhood growth and development are fundamental for future well-being and success. In this context, early nutrition plays a pivotal role in ensuring proper development. The most critical periods for growth are the prenatal phase, infancy, and early childhood when the body requires a variety of nutrients for optimal development [1,2], Certain fatty acids (FA), particularly omega-3 and omega-6 polyunsaturated fatty acids (PUFA), have garnered significant attention. Omega-3 FA, in particular, is essential for healthy growth and development, especially during early childhood and adolescence (**Figure 1**). During these formative years, these fatty acids support brain development, cognitive function, and overall physical health.

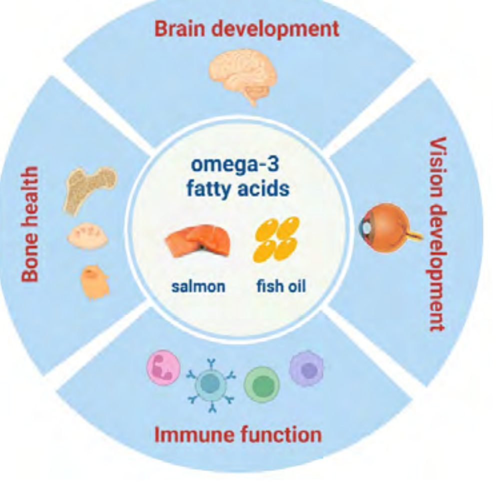

Figure 1. Role of omega-3 fatty acids during growth and development.

In this review, we updated the current knowledge on the role of omega-3 PUFA in growth and development.

BRAIN DEVELOPMENT

Almost 50–60% of the brain's weight consists of lipids, with omega-3 PUFA constituting around 35% of these lipids. Among them, docosahexaenoic acid (DHA) represents over 40% of the total in neuronal tissues, particularly within the grey matter [3]. DHA is highly concentrated in the frontal lobe, a region responsible for complex cognitive functions. In this area, DHA plays a crucial role in maintaining membrane fluidity and facilitating efficient signal transmission. In contrast, eicosapentaenoic acid (EPA) is about 300-fold lower than DHA and comprises less than 1% of the brain's total fatty acids [4]. However, EPA also plays an important role, primarily through its anti-inflammatory and neuroprotective effects.

Nevertheless, intensive accumulation of omega-3 PUFA in the brain starts during the intrauterine stage, continues up to two years of age, and then maintains life needs to adequate continual supply [5]. These facts underscore the importance of DHA in early neurodevelopment and its potential implications for long-term cognitive health [6]. A recently published systematic review showed that omega-3 long-chain PUFA supplementation during the earliest developmental stage—*in utero*, the first year of life, and childhood to adolescence—shows some benefits in visual attention, working memory, executive function, and communication [7]. Further, omega-3 PUFA can improve attention, reduce impulsivity, and enhance overall cognitive abilities in children and adolescents. However, these effects are often short-term and limited to specific cognitive domains, suggesting that supplementation is recommended during life and can be beneficial against neurodegenerative diseases [7,8]. Additionally, the intake of omega-3 PUFA supports brain plasticity and mental health, helping with memory, focus, and learning, especially in adolescents. For example, Lehner *et al*. demonstrate that consuming 8 g of fish daily improves learning in German adolescents compared to those without fish consumption [9]. Moreover, supplementation with 1g/day of omega-3 PUFA for 6 months, improves cognitive function, including attention span and focus, in adolescents with lipid metabolism disorders [10]. Also, Bozzatello *et al*. suggested that omega-3 FA may be beneficial as a supplement to therapy for treating depressive and manic symptoms in adolescents with bipolar disorder, with a recommended dosage of 1-2 g/day [11].

On the other hand, deficiencies in omega-3 PUFA have been implicated in the etiology of psychiatric disorders like autism, attention-deficit/hyperactivity disorder (ADHD), and psychosis in children and adolescents [12–14]. Studies have shown that children with hyperactivity exhibit significantly lower blood levels of omega-3 PUFA [13]. Although it remains unclear whether reduced dietary intake of PUFA directly contributes to impaired PUFA status, evidence suggests that increasing DHA intake may alleviate symptoms of inattention in children with ADHD [12]. Additionally, growing research indicates that PUFA deficiencies during childhood may pose a risk for the development of psychopathologies later in life [15]. Also, in comparison with typically developed, ASD populations had a lower level of omega-3 PUFA. In the cross-section study on the dietary habits of children with developmental disabilities in Croatia, North Macedonia, and Serbia, parents stated that the most common dietary supplements consumed by their children were omega-3 FA and fish oil [16]. However, the beneficial effects of omega-3 PUFA supplementation in autism spectrum disorder are limited and inconclusive, with existing studies varying greatly in their methods and findings [17]. Similarly, omega-3 PUFA supplementation may be beneficial in preventing the transition to psychosis and improving symptoms and functioning in those with first-episode psychosis [18].

Human milk is the optimal food for infants. Fat in human milk is the main energy source, a source of omega-3 PUFA, crucial fat-soluble vitamins, and key nutrients for infant development. Fatty acids, including long-chain PUFA, in human milk may originate either from the maternal dietary lipids, from FAs released from maternal adipose tissue, or from *de novo* synthesis in maternal tissues [19]. In line with this, DHA is often included in infants' formula, ensuring normal growth and development.

The European Food Safety Authority (EFSA) recommends: 0.3% DHA of total FA for infants from 0-12 months and 100 mg/day as an adequate intake of DHA for older infants and young children. Due to rapid growth and development during childhood, requirements for PUFA are higher than at other times later in life. The recommended dietary intake of EPA+DHA, according to the EFSA, is 150 mg/day between 1 and 2 years of age and 250 mg/day after 2 years of age.

VISION DEVELOPMENT

Similar to brain development, DHA is a crucial omega-3 PUFA for photoreceptor development, function, and survival. It accounts for over 50% of the photoreceptor outer segment phospholipid [20,21]. Animal research showed that mice with defects in PUFA metabolism or transport show retinal degeneration, confirming the importance of DHA in photoreceptor biogenesis and function [22]. Also, several human diseases, such as age-related macular degeneration [23], diabetic retinopathy [24], and retinitis pigmentosa [25], are associated with reduced retinal DHA levels. Additionally, DHA has an important role in phototransduction i.e. transduction of light into an electrical signal, and it is involved in the activation of the visual cycle [22]. Also, it is converted into neuroprotectin D1 and other lipid mediators that protect the retina against injury-induced oxidative stress and inflammation [26].

Adequate omega-3 PUFA intake, particularly during pregnancy is associated with improved visual function in both infants and school-age children [27]. On the other hand, inadequate omega-3 PUFA intake during pregnancy and early life can lead to decreased DHA levels in the brain, potentially affecting learning and visual function [28].

Although several studies reported that supplementation with omega-3 PUFA during pregnancy showed favorable effects on visual activities in infants aged 2 months [28,29], the other did not find these improvements. Thus, Nevins *et al*. suggested that omega-3 PUFA supplementation during pregnancy may improve cognitive development in children, but not visual development [1]. Also, there is evidence that the benefits of visual acuity were stronger for supplementation in infants compared to maternal supplementation [2].

Preterm infants are certainly at the greatest risk of reduced visual acuity, especially those who have been treated with cryotherapy [30]. In line with these, several studies have examined the impact of supplementing human milk with DHA on visual function in preterm infants but the obtained results did not show a positive effect [31].

IMMUNE FUNCTION

As integral components of all biological membranes, omega-3 FA are essential constituents of the cell membranes within the immune system. Specifically, EPA and DHA typically account for up to 1% and 3% of the membrane lipid composition of these cells, influencing their fluidity and function. Beyond their structural role, these fatty acids serve as precursors to bioactive lipid mediators, including prostaglandins (PGs), thromboxanes, and leukotrienes (LTs), key modulators of inflammation and immune responses [32].

EPA is metabolized through cyclooxygenase (COX) and lipoxygenase (LOX) pathways, generating distinct lipid mediators. In the COX pathway, EPA is converted into 3-series PGs and thromboxanes, while in the 5-LOX pathway, it produces 5-series LTs. These mediators exhibit weaker pro-inflammatory actions than those derived from omega-6 FA such as arachidonic acid, suggesting that EPA-derived mediators may dampen inflammatory processes [33].

In addition to these inflammatory mediators, EPA and DHA are precursors of specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, which are critical in the resolution of inflammation and the promotion of immune function. These SPMs are considered anti-inflammatory and immune-regulatory agents that “turn off” ongoing inflammation [34] and support the restoration of tissue homeostasis following immune activation. Additionally, SPMs increase the capacity of phagocytosis bacteria and cellular debris and the production of reactive oxygen species, thus supporting innate immunity [35].

Maternal intake of long-chain PUFA influences some immune markers in umbilical cord blood and can stimulate immune maturation [36]. Also, there is evidence that maternal DHA supplementation (0.4 g/day) from week 12 of pregnancy and during 4 months of lactation alters some immune markers in the infants’ blood at age 4 months [37]. Additionally, maternal supplementation with 1.5 g EPA + DHA/day solely during the first 4 months of lactation leads to faster immune system maturation in the offspring at age 2.5 years [38].

The ratio of omega-3/omega-6 FA plays a crucial role in modulating the development and function of the immune system, influencing immune cell activity, and regulating inflammatory responses and allergic phenomena [39]. Unfortunately, about 30% of children have been diagnosed with an allergy linked to foods, environmental or genetic factors [40]. The most prevalent allergies in children include symptoms of skin rashes associated with atopic dermatitis or eczema, respiratory distress in the form of asthma, and allergic rhinitis characterized by sneezing, coughing, a runny nose, or itchy eyes. Additionally, gastrointestinal disturbances such as nausea or vomiting may occur in cases of food allergies.

Animal studies have demonstrated that diets enriched with EPA and DHA, or DHA alone, can attenuate allergic symptoms and offer protection against allergic sensitization in mice with food allergies, atopic dermatitis, and arthritis [41-43]. These findings are further supported by clinical studies that reported that term infants receiving formula supplemented with PUFA exhibited a lower risk of upper respiratory infection and other allergies at a 3-year follow-up [44]. Moreover, Foiles *et al*. found that infants who consumed formula supplemented with PUFA during the first year of life had a reduced prevalence of asthma compared to those who received standard formula, with the benefits observed up to age 4 [45]. Additionally, supplementation with 180 mg EPA and 120 mg DHA daily for 3 months has been shown to improve symptoms in children with asthma [46].

BONE HEALTH

The relationship between omega-3 PUFA intake and bone health is well-established [47]. Bone mineral density (BMD), a key predictor of osteoporotic fractures, is crucial for maintaining bone health [48]. The primary determinant of BMD is the amount of bone (peak bone mass) developed during early life. Maternal nutrition during pregnancy and lactation plays a critical role in determining peak bone mass and influencing the onset of osteoporosis in offspring [49].

However, most studies have focused on the role of omega-3 PUFAs in secondary prevention, such as after the development of osteopenia, osteoporosis, or fractures. Few studies have investigated the impact of omega-3 supplementation on bone development during periods of rapid growth. In their studies conducted on mice and *in vitro*, Koren *et al*. demonstrated that exposure to high concentrations of omega-3 fatty acids during early life accelerates bone growth by modifying the growth plate, which is associated with increased chondrocyte proliferation and differentiation [47]. Similarly, improved bone micro-architecture and enhanced mineralization were detected in mice fed diets rich in flaxseed and fish oils, respectively [50]. Other animal research has also highlighted that maternal nutrition affects bone quality and strength. For example, a diet high in fat and sugar can impair bone quality [51]. These findings suggest that dietary interventions during pregnancy could positively influence bone quality in later life. Maternal omega-3 and omega-6 status in late pregnancy have been found to influence bone development during early childhood [52]. DHA supplementation during pregnancy and lactation decreased bone loss in mothers and promoted bone formation and mineralization in neonates [53], Moreover, supplementation with omega-3 PUFA (fish oil) in the third trimester of pregnancy increased bone mass and bone mineral density in children at 6 years of age [54]. However, despite a positive association between increased DHA in erythrocytes and plasma insulin-like growth factor-1, no association between fish oil supplementation and DHA status and bone mass and formation in adolescent boys has been found [55].

CONCLUSION

Omega-3 FAs are essential components of all biological membranes, playing a pivotal role in the structural integrity and functionality of neurons, retinal cells, and immune cells. They are particularly influential in the proliferation and differentiation of chondrocytes, which are critical for maintaining bone health. Adequate maternal intake of omega-3 FA during pregnancy and lactation is vital for normal fetal and infant development, encompassing the formation of the central nervous system, visual pathways, and immune system maturation. During childhood and adolescence, omega-3 FA supplementation has a significant positive influence on neurodevelopment, immune function, and skeletal health. These findings have important implications for the prevention and treatment of developmental disorders linked to insufficient omega-3 fatty acid levels. Nevertheless, more extensive trials are needed across these areas to provide guidelines for the use of omega-3 FA in therapeutic interventions.

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Omega-3 masne kiseline tokom detinjstva i adolescencije

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Kratak sadržaj

Omega-3 masne kiseline (MK), posebno eikozapentaenska i dokozaheksaenska kiselina, igraju važnu ulogu tokom čitavog života. Ovi esencijalni molekuli sastavni su deo ćelijske membrane i služe kao prekursori za različite bioaktivne metabolite koji mogu doprineti prevenciji razvoja brojnih hroničnih nezaraznih bolesti. Pošto naš organizam ne može efikasno da proizvode omega-3 masne kiseline, ove hranljive materije se prvenstveno moraju unositi ishranom, a morski plodovi su glavni njihov izvor. Nakon rođenja, novorođenčad dobijaju omega-3 MK kroz majčino mleko. Optimalan unos omega-3 MK tokom trudnoće i dojenja, često uz dodatak ribljeg ulja, obezbeđuje normalan rast i razvoj i smanjuje učestalost alergija kod odojčadi. Neadekvatan unos omega-3 FA kod dece i adolescenata povezan je sa astmom i kožnim oboljenjima, kao i različitim neurološkim i psihijatrijskim bolestima. Nasuprot tome, veći unos omega-3 FA poboljšava kognitivne funkcije i zdravlje kostiju, a povezana je i sa boljom kontrolom depresivnih i maničnih simptoma kod adolescenata sa bipolarnim poremećajem. S obzirom na njihove velike zdravstvene prednosti, obezbeđivanje adekvatnog unosa omega-3 MK kroz ishranu ili suplemente je ključno za ove populacione grupe tokom života.

Ključne reči: *omega-3 MK; eikozapentaenska kiselina; dokozaheksaenske kiseline; ishrana; deca; adolescenti; mozak; inflamacija..*