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# Omega-3 fatty acids and fetal brain development: implications for maternal nutrition, mechanisms of cognitive function, and pediatric depression

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## Abstract

Polyunsaturated fatty acids (PUFAs) are critical for human health, serving as key components of cellular membranes and regulators of various physiological functions. Since the body can endogenously synthesize only a small amount of these fatty acids from precursors, adequate dietary intake is essential. This article discusses the vital role of omega-3 fatty acids, particularly docosahexaenoic acid (DHA), in fetal brain development, with maternal omega-3 intake during pregnancy linked to improved neurodevelopment and long-term cognitive outcomes. However, variability in study findings highlights the need for further research to clarify DHA's mechanisms of action. This article explores recent findings indicating that insufficient omega-3 levels during pregnancy disrupt key neurodevelopmental processes, particularly microglial function, potentially elevating the risk of cognitive impairments and neurodevelopmental disorders, highlighting the need for further research to confirm these effects and elucidate underlying mechanisms and long-term consequences. Ensuring adequate maternal omega-3 intake is vital for supporting healthy brain development and reducing these risks. Additionally, DHA and eicosapentaenoic acid (EPA) show promise in treating pediatric depression by modulating the gut-brain axis, reducing neuroinflammation, and restoring autonomic nervous system function—mechanisms implicated in depression. While omega-3 supplementation holds potential as an adjunctive treatment for pediatric major depressive disorder (MDD), further research is necessary to refine dosing strategies and explore underlying mechanisms, ultimately advancing neuropsychiatric care.

## Keywords

Omega-3 fatty acids, polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), cognitive impairments, fetal brain development, gut-brain axis, pediatric major depressive disorder (MDD)

## Introduction

Fatty acids are essential components of complex lipids, playing crucial roles in metabolism, gene regulation, and cellular signaling. Although the human body can endogenously synthesize most fatty acids, it lacks the necessary enzymes for the de novo production of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs). Therefore, it relies on dietary intake of their essential precursors, α-linolenic acid and linoleic acid, which are subsequently metabolized through elongation and desaturation pathways. These PUFAs are primarily obtained from sources such as fatty fish and plant oils [1, 2]. Their biosynthesis and metabolism are tightly regulated by specific enzymes. Genetic variations in these enzymes can lead to significant interindividual and interpopulation differences in PUFA processing, further underscoring the importance of adequate dietary intake [3, 4].

PUFAs are structurally integral to cell membranes and are functionally critical for maintaining cellular homeostasis. They are classified into two main families based on their precursor molecules: omega-6 PUFAs, which are derived from *cis*-linoleic acid (LA, 18:2 omega-6), and omega-3 PUFAs, which originate from *alpha*-linolenic acid (ALA, 18:3 omega-3) [5, 6]. These precursors undergo enzymatic transformations to produce bioactive metabolites with diverse physiological roles. For instance, LA is converted into *gamma*-linolenic acid (GLA, 18:3 omega-6) and subsequently metabolized into *dihomo*-GLA (DGLA, 20:3 omega-6), which can be further converted into arachidonic acid (AA, 20:4 omega-6), a key precursor of pro-inflammatory prostaglandins. In contrast, ALA is converted into eicosapentaenoic acid (EPA, 20:5 omega-3) and docosahexaenoic acid (DHA, 22:6 omega-3). These metabolites have well-established anti-inflammatory properties and play a significant role in cardiovascular, metabolic, and neurological health [7–9].

Recent studies underscore the therapeutic potential of omega-3 fatty acids, particularly EPA and DHA, in treating a wide range of nervous system disorders, including depression, neuropsychiatric conditions, and neurodegenerative diseases. These findings highlight the critical importance of dietary intake, bioavailability, and the mechanisms of action of these fatty acids in promoting neuronal health [10].

Among the physiological processes influenced by PUFAs, pregnancy represents a particularly critical period. Maternal nutrition during gestation plays a pivotal role in fetal growth and development, with long-lasting implications for the health of both mother and child [11, 12]. Omega-3 fatty acids, especially DHA, are particularly important during this time due to their essential role in fetal brain development and neurogenesis [13, 14].

The importance of maternal nutrition extends beyond pregnancy into the first three years of life, a critical period that encompasses conception through a child's second birthday [15]. This phase is marked by rapid brain growth and structural organization, during which the developing nervous system is highly sensitive to external influences, particularly maternal dietary intake [16]. Omega-3 fatty acids, particularly DHA, emerge as cornerstone nutrients during this foundational period, underscoring their vital role in shaping neurodevelopmental outcomes [17, 18].

This article examines the multifaceted role of omega-3 fatty acids in prenatal development, with a particular focus on DHA's impact on fetal brain growth, long-term cognitive outcomes, and behavioral trajectories. It explores the essential functions of PUFAs in human health, highlighting their roles in cellular function, inflammation regulation, and neurological development. DHA, a key omega-3 fatty acid, is crucial for fetal brain maturation, with maternal intake associated with improved neurodevelopmental outcomes. The article underscores the need for further research to optimize DHA supplementation during pregnancy

and investigate its therapeutic potential in pediatric neurodevelopmental disorders, including depression. Additionally, it emphasizes the importance of personalized nutrition strategies and the role of PUFAs in shaping lifelong cognitive and mental health.

## Role of omega-3 fatty acids in fetal neurodevelopment

### Optimizing maternal and fetal health: the critical role of EPA and DHA monitoring and personalized supplementation

EPA and DHA, long-chain omega-3 fatty acids, play pivotal roles in maternal and fetal health during pregnancy. These essential fatty acids are crucial for fetal development, maternal well-being, and minimizing the risks of adverse pregnancy outcomes, such as preterm birth [19]. Scientific research indicates that blood concentrations of EPA and DHA are more accurate indicators of health outcomes than dietary intake alone [20], emphasizing the need for precise monitoring techniques.

Factors like bioavailability, dietary interactions, and metabolic variability underscore the necessity of personalized supplementation strategies to achieve optimal omega-3 levels in pregnant women [19, 21]. Analysis of the works reveals that while dietary intake data is widely available, it does not adequately capture interindividual variability in omega-3 absorption, metabolism, and functional impact, making blood-based measurements superior metric. Moreover, metabolic differences in fatty acid elongation and desaturation enzymes (e.g., FADS1 and FADS2 polymorphisms) significantly affect DHA synthesis from ALA, leading to considerable variability in omega-3 status across populations.

These individualized approaches are essential for improving maternal and fetal health outcomes, particularly for women facing challenges in meeting the recommended omega-3 intake, such as vegetarians and vegans.

The literature highlights key aspects of omega-3 research during pregnancy, including their physiological significance and the benefits of blood-based assessments over dietary intake data. It also addresses the challenges involved in supplementation and intervention trials (Table 1). Notably, blood-based measurements such as the Omega-3 Index and HS-Omega-3 Index® demonstrate a strong inverse correlation with preterm birth risk, whereas dietary intake data alone exhibits weaker or negligible associations [22, 23]. Furthermore, recent meta-analyses suggest that achieving an Omega-3 Index above 5% could reduce the risk of early preterm birth by nearly 50%, underscoring the need for more targeted intervention strategies [24, 25]. The growing body of evidence stresses the importance of refining research methodologies and enhancing individualized interventions. For example, bioavailability varies up to 13-fold among individuals due to dietary interactions and metabolic differences, necessitating personalized supplementation to optimize maternal and fetal health [26, 27]. Additionally, the source of omega-3 intake plays a critical role. Phospholipid-bound DHA from krill oil has been shown to have superior absorption compared to triglyceride-bound DHA from fish oil, suggesting that formulation choice may be a crucial determinant of efficacy. Standardizing measurement techniques and adopting blood-based monitoring will facilitate the effective optimization of maternal and fetal health.

Additionally, the significant depletion of maternal DHA stores during pregnancy, particularly in longer gestations where fetal erythrocyte DHA levels reach 8–9%. This underscores the importance of ensuring adequate maternal DHA intake to support fetal neurodevelopment [31, 32]. Furthermore, vegetarians and vegans exhibit lower plasma EPA and DHA levels, demonstrating the critical need for tailored supplementation strategies in these populations [36, 37]. Epidemiological studies indicate that low maternal DHA levels are associated with increased risks of neurodevelopmental disorders in offspring, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). This reinforces the necessity of sufficient prenatal DHA intake.

Intervention trials face ethical and methodological challenges, particularly due to the necessity of maintaining a minimum Omega-3 Index (~2%) for survival [29]. This highlights the difficulty in designing placebo-controlled trials, which may explain inconsistencies in omega-3 supplementation research.

**Table 1. Key insights and considerations in omega-3 supplementation for maternal and fetal health**

| Section | Key insights | Evidence/Examples | Implications | References |
|---|---|---|---|---|
| Role in pregnancy | EPA and DHA levels critically influence maternal and fetal health. | • Low blood levels associated with preterm births (especially < 34 weeks).<br>• Blood-based measurements (e.g., erythrocytes, whole blood, plasma) show strong inverse correlation with preterm birth risk.<br>• Dietary data shows weaker or negligible associations. | Monitoring blood EPA and DHA levels is essential for reducing adverse pregnancy outcomes. | [22, 23] |
| Dietary intake vs. blood levels | Blood levels are better predictors of outcomes than dietary intake. | • Dietary intake may not reflect bioavailability due to variability (e.g., fat content of meals enhances absorption up to 13-fold).<br>• Obesity further reduces the response to omega-3 supplementation. | Blood measurements offer a more accurate guide for clinical decisions and intervention strategies. | [24, 25] |
| Bioavailability factors | Bioavailability varies greatly among individuals. | • Interindividual variation in omega-3 uptake (up to 13-fold).<br>• Dietary interactions can alter bioavailability by up to 10-fold. | Tailored supplementation is required to address individual differences in omega-3 uptake. | [26, 27] |
| Measurement methods | Accurate evaluation of omega-3 status relies on blood assessments. | • Omega-3 Index: Reliable long-term marker with low biological variability.<br>• HS-Omega-3 Index®: Standardized and validated as the gold standard.<br>• Short-term indicators (e.g., plasma) reflect recent dietary changes but show high biological variability. | Regular blood testing provides precise data for monitoring and optimizing omega-3 status. | [28–30] |
| Maternal-fetal transfer | DHA transfer via the placenta supports fetal development. | • Fetal erythrocyte membranes reach DHA levels of 8–9%, depleting maternal stores.<br>• Longer pregnancies correlate with higher fetal DHA levels. | Ensuring adequate maternal DHA levels is crucial for fetal health and development. | [31, 32] |
| Breast milk composition | Maternal DHA status directly impacts breast milk composition. | • Optimal Omega-3 Index (8%) corresponds to ~1% EPA and DHA in breast milk.<br>• Many women fail to meet recommended levels (e.g., German pregnant women: average Omega-3 Index = 6.23). | Targeted supplementation improves maternal DHA status and breast milk quality, benefitting infants. | [33–35] |
| Challenges in vegetarian and vegan diets | Plasma EPA and DHA levels are lower in vegetarians and vegans. | • These groups face greater challenges in meeting recommended omega-3 levels. | Supplementation and monitoring are vital for these populations. | [36, 37] |
| Intervention trials and challenges | Omega-3 studies face unique ethical and methodological challenges. | • Cannot ethically deprive participants of omega-3 (minimum Omega-3 Index ~2% necessary for survival).<br>• Baseline variability and bioavailability differences complicate trial outcomes. | Standardized methods and tailored interventions enhance trial effectiveness and clinical relevance. | [29] |
| Future research directions | Addressing methodological gaps can unlock the full potential of EPA and DHA. | • Studies with standardized blood measurements show more consistent results.<br>• Personalized supplementation strategies offer promise, especially for vulnerable populations like pregnant women. | Improved methodologies can maximize the health benefits of EPA and DHA supplementation. | [38, 39] |

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid

Analysis also reveals that obesity reduces the effectiveness of omega-3 supplementation, further emphasizing the importance of blood-based monitoring over dietary intake data to guide clinical decisions. Specifically, increased adiposity leads to greater sequestration of DHA in fat tissue, thereby reducing its bioavailability for fetal development. Moreover, individuals with metabolic syndrome may exhibit impaired omega-3 incorporation into cell membranes, further complicating supplementation strategies.

## Impact of PUFA supplementation during pregnancy on perinatal outcomes and cognitive development

DHA supplementation during pregnancy has garnered considerable attention due to its potential impact on fetal neurodevelopment [33]. As a primary structural component of neural membranes, DHA plays a critical role during periods of rapid brain growth, particularly in the third trimester. Numerous studies, including randomized controlled trials (RCTs), meta-analyses, and observational research, have investigated DHA's effects on pregnancy outcomes and cognitive development (Table 2) [31, 40, 41]. However, despite the extensive research, the evidence on DHA's influence on cognitive outcomes remains inconclusive, reflecting the complexity of its effects. An analysis of the studies presented in Table 2 highlights the nuanced and often contradictory findings concerning DHA supplementation during pregnancy, particularly regarding its effects on cognitive development.

**Table 2. Efficacy of DHA and EPA supplementation during pregnancy: insights from clinical trials, meta-analyses, and observational studies**

| Study/Analysis type | Key findings | Participants | DHA dosage | Outcomes | Limitations | References |
|---|---|---|---|---|---|---|
| DOMINO trial (RCT) | Investigated DHA (800 mg) + EPA (100 mg) supplementation. Significant reductions in preterm births, low birth weight, and perinatal deaths. Cognitive benefits were observed in offspring, but no reduction in postpartum depression. | 2,399 pregnant women | 800 mg DHA + 100 mg EPA | 51% reduction in preterm births < 34 weeks, 35% reduction in low birth weight, mean birth weight increased by 68 grams, 3 perinatal deaths in supplementation group vs. 12 in placebo, no increase in bleeding complications. | Primary endpoint (postpartum depression) not met; mixed results in cognitive development. | [42] |
| Cochrane meta-analysis (RCTs) | Analyzed 70 RCTs (19,927 participants). Found modest effects on preterm births and low birth weight. No significant improvement in cognitive development or perinatal mortality. | 19,927 participants | Varies | 42% reduction in preterm births < 34 weeks, minor reductions in low birth weight, and neonatal care needs. No significant effects on perinatal mortality or cognitive development. | Limited evidence for cognitive development benefits; variability in trial designs and results. | [23] |
| Meta-analyses (RCTs) | Reported stronger effects, particularly dose-dependent benefits. Stronger reduction in preterm births and perinatal mortality. | Various participants | Varies | Stronger reduction in preterm births and perinatal mortality with higher doses of DHA and EPA. | Inconsistent findings between studies; insufficient for definitive conclusions on cognitive effects. | [43, 44] |
| Observational studies | Maternal DHA intake (especially from fatty fish) is linked to improved psychomotor and cognitive outcomes in offspring. | Varies by study | Natural dietary DHA sources | Higher DHA levels in maternal serum are associated with better cognitive and psychomotor development in infants. | Variability in study design, timing, and confounding variables (socioeconomic status, diet). | [18, 45, 46] |

RCT: randomized controlled trial; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid

The DOMINO trial, a large-scale RCT, investigated the effects of DHA (800 mg) + EPA (100 mg) supplementation during pregnancy, involving 2,399 pregnant women. This study found significant reductions in preterm births (51% reduction), low birth weight (35% reduction), and perinatal deaths, alongside a slight increase in mean birth weight (68 grams). However, cognitive benefits in offspring were

not consistently observed, and the primary endpoint—reduction in postpartum depression—was not met [42]. The findings from the DOMINO trial provide evidence for DHA's potential to improve pregnancy outcomes such as preterm birth and low birth weight. However, the lack of consistent cognitive benefits underscores the complexity of the relationship between DHA supplementation and neurodevelopment. This highlights that other factors may play a role in influencing cognitive outcomes. Additionally, the trial did not observe any significant increase in bleeding complications, suggesting that DHA supplementation at the dosages tested is safe with respect to maternal health.

The Cochrane meta-analysis, which synthesized data from 70 RCTs involving 19,927 participants, found modest effects of DHA supplementation on preterm births and low birth weight. Specifically, it reported a 42% reduction in preterm births before 34 weeks and minor reductions in low birth weight and neonatal care needs. However, it noted no significant effects on perinatal mortality or cognitive development [23]. This meta-analysis underscores the variability in the outcomes associated with DHA supplementation. While the reductions in preterm births and low birth weight are noteworthy, the lack of improvement in cognitive development suggests that DHA's impact may be more prominent in addressing pregnancy complications. This indicates that DHA may be more effective in mitigating prenatal risks than in enhancing neurodevelopment.

Other meta-analyses indicated dose-dependent benefits, with stronger reductions in preterm births and perinatal mortality observed at higher doses of DHA and EPA. However, these studies emphasized the inconsistency of findings across different trials, making it difficult to draw definitive conclusions about the cognitive benefits of DHA supplementation [43, 44]. This variability further complicates our understanding of DHA supplementation's role in pregnancy outcomes. While higher dosages may lead to more pronounced effects on certain outcomes, the cognitive benefits remain unclear, suggesting that the relationship between DHA and cognitive development may not be straightforward. The inconsistencies across studies may be attributed to differences in study design, sample populations, and the timing of supplementation, all of which warrant further exploration.

Observational studies have focused on maternal DHA intake from natural dietary sources, such as fatty fish, and have linked higher maternal DHA levels to improved psychomotor and cognitive outcomes in offspring. Specifically, higher DHA levels in maternal serum were associated with better cognitive and psychomotor development in infants [18, 45, 46]. However, these studies are limited by confounding variables such as socioeconomic status, maternal diet, and other lifestyle factors, which complicate the interpretation of results. While observational studies provide valuable insights into the potential long-term benefits of DHA, they cannot definitively establish causality due to the inherent limitations of their design. The relationship between maternal DHA levels and cognitive development is likely influenced by a complex array of factors, underscoring the need for more controlled experimental studies.

A thorough and systematic analysis of the studies presented in Table 2 reveals the complexity of DHA supplementation's effects on pregnancy and neurodevelopment. While several studies demonstrate a positive impact on pregnancy outcomes, particularly in reducing preterm births and low birth weight, the effects on cognitive development are less clear. The inconsistency of findings across trials indicates that DHA supplementation may not uniformly benefit all pregnant women or all offspring, particularly in terms of cognitive outcomes. Several factors contribute to this variability, including differences in study designs, participant characteristics, and the timing and dosage of supplementation.

Clarifying the specific conditions under which different outcomes occur, the practical implications of the research conclusions are somewhat limited. While DHA supplementation appears to have a more significant impact on certain pregnancy outcomes, such as reducing preterm birth and improving birth weight, the evidence for its influence on cognitive development is weaker. This discrepancy suggests that the benefits of DHA supplementation may be more pronounced in the context of improving pregnancy health rather than neurodevelopment, highlighting the need for more targeted research. Furthermore, the effectiveness of DHA supplementation may be influenced by maternal DHA levels at baseline, with women who have lower DHA levels potentially benefiting more than those with higher levels.

The benefits of DHA supplementation for perinatal outcomes are well-established, including reductions in the risks of preterm birth, low birth weight, and perinatal mortality (Table 3) [47, 48]. These findings underscore DHA's essential role in supporting both maternal and fetal health. However, its impact on cognitive development remains less definitive. Differences in study design, such as variations in DHA dosage, supplementation timing, maternal nutritional status, and measurement methods for cognitive outcomes, contribute to inconsistent findings [40, 49]. These discrepancies complicate efforts to fully understand DHA's role in neurodevelopment and highlight the need for more nuanced and targeted research.

**Table 3. Key insights and research directions on DHA supplementation: mechanisms, implications, and future perspectives**

| Topic | Key insights | Mechanisms | Implications | Challenges and considerations | References |
|---|---|---|---|---|---|
| Nonlinear effects of DHA | The relationship between maternal omega-3 LC-PUFA levels and fetal neurodevelopment may follow a nonlinear pattern. | Lower DHA may support fetal brain development while excessive DHA may lead to oxidative stress. | Excessive DHA intake can impair neuronal function by generating ROS. | Animal studies show that high DHA levels result in oxidative damage, affecting cellular function. | [12, 33, 50] |
| Tailored strategies for maternal intake | Tailored DHA intake strategies are critical to optimize maternal and fetal health. | DHA levels need to be adjusted based on baseline maternal DHA and specific needs for preterm infants. | Ensures adequate DHA intake while preventing over-supplementation, avoiding risks associated with excessive intake. | Customizing DHA intake reduces risks, but high-dose supplementation for women with sufficient omega-3 intake could be unnecessary and risky. | [43, 44, 51, 52] |
| Optimizing DHA supplementation: timing, dosage, and population considerations | Understanding the timing, dosage, and population-specific needs of DHA during pregnancy is essential. | Maternal-fetal nutrient exchange varies due to genetic, nutritional, and metabolic factors. | Identifying optimal DHA and EPA concentrations at different gestational stages is key for neurodevelopment. | Variability in needs across populations makes it difficult to recommend one-size-fits-all supplementation. | [33, 53, 54] |
| Safety and tolerability | Omega-3 supplementation up to 5 g/day of EPA and DHA is considered safe for pregnant and lactating women. | Clinical trials show doses up to 2.7 g/day of DHA are well tolerated with minimal adverse effects. | High doses may increase bleeding risks, but these are rare and typically not clinically significant. | Despite potential bleeding risks, higher doses of DHA during pregnancy may have limited clinical significance. | [22, 43, 55, 56] |
| Limited evidence on lactation | Research on DHA supplementation during lactation is limited. Effects on child cognitive outcomes remain inconclusive. | Evidence linking DHA supplementation during lactation to improved neurodevelopmental outcomes is scarce. | The role of DHA supplementation during lactation is unclear and needs more research. | Variability in study design, sample sizes, and outcomes makes it difficult to assess the impact of DHA during lactation. | [18, 57, 58] |
| Population-specific interventions | DHA supplementation benefits vary based on baseline omega-3 status. Populations with low DHA levels may benefit more. | Lower doses of DHA (300–400 mg/day) may be as effective as higher doses (e.g., 1,440 mg/day) in supporting neurodevelopment. | Personalized nutritional strategies based on baseline omega-3 levels could optimize neurodevelopmental outcomes. | Individual responses to DHA supplementation may vary significantly, requiring personalized approaches to intervention. | [40, 59, 60] |
| Cognitive and behavioral outcomes | DHA supplementation may have lasting cognitive and behavioral effects, such as attention regulation and academic performance in childhood. | DHA supports brain development, influencing attention, academic performance, and social behavior. | Long-term studies are necessary to fully understand DHA's impact on cognitive and behavioral outcomes. | Findings on long-term cognitive effects of DHA supplementation are inconsistent, and further studies are needed to clarify these effects. | [40, 61–63] |

**Table 3. Key insights and research directions on DHA supplementation: mechanisms, implications, and future perspectives** (*continued*)

| Topic | Key insights | Mechanisms | Implications | Challenges and considerations | References |
|---|---|---|---|---|---|
| Neural plasticity and lifelong development | DHA supports neural plasticity, neurogenesis, and synaptic plasticity, suggesting long-term benefits for brain health and cognitive development. | DHA enhances neural circuits, supporting lifelong cognitive and behavioral development. | Supplementation during critical brain development periods may influence cognitive and behavioral trajectories. | The full extent of DHA's impact on long-term brain development remains understudied, and more research is needed. | [33, 64–66] |

DHA: docosahexaenoic acid; LC-PUFA: long-chain polyunsaturated fatty acids; ROS: reactive oxygen species; EPA: eicosapentaenoic acid

The relationship between maternal omega-3 long-chain PUFAs (LC-PUFAs) levels and fetal neurodevelopment may follow a nonlinear pattern. While insufficient DHA levels impair fetal brain development, excessive DHA intake may generate oxidative stress and impair neuronal function through the overproduction of reactive oxygen species (ROS). Animal studies suggest that high DHA levels can lead to oxidative damage, thereby affecting cellular function. Recent studies have indicated that excessive DHA intake may also influence epigenetic modifications, altering gene expression related to neurodevelopment [12, 33, 50].

Tailored DHA intake strategies are essential for optimizing maternal and fetal health. Current evidence suggests that DHA levels should be adjusted based on baseline maternal DHA status and the specific needs of preterm infants. While ensuring adequate DHA intake is critical, excessive supplementation in women with sufficient omega-3 intake may be unnecessary and could pose potential risks. Customizing DHA intake can mitigate such risks, but further research is needed to define personalized supplementation guidelines based on maternal baseline levels and risk factors to establish safe upper intake limits for different populations [43, 44, 51, 52].

The timing, dosage, and population-specific needs of DHA supplementation during pregnancy remain critical considerations. Maternal-fetal nutrient exchange is influenced by genetic, nutritional, and metabolic factors, making it essential to determine the optimal DHA and EPA concentrations at various gestational stages. The heterogeneity in requirements across populations complicates the establishment of universal supplementation recommendations. Emerging evidence highlights that genetic polymorphisms affecting DHA metabolism may further modulate individual responses to supplementation [33, 53, 54].

Regarding safety, omega-3 supplementation up to 5 g/day of combined EPA and DHA is generally considered safe for pregnant and lactating women. Clinical trials indicate that doses up to 2.7 g/day of DHA are well tolerated, with minimal adverse effects. Although higher doses may slightly increase bleeding risks, these effects are rare and not typically clinically significant. However, recent meta-analyses suggest that excessive omega-3 intake might influence immune system development in infants, necessitating further investigation [22, 43, 55, 56].

Despite growing interest, research on DHA supplementation during lactation remains limited, and its effects on child cognitive outcomes are inconclusive. While it is hypothesized that DHA supplementation enhances neurodevelopment via breast milk enrichment, strong evidence supporting this claim is lacking. The variability in study design, sample sizes, and cognitive outcome measures further complicates interpretation. Some studies suggest that DHA-enriched breast milk may contribute to improved visual acuity and early cognitive function, but these findings require validation in larger cohorts [18, 57, 58].

The impact of DHA supplementation appears to be most pronounced in populations with low baseline omega-3 levels, where the greatest benefits in neurodevelopment are observed. While higher DHA doses (e.g., 1,440 mg/day) have been investigated, lower doses (300–400 mg/day) may be equally effective in supporting neurodevelopment. Personalized nutritional strategies based on baseline omega-3 levels could optimize neurodevelopmental outcomes. However, individual responses to DHA supplementation vary significantly, requiring a tailored approach. Recent research suggests that maternal DHA status during

pregnancy might also influence offspring metabolic health, highlighting a potential area for further exploration [40, 59, 60].

DHA supplementation may also have lasting cognitive and behavioral effects, including improved attention regulation and academic performance in childhood. Through its role in neural circuit formation, DHA supports cognitive functions such as attention, memory, and social behavior. However, evidence regarding the long-term cognitive effects of DHA supplementation remains inconsistent. Recent findings suggest that early DHA exposure may influence stress reactivity and emotional regulation later in life [40, 61–63].

DHA plays a crucial role in neural plasticity, neurogenesis, and synaptic remodeling, suggesting potential lifelong benefits for brain health. By enhancing synaptic connectivity and neuronal function, DHA may influence cognitive and behavioral development beyond infancy. However, the long-term impact of DHA supplementation during critical neurodevelopmental windows remains insufficiently studied. Recent advancements in neuroimaging have provided preliminary evidence linking prenatal DHA exposure to structural and functional changes in brain connectivity [33, 64–66].

To clarify these inconsistencies, it is crucial to investigate the mechanisms and implications of DHA supplementation during pregnancy. Important areas of exploration include identifying optimal dosing strategies, customizing intake recommendations based on maternal health profiles, and evaluating the long-term safety of DHA supplementation. Research should also focus on filling critical gaps, such as understanding the effects of sustained DHA use beyond the perinatal period. These insights are essential for refining research methodologies and clinical guidelines.

Beyond neurodevelopment, clinical evidence highlights the therapeutic potential of DHA and EPA supplementation in managing neuropsychiatric conditions [67]. Deficiencies in DHA have been closely linked to impaired synaptic signaling and mood dysregulation, which are characteristic features of disorders such as depression [68, 69]. Supplementation studies have shown significant cognitive and emotional benefits, including enhanced memory and executive function in individuals with mild cognitive impairment and dementia, as well as improved mood stability in those with depression.

These findings emphasize the dual role of omega-3 fatty acids in both the prevention and treatment of neuropsychiatric conditions, reinforcing their importance as essential dietary components for mental health [70]. The exploration of these benefits and their underlying mechanisms is addressed in subsequent sections.

Despite these promising findings, several challenges remain in establishing definitive recommendations for DHA supplementation during pregnancy. A major limitation is the lack of standardized methods for measuring omega-3 plasma levels across studies. This inconsistency affects the ability to assess adherence to supplementation protocols and evaluate the efficacy of different dosages. Additionally, variability in trial outcomes highlights the need for further investigation into maternal factors—such as diet, genetics, and environmental influences—that may modulate DHA's effects.

In addition, understanding the molecular and cellular mechanisms by which DHA supports fetal brain development remains a critical area of research. Key neurodevelopmental processes, including neurogenesis, synaptogenesis, and myelination, depend on adequate DHA levels, and exploring these pathways will provide a solid scientific foundation for DHA supplementation strategies [71, 72]. Longitudinal studies are essential for evaluating the lasting effects of prenatal DHA intake on cognitive and behavioral outcomes, particularly in areas such as executive function, attention, and sleep patterns. These studies will help determine whether the benefits of early DHA supplementation extend into later life stages, offering valuable insights into the long-term impacts of maternal DHA intake.

Increasing the representation of diverse populations in research is vital for ensuring the broader applicability of findings. Including individuals from varied genetic, socioeconomic, and dietary backgrounds will help establish more inclusive dietary recommendations that are relevant across different demographics. Another important focus is the development of personalized dietary guidelines. Tailored recommendations that consider individual maternal and fetal health factors—such as genetics, pre-existing

conditions, and dietary habits—can maximize the benefits of DHA supplementation while minimizing potential risks.

### Role of omega-3 fatty acids in fetal CNS development during pregnancy

Omega-3 fatty acids, particularly DHA, are crucial for the healthy development of the fetal central nervous system (CNS) during pregnancy. DHA is mobilized from maternal adipose tissue and transported across the placenta, accumulating in the fetal brain [73]. This accumulation supports brain structure formation and function, with significant increases in maternal plasma DHA concentrations occurring throughout pregnancy, especially during the second trimester—a critical period of neurodevelopment [32, 33, 73]. Given the essential role of DHA in this phase, ensuring adequate maternal DHA levels is vital for optimal CNS development.

Research into DHA supplementation during pregnancy has examined its effects on visual, cognitive, and motor development in offspring. However, findings remain inconsistent. While some studies suggest positive developmental outcomes, others report no significant improvements, indicating that factors such as maternal diet, genetics, and environmental influences may modify the effects of DHA supplementation [17, 48, 63, 74]. These inconsistencies highlight the need for further research to better understand the role of omega-3 fatty acids, particularly DHA, in prenatal development.

During pregnancy, maternal levels of DHA and AA decline as these and other essential fatty acids are preferentially transferred to the fetus via the placenta to support fetal neurodevelopment, particularly the growth and maturation of the CNS [75]. Maternal-infant DHA equilibrium is thought to be achieved when DHA transfer from maternal stores adequately meets fetal neurodevelopmental demands, reflecting an optimal DHA status for both mother and newborn [76]. Maintaining higher maternal DHA levels at delivery may further support DHA transfer during lactation, which remains critical for postnatal brain development [77]. This pattern suggests that fetal brain DHA levels rise rapidly during pregnancy and continue accumulating throughout the first year of life, emphasizing the importance of sufficient maternal omega-3 intake for promoting optimal neurodevelopment and cognitive outcomes in offspring [33, 78, 79]. Prenatal DHA supplementation can further influence these outcomes by optimizing maternal omega-3 status and enhancing the child's capacity to convert precursor fatty acids into LC-PUFAs, which are essential for CNS development [33, 80–82]. However, many studies fail to account for baseline maternal omega-3 status, excluding participants who already take DHA-containing supplements. Health organizations recommend regular consumption of DHA-rich foods, such as fish, to ensure sufficient intake. For example, the American Academy of Pediatrics advises consuming 1–2 servings of DHA-rich fish per week, and the 2020 Dietary Guidelines for Americans recommend 8–12 ounces of seafood weekly, providing 250–400 mg of omega-3 fatty acids [83, 84].

DHA and EPA are essential for maintaining neuronal membrane integrity, facilitating neurotransmitter signaling, and promoting neurodevelopment. Deficiencies in omega-3 fatty acids are associated with impaired synaptic function, disrupted neurotransmitter systems, and hindered neurodevelopment, all of which are linked to neurodevelopmental and neuropsychiatric conditions, such as depression, and dementia [40, 85–88]. Omega-3 fatty acids are especially important during early neurodevelopment, as DHA and EPA contribute to the structural and functional integrity of neuronal membranes, promote synaptic connectivity, and enhance neurotransmitter efficiency [21, 88, 89].

Maternal omega-3 intake has a significant impact on offspring neurodevelopment, although clinical findings vary due to differences in supplementation timing, dosage, and study populations. Standardized research methodologies are needed to clarify the relationship between maternal omega-3 intake and offspring neurodevelopment [17, 50, 90, 91]. Omega-3 fatty acids also influence behavioral development, including sleep regulation and circadian rhythm establishment. DHA supports the maturation of neural pathways necessary for organized sleep patterns in infants, with supplementation during pregnancy associated with longer gestational periods and improved neurodevelopmental and behavioral outcomes [19, 50, 92–94].

The placenta plays a vital role in supplying essential nutrients, including PUFAs, which are critical for fetal brain development. Emerging evidence suggests that maternal PUFA levels during pregnancy can have lasting effects on neonatal and childhood outcomes, including fetal growth, respiratory function, adiposity, and neurodevelopment [12, 32, 95–97]. Maternal PUFA status has been linked to cognitive function, behavioral health, and other neurodevelopmental markers [73, 98]. Additionally, the omega-3 to omega-6 PUFA ratio in the maternal diet influences emotional and behavioral outcomes in children [99, 100]. A lower omega-3 to omega-6 ratio has been associated with an increased risk of emotional issues and autistic traits, while higher maternal omega-3 levels correlate with improved cognitive outcomes, such as higher IQ scores and enhanced sequential processing abilities [67, 101–103]. These findings suggest that both the quantity and balance of omega-3 and omega-6 PUFAs are crucial for fetal brain health.

### Mechanisms of PUFA-mediated neurodevelopment: roles of DHA and EPA in fetal brain growth and CNS function during pregnancy

The mechanisms through which PUFAs influence neurodevelopment remain partially understood. However, certain fatty acids, including DHA, EPA, AA, and adrenic acid, play essential roles in neuronal membrane structure, neurogenesis, and myelination [96, 104]. DHA, in particular, is critical for synaptic function, axonal growth, and the establishment of neural networks during pregnancy [33, 105]. The second half of gestation is marked by rapid brain growth, involving neurogenesis, axonal elongation, dendritic differentiation, and synaptogenesis—all of which depend on the availability of omega-3 PUFAs [96, 106, 107]. Insufficient omega-3 PUFA intake during pregnancy may disrupt these processes, potentially leading to reduced brain volume and impaired neurodevelopment [33, 69].

DHA may also regulate the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and leukemia inhibitory factor (LIF), which are critical for neurogenesis and brain volume [64, 96, 108]. The expression of these factors may be influenced by epigenetic mechanisms, including DNA methylation [109, 110]. Low maternal omega-3 PUFA levels could impair neurotrophic factor expression, negatively impacting neurogenesis and brain development [111, 112]. Moreover, insufficient omega-3 PUFA intake may alter metabolic pathways, increasing the risk of childhood obesity and lowering HDL cholesterol, further affecting brain development [21, 69].

DHA and AA support synaptic connectivity and help maintain membrane fluidity in the brain's gray matter. While these fatty acids can be synthesized endogenously from dietary precursors like ALA and linoleic acid, direct dietary sources, such as fatty fish, fish oil, and algae, provide more bioavailable and efficient forms [104, 113, 114]. Modern Western diets, characterized by an excessive linoleic acid to ALA ratio, tend to elevate AA levels while reducing the availability of DHA. This imbalance disrupts the essential equilibrium between omega-3 and omega-6 fatty acid and has been implicated in the pathophysiology of various neurodevelopmental disorders, including depression [1, 69, 115]. The homeostasis between omega-6 and omega-3 fatty acids is tightly regulated by shared enzymatic pathways—namely Δ6-desaturase, Δ5-desaturase, and elongase—which convert linoleic acid and ALA into their bioactive metabolites, AA and DHA, respectively [116, 117]. However, the disproportionately high intake of linoleic acid in Western dietary patterns shifts this enzymatic competition toward omega-6 metabolism, thereby promoting the excessive synthesis of AA and limiting the conversion of ALA into DHA. This metabolic shift fosters a pro-inflammatory milieu, as AA-derived eicosanoids—such as prostaglandins and leukotrienes—exert potent pro-inflammatory effects, whereas DHA and other omega-3 metabolites exert anti-inflammatory and neuroprotective functions [6]. Consequently, the disrupted fatty acid balance may contribute to the onset and progression of neurodevelopmental and neuropsychiatric disorders by altering neuronal membrane composition, impairing synaptic plasticity, and exacerbating neuroinflammatory responses. Addressing these dietary imbalances is therefore critical for reducing the risk associated with omega-3 deficiencies and their neurobiological consequences.

In addition to their structural roles, bioactive mediators derived from DHA and AA, such as the oxylipins, play a key role in regulating CNS functions. These mediators are produced through enzymatic pathways involving cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes,

modulating inflammation and immune responses [118–120]. These bioactive lipids underscore the physiological importance of dietary fatty acids in maintaining CNS homeostasis and supporting neurodevelopmental processes.

Research suggests that maternal PUFA levels during pregnancy influence the morphology of the offspring's brain, including brain volume and white matter integrity. Higher maternal omega-3 PUFA levels, particularly DHA, have been linked to larger brain volumes and improved white matter microstructure in children. These effects are especially evident in gray matter. However, omega-6 PUFAs, particularly long-chain omega-6 fatty acids, do not appear to exert similar benefits on brain morphology. In fact, certain omega-6 fatty acids, such as linoleic acid, may be inversely associated with white matter volume. Despite evidence supporting the role of omega-3 PUFAs in brain development, the relationship between maternal PUFA status and brain morphology remains complex and requires further exploration.

### Maternal omega-3 PUFAs and offspring brain development: unraveling public health implications

Maternal omega-3 PUFAs are essential for optimal fetal brain development. However, significant gaps remain in understanding the specific mechanisms driving these effects. Existing research highlights the critical role of omega-3 fatty acids, but further studies involving larger and more diverse populations are needed to better understand how prenatal omega-3 exposure influences brain morphology and cognitive outcomes. Investigating omega-3 levels during key neurodevelopmental windows is essential for assessing their cumulative impact on brain health throughout pregnancy.

Understanding the causal relationship between maternal PUFA levels and fetal brain development has important public health implications. This knowledge could inform targeted interventions, such as dietary recommendations or supplementation programs, aimed at optimizing maternal and fetal health. Such strategies could promote healthy brain development, reduce the risk of neurodevelopmental disorders, and address long-term concerns like cognitive impairments and mental health disorders later in life.

Identifying the populations most likely to benefit from omega-3 supplementation remains an area of significant research gap, particularly when considering factors such as baseline omega-3 levels and dietary habits. For instance, data from the National Health and Nutrition Examination Survey (NHANES) reveal that while a considerable number of pregnant and lactating women in the U.S. use dietary supplements, a relatively small proportion specifically consume DHA or EPA supplements [84, 121, 122]. Furthermore, genetic factors, such as variations in fatty acid desaturase genes, can influence omega-3 metabolism [123, 124], underscoring the need for personalized nutritional approaches. Addressing these gaps is critical for optimizing omega-3 supplementation strategies and ensuring that individuals who are most likely to benefit receive adequate intake.

The determination of the optimal timing and form of omega-3 supplementation remains underexplored. While most studies have compared omega-3 supplements to placebos, alternative methods, such as multivitamins, fortified foods, or natural sources like seafood, merit further investigation. Additionally, examining the combined effects of omega-3 supplementation during pregnancy and lactation, along with identifying critical supplementation windows, could offer valuable insights. To ensure findings are broadly applicable, future studies should include diverse populations, encompassing various ethnicities, socioeconomic backgrounds, and geographic locations. These considerations are essential for developing tailored guidelines to promote public health and reduce the burden of neurodevelopmental disorders.

## Implications of maternal omega-3 PUFA deficiency on microglial function, hippocampal dysfunction, and cognitive impairment

Sections Maternal omega-3 deficiency and microglial dysregulation in neurodevelopment and The impact of omega-3 PUFA deficiency on hippocampal development and cognitive function examine the impact of maternal omega-3 PUFA deficiency on neurodevelopment, with a focus on microglial dysfunction. Microglia play a critical role in neural circuit formation, synaptic pruning, and brain homeostasis. Omega-3 PUFA deficiency during pregnancy may disrupt microglial function, impair neurodevelopment, and increase the

risk of cognitive deficits and neurodevelopmental disorders. Notably, studies investigating the role of omega-3 PUFAs in supporting microglial function and synaptic pruning have been primarily conducted in animal models, limiting their direct applicability to human neurodevelopment. This discussion also explores the broader role of omega-3 PUFAs in brain development, particularly during critical periods, and their connection to major depressive disorder (MDD) and the gut-brain axis. While research on omega-3 supplementation for pediatric neurological disorders remains limited, its anti-inflammatory properties and neuroprotective potential offer promising avenues for future investigation.

## Maternal omega-3 deficiency and microglial dysregulation in neurodevelopment

Neurodevelopment is a complex process orchestrated by cellular and molecular mechanisms that establish functional neural circuits, essential for cognitive, behavioral, and motor functions [125, 126]. Microglia play a pivotal role in brain homeostasis and neuroinflammation regulation during development [127]. A key function of microglia in brain maturation is synaptic pruning—the selective elimination of redundant synapses to refine neuronal circuits—which is critical for cognitive and behavioral function maturation [128]. Dysregulated synaptic pruning has been linked to neurodevelopmental disorders, including depression [129].

Recent research underscores the significant influence of maternal nutrition on offspring neurodevelopment, with omega-3 PUFAs, particularly DHA and EPA, being essential for synaptic plasticity, neuronal membrane integrity, and anti-inflammatory signaling [87, 89]. Maternal deficiencies in omega-3 PUFAs during gestation and lactation disrupt neurodevelopment, particularly by impairing microglial function. Notably, omega-3 PUFA deficiency is associated with excessive microglial pruning in key brain regions such as the hippocampus, a structure critical for learning and memory [73, 130, 131].

Microglia function as both immune sentinels and regulators of neural circuit refinement [132]. During neurodevelopment, they facilitate apoptotic cell removal and synaptic pruning, processes crucial for the maturation of functional neural circuits [133]. At the cellular level, microglia rely on intricate intracellular signaling cascades, such as the PI3K/Akt and MAPK pathways, to modulate phagocytic activity and inflammatory responses. These molecular mechanisms are tightly regulated by cytokines, lipid mediators, and neurotransmitters, ensuring a balance between synapse elimination and preservation [134, 135]. Synaptic pruning is particularly active postnatally, ensuring the precise refinement of brain circuits through signaling pathways such as the complement cascade and fractalkine receptor interactions, which selectively eliminate redundant synapses while preserving essential neural pathways [136, 137]. Dysregulated pruning, whether excessive or insufficient, disrupts neural circuit formation, leading to cognitive deficits and behavioral disorders [138].

Maternal omega-3 PUFA deficiency has been shown to drive overactive microglial pruning [130, 131], primarily through the 12/15-LOX pathway. This pathway metabolizes AA into bioactive lipid mediators such as 12-hydroxyeicosatetraenoic acid (12-HETE), which enhances microglial phagocytosis, resulting in excessive synaptic pruning [139, 140]. Omega-3 PUFAs regulate microglial activation through peroxisome proliferator-activated receptors (PPARs) and retinoid X receptors, which modulate gene expression related to neuroinflammation [141, 142]. These nuclear receptors help ensure that microglia maintain homeostatic functions rather than transitioning into a hyperactive state [143]. Furthermore, omega-3 PUFA metabolites can counteract the effects of pro-inflammatory lipid mediators derived from AA, thus suppressing excessive synaptic pruning [131, 144]. In normal conditions, microglial activity is balanced to maintain synaptic connectivity, but omega-3 PUFA deficiency disrupts this balance, shifting toward an overactive pruning response [131].

At the molecular level, the upregulation of the LOX pathway alters the lipid microenvironment within microglial cells, leading to increased production of pro-inflammatory lipid mediators that exacerbate synaptic engulfment [145, 146]. These changes are accompanied by enhanced expression of complement proteins, further amplifying the process of synapse elimination. Additionally, maternal omega-3 PUFA deficiency disrupts microglial metabolic pathways by altering lipid raft composition in the cell membrane. This results in dysfunctional signaling cascades, leading to an overproduction of ROS and increased

activation of the NF-κB pathway, which perpetuates neuroinflammation and exacerbates synaptic loss [130, 147]. Elevated 12-HETE levels promote synaptic spine engulfment, reducing spine density and impairing synaptic connectivity and function [131].

The interaction between the 12-HETE pathway and the complement cascade exacerbates excessive synaptic pruning. The complement system marks synaptic elements for removal, and its activation alongside 12-HETE signaling amplifies microglial pruning activity [138, 148, 149]. On a cellular level, microglial engulfment of synaptic elements is driven by upregulated expression of complement receptor 3 and triggering receptor expressed on myeloid cells 2, both of which become hyperactivated under omega-3 PUFA-deficient conditions [131, 145, 150]. This heightened activity leads to an imbalance in synaptic homeostasis, ultimately compromising neural network stability and connectivity.

This synergistic effect leads to disrupted neural connectivity, highlighting the critical role of maternal omega-3 PUFA intake in maintaining microglial function and synaptic integrity during neurodevelopment. Ensuring optimal maternal nutrition, particularly sufficient omega-3 PUFA consumption, is essential for proper neural circuit development and the prevention of neurodevelopmental disorders.

### The impact of omega-3 PUFA deficiency on hippocampal development and cognitive function

The hippocampus, a brain region crucial for learning and memory, is particularly vulnerable to the effects of maternal omega-3 PUFA deficiency [151, 152]. Structural impairments, such as reduced dendritic length and decreased expression of key synaptic proteins like PSD-95 and cofilin, have been observed in the hippocampi of offspring from omega-3 PUFA-deficient mothers [131, 153]. These structural changes are accompanied by functional impairments, including deficits in spatial memory and cognitive flexibility, which become apparent even at early developmental stages such as weaning. The excessive pruning of synaptic elements in the hippocampus contributes to these abnormalities, ultimately leading to long-term cognitive deficits [154].

These findings imply maternal omega-3 PUFA deficiency in the pathogenesis of neurodevelopmental disorders characterized by hippocampal dysfunction, such as depression [155]. The observed structural and functional impairments in the hippocampus highlight the critical importance of maternal nutrition during key windows of neurodevelopment, particularly in the context of synaptic remodeling. At a cellular level, hippocampal neurons exposed to omega-3 PUFA deficiency exhibit reduced spine density and altered expression of synaptic adhesion molecules, impairing synaptic transmission [89, 156]. This results in decreased long-term potentiation, the primary mechanism underlying learning and memory. Additionally, maternal omega-3 PUFA depletion disrupts hippocampal neurogenesis, leading to reduced neuronal proliferation and survival in the dentate gyrus, a crucial region for memory encoding [89, 157].

On a molecular scale, omega-3 PUFA deficiency induces alterations in synaptic protein composition, reducing the availability of AMPA and NMDA receptor subunits necessary for excitatory neurotransmission [158, 159]. Additionally, deficits in DHA incorporation within neuronal membranes impair membrane fluidity, weakening synaptic signal transduction and plasticity [160]. The imbalance between omega-3 and omega-6 PUFAs during pregnancy can have lasting effects on offspring brain development, influencing cognitive outcomes and increasing the risk of neurodevelopmental disorders [107].

The balance between maternal omega-3 and omega-6 PUFAs is essential for healthy brain development, as deficiencies and imbalances can disrupt microglial function, synaptic pruning, and hippocampal activity. Addressing these imbalances through targeted nutritional and therapeutic interventions holds promise for optimizing neurodevelopment and supporting lifelong brain health.

### Maternal omega-3 PUFA deficiency and its impact on neurodevelopment: implications for cognitive health and therapeutic strategies

Epidemiological studies have consistently demonstrated a strong link between maternal omega-3 PUFA deficiency and impaired neurodevelopment, with lasting cognitive consequences for offspring [69, 80]. Reduced levels of DHA and EPA during pregnancy are associated with smaller brain size, altered neural

connectivity, and cognitive deficits in the offspring [33]. The omega-3 PUFA index, which measures DHA and EPA levels in erythrocytes, has emerged as a promising biomarker for assessing the risk of neurodevelopmental impairments. This index could potentially guide public health initiatives aimed at improving maternal nutrition and reducing the risk of neurodevelopmental disorders [21, 38, 161].

Supplementing maternal diets with DHA and EPA during pregnancy and lactation holds considerable potential for mitigating the effects of omega-3 PUFA deficiency. Such dietary interventions are critical in preserving synaptic connectivity and preventing the cognitive impairment associated with excessive microglial pruning [60, 105, 162]. Therapeutic approaches targeting neuroinflammatory pathways, such as pharmacological inhibitors of the 12/15-LOX pathway or dietary interventions aimed at restoring lipid homeostasis [163], represent promising strategies for mitigating the adverse effects of omega-3 PUFA deficiency. Additionally, modulating maternal gut microbiota composition through probiotics and prebiotics may enhance omega-3 PUFA bioavailability [164], further supporting neurodevelopment. Targeting early-life nutritional strategies, particularly for at-risk populations, such as pre-term or low-birth-weight infants, can significantly improve neurodevelopmental outcomes and reduce the risk of neurodevelopmental disorders in these vulnerable groups.

## Omega-3 PUFAs in pediatric depression: early-life deficiency, central mechanisms, and therapeutic implications

The early stages of life are critical for brain growth and maturation, characterized by an increased demand for omega-3 PUFAs, particularly DHA and EPA. Deficiencies in omega-3 PUFAs during this vulnerable period can disrupt these vital processes, resulting in long-lasting cognitive and emotional impairments, with an elevated risk of pediatric depression [165, 166].

Maternal omega-3 PUFA deficiency also poses a significant risk, as it is linked to a higher likelihood of maternal depression, further exacerbating health challenges for both mother and child [167, 168]. Research in animal models suggests that maternal immune activation, combined with an omega-3 PUFA-deficient diet, can intensify neuroinflammation and cognitive deficits in offspring. This combination may increase the likelihood of neurodevelopmental and psychiatric disorders, including depression [169–171]. Epidemiological studies further support this association, showing that low maternal seafood consumption correlates with poorer neurodevelopmental outcomes and a heightened risk of neuropsychiatric conditions, such as depression [172, 173].

DHA deficiency is consistently linked to structural and functional abnormalities in the brain, contributing to enduring learning and memory deficits [33, 174]. These deficits are associated with a heightened vulnerability to mood disorders, including depression. Ensuring adequate DHA intake during early life is crucial for fostering long-term cognitive and emotional health, thereby mitigating the risk of pediatric depression.

### The potential role of omega-3 PUFA in managing major depressive disorder in children and adolescents

MDD is a leading cause of morbidity among children and adolescents, with prevalence rates ranging from 5% to 12% [175]. Despite the substantial public health burden, current treatment options for pediatric MDD are limited, and traditional pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRIs), often demonstrate insufficient efficacy [176]. This has prompted growing interest in alternative therapeutic approaches, particularly the potential role of omega-3 PUFAs, such as EPA and DHA, in alleviating the pathophysiology of depression. Deficiencies in these fatty acids have been observed in individuals with depression, leading to investigations into their therapeutic benefits.

Epidemiological studies consistently suggest that higher dietary intake of omega-3 PUFAs is associated with lower rates of depression, highlighting a potential protective role for these fatty acids in mental health [177, 178]. Clinical trials have confirmed the antidepressant effects of EPA and DHA, not only in MDD but also in other mood disorders, such as bipolar disorder [55]. Interestingly, these fatty acids appear to exert a

more pronounced effect during depressive episodes compared to manic phases, emphasizing their selective benefit for mood regulation. Various mechanisms have been proposed to explain these effects, including their impact on the gut-brain axis, their ability to restore autonomic nervous system (ANS) function, and their role in reducing systemic inflammation.

One of the key mechanisms through which omega-3 PUFAs influence depression is by modulating the ANS. Depression is often associated with vagal withdrawal, which leads to reduced heart rate variability (HRV)—a marker of emotional dysregulation and impaired psychological flexibility [171, 179, 180]. Research has shown that HRV is significantly lower in adolescents with depression compared to healthy controls. Supplementation with omega-3 PUFAs has been demonstrated to increase HRV, suggesting that the restoration of autonomic function may help alleviate depressive symptoms. Additionally, omega-3 PUFAs help prevent autonomic dysregulation, improving HRV, reducing arrhythmic risks, and lowering the risk of sudden death [179, 181]. Early-life supplementation with omega-3 PUFAs may be especially critical for promoting healthy autonomic function, which could be pivotal for both the prevention and treatment of depression in children and adolescents.

Beyond their structural and functional roles, omega-3 PUFAs possess potent anti-inflammatory properties that help mitigate neuroinflammation—a key contributor to the pathophysiology of depression [182, 183]. By modulating inflammatory markers such as NF-κB, interleukin-6 (IL-6), interleukin-17A (IL-17A), and tumor necrosis factor-alpha (TNF-α), omega-3 PUFAs support a balanced immune response, creating a favorable environment for neurodevelopment and mental health [184–186]. Specifically, EPA counters inflammation by reducing the levels of AA, a pro-inflammatory omega-6 PUFA, and inhibiting the synthesis of inflammatory mediators such as prostaglandin E2. Animal studies further highlight the protective effects of omega-3 PUFAs, showing that maternal deficiencies in these fatty acids exacerbate inflammatory pathways, which lead to cognitive deficits in offspring [144, 187, 188].

Research also suggests that omega-3 PUFAs exert their antidepressant effects, at least in part, by reducing systemic inflammation. Genetic variations in enzymes involved in PUFA metabolism, such as phospholipase A2 and COX-2, can lead to inflammation-driven depression by lowering the levels of anti-inflammatory omega-3 PUFAs [165, 189]. This phenomenon is observed not only in individuals with MDD but also in patients who develop depression as a result of treatments that induce systemic inflammation, such as interferon-α therapy [190]. Therefore, omega-3 PUFAs may play a vital role in managing depression and promoting brain health by targeting both inflammation and autonomic function, suggesting their potential as a complementary treatment option for pediatric MDD.

### Influence of omega-3 PUFAs on the gut-brain axis: a central mechanism in depression

Recent research has highlighted the crucial role of omega-3 PUFAs in modulating the gut-brain axis—a bidirectional communication network linking the gut microbiota and the CNS. This emerging understanding provides a novel framework for how omega-3 PUFAs exert their neuroprotective and therapeutic effects, particularly in mood and neurodevelopmental disorders [191, 192]. By serving as key modulators of this intricate system, omega-3 PUFAs influence the interplay between dietary components, microbial populations, and CNS function [193].

Diet significantly influences the composition and metabolic activity of the gut microbiome, which is integral to host health, immune function, and nutrient metabolism. Additionally, the gut microbiome is implicated in the development of mental disorders. Different dietary patterns—such as Western, Mediterranean, vegetarian, and ketogenic diets—affect gut microbiota composition and function, with potential implications for neuropsychiatric and psychological disorders within the emerging field of nutritional psychiatry [194].

Early-life supplementation with EPA and DHA has been shown to restore gut microbiota equilibrium by promoting beneficial bacterial populations such as *Bifidobacterium* and *Lactobacillus*, while also enhancing butyrate-producing bacteria known for their anti-inflammatory properties [164, 191]. This microbiota balance correlates with reduced neuroinflammation, improved cognitive performance, and

enhanced behavioral outcomes, underscoring the therapeutic potential of omega-3 PUFAs in supporting brain health via gut-mediated mechanisms.

The human gut microbiome begins to form in utero and matures during the first 2–3 years of life, influenced by factors such as mode of delivery, breastfeeding, antibiotics, chemicals, and maternal stress. Recent evidence highlights the gut microbiome's role in early brain development and its link to neurodevelopmental disorders such as autism, ADHD, Tourette syndrome, and cerebral palsy. Disruptions in the microbiome during early life may contribute to the onset of these disorders and suggest potential avenues for future treatments [195].

Omega-3 PUFAs modulate gene expression through their role as ligands for nuclear receptors, particularly PPARs [141]. PPAR-γ activation by omega-3 fatty acids upregulates anti-inflammatory genes while downregulating pro-inflammatory cytokines such as TNF-α and IL-6 [196]. Additionally, omega-3 PUFAs influence the NF-κB signaling pathway, a critical regulator of inflammation, by inhibiting its nuclear translocation and subsequent transcription of inflammatory mediators [197]. This suppression reduces microglial activation and mitigates neuroinflammatory responses that contribute to mood disorders.

Gut dysbiosis—an imbalance in microbial composition—has been strongly implicated in the pathophysiology of depression. Preclinical models demonstrate that antibiotic-induced dysbiosis leads to depressive-like behaviors, including anhedonia and social withdrawal, which can be alleviated by probiotic interventions such as *Lactobacillus casei* [198]. Similarly, microbiota transplantation from individuals with depression into germ-free rodents induces comparable depressive phenotypes, reinforcing the critical role of the gut microbiome in mood regulation [199].

The gut microbiota influences brain function through microbial metabolites, including short-chain fatty acids (SCFAs) and neurotransmitter precursors [200]. Omega-3 PUFAs enhance SCFA production by supporting the growth of butyrate-producing bacteria [164, 191]. Butyrate, in turn, activates histone deacetylase (HDAC) inhibition, leading to epigenetic modifications that regulate neuronal plasticity and synaptic function [201]. Moreover, omega-3 fatty acids facilitate serotonin biosynthesis by modulating tryptophan metabolism [202, 203], shifting its processing away from neurotoxic quinolinic acid production and toward serotonin synthesis, thereby exerting antidepressant effects.

SCFAs—metabolites produced by gut microbiota through fiber fermentation—are central to this gut-brain connection. SCFAs such as butyrate, acetate, and propionate exert significant immunomodulatory effects, with butyrate and acetate generally reducing neuroinflammation, while propionate has been linked to microglial activation and pro-inflammatory responses [200, 204]. This variability underscores the importance of individual microbiome composition and inflammatory state in shaping SCFA-mediated effects on depression.

Both human and animal studies corroborate the therapeutic potential of omega-3 PUFAs in modulating the gut-brain axis. By reshaping gut microbiota composition and fostering anti-inflammatory conditions, omega-3 PUFAs offer a promising adjunct therapy for neurodevelopmental and psychiatric disorders, including depression. Beyond their direct anti-inflammatory properties, omega-3 PUFAs enhance synaptic plasticity through activation of BDNF signaling [205]. By upregulating BDNF expression via the ERK-CREB pathway, omega-3 fatty acids support neuronal survival, dendritic growth, and synaptic connectivity [206, 207], all of which are crucial for mood stabilization and cognitive function. Their multifaceted role extends beyond neuroprotection, positioning them as systemic regulators of mental health. Continued research into their influence on gut-brain interactions may pave the way for innovative dietary and pharmacological interventions, enhancing resilience and improving outcomes in neuropsychiatric care.

## Clinical evidence for omega-3 PUFA supplementation in pediatric MDD

Preclinical studies have highlighted the potential therapeutic role of omega-3 PUFAs in depression; however, clinical evidence specifically addressing pediatric MDD remains sparse (Table 4). The following studies offer insight into the efficacy of omega-3 PUFA supplementation in this population, with varying results influenced by dosage, population characteristics, and study design.

**Table 4. Impact of omega-3 PUFA supplementation on depression in youth: population, dosage, and efficacy insights**

| Study | Population | Intervention | Duration | Key findings | References |
|---|---|---|---|---|---|
| Pilot study on first-time DD/MADD | Children/adolescents (7–18 years) | Omega-3 PUFAs (1,000 mg EPA + 750 mg DHA) vs. n-6 PUFAs | Not specified | Significant reduction in depressive symptoms with omega-3 PUFAs; greater improvement in DD group vs. MADD group. | [171, 208] |
| Low-dose PUFA study in children | Children (6–12 years) | Omega-3 PUFAs (380–400 mg/day EPA + 180–200 mg/day DHA) vs. placebo | 16 weeks | Greater improvement in depressive symptoms in the omega-3 PUFA group compared to placebo. | [171, 209, 210] |
| Dose-response study in adolescents | Adolescents with treatment-resistant MDD | High-dose (16.2 g) vs. low-dose (2.4 g) omega-3 PUFA supplementation | 10 weeks | 100% remission in high-dose group; 40% remission in low-dose group. | [211–213] |
| Larger trial in medication-free adolescents | Adolescents (12–19 years) | Omega-3 PUFA supplementation vs. placebo | Not specified | No significant differences: authors attributed findings to lack of baseline inflammatory markers. | [209, 211, 214, 215] |

DD: depressive disorder; MADD: mixed anxiety and depressive disorder; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; PUFAs: polyunsaturated fatty acids; MDD: major depressive disorder

Evidence consistently indicates that omega-3 PUFA supplementation is effective in reducing depressive symptoms, particularly in younger children and adolescents experiencing their first depressive episodes or those with treatment-resistant MDD [165, 166, 209, 213, 216, 217]. These findings highlight the therapeutic potential of omega-3 PUFAs, with higher doses demonstrating a greater capacity to achieve symptom remission compared to lower doses. Such dose-dependent efficacy emphasizes the need for optimal dosing to maximize therapeutic outcomes.

Baseline inflammatory profiles may significantly influence treatment response. Adolescents without signs of inflammation appear to benefit less from omega-3 PUFA supplementation, suggesting that inflammatory biomarkers could play a critical role in identifying patients most likely to respond. Incorporating these biomarkers into future studies may enable more personalized and effective treatment approaches.

Treatment efficacy varies depending on factors such as age, baseline symptom severity, and the presence of comorbid conditions, including mixed anxiety-depressive disorder. Tailored interventions that address these individual differences are essential to overcome the heterogeneity within study populations and ensure consistent therapeutic success.

Although current evidence supports the potential of omega-3 PUFAs as an adjunctive treatment for pediatric MDD, further research is necessary. Large-scale, stratified studies are needed to confirm these findings, refine dosing strategies, and explore interactions among omega-3 PUFA metabolism, genetic factors, and gut microbiota.

Omega-3 PUFAs hold promise as a complementary treatment for pediatric MDD, particularly for subgroups with treatment-resistant conditions or specific inflammatory profiles. However, further in-depth exploration is required to optimize supplementation protocols, determine effective dosages, and clarify the mechanisms underlying their therapeutic effects to advance pediatric mental health interventions.

## Conclusions

The reliability and generalizability of omega-3 fatty acid research are often constrained by small sample sizes, which reduce statistical power and increase bias, thereby weakening the strength of conclusions. Additionally, methodological inconsistencies in measuring omega-3 levels introduce variability across studies, complicating direct comparisons and compromising result reproducibility. The absence of standardized measurement protocols further hinders data interpretation, necessitating the adoption of uniform analytical techniques and large-scale, well-controlled studies to enhance validity and comparability.

Despite substantial research highlighting the critical role of omega-3 fatty acids in early brain development, behavior, and cognitive function, significant knowledge gaps remain. One major limitation lies in the incomplete understanding of the biochemical mechanisms governing omega-3 and omega-6 mobilization in brain tissue, particularly the enzymatic activity of phospholipase A2 (PLA2) isoforms. These enzymes, including cytosolic PLA2 (cPLA2), secretory PLA2 (sPLA2), and calcium-independent PLA2 (iPLA2), play pivotal roles in hydrolyzing membrane phospholipids to release PUFAs, such as AA and DHA. Dysregulation of these enzymes has been implicated in neurodevelopmental and neurodegenerative disorders, underscoring the need for further research into their regulatory pathways and interactions within the brain.

Future research should prioritize standardized intervention methodologies and individualized supplementation strategies, particularly for high-risk populations such as pregnant women, individuals with metabolic disorders, and those following restrictive diets. Advances in lipidomics and machine learning-based predictive modeling may facilitate the precise identification of individuals who would benefit most from omega-3 interventions, paving the way for precision nutrition in maternal and fetal health. Furthermore, accounting for confounding factors—such as maternal health, lifestyle, and diet—is essential, as these variables significantly influence DHA's neurodevelopmental effects. Longitudinal studies tracking maternal nutrient levels and fetal development are critical for elucidating DHA's full impact. However, variability in neurodevelopmental assessments and the underrepresentation of diverse populations limit the generalizability of findings. Addressing these challenges through multi-ethnic cohort studies and integrating machine learning approaches for neurodevelopmental assessment will enhance the reliability of future research [16, 218–220].

A key limitation of existing studies on PUFA supplementation, particularly DHA, is the heterogeneity in study designs, sample populations, and assessment methodologies. Genetic variations influencing PUFA metabolism, interindividual differences in dietary absorption, and the potential confounding effects of broader dietary patterns, socioeconomic disparities, and environmental influences further complicate the ability to establish definitive conclusions. Additionally, while observational and epidemiological studies provide valuable insights, they cannot establish causality. To strengthen the evidence base for DHA supplementation, future research should prioritize RCTs with standardized dosing regimens and long-term follow-ups. Moreover, while the therapeutic potential of omega-3 fatty acids is widely recognized, the potential risks associated with excessive supplementation warrant further investigation to refine dietary recommendations and develop personalized nutrition strategies.

PUFAs, particularly omega-3 and omega-6 fatty acids, are essential components of cellular membranes and play crucial roles in neurodevelopment, inflammation, and cardiovascular function. DHA is particularly vital during pregnancy and early development, supporting synaptic connectivity, myelination, and hippocampal function, all of which influence cognitive and behavioral outcomes. However, omega-3 deficiencies during critical developmental periods can increase the risk of neurodevelopmental disorders and depression. Emerging evidence suggests that omega-3 fatty acids modulate neuroinflammatory pathways and the gut-brain axis, highlighting their potential therapeutic role in pediatric depression and overall brain health.

Despite their promise, significant gaps remain in our understanding of PUFAs, particularly regarding standardization of assessment methodologies and the influence of genetic, dietary, and environmental factors. Addressing these challenges requires collaborative, multidisciplinary research efforts integrating advanced technologies such as metabolomics and genomics. By refining study methodologies, increasing study inclusivity, and establishing evidence-based supplementation guidelines, future research can better elucidate the mechanisms underlying PUFA function and optimize their application in neurodevelopmental health.

## Abbreviations

AA: arachidonic acid

ADHD: attention-deficit/hyperactivity disorder

ALA: *alpha*-linolenic acid

ANS: autonomic nervous system

BDNF: brain-derived neurotrophic factor

CNS: central nervous system

COX: cyclooxygenase

cPLA2: cytosolic phospholipase A2

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

GLA: *gamma*-linolenic acid

HRV: heart rate variability

IL-6: interleukin-6

LA: *cis*-linoleic acid

LC-PUFA: long-chain polyunsaturated fatty acids

LOX: lipoxygenase

MDD: major depressive disorder

PLA2: phospholipase A2

PPARs: peroxisome proliferator-activated receptors

PUFAs: polyunsaturated fatty acids

RCTs: randomized controlled trials

ROS: reactive oxygen species

SCFAs: short-chain fatty acids

SSRIs: selective serotonin reuptake inhibitors

TNF-α: tumor necrosis factor-alpha

## Declarations

### Author contributions

RMG and MMN: Conceptualization, Writing—original draft, Writing—review & editing.

### Conflicts of interest

The authors declare no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

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