

# Omega-3 Fatty Acid Deficiencies: How Our Modern Diet Has Made Us Unhappy

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Over the course of the 20<sup>th</sup> century, researchers have documented increased rates of depression and depressive symptoms throughout Western countries. Klerman and Weissman (1989) reveal that changes in diagnostic criteria, increased recognition among health professionals, differential mortality, de-stigmatization and reporting bias cannot explain away the increased prevalence. Some researchers struggling to understand the phenomenon have come to blame the drastic dietary changes seen in Western societies since the onset of industrialization. As researchers link dietary change to coronary heart disease, diabetes, arthritis and other common Western diseases, the relationship between dietary changes and depression has become increasingly evident. More specifically, industrialization has significantly decreased the amount of omega-3 fatty acids consumed by most Westerners. Consequently, deficiencies in dietary-based omega-3 fatty acids may make a significant etiological contribution to depression and depressive symptoms. This paper starts by discussing how industrialization has altered our intake of this essential nutrient, thereby contributing to increased rates of depression. Next, the paper examines a suggested causal mechanism linking omega-3 fatty acids to depression, followed by a review of several empirical studies looking at omega-3s in depressed patients.

## Industrialization and the Increased Prevalence of Depression

Several environmental, social and genetic factors precipitate depressive episodes, affecting their severity and duration. Nutrition forms an important environmental factor affecting depression and several other inflammatory-related diseases. Researchers increasingly turn to changes in our nutritional environment to explain increased rates of depression observed over the course of the past century (Simopoulos, 2002). Although our dietary habits have changed, our genetic makeup has changed little since the Paleolithic era 40,000 years ago (Simopoulos, 2002). In the last 100 years, industrialization has drastically altered our intake of several essential nutrients, including omega-3 fatty acids. Studies on the evolutionary aspect of our diets reveal that mankind evolved consuming an omega 6/3 ratio of 2:1 or 3:1 (Kiecolt-Glaser et al, 2007). As a result of massive dietary changes, that ratio has increased to an estimated 15:1 to 17:1 in the average North American's diet.

The industrialization of food production altered several important aspects of human food consumption, significantly increasing the consumption of omega-6 fatty acids while at the same time markedly decreasing our intake of omega-3 fatty acids. First, industrialization brought the large-scale production of vegetable oils (Pollan, 2008; Simopoulos, 2002). The invention of the Expeller screw press and the steam-vacuum deodorization process made the extraction of cottonseed oil and other vegetable oils inexpensive and efficient. After WWI, these vegetable and seed oils became even more popular. Unfortunately, vegetable and seed oils

are major sources of omega-6 fatty acids and offer little in the way of omega-3s (Simopoulos, 2002).

At the same time, modernization created the need for products that were easily transported over long distances without going bad. Omega-3 fatty acids are less stable than omega-6s and spoil more readily. As a result, even before nutritionists understood the role of omega-3 fatty acids in the body, the food industry began selecting for products containing omega-6 fatty acids for their ability to extend the shelf life of many foods (Pollan, 2008). Producers also learned how to hydrogenate vegetable oils in order to solidify them, further increasing their shelf life. In order to solidify and stabilize the vegetable oils, the process of hydrogenation actually removes alpha-linolenic acid (ALA), a parent form of omega-3 fatty acids, from vegetable oils, leaving high concentration of omega-6 fatty acids (Simopoulos, 2002). Nevertheless, vegetable oils and partially hydrogenated vegetable oils have become an important component of most processed and packaged foods (Pollan, 2008).

Other aspects of industrialization further diminished the amount of omega-3 fatty acids available in most foods. Producers adopted new agricultural methods to produce more food at a faster rate than before. Some of these new methods coincidentally served to increase omega-6 fatty acids and decrease omega-3 fatty acids in the regular animal products we consume. As food production became increasingly industrialized, agribusiness took animals off their accustomed diets of green plants and placed them on richer diets of seed and grain (Pollan, 2008; Simopoulos, 2002). Animals grow faster and bigger on higher-energy seed and grain diets, and without the

need to forage, animals can be kept conveniently in crowded barns that require less maintenance than green pastures (Pollan, 2008). However, animals that graze and forage on green plants containing omega-3s have more omega-3s in flesh (Pollan, 2008; Simopoulos, 2002). For example, wild animals and birds allowed to feed on wild plants may be lean in fat content but contain five times more polyunsaturated fatty acids per gram than do domestic livestock (Crawford et al. 1969). Domestic cattle contain almost undetectable amounts of ALA whereas up to 4% of the fat of wild animals contains certain kinds of omega-3 fatty acids (Crawford 1968, Simopoulos, 2002). The same logic applies to animal products as well. In one study, egg yolks from pasture-raised chickens exhibited an omega 6/3 ratio of 1:3 whereas the standard USDA egg generally contains a ratio of 19:9 (Simopoulos, 2002). Furthermore, studies show that milk and cheese from grazing animals contain significant amounts of omega-3 fatty acids whereas products from grain-fed animals do not (Simopoulos, 2002).

One final piece of evidence involves research from the 1950s on the potential role of omega-6 fatty acids in lowering cholesterol. In response to concerns over rising rates of coronary heart disease, health officials began encouraging the replacement of saturated fats of animal origin with vegetable and seed oils (Pollan, 2008; Simopoulos, 2002). However, these vegetable and seed oils served to greatly increase omega-6 fatty acids consumption.

In sum, humans evolved eating omega-3 fatty acids in most everything they consumed: meat from wild game, wild plants, eggs, fish and nuts. However, as industrialization has worked to decrease the omega-3 fatty acids in these foods and replace many of these foods with high omega-6 foods, the ratio of omega-6 to omega-3s in our diet has skyrocketed (Simopoulos, 2002; Pollan, 2002). The altered ratio undoubtedly affects many of the body's cellular processes, including those implicated in depression. Research linking deficiencies in omega-3 fatty acids to depression may deepen our understanding of the biological processes involved in depressive disorders, providing new types of treatment and prevention options.

### **Causal Mechanisms: How Omega-3 Fatty Acid Deficiencies Are Implicated in Depression**

Omega-3 fatty acids are long-chain polyunsaturated fatty acids produced by plants during photosynthesis. They occupy space in cell membranes of chloroplasts, playing a vital role in light collection. Omega-3 fatty acids are considered essential fatty acids because the body cannot produce them and they must be obtained from the diet (Pollan, 2008). Many people associate omega-3 fatty acids with seafood because fish and other marine creatures contain large amounts of omega-3 fatty acids in their flesh. These animals actually acquire the large amounts of omega-3 fatty acids in their bodies from the algae they feed upon.

Omega-3 fatty acids come in several nutritionally important forms. Marine-based omega-3 fatty acids consist primarily of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). The body readily utilizes these two forms of omega-3 fatty acids. In contrast, omega-3 fatty acids from plants come in the parent omega-3 fatty acid alpha-linolenic acid (ALA). Higher up on the metabolic path, ALA must be converted into EPA and DHA for use by the human body. This conversion process is high inefficient, with only 10-15% of ALA converting into EPA and DHA (Parker et al, 2006). Consequently, researchers focus on the intake of omega-3 fatty acids as EPA and DHA in the context of depression research.

In the past, researchers looked mostly at the amount of omega-3 fatty acids present in the body to explain disease. However, an important part of the story includes the relationship that omega-3s have with omega-6 fatty acids in the body (Pollan, 2008). Omega-6 fatty acids are another type of essential fatty acid that serve different functions in the body. Omega-6 fatty acids come primarily in the form of arachidonic acid (AA). The ratio of the two types of fatty acids in the body becomes physiologically significant because AA competes with DHA and EPA for space in the cell membrane (Pollan, 2008).

Once in the cell membranes, AA, DHA and EPA trigger a cascade of activities not yet completely understood by scientists. However, many of these responses implicate several of the pathophysiological domains related to depression such as neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior (Raison et al, 2005). Most importantly, scientists implicate EPA and DHA in the calming of inflammation and AA in the instigation of the inflammatory response system

(Pollan, 2008). Arachidonic acid serves as the precursor of two types of signaling molecules responsible for initiation inflammation: eicosanoids and pro-inflammatory cytokines. In cell membranes, AA competes with EPA for the cyclo-oxygenase system, which enhances the production of pro-inflammatory eicosanoids. The production of pro-inflammatory cytokines depends on eicosanoid release from the cyclo-oxygenase system (Parker et al, 2006). Studies have shown that the administration of omega-3 fatty acids leads to the replacement of AA in the cell membrane by EPA. This alters the balance of eicosanoids produced, reducing the number of eicosanoids responsible for initiating the production of pro-inflammatory cytokines and thus reducing the concentration of pro-inflammatory cytokines (Maes et al, 2000).

Although many studies document increased serum concentrations of pro-inflammatory cytokines in depressed patients (Raison et al, 2005), the question of how inflammation leads to depression remains unresolved. One causal link lies in the overlap of depressive symptoms and sickness behaviors. Both depression and sickness can cause anhedonia, impaired sleep, reduced physical activity, anorexia and insomnia (Raison et al, 2005). Omega-6 fatty acids in cell membranes stimulate the production of interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$ , the main pro-inflammatory cytokines involved in sickness behavior (Dantzer et al, 2008; Kiecolt-Glaser et al, 2007). Experiments demonstrate that administering IL-1 $\beta$  and TNF- $\alpha$  to rats and mice produces significant signs of sickness behavior (Dantzer, 2001). For example, administration of the two pro-inflammatory cytokines leads the rats and mice to hunch in their cages, demonstrating little interest in the environment around them. This behavior is thought to mimic the anhedonia demonstrated by many depressed patients. Additionally, the rats and mice show decreased physical activity, reduced food and water intake, decreased slow-wave sleep, fatigue, and social withdrawal.

In humans, this phenomenon has been labeled cytokine-induced sickness behavior. The body responds to potentially infectious agents with inflammation, producing a whole series of sickness behaviors seen in both humans and animals (Kelley et al, 2003). However, researchers consider sickness

behavior as an evolutionary advantage, encouraging the organism to seek rest and recover from infection. Consequently, depression may be viewed a prolonged sickness response that becomes maladaptive for the individual (Dantzer & Kelley, 2007). Depression may occur when the immune system becomes activated for long durations or at high intensities. Other researchers suggest that depression may arise in response to the initiation of the inflammatory response system when other vulnerabilities to depression already exist within the individual (Dantzer et al, 2005). The ratio of omega-6 to omega-3 fatty acids in the body serves as a risk factor for depression susceptibility. Two types of studies further elucidate the issue: epidemiological studies examining how rates of depression in different countries relate to omega-3 consumption and individual level studies assessing whether depressed patients show physiological differences relative to non-depressed patients.

### **Why Study Omega-3s: Preliminary Evidence in Community Studies**

Large amounts of omega-3 fatty acids can be found in fish and other seafood. Much of the justification for studying omega-3 fatty acids in relation to depression comes from community studies documenting the apparent protective effect against depression found in societies with high rates of seafood consumption. Several community studies link high rates of seafood consumption to lower occurrence of depression.

When comparing rates of seafood consumption across nations, Hibbeln (1998) found a strong negative correlation between fish consumption and annual rates of depression ( $r=-0.84$ ,  $p<0.005$ ). Other studies also find indirect evidence that high seafood consumption protects against certain types of depression. A study conducted in Iceland found low rates of seasonal affective disorder despite harsh winter conditions, with depression and anxiety scores for men and women remaining constant year round (Magnusson et al, 2000). Building on this study, Cott and Hibbeln (2001) suggested that Iceland's high rate of fish consumption (225 lb per person per year) explains the finding. The authors also point to low rates of seasonal affective disorder in Japan, another society with high fish consumption (147 lb per person per year). When they compared the data from Iceland and Japan to other countries with much lower intakes of seafood, they found higher rates of seasonal

affective disorder in countries with fish consumption of only 50 to 70 lb per person per year despite milder climates.

Other studies focus more on fish consumption in individuals. Tanskanen et al. (2001) surveyed a random sample of 3,204 Finnish adults for rates of fish consumption. Using the Beck Depression Inventory, they found that infrequent fish consumers were more likely to have depressive symptoms than frequent fish consumers. In addition, Silvers and Scott (2002) found in a survey of New Zealand adults that increased consumption of fish correlated to higher self-reported mental health status. The relationship held true even when controlling for age, income, eating habits and alcohol and drug use. Although the survey scale did not assess depressive symptoms, several questions evaluated mood. Fish consumption was inversely correlated with negative mood.

### **Physiological Correlates of Increased Omega-6 Fatty Acids in Depressed Patients**

One of the first studies that looked at omega-3 fatty acids and depression measured levels of omega-3 fatty acids in red blood cell (RBC) membranes of depressed and non-depressed individuals. Edwards et al. (1997) expected to see lower levels of omega-3 fatty acids in depressed patients compared to healthy controls. The study recruited 10 patients with a diagnosis of major depressive disorder according to DSM IV criteria. None of patients suffered from a comorbid physical illness and all took antidepressant medication. The depressed patients were matched to 14 healthy controls on the basis of age, gender, social class, recent life events, smoking habits and alcohol consumption. Researchers used the Beck Depression Inventory to rate both patients and controls for symptom severity and a 7-day weighted method to appraise dietary habits.

The study showed that depressed individuals had statistically significant lower levels of RBC membrane omega-3 levels compared to control subjects. Omega-6 fatty acids showed no significant difference in the patient group compared to the control. Unfortunately, the study did not examine the ratio of the two fatty acids present in the red blood cells of the subjects. The dietary analysis conducted in the Edwards et al. study also provided support for the hypothesis. The study revealed a significant negative correlation between RBC membrane omega-3 fatty acid levels and dietary intake of omega-3 fatty acids,

providing evidence that increased dietary intake of omega-3 fatty acids increases their presence in the red blood cell membranes.

More recently, studies incorporated suggested a causal mechanism, testing the hypothesis that depleted levels of omega-3s lead to inflammation, causing depression and depressive symptoms. To expand on existing data, Kiecolt-Glaser et al. (2007) hypothesized that higher omega-6/3 ratios and higher levels of depressive symptoms would predict higher levels of certain pro-inflammatory cytokines than either alone in older adults. The authors point to a possible bi-directional relationship as explanation. While pro-inflammatory signaling molecules can lead to depression, it is also true that depression and depressive symptoms can stimulate the production of the pro-inflammatory signaling molecules.

The study recruited 43 participants from a larger project examining stress and health in older adults. Kiecolt-Glaser et al. excluded subjects taking statins, steroids or diabetes medication from the larger cohort. Researchers also excluded participants with immunologically related health problems and those taking medications with immunological consequences. Trained graduate psychology or nursing students administered the Diagnostic Interview for Genetic Studies to obtain data on mood and psychotic disorders, and the Center for Epidemiological Studies Depression Scale to appraise the severity of depressive symptoms. The Older Adults Resources Survey collected information on health behaviors and researchers asked questions about smoking, medications, alcohol consumption and exercise habits. Lastly, patients were asked to complete the Pittsburg Sleep Quality Index, a measure of several dimensions of sleep quality.

Researchers drew blood samples from the patients, testing for the presence of three pro-inflammatory signaling molecules (TNF- $\alpha$ , IL-6 and sIL-6r). Researchers then ran linear regression models for each cytokine, controlling for several potential confounders. Control variables included age, gender, health behavior and medication usage. The researchers found that higher omega 6/3 ratios and higher levels of depressive symptoms predict increased pro-inflammatory cytokine production than either factor alone. The researchers took this as evidence of the bidirectional relationship between depression and pro-inflammatory cytokine production. Additionally, as expected, the researchers also found

that individuals with major depression had markedly higher omega 6/3 ratios compared to healthy subjects. Kiecolt-Glaser et al. concluded that diets containing higher omega 6/3 ratios increase risk for depression and other inflammatory-related diseases.

Other studies incorporate common risk factors for depression when considering effects of inflammation. Researchers suspect that other factors may combine with higher omega 6/3 ratios to stimulate even greater production of pro-inflammatory cytokines. Stress and negative life events are strong predictors of depressive episodes (Raison et al, 2005). Stress may initiate an immune response, producing increased inflammation. Raison et al. documented studies showing that psychological stress stimulates the production of pro-inflammatory cytokines. In 2000, Maes et al. (2000) hypothesized that a higher ratio of omega 6/3 fatty acids would predict greater production of pro-inflammatory cytokines in response to a stressful event. The researchers recruited 27 medical science students aged 19-22 from the University of Antwerp. The subjects had no history of past psychological disorder or major negative life events prior to the study. None of the subjects were on psychotropic medications and none took psychotropic drugs during the study. Subjects had serum samples taken a few weeks prior to and after as well as the day before a difficult oral examination. Students also completed the 14-item Perceived Stress Scale during these three visits.

The study revealed that omega 6/3 ratios predict the production of pro-inflammatory cytokines. Following psychological stress, students with higher omega 6/3 ratios had increased production of pro-inflammatory cytokines compared to students with lower omega 6/3 ratios. These results support the idea that stress may play an important role in stimulating the immune system. Furthermore, a balanced omega 6/3 may protect individuals from a pro-inflammatory response following stress.

As the empirical research increasingly implicates the inflammatory response of the immune system in depression and other major diseases, researchers will need to be able to understand the relationship between the dietary intake of omega-3 fatty acids and the roles that these fatty acids play at the cellular level. By synthesizing research from a variety of disciplines, I discussed how our dietary intake of omega-3 fatty acids has changed drastically

over the course of industrialization, suggested how this affects cellular processes regulating inflammation and examined how pro-inflammatory immune responses are implicated in depression. This paper serves only as a starting point but intends to convey the significance of this new and exciting research.

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