The Potential for Military Diets to Reduce Depression, Suicide, and Impulsive Aggression: A Review of Current Evidence for Omega-3 and Omega-6 Fatty Acids

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ABSTRACT The current burden of psychological distress and illness poses as a significant barrier to optimal force efficacy. Here we assess nutrients in military diets, specifically highly unsaturated essential fatty acids, in the reduction of risk or treatment of psychiatric distress. Moderate to strong evidence from several meta-analyses of prospective cohort trials indicate that Mediterranean diet patterns reduce risk of clinical depressions. Specific nutrients and foods of biological interest in relation to mental health outcomes are then discussed and evaluated. Moderate evidence indicates that when fish consumption decreases and simultaneously omega-6 increases, the risk of clinical depressive symptoms are elevated. One meta-analysis examining tissue compositions provides moderate to strong evidence that higher levels of omega-3 highly unsaturated fatty acids (HUFAs) (eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid) are associated with decreased risk of clinical depressions. Other meta-analytic reviews of randomized placebo-controlled trials provide moderate to strong evidence of significantly improving clinically depressive symptoms when the formulation given was >50% in eicosapentaenoic acid. Finally, a meta-analysis of omega-3 HUFAs provides modest evidence of clinical efficacy for attention-deficit hyperactivity disorder. This article recommends that a rebalancing of the essential fatty acid composition of U.S. military diets, achieve tissue compositions of HUFAs consistent with traditional Mediterranean diets, may help reduce military psychiatric distress and simultaneously increase force efficacy substantially.

INTRODUCTION

The high prevalence of psychiatric disorders among the U.S. military may undermine optimal total force readiness. The prevalence of reporting a mental health problem was 19.1% among service members returning from Iraq compared with 11.3% after returning from Afghanistan and 8.5% after returning from other locations ($p < 0.001$). Mental health problems reported on the postdeployment assessment were significantly associated with combat experiences; mental health care referral, and utilization and attrition from military service. Thirty-five percent of Iraqi war veterans accessed mental health services in the year after returning home and 12% per year were diagnosed with a mental health problem.[1] In addition, 10% to 18% of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) troops returning home are estimated to suffer from post-traumatic stress disorder (PTSD).[2] Estimates of depression in returning troops range from 3% to 25%, although exact figures are difficult to determine as methods across studies vary widely. Emerging research also suggests that those soldiers, sailors, and marines who had a higher number of combat stressors (e.g., seeing dead bodies, being shot at, being attacked or ambushed, receiving rocket or mortar fire and knowing someone who had been killed or seriously injured) were found to have significantly higher levels of mental health problems.[2] Those who served in Iraq were found to have higher rates of PTSD than those who served in Afghanistan.

There are many other challenges to optimal mental health, including high information dense positions, multiple deployments, and stressful environments. Specific risk factors for the development of PTSD have now been identified and include: a longer deployment time, more severe combat exposure, such as deployment to "forward" areas close to the enemy, seeing others wounded or killed, more severe physical injury, traumatic brain injury, a lower rank or lower level of schooling, low morale and poor social support within the unit, being unmarried, family problems, a member of the National Guard or Reserves, prior trauma exposure, being female gender, and finally being a member of a Hispanic ethnic group.[2] Enhancing force effectiveness with support of the cognitive, emotional, and physical performance of the warfighter are among the top four investment categories identified in a recent report.[3] The report noted that the U.S. military diet mirrors the typical U.S. diet and in "this situation - the lack of fact based nutritional support to match the demanding high-level cognitive and physical performance requirements of the modern warfighter—may contribute to a force that is overburdened, stressed out, less healthy, and less effective than those in generations past."[3] Evaluated here are

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some of the critical issues regarding what is known about the role of omega-3 and omga-6 fats in the brain and body to inform consideration of modifying U.S. military dietary intakes. The tissue composition of omega-3/6 fats is particularly relevant when considering that the mammalian brain is primarily composed of fats and lipids, usually 60% wet weight. Approximately, 30% of fatty acid pool cannot be made *de novo* and must be obtained through the diet—hence the term—essential fatty acids.

Seafood, fish oils, and fortified foods are rich sources omega-3 highly unsaturated fatty acids (HUFAs). Docosahexaenoic acid (DHA) is selectively concentrated in neuronal membranes comprising approximately 15% to 20% of total fatty acids and has an absolute requirement for brain function.[4,5] Therefore, omega-3 fatty acids from fish or marine sources and omega-6 fats from seed oils are potential candidates for the decreased and increased risk of major depression and psychological distress respectively. This article raises issues pertaining to: (1) diet patterns, (2) specific foods and specific nutrients within those patterns, (3) tissue compositions, (4) specific mechanisms of action, and (5) an evaluation of meta-analyses of randomized clinical trials primarily for major depression. The authors have assessed pertinent research findings according to the *Criteria for Assessing Evidence Level for Best-Evidence Synthesis* model (see Table 1). The critical perspective of the authors is that dietary intakes (except severe deficiencies) are clearly not sole determinants for neurological and mental health impairments. However, if nutritional insufficiencies or excesses can be identified that impair optimal functioning, actions can easily be made, targeted and executed.

Mediterranean and Healthy Dietary Patterns in Depression

Several meta-analytic and systematic reviews have assessed relationships between dietary patterns and risk of major depression and psychological distress. Candidates include Mediterranean, traditional (specific for each country) and Western diet. Dietary pattern analysis has become more frequent in recognizing that nutrients intact together and therefore dietary advice is often provided as optimally consuming patterns of foods, in addition to specific foods. In a meta-analysis of nine prospective cohort studies, Psaltopoulou et al[6] examined the association between adherence to a Mediterranean diet and risk of depression and cognitive impairment. High adherence to Mediterranean diet was consistently associated with reduced risk for depression (relative risk [RR] 0.68; 95% confidence interval [CI] 0.54–0.86) and cognitive impairment (RR 0.60; 95% CI 0.43–0.83). Moderate adherence was similarly associated with reduced risk for depression and cognitive impairment.

Lai et al[7] pooled results from 13 observational studies and identified two dietary patterns of interest. The first was the "healthy diet" pattern that was significantly associated with reduced odds of depression (odds ratio [OR] 0.84; 95% CI 0.76–0.92; $p < 0.001$). Heterogeneity was significant ($I^2 = 81.8\%$; $p < 0.001$). No statistically significant associations were observed between the Western diet (defined in this study as higher loadings of: red and processed meats, high-fat dairy products, french fries, and refined grains) and depression (OR 1.17; 95% CI 0.97–1.68; $p < 0.094$). However, this may be because of the small number of studies examined. The authors concluded that high intakes of fruit, vegetables, fish, and whole grains may be associated with a reduced risk of depression.

If these data indicate that persons adhering to "Mediterranean-inspired" or "healthy diets" have lower risks of clinical depressions and other mental illnesses, then it is critical to examine if these effects are due to the interaction of all nutrients in the dietary pattern or can be attributed to specific nutrients. This question is of critical interest when considering its relevance to the U.S. military diet, especially because the traditional Mediterranean and healthy diets are very low in red meat and protein, both of which are popular with the U.S. military personnel attempting to build muscle mass. The identification of specific nutrients that may optimize brain function is also warranted. Numerous scientists including those in our research team in the Section of Nutritional Neurosciences at the National Institute of Health have previously postulated that an insufficiency of omega-3 and an excess of omega-6 highly unsaturated fats increases risk for major depression and affective disorder.[8] The traditional Mediterranean diet of Crete encourages a greater consumption of fish, which are rich in omega-3 HUFAs.[9] Adherence to a Mediterranean dietary pattern will lower the dietary intake of omega-6 linoleic acid (LA) to 2% to 3% of calories or below; simultaneously, it will elevate intakes of omega-3 HUFAs[10] that results in[11] a blood composition with higher omega-3 HUFAs and lower omega-6 HUFAs.[12,13] A tissue composition of 50% n-3 HUFAs compared to 50% n-6 HUFAs is predicted by Lands et al[11] to improve both physical and mental health.

TABLE I. Criteria for Assessing Evidence Level for Best-Evidence Synthesis

Level of Evidence	Criteria for Inclusion in Best Evidence Synthesis
Strong Evidence	Generally Consistent Findings in: Multiple High-Quality Cohort Studies
Moderate Evidence	Generally Consistent Findings in: One High-Quality Cohort Study and >2 High Quality Case-Control Studies
Limited Evidence	Generally Consistent Findings in: Single Cohort Study One or Two Case–Control Studies or Multiple Cross-Sectional Studies
Conflicting Evidence	Inconsistent Findings in <75% of the Trials
No Evidence	No Studies Could be Found

Fish Consumption Dietary Patterns and Mental Illnesses

The relationship of low omega-3 HUFA status and greater risk of affective illnesses appears to be fairly consistent across ecological studies, epidemiological studies, and case–control studies. Ecological studies indicate that in comparison to countries with the highest seafood consumption, low seafood consumption is associated with a 65-fold higher risk for lifetime prevalence of major depression ($r = -0.84$; $p < 0.0001$),[14] a 50-fold higher risk for postnatal depression ($r = -0.81$; $p < 0.0001$),[15] a 30-fold higher risk for bipolar spectrum disorder ($r = -0.80$; $p < 0.0003$),[16] and a 10-fold higher risk of death from homicide mortality ($r = -0.63$; $p < 0.0006$).[17] Correlation coefficients in these ranges are considered to be very robust.

Epidemiological studies within countries have reported strong associations between low fish and seafood intake and greater risk of depression with a high degree of consistency. Meta-analyses specifically evaluating fish or seafood consumption could not be identified. Therefore, an overview of studies, without systematic analysis is presented here. In 2001, among just under 2,000 participants in Northern Finland, Tanskanen et al[18] reported that both the risk of being depressed (OR 0.63; 95% CI 0.43–0.94; $p < 0.02$) and the risk of having suicidal ideation (OR 0.57; 95% CI 0.35–0.95; $p < 0.03$) were significantly lower among frequent lake-fish consumers compared with more infrequent consumers. In a birth cohort of 5,689 Finnish participants, the risk of depression was 2.6-fold (95% CI 1.4–5.1) greater and risk of suicidal thinking was 1.5-fold (95% CI 1.0–3.0) greater comparing females with rare fish consumption to regular consumers.[19] Finnish fishermen ($n = 6,410$) consume twice as much fish and have a lower risk of mortality from alcohol-related diseases (OR = 0.59; 95% CI 0.41–0.82) and suicides (OR 0.61; 95% CI 0.39–0.91) compared to the general population, after adjustment.[20] Some studies reported no association, for example, Hakkarainen et al[21] found no associations between either the dietary intake of omega-3 fatty acids or fish consumption and self-report of depressed mood; hospitalization for a major depressive episode, or suicide among 29,133 Finnish men. However, there was a high covariance with fish and omega-6 LA consumption, which was 20-fold higher than omega-3 HUFA from fish.[22] Thus, it is difficult to determine which factor was specifically associated with an increased risk of depression. Among 21,835 Norwegians, users of cod liver oil were significantly less likely to have depressive symptoms than nonusers after adjusting for multiple possible confounding factors (OR = 0.71; 95% CI 0.52–0.97).[23] A longitudinal follow-up study in France of nearly 14,000 participants reported that consuming fatty fish, or having an omega-3 HUFA intake >1% energy (en%), was significantly associated with a reduced risk of single or recurrent depressive episodes.[24] In the Zutphen Study of the Elderly, high intakes of omega-3 HUFAs (mean 407 mg/d) were associated with lower risk of depressive symptoms (OR 0.46; 95% CI 0.22–0.95) compared with low intakes (21 mg/d).[25] Among 7,903 Spanish participants, moderate consumption of fish had a relative risk reduction of >30%.[26] Among 10,602 men from Northern Ireland and France, higher depressed mood scores were associated with lower fish intake in a nonlinear relationship.[27] Likewise, a nonlinear relationship was reported between depression and fish intake among a United Kingdom population ($n = 2,982$).[28] Conversely, Jacka et al (2004)[29] reported no association between fish consumption and depression defined by DSM-III criteria in a New Zealand population ($n = 755$), whereas Murakami et al[30] found no association between fish intake and lower risk of depressive symptoms among 618 adults. However, the mean omega-3 HUFA intake was approximately 0.37 en%, which is far above the putative estimated average requirements and recommended dietary allowances presented here. Thus the majority of the population may have had adequate intakes. Overall, epidemiological studies have fairly consistently reported a relationship between low omega-3 HUFA intake and depressive symptoms.

Tissue Compositional Studies

Case–controlled studies comparing differences in tissue compositions among psychiatrically ill and healthy participants are useful but must be interpreted with caution as it is commonly known that psychiatric illnesses can change eating habits. When illnesses are severe enough to impair social function they may reduce access to more expensive foods, especially fish. Progress toward a biomarker index of omega-3 fatty acid status for mental health was proposed by Milte et al.[31] Their review examined whether n-3 polyunsaturated fatty acid (PUFA) levels are abnormal in people with three prevalent mental health problems—attentiondeficit hyperactivity disorder (ADHD), depression and dementia, but found an insufficient number of studies to form clear conclusions. Lin et al[32] subsequently conducted a systematic review and meta-analysis of 14 studies comparing the levels of PUFAs among depressive patients to controls. Patients with clinical diagnoses of a depressive disorder had lower levels of eicosapentaenoic acid (EPA) (Hedges g 0.42; 95% CI 0.67–0.18; $p < 0.0008$), DHA (Hedges g 0.52; 95% CI 0.85–0.22; $p < 0.0008$) and total omega-3 PUFAs (Hedges g 0.85; 95% CI 0.1.21–0.49; $p < 0.0008$). Differences were significant, but of lesser magnitude among all participants described as depressed, but they found no significant differences in AA or total omega-6 PUFAs. The large effect sizes for omega-3 tissue compositional differences among participants with clinical depressions compared to the weaker effect sizes among participants with less severe mood ratings are strikingly consistent with the findings of clinical interventions trials when they distinguish participants with clinically defined depressions from those with low to moderate depression scores.

Neuro-Inflammation and Affective Disorders

The mechanisms of action of EPA/DHA in neuronal function are incredibly diverse, complex and far-reaching. It has been proposed that EPA and DHA may improve affective disorders by regulating neuro-inflammatory responses. There is evidence to suggest that neuro-inflammation may be associated with the pathophysiology of depression and has been the subject of several excellent reviews.[33,34] However, the interaction of essential fatty acids in neuro-immune responses and their subsequent relationships to risk of affective disorders is beyond the scope of this analysis. A framework of interaction has been proposed by Smith[35] in his Macrophage Hypothesis of Depression. This hypothesis, in short, proposes that excesses in arachidonic acid (AA) levels, relative to omega-3 HUFAs, predispose macrophages to disproportionately release AA derived eicosanoids (e.g., prostaglandin E_2 stimulating an excessive release of cytokines IL-6 and tumor necrosis factor-α (TNF-α). Elevated levels of these cytokines act across the blood brain barrier, or as microglia, to induce mRNA expression of c*orticotropin-releasing hormone*, which in turn stimulates the "stress axis" hyperactivity. Recently, Lu et al[36] reported that DHA reduced expressions of TNF-α, interleukin-6, nitric oxide synthase, and cyclooxygenase-2, which were induced by interferon-γ, and facilitated the upregulation of heme oxygenase-1 (HO-1) in BV-2 microglia.[36] Song et al,[37] conducted a very specific test of this hypothesis isolating EPA as a dietary variable in an olfactory bulbectomy model of depression. EPA was able to revert the entire neuroinflammatory cascade to near control levels in addition a 2- to 3-fold elevation in PLA2 mRNA expression and activity was achieved, a 2-fold increase in prostaglandin E_2 levels, a 5-fold increase in Il-6 cytokine levels, a 3-fold increase in mRNA expression and activity of corticotropin-releasing hormone subsequent activation of the hypothalamic–pituitary–adrenal axis and the initiation of depressive behaviors as measured by the Porsolt swim test.

In addition, there is evidence linking HUFA metabolites with neuro-inflammation. For example, a recent meta-analysis reported that cytokine IL-6 and TNF-α are increased in participants with major depressive disorder.[38] Likewise, Keicolt-Glaser et al[39] were able to low scores of anxiety among 205 medical students following supplementation with omega-3 HUFA (2.5 g/d) and also observed concomitant decreases in IL-6 and TNF-α cytokine production. The disproportionate release of AA by phospholipase A_2 and cascade of bioactive metabolites of AA is central to all models of essential fatty acids in excessive neuroinflammatory responses. In 2007, Wada et al[40] elegantly demonstrated that AA eicosanoid metabolites are released relative to the proportion of AA to n-3 HUFAs in the phospholipid precursor pools. Thus, an alternative approach to reducing omega-6 derived eicosanoids such as prostaglandin E_2 is to reduce dietary intakes of omega-6 fats to classical Mediterranean levels of 2 to 3 en%, perhaps by replacement with linolenic acid and increasing dietary intakes of omega-3 HUFAs.

Arachidonic Acid Cascade Hypothesis

The arachidonic cascade is thought to play a key role in the development of negative affect and major depressive disorder. Hibbeln et al[41] were the first to propose that excessive activity of phospholipase A_2, had subsequent effects on membrane biophysical properties and that the release of AA were key components in the pathophysiology of affective disorders. The specific mechanism(s) of antidepressant and anticycling pharmaceuticals including lithium, carbamazepine, and valproic action, as well as the hormones cortisol and progesterone, can be understood in terms of their regulation of phospholipase A_2 activity. Chang et al[42] suggested that a major therapeutic effect of lithium is to specifically reduce the turnover of AA possibly by inhibition of phospholipase A_2 involved in signal transduction. Several authors including Rapoport and Bosetti[43] and Bazinet[44] have proposed that lithium and antimanic anticonvulsants act by targeting parts of the "arachidonic acid cascade," which may be functionally hyperactive in mania and more generally in affective disorders.[45] They have predicted that drugs that target enzymes in the cascade, such as cyclooxygenase 2 inhibitors, might indeed be candidate treatments for mania. Consistent with this prediction, the cyclooxygenase-2 inhibitor Celecoxib has been observed to augment the noradrenergic antidepressant reboxetine and in doing so improve scores of depression in comparison to reboxetine plus placebo.[46] In an animal model, Celecoxib enhanced the effect of fluoxetine on cortical noradrenaline and serotonin.[47] However, perhaps more compelling is the examination of the function of genetic variation in phospholipase A_2, cyclooxygenase, and other components of the AA cascade. In 2010, Su et al[48] examined the effects of seven single nucleotide polymorphisms in cyclooxygenase-2 and phospholipase A_2 genes on the development of depression during interferon (IFN)-α treatment among patients with chronic hepatitis C viral infection (n = 132). Participants with the phospholipase A_2, BanI GG or the COX2 rs4648308 AG genotypes had a higher risk of IFN-α-induced depression (OR = 3.1 and 3.5, respectively). The "at-risk" phospholipase A_2 genotype was also associated with lower EPA levels, and the "at-risk" cyclooxygenase-2 genotype was associated with lower DHA levels.

These studies are consistent with a generalized over activation of the AA cascade or an excess of omega-6 derived eicosanoids such as prostaglandin E_2. Prostaglandin E_2 has been of particular interest since an earlier finding that levels were elevated among depressed participants, in the monoamine oxidase pathway and they are also implicated in the regulation of sleep wake cycles.[45] Interestingly, Bosetti et al[49] reported that lithium down regulates cyclooxygenase-2 activity and prostaglandin E_2 concentrations. Remarkable decreases in cytosolic prostaglandin E_2 synthase protein levels in the frontal cortex has been observed in all psychiatric groups relative to control tissues ($p < 0.05$), with an effect of medication found only among bipolar participants.[50] Curiously, cyclooxygenase-2 inhibitors may aggravate the pathophysiology of depression

by: inducing neuro-inflammation, increasing lipid peroxidation, decreasing the levels of key antioxidants, damaging mitochondria, and aggravating synaptoneogenesis.[51] Some protective eicosanoids, which may be derived from omega-3 fatty acids, may also be impaired by cyclooxygenase inhibition.

Dietary Intakes of Omega-6 Fatty Acids and Relevance for Depression and Aggression

Focusing solely on dietary intakes of omega-3 HUFAs is not sufficient. This is because when dietary intakes of omega-6 fats are below 4 en% fewer omega-3 HUFAs are needed in the diet to reach healthy tissue compositions of omega-3 HUFAs.[52,53] LA intakes of 2 to 3 en% are typically found in Mediterranean diets[10] and this 2 en% intake is also recommended by an international body of essential fatty acid scientists (ISSFAL).[54] For example, Cleland et al reported higher incorporation of EPA into neutrophil membranes after fish oil supplementation among participants eating a diet low in LA and high in oleic acid compared to participants on a diet high in LA.[55,56] We have estimated that to achieve a 50/50 balance of n-3 HUFAs to n-6 HUFAs in blood and tissues, 2178 mg/d of n-3 HUFAs are needed when the background diet contains 8.91 en% of omega-6 LA, but only 133 mg/d of n-3 HUFAs when the diet contains .8 en% of omega-6 LA[57]. This provides an approximate omega-3 index of 12. Our research team were also able to calculate that during the 20th century omega-6 LA consumption rose from 2.23 en% to at least 7.21 en% and that this was primarily due to an increased consumption of soybean oil.[58] Strong temporal relationships have been reported between higher intakes of the omega-6 fatty acid, LA and greater prevalence rates of major depression[8] and homicide mortality in five different countries between 1960 and 2000 (20-fold higher risk; $r = 0.94$; $p < 0.0001$).[59] Thus, in agreement with the view that nutrients work synergistically, it was contended that an excess of n-6 fatty acids, at the detriment of n-3 HUFAs, may increase the risk of depressive and aggressive disorders.

LA and Depressive Symptoms

To date, no identifiable meta-analyses have been conducted evaluating the interaction of LA and depression Therefore, an overview of data from the available studies is presented here. Wolfe et al[60] prospectively assessed the association between dietary linoleic and oleic fatty acids and the risk of severe depressed mood among 4,856 adults who originally took part in the NHANES survey study (1971–1975) after an average of 10.6 years of follow-up. Dietary intakes of LA were classified into three groups: low (1.6 en%), middle (3.9 en%), and high (8.7 en%). Compared to the lowest tertile of LA intake, men were at higher risk for depressive symptoms in the middle (OR 1.64, 95% CI 1.06–2.54) and high (OR 2.34, 95% CI 1.41–3.87) groups (p for trend across tertiles = 0.001). A similar relationship was found among women.

Beydoun et al[61] examined dietary intake data from 1,746 adults in the Baltimore based HANDELS study. They reported that women with higher intakes of n-3 fatty acids (absolute [n-3] and relative to n-6 fatty acids [n-3:n-6]) had a lower risk of depressive symptoms.[61] Collectively, these two epidemiological studies provide support for the assertion that excessive omega-6 fat consumption may be associated with a greater risk of depressive illnesses.

Tissue Compositions and Raising n-3 HUFA Tissue Levels

Jadoon et al[62] examined participants ages 60 and over with previous major depression, but were in remission. They reported that erythrocyte membrane LA levels were curvilinear related to depressive and anxiety symptoms.[62] Plasma LA levels were found to have a negative linear relationship with depressive symptoms. Evans et al[63] examined symptom severity among bipolar patients and found that specific omega-6 fatty acids (LA and AA) and the enzymes that control their biosynthesis may be useful biomarkers in measurements of depressive disorders and the burden of disease. Vas et al[64] evaluated the relationship of serum fatty acid status to suicide risk and major depressive episodes in a cross sectional analysis of 234 pregnant women in Rio de Janeiro, Brazil. In the adjusted logistic regressions, a higher likelihood of suicide risk was observed among women with higher AA levels (AA or 20:4 n-6) (OR 1.45; 95% CI 1.02–2.07) and adrenic acid levels (AdA or 22:4 n-6) (OR 1.43; 95% CI 1.01–2.04). A higher likelihood of a major depressive episode was also observed among women with higher AA levels (OR 1.47; 95% CI 1.03–2.10) and AdA levels (OR= 1.59; 95% CI 1.09–2.32). These tissue compositional studies support the hypothesis that excessive n-6 HUFAs may contribute to the risk of depressive symptoms.

Meta-Analyses of Omega-3 HUFAs for Major Depression

The gold standard of all medical research are randomized controlled trials. Arguably, they provide the clearest evaluation for treatment efficacy and are useful for comparing omega-3 HUFAs to placebos among participants with well characterized psychiatric illnesses. Clearly, such trials need to adequately powered to obtain quality data in cohorts representative of clinical populations of interest. Such future trials need to be well-designed to avoid common errors that have previously been identified in trials of omega-3 HUFAs for significant depressive symptoms. Namely, heterogeneity has arisen for matters pertaining to: study design, participant selection, duration of supplementation, dose, formulation and background omega-3 and omega-6 HUFA status. Until these trials are conducted, meta-analysis is the best tool available for evaluating the effectiveness of n-3 HUFAs for major depression. However, the confounding effects of heterogeneity, must be considered when interpreting such studies, as the current observed lack of effect might be due to the inclusion of a subpopulation of unresponsive participants or the inappropriate pooling of effective and ineffective formulations.[65]

Thus, we have examined the currently available meta-analyses of omega-3 HUFAs in depressive symptoms, paying particular attention to identify sources of heterogeneity.

The first meta-analysis was published as part of the American Psychiatric Association treatment recommendation for use of omega-3 HUFAs for all psychiatric patients, primarily for medical benefits.[66] This analysis of 8 studies included both bipolar and unipolar depression and reported a positive effect size of g = 0.34, $p < 0.02$. However, it did not differentiate between the formulation of omega-3 HUFAs. Appleton et al[67] reported only a small effect magnitude of omega-3 on depression when all participants were pooled together, but also identified a substantial source of heterogeneity, namely, participants with major depression versus nonclinical depressive symptoms. When trials of participants with major depression were pooled separately, there was a substantially stronger effect size standardized mean difference (SMD) = 0.73, $p < 0.04$, with lower heterogeneity.[67] Lin et al[68] also differentiated studies by those that included participants with clearly defined depression or bipolar disorder and found a similarly large clinical effect size (SMD 0.69; $p < 0.002$ and SMD 0.69; $p < 0.0009$, respectively).[68] Neither Appelton et al nor Lin et al found any evidence of treatment efficacy when pooling healthy participants or participants together with mild or clinical depressive symptoms. These findings are strongly consistent with the well-established observation that the likelihood of finding efficacy for any treatment depends on the initial severity of depressive symptoms of participants in the trial, regardless of whether the intervention is pharmacological, psychotherapeutic, or nutritional.[69] Arguably, this is due to both the high placebo response rate among participants with mild to moderate depressions and to floor effects. In other words, it is not possible to reduce depressive symptoms among psychiatrically healthy participants.

A second problem and source of heterogeneity has been pooling studies with noneffective omega-3 HUFAs formulations with ones that have supposed strong clinical effects. Ross et al[70] was among the first to identify that that differences in formulation accounted for substantial heterogeneity and that studies using predominantly EPA formulations had larger effect sizes (SMD 1.18) compared to predominantly DHA-rich formulations (SMD 0.06; $p < 0.009$). Martins[71] observed that when pooling 28 studies, there was a modest effect size of 0.29 (95% CI 0.46–0.12; $p < 0.001$), but with significant heterogeneity. However, using a type of subgroup analyses, Martins[71] identified four primary sources of heterogeneity, namely: (1) diagnostic category (unipolar versus bipolar); (2) therapeutic versus preventative interventions; (3) adjunctive versus monotherapy and (4) supplement type. Symptoms of depression were not reduced using formulations with pure DHA or 50% DHA. In contrast, 13 studies with supplements containing greater than 50% EPA (SMD 0.46; 95% CI 0.75–0.14; $p < 0.005$) and 8 studies with pure ethyl ester EPA (SMD 0.40; 95% CI 0.65–0.14; $p < 0.002$) had significantly reduced depressive symptoms.[71] Both Lin et al and Sublette et al. (2011) reported no efficacy of pooled studies using predominantly DHA formulations yet significant efficacy when pooling studies using predominantly EPA formulations. Clearly, this data supports "supplement type" as a significant source of heterogeneity. Table II presents the results from meta-analyses distinguished by diagnosis and omega-3 HUFA formulation. Both the clinical severity and omega-3 HUFA formulation appear to predict study efficacy.

Critique of the Bloch and Hannestead Meta-Analysis

Bloch and Hannestead[72] evaluated a similar accumulation of studies and somewhat surprisingly advised that public resources should not be used to conduct further clinical trials of omega-3 HUFAs in depression. They justified this by identifying considerable heterogeneity in their pooled analyses of published trials and attributed this heterogeneity to publication bias. The originators of the funnel plot evaluation cautioned against an over interpretation of heterogeneity as publication bias especially in new fields when most of the trials were small and investigators were only beginning to determine the sources of heterogeneity in results.[65,73] This caution is especially important as Bloch and Hannestead[72] failed to recognize from the prior literature that trials predominantly rich in EPA showed strong positive effects compared to trials predominantly rich in DHA. In addition, prior studies also identified that the severity of depressive symptoms was a significant source of heterogeneity in pooling participants with significant depressive symptoms demonstrating strong positive effects compared to trials pooling participants with mild or no symptoms. Bloch and Hannestead[72] also had an unusual criterion of study selection with the inclusion of perinatal and postnatal depression trials, but exclusion of studies in childhood depression, and participants with episodes of deliberate self-harm and significant depressive symptoms. We therefore feel that it was inappropriate of Bloch and Hannestead to discourage the conduct of future, well-designed and adequately powered clinical trials and premature to conclude that omega-3 HUFAs have no therapeutic effects in treating depressive symptoms.

In contrast, we contend that these meta-analyses can be utilized directly as evaluations of efficacy and are useful for identifying sources of heterogeneity so that future trials can be designed appropriately, avoiding the mistakes of the past. Recommendations for future research in this area include that clinical trials should enroll participants who have substantial depressive symptoms at baseline and employ formulas that are predominantly rich in EPA. If these two criteria of study design are not met, failure to demonstrate efficacy and persistent heterogeneity in future meta-analyses can be predicted. However, when these criteria are met in a well-designed study, it may be reasonable to expect effect sizes of between (SMD) 0.5 and 0.6.

TABLE II. Studies Evaluated by Symptom Severity and Formuation of Intervention

Study	Number of Studies	Number of Subjects	Effect size (SMD)	95% CI	$p<$	I_2 (%)	$p<$	Notes
No Distinctions								
Freeman et al (2006)	8	320	0.34		0.02			
Appelton et al (2006)	11		0.57	0.25–0.89		79	0.001	Excluding Ness et al
Ross et al (2007)	9	664	0.91	0.41–1.42		75	0.01	
Lin et al (2007)	10	329	0.61	0.21–1.01	0.003			Positive Dose Response to EPA, Significant Heterogeneity Noted
Martins (2009)	28	1,953	0.29	0.12–0.46	0.001	64	0.0001	Broad Spectrum of Primary Psychaitric Diagnoses
Appelton et al (2010)	35	2,949	0.1	0.02–0.17		65	0.01	Broad Spectrum of Primary Psychaitric Diagnoses
Bloch and Hannestad (2012)	13	731	0.11	–0.04 to 0.26	0.14	73	0.00001	All Benefits Removed After Adjustment for Publication Bias
Lin et al (2012)	12	502	0.23	0.05–0.42	0.01	55	0.001	Excluded Rogers et al From Bloch and Hannestead 2012
Sublette et al (2013)	15	916						
EPA Predominant >50%								
Ross et al (2007)	6		1.18					Difference Compared to DHA Predominant Studies $p < 0.009$
Martins (2009)	13		0.41	0.75–0.13	0.005			Heterogeneity Noted for EPA >50% Studies
Martins (2009)	8		0.4	0.65–0.14	0.002			No Significant Heterogeneity Among Pure Ethyl Ester EPA Studies
Lin et al (2012)	7		0.58	0.29–0.87	0.0001	77	0.0002	
Sublette et al (2013)	12		0.53	0.27–0.73	0.001			
DHA Predominant >50%								
Ross et al (2007)	3		0.06					
Martins (2009)	3		0.001	–0.33 to 0.33	0.99			DHA Predominant, No Significant Heterogeneity
Martins (2009)	4		0.14	–0.19 to 0.48	0.47			DHA > 50%, No Significant Heterogeneity
Lin et al (2012)	5		0	–0.24 to 0.23	0.99	32	0.99	
Sublette et al (2013)	7		–0.03	–0.20 to 0.19	0.76			
Significant Depression								
Appelton et al (2006)			0.73	0.05–1.41		66	0.001	
Lin et al (2007)	3		0.69	0.24–1.13	0.003			
Martins (2009)			0.6	0.87–0.34	0.0001			
Appelton et al (2010)[104]	16		0.57	0.29–0.85		71	0.01	
Bloch and Hannestad (2012)	8		0.42	0.19–0.65	0.0004	63	0.008	
Mild/Other Depression								
Appelton et al (2006)			–0.13	–0.29 to 0.02		3	0.38	
Martins (2009)			0.07	0.32 to 0.17	0.55			
Appelton et al (2010)	4		0.24	–0.04 to 0.52		32	0.2	
Bloch and Hannestad (2012)	5		–0.11	–0.30 to 0.09	0.28	73	0.005	

The top of the table displays results of meta-analyses when studies were not distinguished by participant severity or type of omega-3 HUFA formulation. EPA predominant >50% indicates that the formulation was more than 50% EPA in relation to DHA. Distinctions by the author of the individual meta-analyses into participants with significant, or clinical depression or mild/ other depressions are indicated. Effect sizes are indicated by SMD, 95% confidence intervals (95% CI) and corresponding p value. Heterogeneity is indicated by I^2 and corresponding p value.

Suicide in the United States and Among U.S. Military

The prevalence of suicide is particularly high among the nation's military veterans.[74] Deaths by suicide, suicide attempts, and self-reports of attempted suicide are reported to have continued to increase among persons who have not been combat deployed.[74,75] Of the patients using the Veterans Health Administration services in the fiscal year of 1999, 7684 died of suicide in the following 7 years.[75] Rates for Veterans are almost twice as high as the suicide rates in the general population, which equate to approximately 23 (males) and 6 (females) deaths by suicides per 100,000.[75] Reducing high rates of U.S. military suicide deaths, the incidence of impulsive/aggressive, high-risk behaviors, and mental health conditions is a top priority for the military.

Suicide Risk Traits and Omega-3 Fatty Acids

Deficiencies in omega-3 fatty acids may result in neurobiological abnormalities which are in turn associated with an increased risk of suicide. The effects of omega-3 deficiencies

in the brain have been well replicated in animal studies and include: hypofunction of the serotinergic system and/or dopaminergic neurotransmitter systems that regulate reward, increased stress reactivity of the hypothalamic–pituitary–adrenal "stress" axis and hyperfunction of the endocannabinoid system. Sublette et al[76,77,78] demonstrated that low-DHA plasma levels were a strong predictor of future suicide risk. Furthermore, low DHA levels were associated with hyperfunction of the limbic forebrain and hypofunction of the parietal and temporal cortex. It is estimated that deficiencies in omega-3 HUFAs lead to a 50% reduction in serotonin and dopamine in the frontal cortex and nucleus accumbens of animal brains.[79,80] In human studies, lower levels of plasma DHA have been correlated with lower levels of CSF 5-HIAAA.[81]

Data from epidemiological studies have also indicated that low fish consumption may be a risk factor for suicide mortality. For example, in a longitudinal study that followed up 256,118 Japanese participants for 17 years[82] those who ate fish daily had a lower risk of death from suicide (OR 0.81; 95% CI 0.27–0.91) compared to participants eating fish less than daily. However, the results were not adjusted for confounding variables.

Another study in Northern Finland examined data from 1,767 participants and found that frequent fish consumption (that is at least twice per week or more) significantly reduced the risk of depressive symptoms (OR = 0.63; $p < 0.03$) and suicidal thinking (OR = 0.57; $p < 0.04$) after adjustment for confounding variables.[18] De Vriese et al[83] reported that the seasonal variation in omega-3 plasma status closely correlated with the seasonal variation in suicide rates in Belgium.

These epidemiological observations based on dietary intakes are consistent with the assessment of omega-3 HUFA body compositions directly among patients. Huan et al[84] reported a 30% lower red blood cell concentrations of EPA among suicide attempters ($n = 200$) and a dose–response association of low EPA status and greater risk of suicide compared to control participants. Low DHA status also predicted greater risk of a new suicide attempt in a follow-up study of more than 800 days, 5% of participants above the median split had new attempts compared to 50% of those below the median split.[76] Another case-control study ($n = 1,600$) among active duty U.S. military, identified low DHA status as a significant risk factor for suicide death.[85] All U.S. military personnel in this study had low n-3 HUFA status in comparison to a range of control participants from North America,[86] Australia,[87] Mediterranean,[88] and Asian[84] countries. For example, the DHA status of the U.S. military had only a 5% overlap with the lowest quartile of the Chinese population, (see Fig. 1) who had a significantly higher odds of suicide attempt (OR = 4.8; 95% CI 1.67–14.28; $p < 0.0003$) compared to the highest quartile.[84] A great diversity in DHA in red blood cells can be seen from the lowest octile of the U.S. military (mean 0.7%) to the highest quartile of a Chinese population (mean 6.9%). This diversity may potentially correspond to a 6- to 7-fold increased risk for suicidal behaviors (see Fig. 1). We are aware of only 1

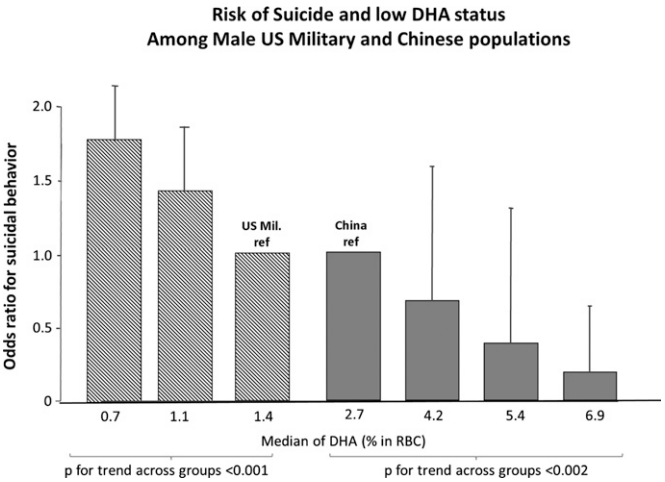

FIGURE 1. Mean erythrocyte levels of DHA (%) are indicated for quartiles of a Chinese population[84] of suicide attempters and representative octiles of U.S. military suicide completers.[85] Odds ratios for suicidal behavior are represented for Chinese (solid bars) and U.S. military (hashed bars) with 95% confidence intervals. ANOVA p for trend is indicated across Chinese and U.S. military population groups separately.

randomized controlled intervention trial by Hallahan et al[89] with omega-3 HUFAs in suicidal patients. In the group receiving omega-3 supplementation suicidal thinking was reduced by 45%; depressive symptoms were reduced by 50%, perceived stress was reduced by 30%, and reports of happiness increased by 33%.[89]

Violence and Aggression

There is growing evidence that low levels of omega-3 HUFA alongside other micronutrient (vitamins and minerals) deficits may be linked to antisocial and aggressive behaviors.[90–94]

Gesch et al[95] conducted a randomized double-blind placebo-controlled trial investigating the effects of combined omega-3/6 and micronutrients supplementation in a population of 231 young adult prisoners (ages 18 and over). The results revealed that nutrient supplementation at routine low daily doses produced a marked reduction (35%–37% versus 7%–10% in the placebo group) in antisocial behavior and violent offences in the active group compared to baseline. This study is instrumental in demonstrating that nutritional supplementation can significantly improve antisocial and aggressive behaviors, although it does not isolate the role of HUFAs in producing this benefit. The findings of Gesch et al[95] were later replicated and confirmed in an almost identical randomized controlled nutritional supplementation trial in the Netherlands of 221 young adult prisoners (mean age 21.0, range 18–25 years) ($n = 115$) over a period of 1 to 3 months.[96] The results of this study yielded comparable findings of a nearly 30% reduction in major behavioral and conduct incidents. Consistent with these findings, anger scores were reduced among substance abusers and participants with borderline personality disorder in randomized clinical trials of omega-3

HUFAs.[97,98] A study by Gow et al conducted in children and adolescents with ADHD and symptoms of conduct-disorder found that low blood levels of omega-3 were negatively associated with high scores of callous and unemotional (CU) traits. Callous and unemotional traits are a sizeable risk factor for the later development of psychopathy and antisocial behaviors. There is a necessity for additional clinical research trials in youths at risk for conduct-disorder/delinquent behaviors to establish whether omega-3 HUFAs with or without micronutrients may help reduce criminal delinquency and the progression of more serious violent and criminal behaviors.

Several investigators have also examined the relationship between maternal diets during pregnancy and internalizing and externalizing behavioral outcomes among the children. Early nutrition may be important because these behaviors are established as early markers for later mental health problems. Hibbeln et al[99] found that consumption of fish in accordance with the 2004 Food and Drug Administration EPA advisory was associated with greater risk of suboptimal verbal IQ, and problems with peer relationships and social interactions. In 2013, Steenweg-de Graaff et al[100] examined maternal diets in pregnancy and behaviors at age 4 and 6 of 3,101 mother–child pairs. The Mediterranean diet was negatively associated ($OR_{\text{per SD in Mediterranean score}}$ 0.90; 95% CI 0.83–0.97) and the traditionally Dutch diet was positively associated with child externalizing problems ($OR_{\text{per SD in traditionally Dutch score}}$ 1.11; 95% CI 1.03–1.21), after adjustment. Neither diet was associated with internalizing problems. In 2013, Jacka et al[101] examined 23,020 eligible women and their children in the Norwegian Mother and Child Cohort Study. Compared to an "unhealthy" dietary pattern greater adherence to "healthy" dietary pattern (which was rich in fish products) was associated with a lower risk of both internalizing and externalizing behavioral scores throughout development. Although these studies do not directly assess the reduction of risk of depressive disorders or aggression in adults, they provide an important proof of concept useful for the development of studies to benefit military families.

PTSD

Few studies have examined the impact of n-3 HUFAs in the prevention or treatment of PTSD. In an open trial of Japanese participants who had been involved in an automobile accident, only 1 of 15 of those treated with 7 g of omega-3 HUFAs /d developed significant PTSD symptoms in contrast to the historically expected rate of 25%.[102] More studies are needed to evaluate the potential utility of omega-3 HUFAs in preventing and treating PTSD.

Considerations for Achieving Mediterranean Tissue Compositions of Essential Fatty Acids

Our evaluation of the data presented here proposes that current dietary intakes of omega-3 and omega-6 fatty acids result in tissue compositions that are insufficient for optimal mental health, resilience and force efficacy. A study by Lewis et al[85] suggested that the U.S. military population is excessively low in n-3 HUFAs in comparison to recommended compositions and other parts of the world.

Thus it is appropriate to consider how U.S. military dietary intakes of omega-3 and omega-6 fats can be modified and if a target tissue composition consistent with healthy Mediterranean dietary patterns is reasonable. It is clear that dietary supplements or eating more seafood can successfully raise omega-3 HUFA tissue compositions. However, lowering the high levels of omega-6 fats in the background can reduce competition between these fatty acids. For example, Ramsden et al[103] demonstrated that blood levels of n-3 HUFAs can be raised by selectively lowering dietary intakes of LA from 7.42% to 2.45% of energy, but without increasing dietary intakes of n-3 HUFAs. However, other studies have failed to show an increase in n-3 HUFAs with omega-6 LA lowering; a critical difference in this study was that LA was lowered to <2.5% of energy. Basic enzyme kinetic equations predict that LA must be lowered to less than 4% of energy to change the amount of conversion from linolenic acid to EPA and DHA.[52] An accompanying article in this volume models how nutrients in foods served in recipes in a U.S. military garrison can be rebalanced to decrease intakes of omega-6 and increase intakes of omega-3 fatty acids (Marriott et al 2014, submitted). An actual translation of this modeling is currently being conducted in the Optimal Omega-3 Study, which is a randomized controlled metabolic kitchen trial in collaboration with the U.S. Army Natick Soldier RD&E Center; the U.S. Army Research Institute of Environmental Medicine the Pennington Biomedical Research Center; DFM Frontiers; the Samueli Institute and the National Institute on Alcohol Abuse and Alcoholism (please see The Optimum Omega -3 (003) Diet Study on http://clinicaltrials.gov/show/NCT01642368). For this trial, the feed for chickens were redesigned to produce high omega-3 HUFA and low omega-6 meat and eggs (Super Chicken products). Alternative salad dressings, mayonnaise, pasta sauces, and peanut butter and other foods with low omega-6 and high omega-3 contents were also sourced. These foods were substituted into a repeated 7-day selection of U.S. military menus so as to elevate tissue compositions of omega-3 HUFAs without the use of supplements. In a separate study, Bernadette Marriott, PhD, and members of our research team are also currently evaluating the efficacy of 3 g/d of omega-3 HUFA supplements to reduce suicidal behaviors among U.S. military veterans. The study which is named The Better Resilience Among Veterans on Omega-3's (BRAVO) is being conducted at the Medical College of South Carolina.

CONCLUSION

Collectively, the research demonstrates potential efficacy for improving mental ill-health outcomes including reducing symptoms of depression and aggression and lowering the risk of suicide ideation among the U.S. military by raising blood

levels of omega-3 HUFAs. Although, more studies need to be conducted to confirm mental health benefits, there are few harms raising the omega-3 and lowering the omega-6 content of U.S. military diets. One target for intake of essential fatty acids might be to achieve consistency with Mediterranean dietary patterns that are increasingly being recommended for multiple health outcomes. The core components of Mediterranean diets are the use of olive oil, which is low in omega-6 LA, instead of vegetable oils, and increasing fish consumption, which raises omega-3 HUFA intakes. A potential biomarker goal for mental health outcomes may be a typical Mediterranean body composition of 50% omega-3 HUFAs. We caution that omega-3 HUFAs should not be considered as a sole cause or redeemer of mental ill-health impairments. However, programs of education and the provision of foods with altered essential fatty acid contents, followed by careful monitoring of blood compositions have the promise of significantly improving the mental health status and force efficacy of the U.S. military.

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