Omega-3 fatty acid deficiencies and the global burden of psychiatric disorders

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Abstract

Neuropsychiatric illnesses constitute a large burden of global ill health and nutritional deficiencies of omega-3 essential fatty acids are emerging as reversible and preventable risk factors. Recommendations by the American Psychiatric Association support treatment efficacy for major depression in adulthood. Emerging clinical intervention data indicate that homicide, personality and substance abuse disorders respond to alleviation of these deficiencies. Neuropsychiatric manifestations deficiencies in long chain omega-3 in the fetus may include low verbal IQ in childhood and abnormal social behaviors, potential developmental indicators of a deviant social trajectory towards substance abuse and violence. Public advisories for fertile or pregnant women to limit seafood intake may encourage nutritional deficiencies in lipids critical to optimal neural development and inadvertently increase risk for the harm they intent to prevent. In the US alone supplementation with 1,800 mg/d of long chain omega-3 fat is estimated to prevent 384,303 hospitalizations due to cardiovascular disease and save USD 3.1 billion over 5 years. Similar reductions in misery and economic costs could be expected for the reduction in neuropsychiatric illnesses.

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Introduction: World burden of illness potentially attributable to omega-3 deficiencies

Neuropsychiatric disorders, primarily major depression, substance abuse disorders and violence, currently account for 14% of the global burden of disease (Prince *et al.*, 2007). In 2020, the top three leading causes of disability-adjusted life-years are projected to be ischemic heart disease, unipolar major depression and motor vehicle accidents which are often substance abuse related (Murray and Lopez, 1997). Violent and excessively aggressive behaviors are significant threats to public health, and the prevention of injury has been identified as a policy priority by the U.S. Surgeon General (Satcher, 1995; US Department of Health and Human Services, 2005). Developmental pathologies of the brain (Liu and Wuerker, 2005), potentially exacerbated or caused by nutritional deficiencies in omega-3 essential fatty acids

(Hibbeln and Salem, 1995) may in part explain the increased prevalence of these prevalent afflictions. While other major morbidities, such as cardiovascular disease, are wide accepted to be linked to dietary factors (Hu and Willett, 2002) the perception of mental ill health as an emergent symptomotology of nutritional deficiencies of omega-3 essential fatty acids has been slow to emerge despite knowledge of their importance to biophysical, biochemical and neurodevelopmental mechanisms (Salem *et al.*, 2001). Omega-3 long-chain fatty acids (omega-3 LCFAs: eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids), found primarily in fish oil, are essential nutrients for humans and therefore must be obtained through the diet. Western society may be in a global state of nutritional deficiency of these nutrients, especially compared to diets which permitted evolution of hominid encephalization and optimal neuronal function (Crawford and Sinclair, 1971; Cunnane *et al.*, 2007). Global economic changes in the use of seed oils rich in the omega-6 fatty acid linoleic acid may cause functional deficiencies in omega-3 fatty acids by displacing eicosapentaenoic acid and docosahexaenoic acid from membranes and preventing efficient elongation and desaturation (Hibbeln *et al.*, 2006). The understanding on the utility of long chain omega-3 fatty acids and the competitive effects of omega-6 fatty acids could lead to the development of treatments and prevention strategies to reduce the burden of depressive and aggressive disorders at low cost with global applicability. Here we will examine the hypothesis that omega-3 fatty acid deficiency in at least two developmental periods increases risk for aggressive and depressive behaviors.

Treatment efficacy for major depression

First, the treatment efficacy for long chain omega-3 fatty acids in major depression in adults has recently been supported by treatment recommendations issued by the American Psychiatric Association (Freeman *et al.*, 2006). The large effect size ($g=0.57$, $p<0.0008$) confirmed in a meta-analysis of 9 randomized placebo controlled trials, which was a larger treatment effect size for most antidepressant medications. Because depression is frequently co-morbid with cardiovascular disease and obesity, the treatment recommendations were formulated to follow the American Heart Association Recommendations for primary and secondary prevention (Kris-Etherton *et al.*, 2003). Three similar meta-analyses have found similar effect sizes for the treatment of major depressive illnesses (Appleton *et al.*, 2006; Lin and Su, 2007; Ross *et al.*, 2007). These data indicate that major depressive illnesses may, in part, be a reversible manifestation of omega-3 fatty acid deficiency in adulthood. Given this evidence of treatment efficacy, a new perspective can be taken on the ecological data which indicates that the risk of major depression is 50-fold greater among countries with the lowest seafood consumption (Hibbeln, 1998). Causal interpretations need not be debated regarding these ecological data; alternatively they can be used to estimate the burden of depression potentially treatable by ensuring adequate essential fatty acid nutrition.

Emerging data in homicide, personality disorders and substance abuse

Additional neuropsychiatric manifestations deficiencies in long chain omega-3 in adults may include a predisposition for personality disorders, substance abuse and impulsive or violent behaviors. Treatment effect sizes for the reduction of violent and impulsive behaviors appear to be a large as for major depression: for example a 50 % reduction in anger among 35 aggressive polysubstance abusers (Budens-Branchey Hibbeln *et al.*,

in press) and a 45 % reduction in time contemplating suicide among patients who had been referred to an emergency room for self injury (Hallahan *et al.*, 2007). In ecological studies homicide can be considered as a surrogate measure of aggression as it is an extreme case of violent behavior. Mortality data are particularly useful as the definition of homicide is consistent across countries and data are prospectively collected for whole populations. Cross-national ecologic data indicate that there is an inverse relationship between seafood consumption, a surrogate of omega-3, LCFA intake, and rates of death by homicide ($r = 0.63$, $p<0.0006$, $n = 36$ countries) (Hibbeln, 2001). Whereas tissue compositions of EPA and DHA can be increased by greater seafood consumption, these levels can be decreased by greater consumption of competing omega-6 fatty acids, in particular linoleic acid, found principally in seed oils (Lands *et al.*, 1992). In addition, greater linoleic acid consumption, estimated from economic disappearance data, has been found to have a direct relationship with homicide rates across five countries ($r=0.93$, $p<1 \times 10^{-40}$) between 1960 and 1999 (Hibbeln *et al.*, 2004). Differences in apparent intake of linoleic acid ranged from approximately 1% of calories in the United Kingdom in 1960 to nearly 10% of calories in the U.S. in 1999 and represent the world's diversity of linoleic acid intake (Hibbeln *et al.*, 2006) and correlates with a 100-fold difference in rates of homicide mortality (Hibbeln *et al.*, 2004).

Observational and intervention studies of human subjects are consistent with the cross-national data described above, suggesting that low omega-3 levels are associated with aggression. Virkkunen and others were the first to report that violent and impulsive offenders had lower plasma concentrations of DHA than non-impulsive offenders and healthy controls (Virkkunen *et al.*, 1987). Previously, Fiennes *et al.* (1973) has reported severe behavioural pathology and hepatic lipid infiltration in a primate model of omega-3 deficiency in the presence of excess linoleic acid. Higher adipose concentrations of linoleic acid were strongly associated with Type A personality among Cretan adults (Mamalakis *et al.*, 1994). Lower plasma DHA correlated with greater neuroticism and lower agreeableness on the NEO personality inventory in a normative population (Conklin *et al.*, 2007). In 6- to 12-year old boys, a greater number of behavior problems, temper tantrums and sleep problems were associated with lower total omega-3 fatty acid concentrations in comparison to controls (Stevens *et al.*, 1996). The CARDIA study found that greater seafood consumption amongst 4,000 subjects was associated with lower scores on the Cook-Medley hostility scale, irrespective of gender or ethnicity (Iribarren *et al.*, 2004). Several double-blind, placebo-controlled intervention trials have been conducted to assess the efficacy of omega-3 fatty acids in reducing hostility, an affective state closely related to anger and aggression. Although not specifically designed to assess psychometric changes, hostility and depression scores were reduced by a high fish diet over the course of five years (Weidner *et al.*, 1992). Hamazaki *et al.* (1996), reported that 1.5 to 1.8 g/d of DHA reduced measures of hostility in a picture frustration test among Japanese students, indicating that omega-3 fatty acids may reduce aggression during stress in normal subjects. It is interesting to note that the baseline plasma DHA composition of this group was 3.0%, compared to typical American levels of approximately 1.5%. Small decreases in hostility measures among Thai University employees after two months of supplementation with 1.5 g/d of DHA compared to placebo (Thienprasert *et al.*, 2000). Investigators in Boston (Zanarini and Frankenburg, 2003) reported large decreases in verbal and physical aggression among women with borderline personality disorder with EPA monotherapy. Although not primarily examining aggression, investigators at Oxford, UK (Richardson and Montgomery, 2005) found decreases in

disruptive behavioral disorders among children with developmental coordination disorders and a high prevalence of attention deficit hyperactivity disorder upon supplementation of 558 mg/d EPA and 174 mg/d DHA. In a study of Japanese children (9-12 y/o), (Itomura *et al.*, 2005) one group supplemented with fortified foods providing 840 mg/week EPA and 3,600 mg/week DHA, while the control group ate unfortified foods. Measures of hostility and symptoms of attention deficit hyperactivity increased in girls in the control group who had no changes in EPA and DHA from baseline, but whose RBC linoleic acid levels increased. These data may indicate that foods low in EPA/DHA and high in linoleic acid increase the risk of hostility and attention deficit hyperactivity disorder. One of the most provocative reports has been that a cocktail of multivitamins, mineral and essential fatty acids (including about 180 mg of EPA plus DHA) reduced felony level violence among prisoners by 37% (Gesch *et al.*, 2002). These studies suggest that residual behavioral problems may be reduced or reversed in childhood, adolescence and adulthood or at least concurrently treated by the increased use of omega-3 and decreased use of omega-6 essential fatty acids.

Early development

Neuropsychiatric manifestations deficiencies in long chain omega-3 in the fetus may include low verbal IQ in childhood and abnormal social behaviors, potential developmental indicators of a deviant social trajectory towards substance abuse and violence. Deficiencies in long-chain essential fatty acids during critical periods of prenatal and childhood neurodevelopment may result in a residual predisposition towards aggressive and depressive behaviors (Hibbeln *et al.*, 2006). Possible mechanisms include impaired neuronal migration, connectivity, timed apoptosis, and dendritic arborization, such that there is an irreversible disruption in the neuronal pathways that regulate behavior (Sinclair *et al.*, 2007). Although it is well established that omega-3 fatty acids are important for optimal brain function during infancy (Willatts *et al.*, 1998), data regarding the persistence of these neurodevelopmental effects into childhood and/or adulthood are just beginning to emerge in the literature.

The developing fetal nervous system is especially at risk of neurodevelopmental abnormalities when mothers do not eat sufficient long chain omega-3 fatty acids. The richest sources of long chain omega-3 fatty acids are from seafood for which there is strong (Crawford and Sinclair, 1971; Broadhurst *et al.*, 1998) and increasing (Marean *et al.*, 2007) evidence for the contribution of seafood to the evolution of human encephalzation, socialization and intellect. Marean *et al.* (2007) have recently discovered fossil evidence for what is described as "the earliest appearance of a dietary, technological and cultural package that included coastal occupation, bladelet technology, pigment use and dietary expansion to marine shellfish, and is dated to a time close to the biological emergence of modern humans". In 2004 however, the US Government, advised pregnant women to limit fish intake to less than 340 gm/w to avoid potential harm exposure to trace levels of methylmercury. However, this advisory did not consider the potential harm to the fetus caused by deficient intakes of long chain omega-3 fatty acids. Thus, we considered both the risks and benefits of limiting seafood consumption among a population of 14,541 mother and infant pairs in a large longitudinal study in England (Hibbeln *et al.*, 2007).

When mothers were in compliance with the advisory and consumed less than 340 g/wk of seafood, their children were more likely to have low verbal IQ at age 8, and greater risk of abnormal social behaviors throughout childhood. These findings remained significant after considering 29 potential confounding variables of social class

dietary food group groups and dietary intakes of methyl-mercury. Inclusion of this variable increased the risks of low verbal IQ attributable to low seafood consumption (odds ratio for no maternal seafood consumption 1·98, 95% CI 1·39–2·81, and for 1–340 g/week 1·34, 1·05–1·72, compared with >340 g/week; trend p=0·0001) despite a small risk of low verbal IQ from methyl-mercury exposure (odds ratio for one SD increase 1·14, 95% CI 1·02–1·27, p=0·0229). When expressed as verbal IQ points, children of mothers with no seafood consumption were at risk of having -2.15 (lower) verbal IQ points (95% CI -4.33, -0.04) compared to children whose mothers exceeded 340 g/w and children of mothers who consumed between 1 and 340 g/ w of seafood were at risk of having - 0.61 (lower) verbal IQ points (95% CI -2.08, 0.86) compared to children whose mothers consumed more than 340 g/w, with a three group trend of $p<0.05$. The estimated linear effect for methyl-mercury was –0.14 (lower) verbal IQ points [95% CI -0.82, 0.54] per μg of intake with an overall loss of 0.32 verbal IQ points (despite a gain of 2.15 verbal IQ points) comparing children with no maternal intake to those with more that 340 g/w.

Perhaps if women ate seafood with no methyl-mercury another 0.32 verbal IQ points may have been gained. However, the nutritional benefits of sea food intake outweighed the small adverse effect of methyl-mercury, confirming our conclusion that to limit consumption to 340 g/week is probably detrimental and nutritionally inadequate. Here we consider a minimum to 340 g/w of seafood during pregnancy as necessary to meet criteria for nutritional adequacy as defined by protecting the majority of the population from risk of harm, defined as increased risk of lower verbal IQ.

Calculation of dietary intakes needed to obviate deficiencies

Essential poly-unsaturated fatty acids compete with each other as the same enzyme systems are used by both omega-6 and omega-3 fatty acids for elongation desaturation and transformation in to biologically active eicosanoids and docosanoids. Excessive linoleic acid in the international food supply appears to have created functional deficiency of long chain omega-3 fatty acids (Lands *et al.*, 1992). In order to calculate healthy intakes of omega-3 fatty acids that meet RDA criteria, the worldwide diversity of dietary intakes of omega-6 and omega-3 fatty acids influences tissue compositions of omega-3 LCFA were considered by (Hibbeln *et al.*, 2006). Deficiency in omega-3 LCFA's was defined as attributable risk from 13 morbidity and mortality outcomes, including all causes of death before the age of 75, coronary heart disease, stroke, cardiovascular disease, homicide, bipolar disorder, and major and post-partum depressions. Dietary availability of omega-3 LCFAs from commodities for 38 countries and tissue composition data were correlated by best fit to each illness in deficiency risk models. We found that the potential attributable burden of disease ranged from 20.8% (all-cause mortality in men) to 99.9% (bipolar disorder). Omega-3 LCFA intake for Japan (0.37% of energy, or 750 mg/d) met criteria for uniformly protecting 98% of the populations worldwide. Omega-3 LCFA intakes needed to meet a tissue target representative of Japan 60% omega-3 in LCFA, ranged from 278 mg/d (Philippines, with intakes of 0.8% of energy as linoleate, 0.08% of energy as alpha-linolenate, and 0.06% of energy as arachidonic acid) to 3667 mg/d (United States, with 8.91% of energy as linoleate, 1.06% of energy as alpha-linolenate, and 0.08% of energy as arachidonic acid). With caveats inherent for ecologic, nutrient disappearance analyses, a healthy dietary allowance for omega-3 LCFAs for current US diets was estimated at 3.5 g/d for a 2000-kcal

diet. This allowance for omega-3 LCFAs can likely be reduced to one-tenth of that amount by consuming fewer omega-6 fats. As the availability of omega-6 fatty acids, which compete with omega-3 LCFAs for incorporation in cell membranes, in the international food supply has increased, so have homicide rates in 26 countries. Thus, these ecological data are consistent with current observational and interventional data indicating that a substantial proportion of depressive and violent behaviors may be manifestations of nutritional deficiencies in omega-3 essential fatty acids and considered as targets for public health interventions.

Conclusion

A large global burden of ill health due to cardiovascular disease and neuropsychiatric illnesses appears to be attributable to diets deficient in omega-3 LCFA and potentially exacerbated by excesses in dietary intakes of the omega-6 fatty acid linoleic acid. We note that our estimations of adequate dietary intakes may be conservatively low as we used tissue targets of phospholipid composition in Japan, where in a similar population the JELIS trail reported that supplementation with an additional 2 g/d of ethyl ester EPA resulted in significant reductions in cardiovascular events (Yokoyama *et al.*, 2007). It is remarkable that further prevention effects were seen in this population where plasma EPA levels may be 5-fold higher than in the US (Yokoyama and Origasa, 2003). While efficacy has been well described for reduction in cardiovascular mortality and, from existing trials for major depression, aggressive and substance abuse disorders also seem to be substantially decreased by ensuring nutritional adequacy. The Lewin group Inc. recently used US Congressional budget office techniques to conduct an economic analysis balancing the cost of supplementing seniors in the US alone with omega-3 LCFAs and savings benefit to cardiovascular health (DaVanzo *et al.*, 2006). The estimate of the five year net savings in hospital expenditures and physician charges resulting from a reduction in the occurrence of coronary heart disease among the over age 65 population through daily intake of approximately 1800 mg of omega-3 fatty acids was $3.1 billion. They calculate that approximately 384,303 hospitalizations due to CHD could be avoided across the five years. Perhaps even more money can be saved, and misery prevented, by the simultaneous reduction in neuropsychiatric illnesses which cost the European Union States 386 Billion Euros for the 25 member states at 2004 prices (Andlin-Sobocki *et al.*, 2005).

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