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# Role of Omega-3 fatty acids in the etiology, treatment, and prevention of depression: Current status and future directions

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ABSTRACT

Over the past three decades a body of translational evidence has implicated dietary deficiency in long-chain omega-3 (LC*n*-3) fatty acids, including eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA), in the pathophysiology and etiology of major depressive disorder (MDD). Cross-national and cross-sectional data suggest that greater habitual intake of preformed EPA + DHA is associated with reduced risk for developing depressive symptoms and syndromal MDD. Erythrocyte EPA and DHA composition is highly correlated with habitual fish or fish oil intake, and case-control studies have consistently observed lower erythrocyte EPA and/or DHA levels in patients with MDD. Low erythrocyte EPA + DHA composition may also be associated with increased risk for suicide and cardiovascular disease, two primary causes of excess premature mortality in MDD. While controversial, dietary EPA + DHA supplementation may have antidepressant properties and may augment the therapeutic efficacy of antidepressant medications. Neuroimaging and rodent neurodevelopmental studies further suggest that low LC*n*-3 fatty acid intake or biostatus can recapitulate central pathophysiological features associated with MDD. Prospective findings suggest that low LC*n*-3 fatty acid biostatus increases risk for depressive symptoms in part by augmenting pro-inflammatory responsivity. When taken collectively, these translational findings provide a strong empirical foundation in support of dietary LC*n*-3 fatty acid deficiency as a modifiable risk factor for MDD. This review provides an overview of this translational evidence and then discusses future directions including strategies to translate this evidence into routine clinical screening and treatment algorithms.



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## 1. Introduction

Major depressive disorder (MDD) is a leading cause of disability globally. In the United States (U.S.) severe forms of MDD are estimated to affect between 2 and 7% of the population and up to 16–20% suffer from milder forms [106]. The initial onset of MDD frequently occurs during adolescence and young adulthood [105], and is ~2-fold more prevalent in females after puberty [104]. Outcomes data indicate that MDD is associated with excess premature mortality primarily attributable to suicide and cardiovascular-related disorders [9,152]. Bipolar disorder is also associated with recurrent episodes of depression, and prodromal MDD is a risk factor for mania in at-risk youth [15,55,91]. The first-line treatment for MDD in adolescents and adults is typically a selective serotonin reuptake inhibitor (SSRI). However, approximately 30–40% of adolescent MDD patients exhibit residual symptoms following standard SSRI treatment [58,103], and SSRI treatment may precipitate suicidality and mania in at-risk youth [27,81,124,171]. These and other data highlight an urgent need to identify modifiable risk and resilience mechanisms associated with the etiology of MDD to inform improvements in treatment and ultimately prevention strategies.

While aggressive efforts have been devoted to the identification of genetic risk factors associated with psychiatric disorders including MDD, it has become apparent that both genetic and environmental factors confer vulnerability [56,141]. For example, a meta-analysis of community-based twin studies of MDD yielded a heritability estimate of .37, indicating that approximately two thirds of the liability is attributable to environmental factors [177]. Moreover, environmental factors can regulate gene expression through epigenetic effects (i.e., DNA methylation) independent of DNA sequence polymorphisms [157,192]. Environmental factors can also interact with DNA polymorphisms to increase risk for developing psychiatric disorders [34]. Accordingly, aggressive efforts also need to be devoted to the identification of environmental risk factors, particularly in view of their amenability to modification and prevention.

Over the last three decades a body of translational evidence has emerged which suggests that the habitual diet is relevant to the etiology of MDD. Specifically, evidence has implicated dietary deficiency in essential long-chain omega-3 (LC*n*-3) fatty acids, including eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA), in the pathophysiology and etiology of MDD. This is supported by converging evidence from cross-national and cross-sectional epidemiological surveys, case-control LC*n*-3 fatty acid biostatus studies, prospective observational and LC*n*-3 fatty acid intervention studies, rodent neurodevelopmental studies, and recent neuroimaging findings. Additionally, accumulating evidence suggests that LC*n*-3 fatty acid deficiency may increase risk for suicide and cardiovascular disease, two primary causes of excess premature mortality in patients with MDD. This review provides an overview of translational evidence implicating LC*n*-3 fatty acid deficiency in the pathophysiology and etiology of MDD, and then discusses future directions including strategies to translate this evidence into routine clinical screening and treatment algorithms.

## 2. LC*n*-3 fatty acid biosynthesis and biostatus

As background, omega-3 (*n*-3) and omega-6 (*n*-6) fatty acids are members of the polyunsaturated fatty acid (PUFA) family. Primary dietary sources of the short-chain *n*-3 fatty acid precursor α-linolenic acid (ALA, 18:3*n*-3) include flaxseed, linseed, canola, soy, and perilla oils, and primary dietary sources of the short-chain *n*-6 fatty acid precursor linoleic acid (18:2*n*-6) include safflower, soy, and corn oils. These PUFAs are considered 'essential' because mammals are entirely dependent on dietary sources to procure and maintain adequate concentrations in peripheral and central tissues. The biosynthesis of long-chain *n*-3 (LC*n*-3) fatty acids, including EPA (20:5*n*-3) and DHA (22:6*n*-3), from their short-chain precursors require a series of common and competitive microsomal desaturation and elongation reactions (Fig. 1) [163]. The rate-limiting enzymes regulating LC-PUFA biosynthesis include delta-6 desaturase (delta6-desaturase, *FADS2*) and delta-5 desaturase (delta5-desaturase, *FADS1*), as well as elongases (*e.g., ELOVL5*), and the final synthesis of DHA is catalyzed by β-oxidation within peroxisomes [185]. *FASD1* and *FADS2* genes are primarily expressed in the liver and brain and are co-localized to human chromosome 11q12-11q13.1 [122]. Desaturase enzymes are regulated by several factors including gonadal hormones [18,29,38,70,130], insulin [26], as well as single nucleotide polymorphisms within *FADS2* and/or *FASD1* genes [115]. Recent evidence further suggests that epigenetic effects (*i.e.*, DNA methylation) are associated with delta5/6-desaturase enzyme activity [90] and that PUFA intake can induce DNA methylation resulting in reduced expression of *FADS2* and *ELOVL5* [88,89,148]. Therefore, PUFA homeostasis is ultimately governed by both environmental (i.e., diet) and genetic factors.

In healthy adult subjects ALA→EPA biosynthesis is extremely limited and ALA→DHA and EPA→DHA biosynthesis is negligible [25]. For example, 12-week supplementation with up to 3.6 g/d of flaxseed oil, a rich source of ALA, resulted in moderate increases in erythrocyte (red blood cell) EPA but did not significantly increase erythrocyte DHA levels in healthy adult subjects [19]. Similarly, 4-week supplementation with flaxseed oil resulted in moderate increases in erythrocyte and breast milk EPA but did not significantly increase erythrocyte or breast milk DHA [64]. This limitation in

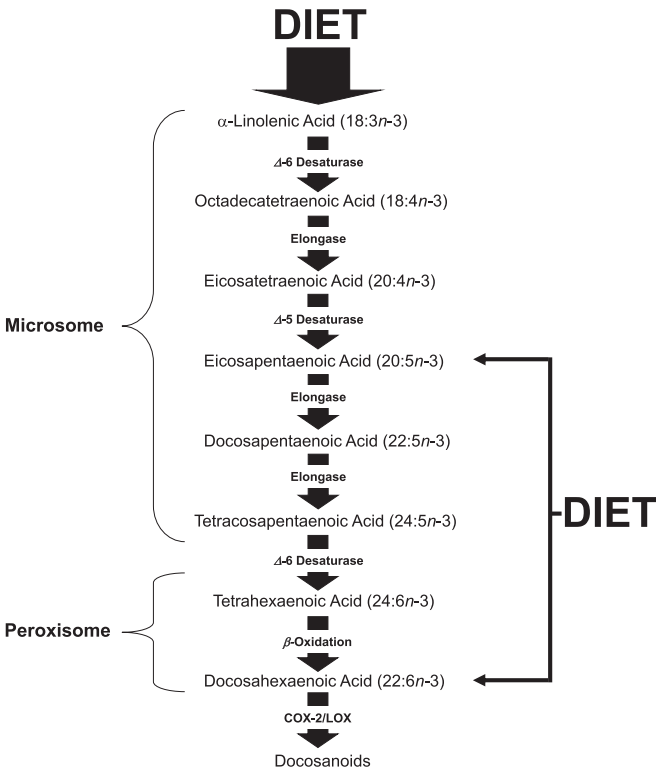


**Fig. 1.** Diagram illustrating the biosynthetic pathway of omega-3 fatty acids. The biosynthesis of docosahexaenoic acid (DHA, 22:6*n*-3) from dietary α-linolenic acid (18:3*n*-3) requires a series of microsomal elongation (*ELOVL5*) and delta-5 (*FADS1*) and delta-6 desaturase (*FADS2*) mediated reactions. The final synthesis of DHA is catalyzed by β-oxidation within peroxisomes. Metabolism of DHA yields inflammation-resolving docosanoids. Preformed DHA and EPA can also be obtained directly from the diet.