



How does the food in the first 1000 days affect infant and toddler brain development?

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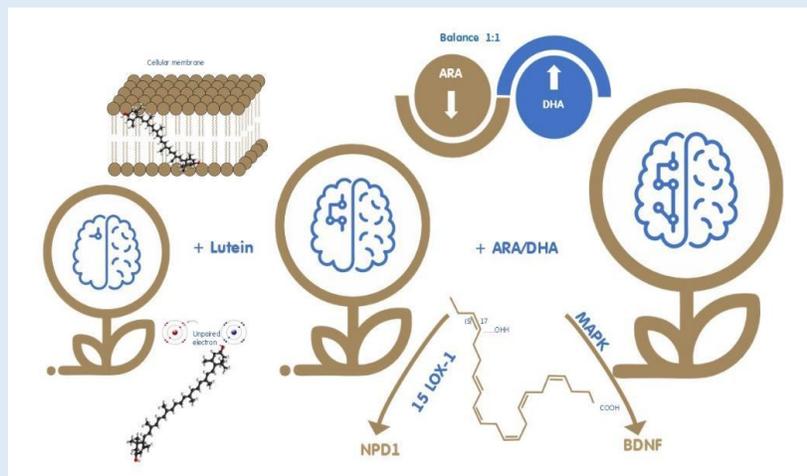
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ABSTRACT

Today, hundreds of millions of children under the age of 5 fall short of their development potential. Advances in neuroscience have confirmed that adult health and well-being are based on the developmental conditions and opportunities they had in early childhood, from conception to 24 months (first 1000 days) and then to the age of



5 (second 1000 days). Young children, who eat a healthy balanced diet, who are treated with care and attention, and who have more opportunities to learn, have a better chance to thrive. Data from a survey of adopted children, as well as experimental and quasi-experimental studies, showed that prevention of stunting is most effective during the first 1000 days and developmental delays in both the first and second 1000 days. External factors affect cognitive development significantly less after this period, and the older a person becomes, the less effective educational programs are, and the longer it takes to learn a new skill. In this regard, it is necessary to identify the degree of influence of nutrient components, such as polyunsaturated fatty acids and lutein, on the cognitive

development of the child in the first year of life, as it determines the intellectual potential of the person throughout life. The goal of this review is to review the existing literature to find out how certain food components (polyunsaturated fatty acids and lutein) affect infant and toddler brain development.

Keywords: omega-3, omega-6, polyunsaturated fatty acids, lutein, cognitive development

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INTRODUCTION

Previous studies have shown that there is a significant difference in the cognitive development of breastfed infants and formula-fed infants. However, these studies used a cow's milk-based powdered infant formula that did not contain lutein and had a suboptimal polyunsaturated fatty acids (PUFA) ratio. During the first 1000 days, external factors can significantly affect cognitive development, and the older a person becomes, the less effective educational programs are, and the longer it takes to learn a new skill [1].

Cognitive development of infants and young children requires external stimuli allowing the brain to grow rapidly through the processes of neurogenesis, axonal and dendritic growth, synaptogenesis, cell death, synaptic pruning, myelination, and gliogenesis [2]. Adequate nutrition through exclusive breastfeeding that is known to be micronutrient-rich together with high-quality complementary and age-appropriate food intake, and intellectual stimulation during infancy and childhood are critical for optimal brain development and function [2, 3, 4].

Despite the indisputable advantage of breastfeeding for the correct and timely cognitive development of children and the fact that in Russia, according to the World Health Organization (WHO), about 80-90% of women begin to breastfeed in the maternity ward of a health care institution, by six

months breastfeeding can be maintained by only 40% of mothers [5]. At the same time, children fed with infant formula need to compensate for the deficiency of macro- and micronutrients as well as other essential components that can be found only in breast milk and are not supplied or are often received in insufficient quantities.

Though most of the infant formulas contain essential macro- and micronutrients, recent research proved that it might not be enough for proper brain development. In order to secure protection of neuronal and glial cells from injury and apoptosis, polyunsaturated fatty acids and lutein should be supplemented in sufficient quantities during the first year of life.

POLYUNSATURATED FATTY ACIDS

Eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6) are omega-3 polyunsaturated fatty acids that are important for brain development [6]. These PUFAs can be synthesized in the body from the precursor, alpha-linolenic acid (ALA, C18:3), and, therefore, are not considered essential (Table 1). Nevertheless, in many cases, the metabolism of ALA into EPA and DHA is insufficient. It is for this reason that physicians recommend including EPA and DHA into the regular/daily diet [6]. As PUFAs play an important role in fetal and infant development, multiple regulatory bodies, medical societies, and unions advise

supplementing the diet of pregnant and lactating women with EPA and DHA [7].

DHA participates in the formation of the human brain and retina [8]. DHA constitutes a the major part of all PUFAs in the retina, and about 60% of the dry weight of the brain accounts for the fatty acids, including DHA [9]. PUFAs deficiency causes a decrease of DHA levels in the cerebral cortex and decreases learning ability in animal models [10]. DHA is accumulated in the grey matter of the human brain and retina during fetal development and after birth [8]. In the third trimester, independent from the ratio of PUFAs intake, neurons of the fetus selectively accumulate DHA at a higher rate [11]. This trend is true during the first 1000 days of development until a child turns 2 years old [12]. Thus, the development of the brain in utero and during the first 2 years of life defines its ability to function later in life.

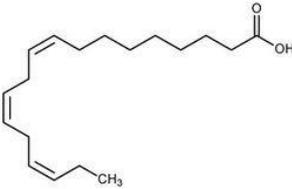
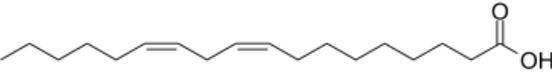
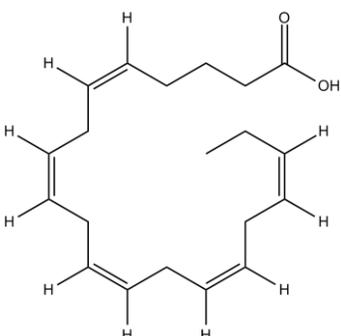
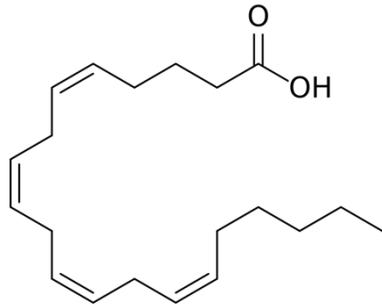
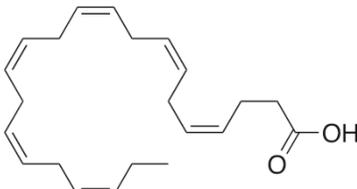
The role of polyunsaturated fatty acids in the brain development:

DHA plays a crucial role in neurodevelopment as it participates in cell signaling, gene expression regulation, and neurotransmission [13]. The experiment showed that in 2-month old rats fed with a diet deficient in omega-3 PUFAs the physiology of neurotransmitters, like serotonin and dopamine, was altered with a noticeable effect on brain function [14]. Besides that, DHA deficiency causes a decrease in the size of neurons in the hypothalamus and hippocampus in the animal model, while the size of neurons is crucial for the proper functioning of the brain [15]. Moreover, in the case of maternal PUFAs deficiency, neurogenesis is disrupted [16]. Insufficient neurogenesis not only slows intellectual development but also may affect the intellectual abilities of an individual later in life [16]. PUFA supplementation during pregnancy allows increasing levels of polyunsaturated fatty acids in the brain of an infant [17].

Long-chain PUFAs are involved in synaptogenesis and myelination, and support membrane function. Behavioral and neuroimaging tests, which measure the electrical activity of the brain, are used in young children to pinpoint the effect of the nutrient deficiencies, both when the child experiences deficiency and while recovering from it. Omega-3 fatty acids such as α -linolenic acid (ALNA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are essential components required for myelination and synaptogenesis. Diet rich with fish oil, DHA or EPA, and EPA is proven to improve visual acuity, attention, and cognitive abilities [2]. Even though most infant formulas contain PUFAs, recent studies have shown that they have a beneficial effect on the cognitive development of a child only in a certain proportion, while in any other case, the effect is insufficient or even absent [5].

While the importance of PUFAs has been long accepted, only recently scientists posed a thesis that the ratio of different PUFAs in nutrition also plays an important role. According to Feuentes-Albero et al. (2019), a certain balance of omega-6 and omega-3 allows an individual to stay physically and mentally healthy by supporting proper neurodevelopment [18]. Several studies showed that supplementation with additional omega-3 PUFAs, like EPA and DHA, can treat attention deficit hyperactive disorder (ADHD) and depression in cases where the deficit had been previously developed [19-21]. One of the explanations of the therapeutic efficiency of omega-3 PUFAs in maintaining mental health is that they play an essential role in multiple neuronal processes and the processes of cell growth, building the cell membrane, hormonal metabolism, and gene expression [22]. Omega-3 PUFAs deficiency has been shown to alter the brain function during the initial developmental stages, which will negatively affect the intellectual ability and mental health of an individual throughout life [23].

Table 1. Polyunsaturated fatty acids that are important for the brain development

n-3 Polyunsaturated fatty acids	n-6 Polyunsaturated fatty acids
<p style="text-align: center;">α-Linolenic acid</p> <p style="text-align: center;">C18:3</p> 	<p style="text-align: center;">Linoleic acid</p> <p style="text-align: center;">C18:2</p> 
<p style="text-align: center;">Eicosapentaenoic acid</p> <p style="text-align: center;">C20:5</p> 	<p style="text-align: center;">Arachidonic acid</p> <p style="text-align: center;">C20:4</p> 
<p style="text-align: center;">Docosahexaenoic acid</p> <p style="text-align: center;">C22:6</p> 	

The role of polyunsaturated fatty acids in the cognitive development of infants: Several studies proved that supplementing human milk with PUFA improved neurodevelopmental outcomes, including problem-solving skills, recognition memory, and

attention scores [24]. Moreover, a study with PUFA-supplemented formula versus non-PUFA-supplemented formula during the hospital stay and after discharge showed an improved cognitive development in infants fed with the formula that

contained high levels of PUFAs [25]. Observational studies revealed that EFA deficiency in mother's milk is associated with lower motor activity at 40 weeks of gestational age, low levels of ARA often indicate low Brazelton Neonatal Behavioral Assessment Score (BNBAS) at 40 weeks of gestational age, and concentration of n-6 PUFAs in breast milk positively correlates with the level of motor, mental and behavioral development at 18 months of age [26].

The role of polyunsaturated fatty acids in the visual development:

Smithers et al. showed that increased DHA intake during the neonatal period improves visual acuity [27]. Other studies registered an improved retinal function as assessed by electroretinography (ERG) in infants with higher PUFA intake [28-29]. Besides that, infant formula supplemented with DHA and/or EPA improved visual acuity, processing speed in the visual zones of the prefrontal cortex, and evoked potentials [28-31]. Therefore, the research shows that to improve the visual development of an infant, supplements should

include a combination of PUFAs (ARA, DHA, EPA) rather than a single polyunsaturated fatty acid [32].

The research shows that it is the ratio between omega-6 and omega-3 unsaturated fatty acids that ensures protection against unwanted outcomes caused by the excessive production of prostanoids, leukotrienes, and harmful lipoxins [22]. The omega-3 fatty acids play an anti-inflammatory and a systemic anti-degenerative role and ensure proper regulation of the immune system. After ingestion, PUFAs are transferred to cells and cellular membranes affecting cellular metabolism and survival. PUFAs are important for proper electrophysiology of neurons in the visual system and play a crucial role in calcium homeostasis, gene expression, respiratory function, ROS production, and mitochondrial apoptosis [33]. The metabolic functions of omega-3 fatty acids, like EPA and DHA, play a crucial role in metabolic cascades in the organism (Table 2) [34], and their importance in the formation of the visual system is well-recognized nowadays.

Table 2. The most important functions of omega-3 PUFAs in health and disease

Biological function	Clinical application
Increase levels of HDL and decrease levels of LDL	Improve neurodevelopment in uteri
Modulate physical properties of membrane lipids and, thus, neuronal transport	Positively affect mental health
Reduce neuroinflammation	Protect neurons from damage and decrease the incidence of sudden infant death (SIDS)

LUTEIN

Lutein is another key factor determining cognitive development and vision maturation in newborns and infants. It is a xanthophyll carotenoid found in many fruits and vegetables that became an attractive supplement in infant nutrition (Figure 1) [35]. The safety of this ingredient is proven in multiple studies and it has been recommended as an addition to food by several regulatory authorities. The nonhuman primates model supported the important role of lutein in the visual system and brain development. Lutein deficiency makes neuronal tissues of the eye susceptible to oxidative damage by blue wavelength light (Figure 2) [35].

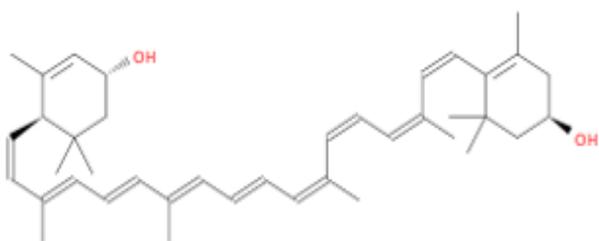


Figure 1. The structure of a xanthophyll carotenoid lutein

To provide formula-fed infants and infants fed both with mother's milk and infant formula with conditions for optimal growth and development, the composition of the formula has to be enriched with lutein [36]. Lutein is an important carotenoid that ensures the correct development of the visual cortex not only in adults but also in children during their first year of life. Research has shown that feeding an infant with infant formula containing lutein ensures its

deposition in the visual cortex, hippocampus, and striatum similarly with breastfed infants [36, 37].

The brain of a newborn is still immature, as the myelination of the white matter continues up to 2 years of age. During this process, the concentration of fats in the brain increases, and the concentration of water decreases. Adequate myelination allows the nerve cells to function with maximum efficiency. If the myelination process is disrupted motor and intellectual development can be violated. Modern research shows that lutein is essential for brain myelination. Lutein deficits can slow down myelination and potentially halt the process of learning [38]. Scientists have shown that feeding an infant with an infant formula that contains lutein increases lutein concentration in the brain significantly compared to children fed with infant formula that does not contain lutein [37]. Moreover, lutein facilitates the exchange of information between nerve cells and increases the speed with which the neuronal signal is transferred. It also protects neuronal damage with free radicals [39]. Also, a high level of carotenoids, including lutein, is associated with more intensive development of cognitive abilities [39]. Scientific research has shown that sufficient concentration of lutein in the brain of the infant during the first year of life secures the proper functioning of multiple metabolic pathways, including fat and energy metabolism, as well as the production of transmitters of amino acids [40].

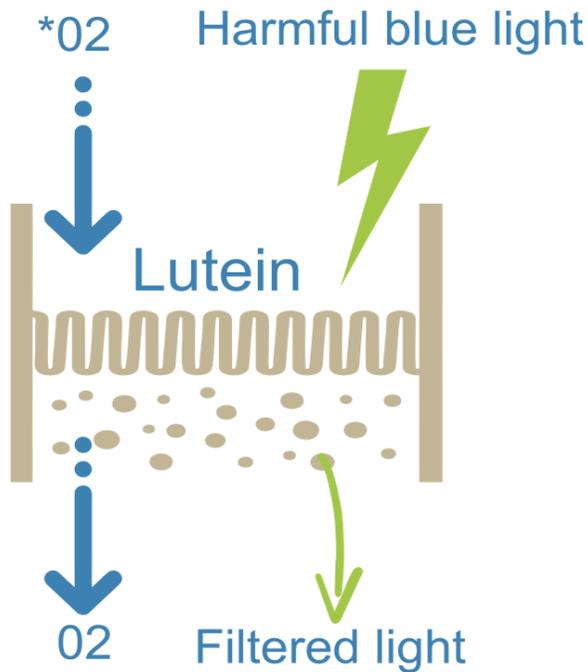


Figure 2. Lutein protects vision from oxidative stress.

Under the influence of the short-wavelength blue light, oxidative damage to the outer segments of the rods occurs, causing the release of mitochondrial components, such as Cytochrome C. As a result, the apoptosis cascade is triggered by the activation of the Caspase 9 enzyme. Lutein in the retina serves as an acceptor of free oxygen radicals and protects tissues under conditions of oxidative stress.

CONCLUSION

Recently, a lot of attention has been paid to the investigation of how nutrition affects the intellectual abilities of adults. Nevertheless, research shows that the choice of nutrition plays the most important role during the first 1000 days of brain development from conception until approximately 2 years of age as during this period neurodevelopmental processes are undergoing the most active phase. For that reason, it is crucial that the baby gets balanced nutrition that satisfies the needs of the developing brain. During pregnancy, a fetus receives all the nutritious components through the placenta from the mother's diet, and the concentration of these nutrients is not

easy to regulate. After birth, the source of the nutritious components depends on whether an infant is breastfed or formula-fed. In case an infant is exclusively breastfed or fed with donor's human milk, the mother should continue taking supplements. Nevertheless, in case an infant is formula-fed, it is crucial to make sure that the formula contains all the nutrients that support neurodevelopment and provide optimal conditions for an infant to thrive intellectually later in life.

While modern infant formulas contain the optimal concentration of proteins, carbohydrates, and fats and are balanced in energy, many of them do not contain polyunsaturated fatty acids, and those that do, do not provide information on the ratio of omega-3 and omega-6 PUFAs. As a result, in formula-fed infants, neurodevelopmental processes can go slower, which halts signal processing speed and decreases the rate of motor and cognitive development. Lutein also determines the rate of neuronal development, especially in the visual system. Playing as an antioxidative component, lutein protects neurons from oxidative stress, providing optimal conditions for myelination that is actively ongoing in the first 1000 days of human development.

Both PUFAs and lutein play a protective role allowing the fast-developing brain to function properly. For that reason, infant formula should not only contain the components that support the physical development and growth of an infant but also be supplemented with additional nutrients that improve the cognitive development of an infant. The lack of objective information in this area suggests that further research is required to allow estimations of how supplementation of PUFAs with omega-3 and omega-6 in optimal proportions and lutein affect the intellectual skills of infants after 18 months of age and later in life. Nevertheless, the results of modern

research, though largely contradictory, allow suggesting introducing PUFAs and lutein into standards and regulations as supplements required in the infant formula.

Competing Interests: The authors have no financial interests or any other conflicts of interest to disclose.

Authors' Contributions: All authors contributed to this review.

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