

# $\Omega$ -3 PUFA DHA: Benefits Associated With Brain

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**Abstract.** DHA and EPA from fish oil are  $\Omega$ -3 polyunsaturated fatty acids which can't be synthesized adequately in human body as the conversion from ALA and ARA is low. Thus, we can only get the recommended dose from marine animals and supplements at the natural ratio. Notably, global warming is predicted to decrease availability of this nutrient, and part of its role in the human body cannot be seen in the form of supplements. This review article summarizes the benefits of DHA on fetal development associated with the maternal supplementation. Fish oil can also influence APOE4-associated Alzheimer's disease through the form of DHA-LPC (lysophosphatidylcholine). This review provides a fresh perspective on DHA.

**Keywords:**  $\Omega$ -3; PUFA; fish oil; fetal development; AD.

## 1. Introduction

Nowadays an increasing number of people take in docosahexaenoic acid(DHA) regularly for its advantages on human body. DHA and EPA(Eicosapentaenoic acid,) which are known as fish oil are  $\Omega$ -3 polyunsaturated fatty acids (PUFAs) from marine animals. They are essential fatty acid which cannot be synthesized in human body itself but only from the conversion of other short chain fatty acids, such as ALA( $\alpha$ -linolenic acid, 18:3  $\Omega$ -3) and ARA(arachidonic acid, 20:4  $\Omega$ -6). It's not that easy for people live in interior to get adequate marine animals everyday, but these short chain fatty acids are much easier to get from common land plants. However, they do not provide the health benefits seen with these long chain fatty acids. Different research has shown various conversion rates, but all have led to the same conclusion that only a small amount of ARA and ALA can be transformed to DHA in human body[2]. It's intriguing to note that a particular research study unveiled an interesting phenomenon: the rise in plasma EPA following DHA supplementation doesn't result from a reversal of conversion, but rather takes place through a gradual metabolic process leading to the accumulation of plasma EPA. This unique finding challenges conventional assumptions about the relationship between these essential fatty acids. The study suggests that the interplay between DHA and EPA in the body is more intricate than previously believed, shedding new light on the mechanisms underlying their effects. This discovery holds significant implications for our understanding of how these compounds interact and contribute to overall health. Furthermore, after ingesting huge amounts of EPA, DHA can be synthesized through the conversion of it[3]. To meet people's demand for fatty acids, which has a positive impact on the play of the role of DHA, it's recommended that the take in of saturated FA, monounsaturated FA and polyunsaturated FA should be at the ratio of 1:1:1.

It is important to highlight that the advantages of  $\Omega$ -3 fatty acids for the human body are acknowledged to have a connection with promoting healthy aging throughout one's lifespan. DHA and EPA, both classified as  $\Omega$ -3 fatty acids, play a pivotal role as precursors to numerous metabolites with robust lipid mediator properties. These metabolites are acknowledged for their potential contribution to the mitigation and management of various diseases spanning the continuum of early to later stages of life. Their influence extends to conditions encompassing cardiovascular health, cognitive function, and even inflammatory responses. As integral components of cellular structures, particularly as key constituents of cell membranes, DHA and EPA exhibit essential functions in maintaining membrane fluidity, structural integrity, and cellular signaling. This intricate interplay underscores their importance in sustaining overall health and supporting longevity, DHA exists extremely abundant in brain and retina, and also has an impact on the viscosity of the cell membrane

[2]. Although this article mainly focuses on its benefits on fetal development and Alzheimer's disease, DHA is also involved in the cardiovascular disease and depression.

## **2. DHA is essential for fetal Development**

The beneficial impact of fish oil in human brain development is first seen in early life. Throughout pregnancy, the placenta facilitates the transfer of nutrients from its own supply to the developing fetus. In terms of the DHA discussed in this article, it is obvious that the amount of  $\Omega$ -3 fatty acids absorbed by the fetus is related to the maternal intake, so mother should ensure adequate nutrition [2]. It is worth noting that the supplementation of fish oil should be the combination of DHA and EPA in a natural proportion. In a group of experiments with mice as subjects, the results proved that acute administration of EPA would impair the learning, memory and hippocampal LTP of prepubescent mice. Therefore, the fetal intake of nutrients should be in a long-term but mild way. While EPA unexpectedly demonstrates adverse impacts on cognitive functions, this outcome can be averted by consuming DHA and EPA in a proportion akin to that found in marine fish oil. [4].

Early studies, in 2010, on the supplementation of DHA and EPA to the mother at different weeks of pregnancy report significantly better problem-solving skills (9 months) when the mother took fish oil (average consumption 1500 mg/week) from week 24 to birth; effects on cognition skills were not obvious. Another research group found higher scores for eye and hand coordination at 2.5 years when the nutrients are supplemented from gestation week 20 to birth [2] (2.2 g/d DHA and 1.1 g/d EPA). These experiments illustrate the neurodevelopmental benefits in brain. However, data are mixed. A study in 2022 by Mireille Guillot concluded Supplementing maternal DHA does not lead to enhanced neurodevelopmental outcomes during the 18 to 22-month period, when corrections are made for age in breastfed, preterm neonates. A potential benefit for language in preterm neonates born before gestation week 27 was suggested [5].

Fish oil is such a vital factor in the development of brain that the amount of this nutrient in the formula for infants is well focused. The recently adopted regulatory standards for infants and new European Union (EU) formula stipulate that all related products marketed in EU must contain 20-25mg  $\Omega$ -3 DHA per 100 kcal, equivalent to 0.5-1% of fatty acids approximately. The nutritional content of the follow-on formula is higher than the usual that in breast milk and current infant formula products, without the requirement of ALA. This has become controversial for the lack of accountable evidence on its safety and suitability. What leads to this outcome is a preceding opinion paper by EFSA, which states formula with DHA but no ALA reduces ALA concentrations in erythrocytes, observing no direct functional consequences. The regulations in Europe also mandate that the EPA content should not surpass that of DHA., based on its low proportion in milk. Another legislation indicates that The ALA content should not go beyond 1% of the overall fat content, while the combined content of all long-chain $\Omega$ -6 PUFAs must not exceed 2% of the total fat.. Through the control experiments using various ratios of DHA and ALA on the formula for fetus, it explains that administering elevated levels of DHA to infants without a harmonized provision of ALA might lead to unforeseen impacts, such as a decrease in the concentration of ALA in brain tissue and unsatisfactory neurodevelopment, which may adversely affect growth and immune function. Therefore, there is an urgent and emphatic call for all infant formulas to unequivocally include both DHA and ALA.. Moreover, the DHA content in formula should be at least equal to the average content of global breast milk, that is, 0.3% of FAs, and to meet the higher demand of some infant subgroups, the figure preferably to be 0.5%, which is equivalent to the average+1 SD content in global human milk [6].

## **3. DHA may inhibit the onset of AD**

Alzheimer's Disease (AD) is medically regarded as a neurodegenerative disease. Its main characteristics include loss of memory and spatial direction, cognitive impairment and obvious changes in behavior. AD has two types: sporadic and familial. The former accounts for more than 95% of the total number of cases; the latter is rare and hereditary. Aging is the central risk in sporadic AD,

as the brain's vulnerability to degeneration increases with time, which is why it is also called late-onset AD and its major genetic factor is a variant of APOE known as APOE4. Approximately 65%-85% of AD patients carry at least one APOE4 allele, which raises the likelihood of disease development by 2 to 3 times., compared with individuals who do not carry APOE4 alleles. What's more, carrying two APOE4 alleles increases the risk by 15 times. Surprisingly, APOE4 is antagonistic, which is reflected in that although it poses a higher risk to AD in later years, it is also related to the improvement of early cognition and intelligence [7].

Neuron membrane phospholipids are the main place of DNA, in which it participates in the proper function of the nervous system, which is why DHA is believed to play an active role in AD[2]. The APOE4 carrier responds well to DHA found in fish, but poorly to the form of DHA dietary supplement. The mechanism behind these opposite results remains unknown. We speculate that marine animals contain DHA in form of phospholipids called DHA-lysoPC, whereas supplements provide DHA in free form. As one of the three major barriers of human body, the blood-brain barrier (BBB), its outer membrane leaflet allows free DHA to pass through passive diffusion, while the transfer of DHA-lysoPC across the inner membrane occurs through the involvement of the protein 2A in the major facilitator superfamily domain.. Disruption of the blood-brain barrier's outer membrane inhibits the transportation of unbound DHA to the brain, while DHA-lysoPC remains relatively unaffected. This divergence in transport mechanisms underscores the intricate regulatory dynamics within brain lipid pathways, potentially impacting neurological health [7]. When maintaining high DHA-lysoPC plasma levels, the best dietary sources of DHA should be in form of phospholipids, that's why deep-sea fish is a good choice in the prevention of AD.

The mechanism of metabolism was present by Phonda P. Patrick and the study by the university of Southern California supports it by their data. By utilizing a method that included 275 participants chosen at random, split into groups to receive either 18 months of DHA supplementation or a placebo, the investigators arrived at a conclusion. They inferred that the reduced elevation of plasma DHA and EPA levels observed in individuals with the APOE4 gene variant, following DHA supplementation, negatively affects the distribution within the brain. Consequently, this interference has implications for the overall efficacy of DHA supplementation. [8].

Findings from another research study indicate the high efficiency of DHA-LPC(DHA-lysoPC), compared to other functional forms of DHA including utilizing techniques involving these three forms of DHA-related compounds, researchers enriched brain DHA levels in normal rats through oral administration for 30 days, each receiving a daily 10 mg DHA dose. This led to the formation of DHA-PC and DHA-TAG compounds. The findings indicate that DHA-TAG exhibits a preference for entering adipose tissue and the heart, excluding the brain. This preference arises from its release as free DHA or monoacylglycerol during digestion, with subsequent absorption as TAG within chylomicrons.. In contrast, DHA-LPC is all stored and used by brain, enhancing brain DHA by a maximum of 100%, but has no effect on adipose tissue. DHA-PC generates both free DHA and DHA-LPC in the digestion process, making the brain, heart and liver rich in DHA. Brain-derived neurotrophic factor is increased by DHA-PC and DHA-LPC rather than DHA-TAG, which not only indicates that the functional effect of the brain is related to the rich content of DHA, but more importantly, it reveals that dietary DHA from TAG or natural PC (sn-2 position) has a weak impact on the brain whereas DHA from LPC (at either sn-1 or sn-2 position) or from sn-1 position of PC are the essential substances that really work efficiently on the enrichment and effectively on the function of the brain [9]. The coincidence of this conclusion and previous evidence leads to the critical statement that DHA is key to the decreasing the risk of AD.

#### **4. Conclusion**

At both ends of the life circle which means birth and death, DHA is crucial to the fetal development and aging disease, AD. Unfortunately, recent studies predicted that at the base of aquatic food chain, the synthesis of DHA by algae will reduce due to the global warming, which further cause the

reduction of DHA transferred to fish. Stefanie M. Colombo concluded that depending on the climate scenario and location, by 2100, rising water temperature may lead to a global loss of about 10 to 58% of available DHA, potentially restricting the accessibility of this vital nutrient [1]. The role played by DHA cannot be supplanted by supplements as they cannot provide the benefits seen in DHA-LPC. The best source of  $\Omega$ -3 fatty acids is fish oil, which provides a combination of DHA and EPA at their natural ratio. Its better problem-solving and coordination of hands and eyes supports the benefits of DHA in brain in children. Although the addition of ARA remains controversial, unless independent relevant scientists thoroughly evaluate this novel formula and exhibit data facts, infants should not be provided with high levels of DHA without ARA. In Alzheimer's disease, DHA is highly associated with LPC on the benefits of its function. The recommended take in of saturated FA, monounsaturated FA and polyunsaturated FA should be at the ratio of 1:1:1. However, only a small amount of people reach this specific value.

## References

- [1] Colombo, S.M., Rodgers, T.F.M., Diamond, M.L. et al. Projected declines in global DHA availability for human consumption as a result of global warming. *Ambio* 49, 865–880 (2020). <https://doi.org/10.1007/s13280-019-01234-6>
- [2] Danielle Swanson, Robert Block, Shaker A. Mousa,  $\Omega$ -3 Fatty Acids EPA and DHA: Health Benefits Throughout Life, *Advances in Nutrition*, Volume 3, Issue 1, January 2012, Pages 1–7, <https://doi.org/10.3945/an.111.000893>
- [3] Adam H Metherel, Maha Irfan, Shannon L Klingel, David M Mutch, Richard P Bazinet, Compound-specific isotope analysis reveals no retroconversion of DHA to EPA but substantial conversion of EPA to DHA following supplementation: a randomized control trial, *The American Journal of Clinical Nutrition*, Volume 110, Issue 4, October 2019, Pages 823–831, <https://doi.org/10.1093/ajcn/nqz097>
- [4] Liu, JH., Wang, Q., You, QL. et al. Acute EPA-induced learning and memory impairment in mice is prevented by DHA. *Nat Commun* 11, 5465 (2020). <https://doi.org/10.1038/s41467-020-19255-1>
- [5] Mireille Guillot, Anne Synnes, Etienne Pronovost, Mosarrat Qureshi, Thierry Daboval, Georges Caouette, François Olivier, Julie Bartholomew, Ibrahim Mohamed, Edith Massé, Jehier Afifi, Leonora Hendson, Brigitte Lemyre, Thuy Mai Luu, Lannae Strueby, Zenon Cieslak, Kamran Yusuf, Gustavo Pelligra, Thierry Ducruet, Aissatou Bintou Khairy Thilor Ndiaye, Georgina Angoa, Thibaut Sériès, Bruno Piedboeuf, Anne Monique Nuyt, William Fraser, Benoît Mâsse, Thierry Lacaze-Masmonteil, Pascal M. Lavoie, Isabelle Marc; Maternal High-Dose DHA Supplementation and Neurodevelopment at 18–22 Months of Preterm Children. *Pediatrics* July 2022; 150 (1): e2021055819. [10.1542/peds.2021-055819](https://doi.org/10.1542/peds.2021-055819)
- [6] Berthold Koletzko, Karin Bergmann, J Thomas Brenna, Philip C Calder, Cristina Campoy, M Tom Clandinin, John Colombo, Mandy Daly, Tamás Decsi, Hans Demmelmair, Magnus Domellöf, Nataša FidlerMis, Ines Gonzalez-Casanova, Johannes B van Goudoever, Adamos Hadjipanayis, Olle Hernell, Alexandre Lapillonne, Silke Mader, Camilia R Martin, Valerie Matthäus, Usha Ramakrishan, Cornelius M Smuts, Sean J J Strain, Conny Tanjung, Patrick Tounian, Susan E Carlson, on behalf of the European Academy of Paediatrics and the Child Health Foundation, Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation, *The American Journal of Clinical Nutrition*, Volume 111, Issue 1, January 2020, Pages 10–16, <https://doi.org/10.1093/ajcn/nqz252>
- [7] Patrick, R.P. (2019), Role of phosphatidylcholine-DHA in preventing APOE4-associated Alzheimer's disease. *The FASEB Journal*, 33: 1554-1564. <https://doi.org/10.1096/fj.201801412R>
- [8] Tomaszewski, Natalie et al. 'Effect of APOE Genotype on Plasma Docosahexaenoic Acid (DHA), Eicosapentaenoic Acid, Arachidonic Acid, and Hippocampal Volume in the Alzheimer's Disease Cooperative Study-Sponsored DHA Clinical Trial'. 1 Jan. 2020 : 975 – 990.
- [9] DhavamaniSugasini, Poorna C.R. Yalagala, Alexis Goggin, Leon M. Tai, Papasani V. Subbaiah, Enrichment of brain docosahexaenoic acid (DHA) is highly dependent upon the molecular carrier of dietary DHA: lysophosphatidylcholine is more efficient than either phosphatidylcholine or triacylglycerol, *The Journal of Nutritional Biochemistry*, Volume 74, December 2019, 108231.