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Letters and editorial comments should be submitted to Nettleton at joyce@fatsoflife.com and technical comments to Dansby at angela@fatsoflife.com. Subscribe to the *PUFA Newsletter* at www.fatsoflife.com

EDITORIAL

New DHA Recommendations for Pregnant and Nursing Women

"At last!" some might say. Indeed, new recommendations from an international working group of experts spell it out: many, if not most, women are not consuming enough DHA, the long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) that matters most for fetal and infant brain development. The report recommends that pregnant and lactating women consume at least 200 mg of DHA/day. Further insights and background on these recommendations are lucidly presented by Gerard Hornstra, a *PUFA Newsletter* Advisory Board member, in a guest commentary. He is one of the most published and respected scientists in the field. The report dismisses the notion that alpha-linolenic acid can meet the DHA requirements of the developing fetus and infant. If there were lingering doubts this, a review by Plourde and Cunnane in *Applied Physiology Nutrition and Metabolism* will bury them.

A review of the DHA and arachidonic acid concentrations of mature human milk from women around the world presents mean values for both these essential fatty acids. Arachidonic acid is more abundant than DHA, but the latter is much more variable–about 10-fold. This overview underscores the need to consume DHA for optimum maternal and infant nutrition.

Whether higher amounts of n-3 LC-PUFAs can substantially lower the risk of atopic conditions remains unsettled, as reports on both sides of the question accumulate. The rough tally in this issue is 2 in favor, 1 against for n-3 LC-PUFAs and childhood allergies. Why are the findings so consistently inconsistent? It may be the timing of the intervention. The earlier the fetus or infant is exposed, the more likely he is to benefit. Possibly, n-3 LC-PUFAs enhance the maturation of the immune system before birth.

Additional confirmation of the benefit to cardiovascular risk of taking both statins and n-3 LC-PUFAs comes from an Australian intervention study with 1 or 2 g/day of DHA from tuna oil. Patients with high cholesterol and triglyceride levels taking the higher dose had a significant drop in their triglycerides as early as 3 months after treatment. An unexpected finding in the cardiovascular area was the report that risk of ischemic stroke was 25% greater in Swedish men, but not women, with high fish intakes. Although this is not the only such report, it has no obvious explanation.

Thinking of the brain, University of Cincinnati scientists found direct evidence that a key region of the brain affected by mood disorders has significantly less DHA in patients suffering from major depression compared with those without the condition. DHA was the only fatty acid to differ in the brains examined. Other studies provided some evidence that cognitive function is at least partly protected when n-3 LC-PUFAs are more abundant. Providing them late in life appears a less than ideal time to boost their intake.

More good news from the back of the eyeball, the retina. Animals experiencing hypoxia (shortage of oxygen), such as occurs in ischemia and diabetic retinopathy, were better protected from damage if they had consumed diets high in n-3 LC-PUFAs. These animals grew more new blood vessels and produced cellular guardians, neuroprotectins and resolvins, whereas the omega-6 PUFA animals had less new vessel growth and none of the protector substances.

Questions and answers go together in PUFA research, but the former always outnumber the latter. We trust this issue provides some of both.

Joyce A. Nettleton
Editor, *PUFA Newsletter* and *Fats of Life*
joyce@fatsoflife.com

GUEST COMMENTARY

Essential Polyunsaturated Fatty Acids and Early Human Development*

Gerard Hornstra

Essential 18-carbon polyunsaturated fatty acids and their longer-chain derivatives (LC-PUFAs) are collectively known as essential fatty acids (EFAs). Since they are indispensable for human development and health, but cannot be synthesized *de novo* by humans, adequate amounts need to be consumed in the diet.

This issue of the *PUFA Newsletter* presents the recent recommendations of an international consensus meeting on dietary fat and fatty acid intakes of pregnant and lactating women. This meeting followed an earlier one on the importance of LC-PUFAs for perinatal development. Although it was previously recognized that the variability in LC-PUFA status among pregnant women is large, it was felt premature to recommend specific LC-PUFA intakes because data showing direct functional benefits of maternal LC-PUFA supplementation were lacking[1]. The present recommendations are largely based on some recent studies showing a functional advantage of maternal LC-PUFA supplementation for later infant development. Because of the great importance of this subject, these comments provide additional justification for these new recommendations.

Maternal PUFA status during pregnancy and lactation is reduced

The EFA status of an individual is reflected in the EFA concentrations in blood and tissues and the amounts of certain status markers. If insufficient EFAs are available to meet the prevailing physiological requirements, the body synthesizes certain fatty acids with a comparable molecular structure, but lacking the specific essential functions. These "surrogate" fatty acids are hardly present under normal conditions and can, therefore, be used as EFA status markers[2]. The best-known marker is Mead acid (20:3n-9), which increases during a shortage of EFA in general and of arachidonic acid (20:4n-6) in particular. If there is a functional shortage of docosahexaenoic acid (DHA, 22:6n-3), the body increases the synthesis of Osbond acid (22:5n-6). Therefore, under steady-state conditions, the ratio between DHA and Osbond acid is a reliable indicator of the functional DHA status.

Pregnancy is associated with a generalized lipemia and between the 10th and 40th pregnancy week plasma phospholipid-associated EFAs increase by 42% on average. However, these changes are less than half the increases observed for the EFA status markers. Thus, pregnancy is associated with a reduction in functional EFA status and of arachidonic acid and DHA in particular.

After delivery, the EFA status in maternal plasma phospholipids gradually normalizes over 6 to 8 months[3]. Lactating women continue to transfer their own EFAs to their infants, whereas non-lactating women do not. As a result, the relative DHA concentrations in plasma and erythrocyte phospholipids of lactating women become significantly lower than their pre-conceptional values. After weaning, maternal DHA values increase rapidly to values comparable to those of non-lactating women[3].

The DHA content in the plasma phospholipids of mothers with first-time pregnancies is significantly higher than in women who have been pregnant before. This observation indicates that certain maternal DHA stores may not be fully replenished after pregnancy, thereby compromising DHA mobilization in subsequent pregnancies. Alternatively, DHA synthesis from precursor fatty acids may diminish as a result of repeated pregnancies[4].

Maternal PUFA status and birth outcome

Maternal LC-PUFA concentrations vary about 3-fold and omega-3 (n-3) fatty acids are positively related to birth weight. In contrast, the concentrations of most n-6 fatty acids are not or are even negatively associated[5]. Interestingly, head circumference at birth is significantly and negatively correlated with maternal linoleic acid (LA, 18:2n-6) intake[6]. Head circumference is a powerful predictor of brain weight. LA concentrations in maternal plasma phospholipids are strongly and negatively related to the concentrations of arachidonic acid and DHA[7], possibly as a result of an overabundance of linoleic acid. This implies that the LA intake may need to be reduced and partly replaced by alpha-linolenic (18:3n-3) and oleic acids.

Neonatal PUFA status may be suboptimal

The fetal EFA supply strongly depends on maternal EFA and LC-PUFA consumption, metabolism and placental transport. This dependence is convincingly illustrated by the significant, positive maternal-fetal correlations for most EFAs and their LC-PUFAs. All fatty acids are much lower in neonatal than maternal plasma, however, due to the smaller neonatal plasma lipid pools.

The reduction in maternal EFA status during pregnancy likely implies a suboptimal EFA status in newborn infants. This view is supported by the observation that the EFA status of neonatal (i.e., cord) blood vessel walls is lower than that of adult blood vessels[8]. In addition, newborn singletons have a higher EFA status than infants born after multiple pregnancies[9].

Early LC-PUFA availability affects later neurodevelopment

Since the brain has its growth spurt during the third trimester of pregnancy and the neonatal period, it seems feasible that fetal and/or neonatal LC-PUFA status could affect early brain growth, maturation and function. However, no significant associations have been observed between DHA or ARA concentrations in cord blood phospholipids–a proxy for fetal LC-PUFA availability–and cognitive performance at 3.5 and 7 years of age[10,11]. Interestingly, DHA concentrations were positively and significantly related to movement quality and visual acuity at 7 to 8 years of age. Speed of visual information processing was also positively related to DHA levels at birth. DHA concentration in cord plasma phospholipids was also significantly related to childhood behavior at age 7; the higher the DHA status at birth, the lower the behavior score for anxiety, withdrawal and depressive symptoms.

None of these functional outcome measures were significantly associated with child plasma DHA levels at follow-up. These results indicate that a higher perinatal DHA availability may promote certain aspects of later neurodevelopment, brain function and infant behavior, as confirmed by the intervention studies reviewed in the Koletzko paper[1]. They also suggest that an ample prenatal DHA supply, and consequently an adequate maternal DHA intake during pregnancy, may be at least of equal importance for cognitive, motor, visual and behavioral development as dietary LC-PUFAs during childhood.

Implications for nutrition during pregnancy

The results reviewed above, together with those summarized by Koletzko and colleagues, provide strong evidence for the necessity to increase the dietary EFA intake of pregnant women in order to prevent the decrease of their EFA status during pregnancy and to optimize that of their newborns. The consensus meeting recommended that pregnant and lactating women aim to achieve a DHA intake of at least 200 mg/day. As the habitual DHA intake in most Western countries is about 100 mg/day, this would imply an additional intake of about 100 mg/day. Based on data from the Maastricht Essential Fatty Acid Birth study, this additional dose can be expected to increase the mean DHA concentration in cord plasma phospholipids from 6.1% to about 6.4%. This is a pretty modest increase, considering that the DHA concentrations in the Maastricht cohort cord plasma phospholipids range from 2.0% to 7.5%.

As Koletzko at al. noted, maternal intakes up to 1 g/d DHA or 2.7 g/d n-3 LC-PUFA did not result in any adverse effect. A bolder recommendation might have been a DHA intake of about 500 mg/day. This increase would require additional sources to the (oily) sea fish mentioned in the 3rd recommendation. Moreover, it may require some additional arachidonic acid as well, to prevent the possible reduction of this fatty acid due to competition[8]. This seems of particular importance with respect to the brain because, so far, the functional importance of n-6 LC-PUFAs in the brain has attracted much less attention than their n-3 counterparts, although their concentration in brain lipids is considerably higher.

**A fully referenced version of this commentary is available upon request from the editor.*

References

1. Koletzko B et al. *Acta Paediatr* 2001;90:460-464.
2. Hornstra G. In: Sinclair A, Gibson R (eds). *Essential Fatty Acids and Eicosanoids*. American Oil Chemists' Society, Champaign, Illinois, 1992, pp. 177-182.
3. Otto SJ et al. *Am J Clin Nutr* 2001;73:1074-1079.
4. van den Ham EC et al. *Am J Cl Nutr* 2001; 73:622-627.
5. van Eijsden M et al. 2007. Submitted.
6. Badart-Smook A et al. *J Am Dietet Assoc* 1997;97:867-870.
7. Rump P and Hornstra G. *Clin Chem Lab Med* 2002;40:32-39.
8. Hornstra G et al. *Lipids* 1989;24:511-517.
9. Zeijdner EE et al. *Prostaglandins Leukot Essent Fatty Acids* 1997;56:395-401.
10. Bakker EC et al. *Eur J Clin Nutr* 2003;57:89-95.
11. Ghys A et al. *Early Human Dev* 2002;69:83-90.

CARDIOVASCULAR HEALTH

DHA Reduces Triglycerides in Statin-Treated Patients with Persistent Hypertriglyceridemia

Recent results from the JELIS study confirmed the ability of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) to reduce cardiovascular risk even in patients taking statin medication. In that study, the addition of 1.8 g of eicosapentaenoic acid (EPA)/day to the statin treatment significantly reduced the likelihood of any major coronary event and of unstable angina by 19% and 24%, respectively, in patients with high cardiovascular risk. The question is, does docosahexaenoic acid (DHA), the other key n-3 LC-PUFA, do the same in hyperlipidemic patients? DHA is thought to be somewhat more potent than EPA in reducing cardiovascular risk factors, but in practice, the two fatty acids are usually consumed together and each may have distinct and complementary functions in protecting against cardiovascular disease.

To determine the effects of DHA in statin-treated patients, Barbara Meyer and colleagues at the University of Wollongong in Australia conducted a randomized placebo-controlled trial in 45 hyperlipidemic patients who had persistent high triglycerides (>1.6 mmol/L) despite taking statins for at least 3 months. They were randomly assigned to consume 1 of 3 treatments: 4 g/day of DHA-rich tuna oil containing 7% EPA and 27% DHA, 8 g/day of DHA-rich tuna oil, or olive oil at either 4 or 8 g/day. These amounts of tuna oil are equivalent to 1.1 and 2.2 g of DHA/day and 0.3 and 0.6 g/day of EPA. The amount of monounsaturated fat in either of the placebo groups was dwarfed by the dietary intake of monounsaturates. Participants maintained their usual statin therapy and consumed the study oils for 6 months. They provided fasting blood samples at the commencement of the trial and after 3 and 6 months. Forty patients completed the trial.

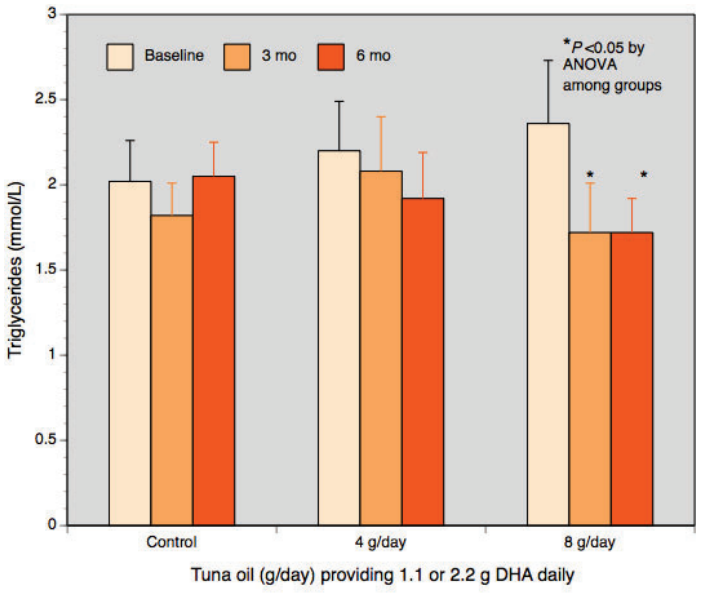

Figure. Changes in plasma TG in hyperlipidemic patients consuming 2 doses of tuna oil for 6 months. Values are means ±SEM.

Patients who consumed 2.2 g of DHA/day experienced a significant (27%) drop in their plasma triglyceride levels as early as 3 months after treatment (Figure). At the end of 6 months, triglycerides showed no further decrease. Consumption of 1.1 g of DHA/day had no significant effect on triglyceride levels, although triglycerides tended to decrease. There was no difference in the two placebo groups and so their results were combined. There were no significant effects of DHA treatment on total, HDL- and LDL-cholesterol levels or on blood pressure.

Like EPA, DHA enhances the effectiveness of statin medication in patients with hyperlipidemia by lowering triglycerides by about 27%.

This trial provides evidence that, just as in the JELIS study using EPA, moderately large amounts of DHA (over 2 g/day) from tuna oil in the presence of a quarter as much EPA are associated with significant reductions in plasma triglycerides in patients with elevated cholesterol levels and persistent high triglycerides. Current medical practice relies on statins to reduce cholesterol with the addition of either fibrates or niacin to lower triglycerides. Both of these adjuncts may have undesirable side effects and be poorly tolerated. In contrast, fish oils rich in either DHA, such as tuna oil, or EPA are well tolerated, although some patients may experience belching or "fishiness." In addition to reducing triglyceride levels, fish oils confer other cardioprotective benefits such as more stable heart rhythms, anti-coagulation, reduced inflammation, lower heart rate and heart rate variability and possibly greater plaque stability. These attributes suggest that fish oils may be the adjunct treatment of choice in managing patients with hyperlipidemia.

Meyer BJ, Hammervold T, Rustan AC, Howe PRC. Dose-dependent effects of docosahexaenoic acid supplementation on blood lipids in statin-treated hyperlipidaemic subjects. Lipids *2007;42:335-344.*

High Fish Intakes Linked to Greater Risk of Ischemic Stroke in Swedish Men

Healthful food habits contribute to a lower risk of many chronic diseases, including stroke. Evidence-based recommendations for stroke prevention have been described and, as with heart disease, the consumption of fatty fish is among them. Fish consumption or the intake of omega-3 long-chain polyunsaturated fatty

acids (n-3 LC-PUFAs) has been associated with significantly reduced risk of stroke in women, men and adults over the age of 65. Lower risks have been reported mainly for ischemic rather than hemorrhagic stroke, the type that prevails in developed countries.

Fish consumption is associated with reduced risk of stroke in several studies, especially in women. Why did things turn out differently in a recent study from Sweden?

Evidence for reduced risk of stroke associated with increased n-3 LC-PUFA intakes has come mainly from epidemiological studies in different populations. Not surprisingly, the data are inconsistent. A recent report from the United Kingdom found no significant relationship between total fish intake and risk of stroke over 8.5 years, although women who had a stroke were more likely to report not eating fatty fish than those who did not have a stroke. A study of male twins in the United States reported that fish or seafood consumption was unrelated to stroke over a 13-year period. Maria Wennberg and colleagues at the Skellefteå Hospital in Sweden wondered whether mercury or eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main n-3 LC-PUFAs in seafood, affected the risk of stroke.

Participants were enrolled in a community intervention program on cardiovascular disease and diabetes and the incidence of stroke was tracked over an approximately 5-year period. Those with transient ischemic attacks, subdural hemorrhages and acute strokes with brain tumors were excluded. There were 388 first-ever stroke cases divided into ischemic (83% of the cases) or hemorrhagic (17%). Two controls for each case–matched for age, sex and date of survey–were randomly selected from the same health surveys. The final analysis included 369 stroke cases and 738 controls. Frequency of eating lean and fatty fish was assessed by food frequency questionnaire and total fish consumption was consolidated into five categories ranging from less than once/month to more than 3 meals/week. Fatty acids were measured in red blood cell membranes, except for the first 113 cases in which plasma phospholipids were used. Total mercury was determined in red blood cells.

On average, study participants ate 1.4 fish meals/week. In multivariate analysis, risk of stroke was 25% greater in men with high fish intakes [OR for ischemic stroke 1.25 (95% CI=1.00-1.56, *P*=0.040)], whereas in women, high fish intake was not associated with stroke. The statistical model was adjusted for smoking, body mass index, diabetes and blood pressure. However, when total EPA and DHA or red blood cell mercury levels were substituted in the analysis model, there was no significant association between stroke and either constituent for men or women.

Risk of ischemic stroke was 25% greater in men with high fish intakes, but in women, fish intake was not associated with stroke. Neither EPA + DHA nor mercury intake was related to the chance of stroke.

The investigators did not expect these results, noting that in the same region of Sweden, EPA+DHA are associated with lower risk of acute myocardial infarction. However, the influence of various factors on each of these conditions is likely different. This observation is not unique, as a study in Spain also reported higher risk of stroke in patients with high fish intakes. Exposure to neither EPA+DHA nor mercury–substances found in fish–was associated with the risk of stroke, suggesting that these are uninvolved. The observations are perplexing, nevertheless, because they are inconsistent with many reports on the benefits of fish consumption and stroke. Until other candidate components in fish appear, these observations remain difficult to explain. This study reinforces the importance of having substantial confirming evidence before reaching a conclusion.

Wennberg M, Bergdahl IA, Stegmayr B, Hallmans G, Lundh T, Skerfving S, Strömberg U, Vessby B, Jansson JH. Fish intake, mercury, long-chain n-3 polyunsaturated fatty acids and risk of stroke in northern Sweden. Br J Nutr *2007;31:1-8*

MATERNAL AND INFANT HEALTH

New Fat and PUFA Recommendations for Pregnant and Nursing Women

The long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) docosahexaenoic acid (DHA) is an essential nutrient for fetal and infant brain growth and development, which must be supplied preformed in the diet or from maternal stores. Yet, few health organizations have devised recommendations for consumption of this nutrient during pregnancy and lactation. Happily, this void has just been filled. Under the auspices of the European Commission, an international group of experts in maternal and child health, nutrition and lipid metabolism, representing several scientific organizations, convened to develop science-based recommendations on the intake of dietary fat, fatty acids and antioxidants during pregnancy and lactation. The group also addressed the safety of fish consumption in the context of environmental contaminants.

The collaborators conducted scientific reviews of the effects of n-3 PUFA intakes for women with low- and high-risk pregnancies, the effect of PUFA consumption on the composition of human milk and infant outcomes, and the

effects of antioxidant intakes in pregnant and lactating women. They also considered recent reviews on the toxicological evaluations of sea fish consumption.

Some noteworthy aspects of these recommendations are their emphasis on consuming preformed DHA rather than its precursor, alpha-linolenic acid; the safety with regard to environmental contaminants of consuming 2 meals of "sea" (presumably marine species) fish/week; and the recommendation to screen pregnant women for dietary shortcomings early in pregnancy. This last recommendation could be especially important in countries and regions where fish consumption is low.

To put these recommendations into the context of how n-3 LC-PUFAs are most commonly consumed, DHA is usually present with eicosapentaenoic acid (EPA) in fish, fish oil supplements and omega-3-fortified foods. Recommended intakes for n-3 LC-PUFAs nearly always specify amounts for all n-3 LC-PUFAs, not just DHA. Two meals of fish/week, preferably of fatty fish, would provide an average of 285 mg to about 485 mg n-3 LC-PUFAs, depending on the serving size and n-3 LC-PUFA content of the fish. These figures are based on a serving of salmon of 3.5 oz (100 g) or 6 oz (168 g) containing about 1 g n-3 LC-PUFAs/100 g. Most fish provide more DHA than EPA, while typical fish oil supplements often provide about 180 mg EPA and 120 mg DHA per capsule. Thus, 2 such capsules daily would meet these new recommended intakes for pregnant women. The key is to read the label carefully to determine how much EPA and DHA each capsule contains.

Recommendations for Fat and Fatty Acid Intakes In Pregnancy and Lactation

On behalf of the Perinatal Lipid Intake Working Group

- ✓ **Fat intake during pregnancy and lactation, as a proportion of energy, should be the same as for the general population.**
- ✓ **The omega-3 fatty acid, docosahexaenoic acid (DHA), must be deposited in adequate amounts in brain and other tissues during fetal and early postnatal life. Several studies have shown a relationship between maternal intake of oily fish or oils during pregnancy and/or lactation and the infant's visual and cognitive development and other functions.**
- ✓ **Pregnant and lactating women should consume enough seafood omega-3s to reach a DHA intake of at least 200 mg/day. Consuming up to 1g/day DHA or 2.7 g/day total seafood omega-3s is without significant adverse effects.**
- ✓ **Women of childbearing age can meet the recommended intake of DHA by eating one to two portions of sea fish per week, including oily fish, which is a good source of omega-3s. This intake of oily fish rarely exceeds the tolerable intake of environmental contaminants. Dietary fish should be selected from a wide range of species without giving preference to large predator fish (such as swordfish and shark), which are more likely to be contaminated with methylmercury.**
- ✓ **Alpha-linolenic acid, the plant-based omega-3, is far less effective with regard to supplying DHA to the fetal brain than the intake of preformed DHA.**
- ✓ **There is no evidence that women of childbearing age whose dietary intake of linoleic acid is adequate need additional dietary arachidonic acid.**
- ✓ **Some studies have shown that mothers who eat fish, fish oils or omega-3s have a slightly longer gestation time, a somewhat higher birth weight and a lower chance of early preterm delivery.**
- ✓ **Mothers should be screened for dietary inadequacies during pregnancy, preferably during the first trimester. If less than desirable dietary habits are detected, individual counseling should be offered during pregnancy and lactation.**

The authors noted the concern about the risks of methylmercury to fetal brain development and recommended not giving "undue preference" to eating predator species, such as marlin, pike, swordfish and shark, known to contain higher concentrations of this contaminant. The report cited the European Food Safety Authority's conclusion that "pregnant women eating up to 2 portions/week of fish are unlikely to exceed the provisional tolerable weekly intake for dioxin and dioxin-like compounds." An exception to this would be herring or wild salmon from the Baltic Sea, which should be consumed by women of childbearing age no more than once/week.

Many other studies of the risks and benefits of eating seafood, such as a series of risk analyses by Joshua Cohen and another by Mozaffarian and Rimm have concluded that the benefits of regular fish consumption providing n-3 LC-PUFAs during pregnancy outweigh the potential disadvantages from contaminants. This is a challenging message to communicate to women of childbearing age, especially during pregnancy and lactation. Well publicized scare campaigns from advocacy groups, especially in the United States, have frightened women away from eating fish, causing them to ask, "why take a chance?" This report should allay those fears.

Koletzko B, Cetin I, Brenna TJ; for the Perinatal Lipid Intake Working Group. Dietary fat intakes for pregnant and lactating women. Br J Nutr *2007;98:873-877.*

Breast Milk DHA and ARA Content Worldwide

A newborn's perfect food, breast milk, depends largely on the mother's diet for its content of docosahexaenoic acid (DHA), one of the primary long-chain omega-3 fatty acids (n-3 LC-PUFAs) and a critical nutrient for brain growth and function. In contrast, the concentration of arachidonic acid (ARA), an omega-6 (n-6) LC-PUFA, is relatively constant among different populations consuming different diets. Studies of the fatty acid concentration of breast milk throughout the world indicate that DHA varies from a low of about 0.1% of total fatty acids in rural South Africa and Canada to over 1% in Japanese women. Vegetarian women, especially vegans, have lower DHA concentrations than omnivore women.

The DHA content of breast milk is largely determined by the mother's fish consumption and can be increased up to 10-fold by eating more fish. A recent study in Brazilian women reported that mothers who consumed 500 g/week of sardines for 30 days increased their breast milk DHA concentration from 0.35% at baseline to 0.61% after 15 days and 0.67% after 30 days. Consumption of the 18-carbon precursor n-3 PUFA, alpha-linolenic acid, increases breast milk eicosapentaenoic acid (EPA) and docosapentaenoic acid concentrations, but does not affect its DHA content.

This report by Tom Brenna of Cornell University, USA, and colleagues, provides the best estimate to date of the worldwide concentrations of ARA and DHA in breast milk. Their analysis of the published literature on breast milk fatty acid concentrations was based on consistent selection criteria and the most accurate fatty acid analytical techniques.

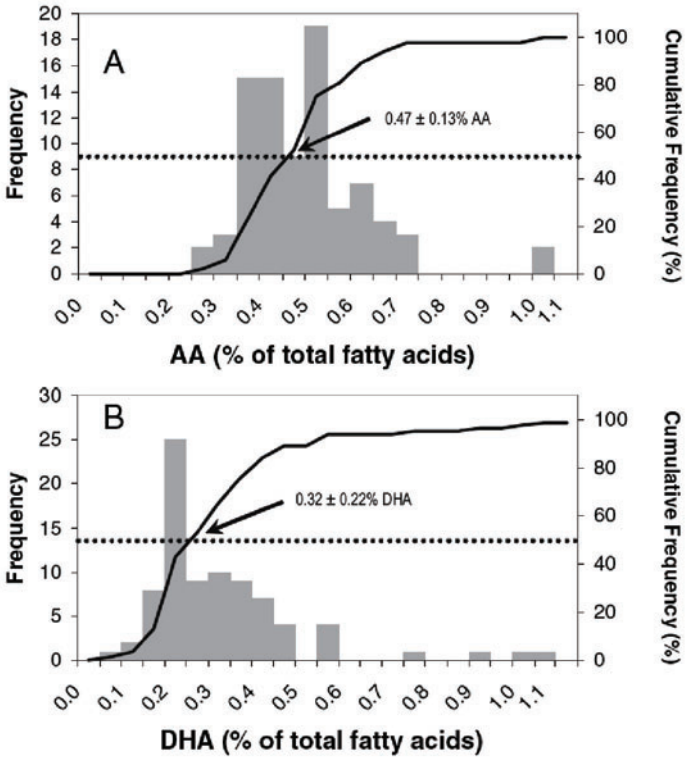

Figure. Human breast milk ARA and DHA concentrations worldwide, determined by capillary gas chromatography. Image © American Society for Nutrition from *Am J Clin Nutr* 2007:85:1457-1464, with permission.

The authors collected data on the distributions of DHA and ARA in mature milk samples from free-living mothers consuming normal or control diets and analyzed them by meta-analysis. Pooled milk samples and milk from mothers consuming experimental diets were excluded. When necessary, values from 2 to 6 months postpartum were used. The primary analysis was based on values determined using capillary gas chromatography. Secondary analysis included data from packed chromatography columns, where complete resolution of DHA and ARA cannot be achieved. Only reports giving the full fatty acid profile were included. The primary analysis included data from 65 reports having 84 mean values from 2,474 women. There were 41 studies in the secondary analysis.

The distributions of ARA and DHA in the primary analysis are shown in the Figure. The mean percent ARA was 0.47 ± 0.13% and for DHA was 0.32 ± 0.22%. The respective medians were 0.46% and 0.26%. The means of these fatty acids from the secondary analysis were somewhat greater, 0.56 ± 0.26% for ARA and 0.40 ± 0.41 for DHA, consistent with overestimated values of these 2 fatty acids using packed columns.

The authors noted that the coefficient of variation for DHA was 69% and for AA, 28%. These values suggest that the AA concentration in breast milk is under tighter control than for DHA and are consistent with greater variability in DHA attributable to maternal diet. Others have also concluded that DHA is more highly variable than ARA in human milk. The report noted that breast milk ARA and DHA were poorly correlated (r=0.25), meaning that neither is a good predictor of the other.

It is now recognized that alpha-linolenic acid, the 18-carbon precursor of n-3 LC-PUFAs, is poorly converted to n-3 LC-PUFAs (less than 1%), especially DHA. Likewise, breast milk ARA comes mainly from maternal stores or preformed in the diet, rather than from conversion of linoleic acid.

This paper provides a useful compilation of the large body of published data on human breast milk fatty acid composition with a careful analysis of the most reliable values for ARA and DHA content in different countries. The overview shows that women in the U.S., Canada Australia and some European countries have the world's lowest breast milk DHA concentrations, usually 0.2% or less. The health implications of these observations are vigorously debated.

Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr *2007;85:1457-1464.*

Fish Oil Supplementation Lowers Risk of Preterm Delivery in High-Risk Pregnancies of Women with Low Fish Intake

The importance of adequate maternal intake of docosahexaenoic acid (DHA) during pregnancy for fetal neurodevelopment is well recognized. There may be additional benefits to ensuring adequate consumption of fatty fish or fish oil in pregnancy, such as lower chance of preterm delivery, preeclampsia, intrauterine growth retardation, atopy in the offspring and improved infant cognitive development and problem-solving. On the other hand, it has been reported that higher fish consumption was linked to increased risk of reduced fetal growth and post-term delivery. Overall, the benefits of moderate fish or fish oil consumption in pregnancy appear to outweigh the potential risks.

Two recent reviews concluded that fish or n-3 LC-PUFA consumption during pregnancy had only modest effects on pregnancy duration and no effect on preterm delivery. However, in Danish women who consumed no fish in the first or second trimesters, risk of preterm delivery was increased 20-fold compared with women eating fish at least once/week in the first 2 trimesters. In their analysis of randomized controlled trials of n-3 LC-PUFA supplementation in pregnancy, Berthold Koletzko's group concluded that such supplementation was associated with a significantly lower rate of early preterm delivery, i.e., before 34 weeks' gestation, and had no effect on the percent of deliveries before 37 weeks' gestation. Sjurdur Olsen's team at the University of Aarhus in Denmark, reasoned that the effects of n-3 LC-PUFA supplementation were likely greater in women with habitually low fish consumption. Previous observations from this laboratory suggested that this was the case. If so, women with low fish intakes at high risk of preterm delivery might benefit most in prolonging their gestation time by consuming n-3 LC-PUFAs or fish oil.

Could background fish intake explain the mixed results of trials on fish oil supplementation and the chance of preterm delivery? This study says "yes."

To obtain a better understanding of the effect of habitual fish consumption on the prevention of preterm delivery, Olsen's group re-analyzed data from a large, multi-center, European intervention trial on the effects of fish oil supplementation in high-risk pregnancies. The original study reported that fish oil supplementation reduced the risk of preterm delivery, but not in women carrying twins or experiencing intrauterine growth retardation. However, information about habitual fish consumption was not available for all participants in the large study. The present analysis re-analyzed the effect of fish oil supplementation in a sub-sample of participants for whom fish consumption data were available.

Women were divided into 3 groups. One comprised 898 women with previous pregnancy complications (past preterm delivery, intra-uterine growth retardation or pregnancy-induced hypertension), a second included 579 women who were carrying twins, and the third consisted of 142 women currently having difficulties, such as pre-eclampsia or intra-uterine growth retardation. Women with diabetes, fetal malformations, drug or alcohol abuse, regular intake of fish oil or anti-inflammatory agents, or allergy to fish were excluded.

Treatment consisted of 3.7 g/day n-3 LC-PUFAs from about week 20 in women with previous pregnancy

problems and those currently carrying twins. Women with current problems were given 6.3 g/day n-3 LC-PUFAs from week 33 of gestation. The control group from each patient category was given the same number of capsules containing olive oil. Baseline dietary and health information was obtained at enrolment and within 4 weeks of delivery, with attention given to fish and olive oil consumption. Analysis of the data on the timing of spontaneous delivery was based on Cox proportional hazards adjusted for maternal smoking, age and parity. Interaction between fish oil supplementation and baseline fish intake was taken into consideration. In addition, the investigators undertook a stratified analysis according to baseline fish intake and whether women habitually consumed olive oil.

As in the original analysis of the entire sample, the likelihood of spontaneous preterm delivery (before 259 days) was significantly lower with fish oil consumption in this subsample of women with previous or current pregnancy difficulties. Risk reductions for each group of women were 31% and 45%, respectively. Fish oil consumption had no effect on spontaneous delivery time in women expecting twins in any of the analyses.

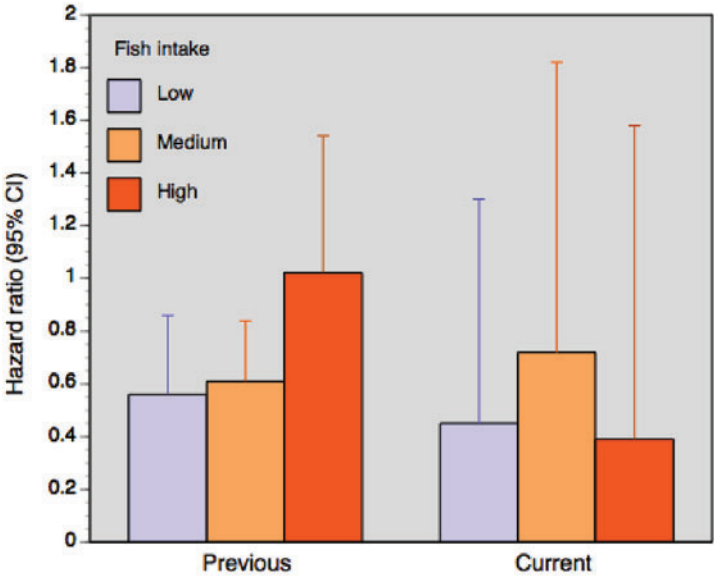

Figure. Hazard ratios for reduced gestational age with fish oil consumption in women with previous or current pregnancy problems according to their habitual fish intake. The reference groups were women who consumed olive oil (Hazard ratio = 1).

When habitual fish consumption was taken into account, women with previous pregnancy problems and low or medium fish consumption had an even lower chance of preterm delivery with fish oil supplementation compared with the overall sample. Risk was reduced by 44% and 39 % in women with low and medium fish intake, respectively (Figure). In women with current pregnancy problems, fish oil consumption had no effect on the risk of preterm delivery. Lack of statistical significance was attributed to the small number of observations and large variability in each fish consumption category.

It should be noted that the frequency or quantity of fish consumed in these women was unable to be determined. However, some perspective may be gained from consumption data in the Danish cohort. In these women, the lowest categories of fish consumption were never or rarely and once in 2 weeks. Women with higher fish consumption ate at least one or more portions/week.

When the data were analyzed accounting for baseline fish consumption and intervention with fish or olive oil, women with previous pregnancy difficulties in the olive oil control group who had low or middle fish intakes had significantly greater risks of preterm delivery, 72% and 55% greater for low and medium fish consumption, respectively, compared with women eating the most fish. In women with current difficulties, baseline fish intake had no significant effect in either the fish or olive oil groups. There were no significant interactions between fish oil supplementation and fish intake.

Habitual fish consumption affects the response to fish oil supplementation in high-risk pregnancies. The lower the maternal fish intake, the greater the risk reduction associated with taking fish oil.

The key finding of this second look at the data is that women at high risk of preterm delivery who do not usually eat fish can reduce their chance of early delivery by consuming supplementary n-3 LC-PUFAs. Risk may be reduced by as much as 44%. The lower the maternal fish intake, the greater the response (and benefit) to fish oil supplementation in reducing risk. On the other hand, women who consumed the most fish obtained no additional risk reduction from taking fish oil. There were no effects in women carrying twins.

The effect of background fish consumption may explain why some earlier studies observed no effect on gestation length with fish oil supplementation. Several previous studies have had small sample sizes, too. Still, revisiting data may introduce its own bias. Nevertheless, these observations suggest a threshold level of n-3 LC-PUFA intake above which additional consumption is without effect on the chance of preterm delivery. As the authors noted, the increased risk associated with olive oil consumption might explain the observations in this study, but there is no evidence that populations consuming

olive oil regularly have shorter gestation times. The bottom line is that fish oil supplementation may prolong gestation in women with a history of preterm delivery whose fish intake is usually modest.

Olsen SF, Osteg JD, Weber T, Tabor A, Secher NJ. Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil. Eur J Clin Nutr *2007;61:976-985.*

IMMUNE FUNCTION

Lower Risk of Allergic Rhinitis with Higher Fish Consumption in Pregnancy

The prevalence of allergic diseases is increasing worldwide, appearing in infants and children as atopic dermatitis, asthma or allergic rhinitis. Suspicion falls on various environmental factors as key contributors, along with urban versus rural living and a family history of allergy. The fetal environment is considered critical to the development of atopic disease and some components of the mother's diet during pregnancy have been linked to risk of infant atopy. For example, in some studies, mothers who consumed fish during pregnancy had infants with reduced risk of atopic allergy or less severe disease, but findings are inconsistent. Children's fish intake was linked to a higher prevalence of asthma in Japan, but a large prospective study reported that regular fish consumption before age 1 was associated with a lower risk of allergic disease and food sensitization.

Allergic rhinitis is especially prevalent in the Japanese population. Does their high consumption of fish have anything to do with it?

The majority of infant atopic allergies occur as eczema and respiratory difficulties, with rhinitis being less common. However, allergic rhinitis affects 19% of the Japanese population, with prevalence higher in urban than rural areas and in the presence of tobacco smoke. Whether fish consumption, typically high in Japan, affects this condition is not known. To find out, Yoshihiro Miyake and colleagues at Fukuoka University in Japan analyzed the relationship between the prevalence of allergic rhinitis and selected high-fat foods and specific fatty acids in the diets of pregnant women participating in the Osaka Maternal and Child Health Study. This is a prospective cohort study to assess the preventive and risk factors affecting maternal and child health, such as allergies and postpartum depression.

At enrolment, the 1,002 participating pregnant women provided information about their dietary habits over a 1-month period and descriptive information on socioeconomic factors, lifestyle and medical history and 2 dust samples collected by vacuum. Participants ranged from <15 weeks to more than 21 weeks of gestation and were 30 years of age, on average. Fourteen percent (141) of the women had used medications for allergic rhinitis at some time in the previous 12 months. Family history of rhinitis (43%) was much more common than for asthma (10%) or atopic eczema (14%). Mean fish consumption was 48 g/day.

Although there was a tendency toward reduced risk of allergic rhinitis with increasing fish consumption, the trend did not reach statistical significance. When the prevalence of allergic rhinitis was examined in relation to fatty acid intakes, there was a significantly lower risk–about 40% less–of the condition as the intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their sum increased (Figure). No other fatty acids were related to the risk of rhinitis.

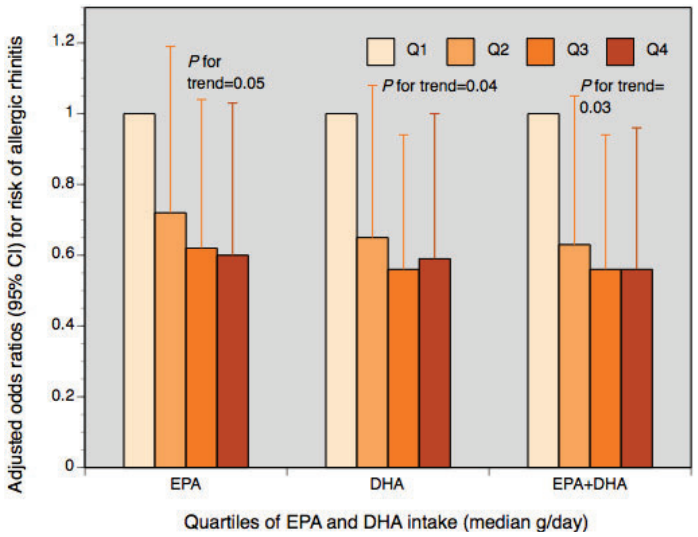

Figure. Odds ratios (95% CI) for risk of allergic rhinitis in pregnant women by quartile of n-3 LC-PUFA consumption.

These observations are consistent with previous reports of an inverse relationship between n-3 LC-PUFAs and atopic conditions. For instance, a cross-sectional study among German adults reported that a high red blood cell membrane content of EPA and a higher food intake of alpha-linolenic acid were associated with significantly lower allergic rhinitis and allergic sensitization, with the risk of rhinitis reduced by about 50%.

In a 4-year study of Norwegian children, fish consumption during the first year of life was associated with a significantly lower risk of allergic rhinitis (55% lower) and asthma (16% reduced). Similar findings were reported for a cohort of children in Sweden who experienced

Fish consumption during pregnancy was unrelated to the risk of maternal allergic rhinitis, but intakes of EPA and DHA were significantly related to about a 40% lower risk of the condition.

significantly lower risk of allergic diseases with fish consumption before age 1.

Fish consumption accounts for the majority of n-3 LC-PUFA intake, although this study did not observe a significant association between the amount of fish consumed and risk of allergic rhinitis. Whether this finding can be attributed to variations in fish intake, the limitations of food estimates in dietary surveys, other substances in fish or other reasons is unknown. However, the inverse association between n-3 LC-PUFAs and significantly lower risk of allergic rhinitis in pregnancy is consistent with other reports of similar associations. This study provides some evidence that risk of allergic rhinitis, like that of eczema and asthma, may be reduced by fish consumption in pregnancy. Nevertheless, there is no substitute for randomized controlled trials. It will be interesting to learn whether rhinitis in the offspring will be related to the mother's fish intake during pregnancy.

Miyake Y, Sasaki S, Tanaka K, Ohya Y, Miyamoto S, Matsunaga I, Yoshida T, Hirota Y, Oda H and the Osaka Maternal and Child Health Study Group. Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka maternal and child health study. J Am Coll Nutr *2007;26:279-287.*

Eating Fish During Pregnancy Lowers Eczema and Atopic Wheeze in Offspring

Sound reasons underlie the rationale for modifying the fetal nutrient environment of pregnant women with a family history of allergic conditions. Their children run a higher risk of allergies that may be affected by maternal fatty acid consumption or metabolism. One reason is the anti-inflammatory effects of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) which are generally consumed in much lower quantities than n-6 PUFAs. Another is the enhanced maturation of the fetus' immune system with increased n-3 LC-PUFA intake. n-3 LC-PUFAs affect T cell function and other immune activities in healthy infants in ways that may diminish the occurrence or severity of atopy in high-risk infants. In addition, prenatal intervention may be more effective than strategies introduced after birth. Other factors besides nutrition affect the manifestation of atopic disease, including genetics, infections and microbial stimulation, antioxidants, tobacco smoke and air pollutants. Thus, dietary modification is just one of several adjustments that may decrease the risk of atopy.

In this study, Isabelle Romieu and colleagues at the National Institute of Public Health in Cuernavaca, Mexico, and the University of Pompeu Fabra, Barcelona, Spain, evaluated the effect of fish consumption in pregnancy on the incidence of atopy and asthma in the offspring. Pregnant women from Menorca, Spain, were recruited during prenatal care and completed a general questionnaire at enrolment. They provided food frequency information 3 months after delivery. From 482 enrollees, 462 provided complete outcome data after 6.5 years of followup. Blood samples from 405 offspring were obtained from cord blood at birth and when the children were 4 years of age. Mothers were interviewed at 6, 14 and 24 months after delivery and yearly thereafter for assessment of their children's allergic conditions. The investigators evaluated atopy by serum IgE levels at 4 years of age and by skin prick tests at age 6. Persistent wheeze and eczema were diagnosed clinically.

Mothers with higher fish consumption during pregnancy had offspring with lower incidence of eczema at 1 year of age, regardless of the mother's own allergic status. Atopic wheeze at age 6 was also significantly lower in children whose mothers ate fish frequently.

Mothers in Menorca typically eat fish regularly, with 86% consuming fish at least once a week. Some 38% ate fish more than once and up to twice a week and 22% had fish more than twice a week. About 37% of mothers reported eating both lean and fatty fish. The mean frequency of fish consumption was 1.5 times/week. Of the parental characteristics potentially related to allergic conditions in the offspring, only maternal asthma was related to fish intake. Asthmatic mothers (6% of the sample) ate significantly less fish than non-asthmatic women. Atopy was present in 12.6% of children at age 4 and in 14.3% by the age of 6.

Frequency of maternal fish consumption was associated with significantly lower incidence (expressed as odds ratios) of eczema at 1 year of age and atopic wheeze at age 6, after adjusting for maternal asthma. For an increase in fish consumption from once to 2.5 times/week, the chance of eczema fell by 37%. Fish intake was also associated with reduced the risk of a positive skin prick test to house dust mites at age 6, but the significance of the association was lost after adjustment for maternal asthma and other confounding variables. Nevertheless, the investigators calculated that increasing maternal fish consumption from once a month to once a week would reduce the risk of a positive skin prick test for house dust mites by 72%.

Boosting consumption from once to 2.5 times/week might reduce atopic wheeze by 82%. These estimates assume, of course, that the observed relationships were causal, but this assumption requires controlled intervention trials to establish. They noted that adjustment for the child's fish intake at age 4 did not modify the results. Breastfeeding had no effect on eczema or atopy risk, but in children who were not breast-fed, maternal fish consumption reduced the risk of persistent wheeze and atopic wheeze at age 6.

Children of mothers with the highest fish intakes were significantly less likely to develop eczema at age 1 and atopy and atopic wheeze at age 6 (Figure). Greater protection potential was observed with more frequent fish intakes compared with less frequent ones. Children of atopic and non-atopic mothers appeared to benefit. These observations agree in part with other observations in non-atopic mothers whose children were less likely to develop positive skin prick responses with higher maternal fish consumption. Fish intake was unrelated to the child's risk of allergic sensitization in atopic mothers. In a different study of maternal supplementation with fish oil, children of the supplemented mothers were 3 times less likely to have a positive skin prick test at age 1 and had less severe eczema.

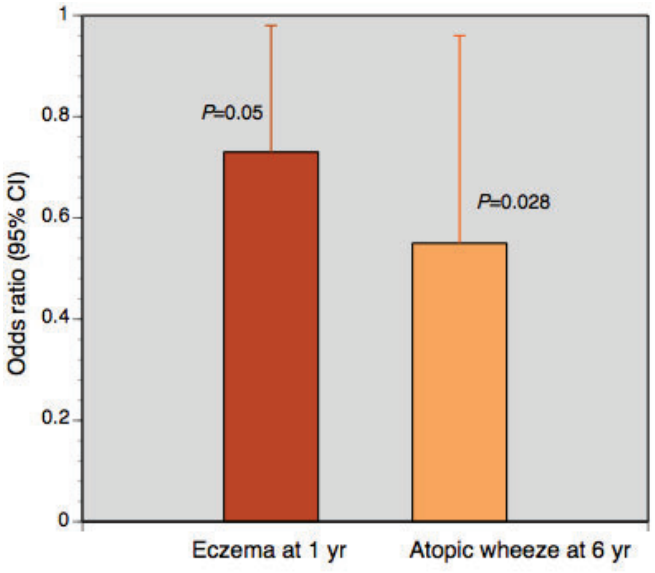

Figure. Adjusted odds ratios for risk of allergic response per unit increased fish consumption (times/wk).

This study was unable to compare the effects of different types of fish consumed by the mothers on their children's outcomes, mainly because there were few who consumed only fatty fish. These findings support other promising studies of the beneficial effects on fish consumption or n-3 LC-PUFA supplementation during pregnancy in lowering the risk of some atopic conditions in children, independent of a family history of allergic conditions. Encouragingly, the investigators will continue to monitor these children for even longer term effects.

Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fito N, Anto JM, Sunyer J. Maternal fish intake during pregnancy and atopy and asthma in infancy. Clin Exp Allergy *2007;37:518-525.*

Omega-3 Supplementation in Early Life Leaves Childhood Asthma or Allergies Unchanged

The increasing prevalence of allergic diseases, especially in children, has prompted research into ways these conditions might be prevented. Some epidemiological studies have reported that fish consumption during pregnancy or early childhood is associated with lower risk of allergies, but others have observed no such effect. Controlled intervention trials are scarce, although there is some rationale for expecting that increased consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) might improve immune responses to allergenic conditions.

A large, randomized, intervention trial in Australia, the Childhood Allergy Prevention Study, was designed to assess whether increased consumption of n-3 LC-PUFAs and reduced intake of n-6 PUFAs in the first year of life would reduce the risk of asthma and childhood allergies. Children with a parent or sibling with asthma were randomized at 6 months of age to consume tuna oil (158 mg n-3 LC-PUFAs) or canola oil capsules. Cooking oils and spreads containing mainly monounsaturated fatty acids were used to prepare the children's food. Three-day, weighed, food intake records were obtained at 18 months of age and food frequency questionnaire data collected from the parents when their children were 3 years old. Clinical outcome assessments were performed when the children were 18 months, 3 and 5 years of age, focusing on atopy by skin prick tests, wheeze and eczema. Plasma fatty acids were determined from blood samples taken at the same time.

Outcome data at age 5 were obtained for 516 of the original 616 participants, with clinical data available for at least 72% of the remaining participants. Plasma and dietary total n-3 PUFAs were significantly higher in the intervention group compared with the controls at all ages (6.2% vs 5.0 % total plasma fatty acids on average). Plasma n-6 PUFAs were significantly lower

Neither dietary intakes nor plasma n-3 fatty acid levels affected the chance of developing asthma or allergic conditions at age 5 in children at high risk for asthma or allergies.

in the n-3 PUFA intervention group, averaging 2.2% less. However, there was no association between plasma levels of n-3 or n-6 PUFAs at any age and allergic outcomes at 5 years. This observation accords with the previous report from this study which failed to find an association between dietary intake of n-3 PUFAs and asthma or eczema. At age 3, there was a reduction in wheeze, but this was not sustained at age 5.

Reasons for the lack of a beneficial effect of n-3 PUFAs on the incidence of any allergy outcome may be related to the dose of n-3 PUFAs consumed. The investigators estimated that the diet supplied 30 mg eicosapentaenoic acid and 128 mg docosahexaenoic acid per day, an amount 3 times the reference intakes for children in Australia and New Zealand. Higher doses might have had an effect, as was observed in one randomized controlled study in which n-3 LC-PUFAs were used to treat children with asthma in a controlled environment. The average proportions of plasma n-6 PUFAs to n-3 PUFAs in the intervention and control groups were 5.3 vs 7.1, differences that may have been too small to detect an effect. Compliance (50% and 56% in the intervention and control groups, respectively) also may have compromised a possible effect of n-3 LC-PUFAs.

This is the largest and one of only a few randomized intervention trials to investigate the primary prevention of childhood asthma with n-3 PUFA supplementation. The study emerged empty-handed at 5 years, but not at 3. Improved childhood allergies in the earliest years of life remain important for the wellbeing of both children and their anxious parents. While these results may not close the case for using n-3 PUFAs in childhood allergies, they suggest that earlier intervention (e.g., during pregnancy) or higher doses may be required for an effect. These results should be considered in the larger context of the many other factors that influence the development of atopic conditions. Primary prevention of childhood allergies remains a black box.

Almqvist C, Garden F, Xuan W, Mihrshahi S, Leeder SR, Oddy W, Webb K, Marks GB; for the CAPS team. Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years. J Allergy Clin Immunol *2007;119:1438-1444.*

MENTAL HEALTH

DHA Deficit Detected in Frontal Cortex of Severely Depressed Patients

The association between intakes of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) and reduced likelihood of major depression is supported by several observational studies and with improved depression ratings in some intervention trials. A benefit of n-3 LC-PUFA consumption has been reported in childhood depression and bipolar disorder, but not all findings have reported improved outcomes.

There is now direct evidence that patients with major depression have significantly reduced levels of DHA in their frontal cortex.

Detailed understanding of n-3 LC-PUFAs, especially of docosahexaenoic acid (DHA) in brain structure and function has revealed altered concentrations of DHA in certain pathologies. For example, patients who die with Alzheimer's disease have reduced levels of DHA and its derivative, neuroprotectin D1 in the hippocampus, the area most damaged by Alzheimer's. Lower DHA in dementia and depression may be reflected in plasma or red blood cell phospholipids as well. Reductions in brain volume with low intakes of n-3 LC-PUFAs have also been reported. To date, there has been no direct evidence of altered brain DHA in depression, although neuroimaging studies have reported significant reductions in the volume of the medial orbitofrontal cortex (gyrus rectus).

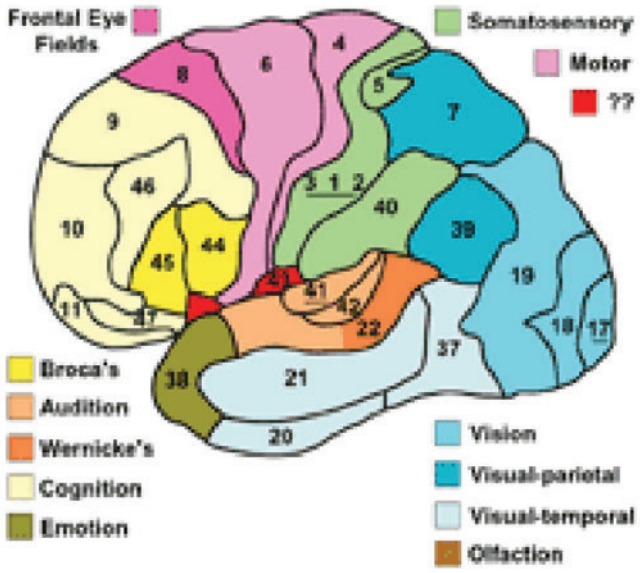

Figure. Cross-section of the human brain showing Brodmann's areas. ***Image reproduced courtesy of Professor Mark Dubin, University of Colorado.***

Dietary deficiency of DHA or n-3 PUFAs is linked to impaired brain function, such as reduced neurotransmission in the frontal cortex. In animals, lower brain DHA has been associated with hyperactivity, altered locomotor activity in male, but not female animals, reduced spatial learning and impaired maze-learning ability. Many

of these handicaps could be overcome with remedial DHA. Provision of DHA attached to the protein albumin conferred significant neuroprotection, reduced subcortical infarction and reduced brain swelling in cerebral ischemia. Thus, diverse evidence indicates that DHA is intimately involved in healthy brain function.

Robert McNamara and colleagues at the University of Cincinnati College of Medicine, USA, decided to find out whether there were alterations in brain DHA in the orbitofrontal cortex of patients with major depression who died. This region is thought to be involved in the hedonic and emotional processes implicated in major depression. All patients had clinically defined major depression and 12 of the 15 had been receiving antidepressant medication at the time of death. Comparisons were conducted with the brains of 27 normal age-matched controls. The average age of patients and controls was 47 years. There were 9/15 males among the patients and 19/27 in the control group. Main causes of death in the patient group were suicide (7) and cardiopulmonary reasons (7), whereas controls died largely from cardiopulmonary (21) causes.

The investigators measured the principal saturated and monounsaturated fatty acids as well as n-6 and n-3 PUFAs in frozen unfixed samples of Brodmann's area 10 in the orbitofrontal cortex (Figure). This is the most anterior part of the frontal cortex. In the control samples, concentrations of the individual fatty acids were consistent with previously published reports. Eicosapentaenoic and alpha-linolenic acids were present in trace or undetectable levels in the majority of samples.

DHA was the only fatty acid that differed significantly between depressed patients and controls, being 22% lower in the depressed patients. Decreases were greater in females than males.

DHA was the only fatty acid that differed significantly between depressed patients and controls, being 22% lower in the depressed patients. There was a trend for lower arachidonic acid (-10%, P=0.03). Difference in DHA was positively correlated with the loss in arachidonic acid, suggesting that these fatty acids may diminish together. Both left and right hemispheres showed similar decreases, but the decrease in the left hemisphere was slightly greater compared to the left hemisphere of the controls (-24%, P=0.009). Cause of death, smoking, substance or alcohol abuse and medication were unrelated to the difference in DHA. However, DHA concentrations were significantly lower in female (-32%), but not male (-16%), depressed patients compared with normal females and males. Age was significantly and negatively correlated with DHA concentrations in controls and in the combined sample, but not in depressed patients.

These observations share some similarities with a previous report from this research group in which fatty acids in the orbitofrontal cortex of schizophrenic patients who died were compared with age-matched normal patients. In that study, significantly lower DHA concentrations (-20%) were found in the schizophrenic patients compared with the normal patients. Unlike in the depressed patients, DHA differences were lower in male, not female schizophrenic patients. The investigators also reported significantly increased concentrations of vaccenic acid (a trans monounsaturated fatty acid, 18:1*trans*-11, found in milk fat) in the schizophrenic patients compared with the normals.

The authors discussed various reasons why the deficits were greater in female than male depressed patients. These may relate to dietary intake (for which no information was available), estrogen, vulnerability to the effects of smoking and possibly alcohol abuse. No answers are forthcoming from this relatively small study, but the findings are among the few in humans to provide direct evidence of DHA depletion in the orbitofrontal cortex in major depression. It is not known whether the difference in DHA is a cause or consequence of the disease. Given the importance of DHA in cell signaling and brain function, understanding its contribution to mental health and pathology is a top research priority.

McNamara RK, Hahn CG, Jandacek R, Rider T, Tso P, Stanford KE, Richtand NM. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. Biol Psychiatry *2007;62:17-24.*

Rate of Cognitive Decline in Elderly Men Slowed with EPA+DHA Consumption

Several epidemiological studies have reported an inverse relationship between fish consumption and age-related cognitive decline. In a small study of patients with early cognitive decline or early Alzheimer's disease who consumed 240 mg/day of docosahexaenoic acid (DHA) and 240 mg/day of arachidonic acid, immediate memory and attention improved in the patients with early cognitive decline, but not in those with early Alzheimer's disease. However, these findings might be attributable to either of the fatty acids or the combination. Not all studies have reported a protective effect of fish or long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) consumption on cognitive decline, but most have. Beneficial effects of n-3 LC-PUFAs

Elderly men with the highest intakes of EPA + DHA had significantly slower loss of cognitive function than men who did not eat fish, the main food source of EPA + DHA.

(mainly eicosapentaenoic acid (EPA) and DHA are plausible because of their anti-inflammatory and neuron-protecting effects. However, the one available intervention trial in patients with Alzheimer's disease reported weak effects only in patients in the early stages of the condition. Preservation of mental function in aging is likely to rely on integrated treatments and healthy lifestyles rather than a single silver bullet from the sea.

In this report from the Zutphen Elderly Study in the Netherlands, Boukje Maria van Gelder and colleagues at the National Institute for Public Health and the Environment re-examined data on fish and n-3 LC-PUFA consumption and cognitive decline over a 5-year period in 210 elderly men. The authors revisited data from the first report because new data on n-3 LC-PUFA composition of fish and other foods became available.

Participants ranged from 70 to 89 years in age (average 75) in 1990 when the baseline dietary data were gathered and mental tests performed. Dietary intakes were assessed using a validated cross-check dietary history method. Repeat assessments were conducted in 1995. Men were excluded if they had myocardial infarction, stroke, diabetes or cancer at baseline. Mental assessment was obtained using the Mini-Mental State Examination for global cognitive functioning. The investigators evaluated depressive symptoms using a self-rating depression scale. Participants with scores less than 24 (maximum score = 30) were excluded because impaired function affects reporting ability.

In this sample of elderly men, 24% did not consume fish, 41% consumed between >0 and 20 g/day and 35% ate more than 20 g fish/day. Men who avoided fish were older and had fewer years of education. Their average intake of EPA+DHA was 15 mg/day from animal and plant foods. At baseline, cognitive function did not differ between those who consumed or avoided fish, after adjustment for confounding variables (e.g., age, education, alcohol intake, smoking, physical activity and energy intake).

Five years later, cognitive function in men who did not eat fish declined by 1.2 points, whereas in fish eaters the decline was 0.3 (P=0.01). There was no significant difference in the decline between the 2 tertiles of fish consumption. In terms of EPA+DHA intake, the cognitive change in the lowest tertile was -0.9 (95% CI=-1.5-0.3)

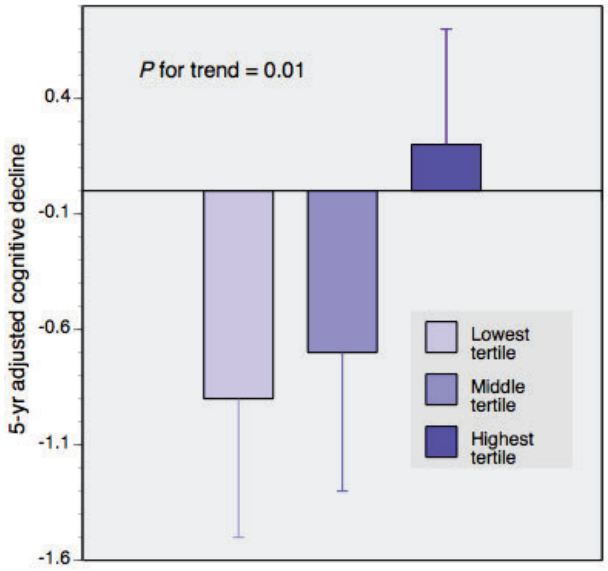

Figure. 5-yr change in cognitive function in elderly men according to intake of EPA + DHA by tertiles.

and in the highest tertile, 0.2 (95% CI=-0.4-0.7), after adjustment for multiple confounding variables (Figure). Thus, higher consumption of EPA+DHA was associated with less cognitive decline.

In a previous cross-sectional analysis of participants in the Zutphen Elderly Study, the authors found a tendency for fish consumption to be inversely associated with cognitive impairment and decline, but the relationships did not reach statistical significance. Now, with improved composition data and a 5-year follow-up, EPA+DHA consumption, but not fish intake, was linked to significantly lower cognitive loss. As the authors noted, EPA+DHA intake was not related to cognitive impairment, just to cognitive decline. In the highest tertile of intake, EPA+DHA consumption was about 347 mg/day. This amount could be obtained from two 4-oz. (116 g) servings of fatty fish/week, the amount recommended by the American Heart Association and other groups. Fish oil supplements, foods fortified with n-3 LC-PUFAs and omega-3-rich eggs also furnish useful amounts of these fatty acids. More detailed evaluation of cognition might reveal specific cognitive effects that were not assessed in this study.

van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr *2007;85:1142-1147.*

Some Fatty Acids Linked to Greater Cognitive Decline, Others to Protection

An association between people's consumption of long-chain omega-3 fatty acids (n-3 LC-PUFAs) and reduced cognitive decline in aging has been reported in several observational studies. However, the reports give no indication of how these fatty acids may protect brain function,

nor which attributes of cognition are better shielded. In the study described here, May Beydoun and colleagues at the University of North Carolina, USA, analyzed data from one set of participants in the Atherosclerosis Risk in Communities Study. This study is examining prospectively the relationship between n-3 LC-PUFA status in plasma lipid fractions and cognitive decline.

Palmitic acid, a saturated fatty acid, and arachidonic acid, an n-6 LC-PUFA, were linked to an increased rate of global cognitive decline. EPA + DHA were protective of verbal fluency, but not other aspects of cognition.

Baseline information from the participants was obtained from 1987 to 1989. At intervals of 3 years, clinical data and blood samples were collected, with measurements of cognitive function determined after 3 and 6 years post-enrolment. The study involved 2,251 participants ranging in age from 50 to 65 years at baseline. Participants were evenly distributed between males and females and all were white with an average age at baseline of 57 years. The investigators measured n-3 LC-PUFAs in plasma cholesteryl esters and phospholipids and evaluated cognitive function in 3 domains: delayed word recall of 10 common words, psychomotor speed and verbal fluency. Dietary intakes were estimated from food frequency questionnaire data. Clinical variables such as blood pressure, dyslipidemia, diabetes and others were obtained at any or all followup examinations.

The participants who exhibited global cognitive decline over the 6-year interval were older (57.7 vs 56.2 years), less physically active and had higher depressive scores on the vital exhaustion scale used in this study (9.7 vs 8.1). They also had better baseline verbal recall on the Delayed Word Recall Test (7.3 vs 6.8) and greater fluency on the Word Fluency Test of the Multilingual Aphasia Examination (45.7 vs 37.1) compared with participants who showed no cognitive decline. Their blood coagulation profile (based on fibrinogen, van Willebrand factor and factor VIII) was also higher (16.4% vs 10.8%).

Those with global cognitive decline had higher concentrations of palmitic and arachidonic acids in their cholesteryl esters, after adjustment for confounding variables. Total PUFAs, total n-6 PUFAs and linoleic acid were inversely related to cognitive decline. A similar, but not statistically significant, pattern was observed in the plasma phospholipids, except that palmitic acid was positively associated with cognitive decline. Neither n-3 PUFAs nor EPA+DHA were related to changes in global cognition.

In subgroup analysis of the 3 domains of cognition, higher concentrations of EPA+DHA in cholesteryl esters and phospholipids were associated with a significantly lower chance (about 25% less) of losing verbal fluency. Word recall and psychomotor speed were unrelated to EPA+DHA concentrations when the analysis was adjusted for other fatty acids. Unlike the global cognitive scores, greater verbal fluency was significantly associated with higher concentrations of EPA+DHA. These relationships appeared to be stronger in participants with hypertension or dyslipidemia, but the odds ratios did not quite reach statistical significance. The authors noted that average changes in cognitive scores over 6 years were relatively small, though they did not report the absolute changes. In addition, cholesteryl ester and phospholipid EPA and DHA concentrations were highly correlated with dietary intakes.

These findings suggest that the fatty acids linked with risk of heart disease may influence cognitive decline in much the same pattern. Too much palmitic and arachidonic acids may promote these scourges, while PUFAs and EPA + DHA can protect against them.

In summary, with fatty acid concentrations in cholesteryl esters as a reflection of fatty acid status, palmitic and arachidonic acids were significantly associated with higher risk of cognitive decline. Higher linoleic acid and total n-6 PUFAs were associated with lower risk. Subgroup analysis of cholesteryl ester EPA+DHA revealed a significantly lower risk of losing verbal fluency with higher concentrations. Other cognitive domains were unrelated to any fatty acid level. Because these effects appeared stronger in participants with hypertension or dyslipidemia, the authors suggest that oxidative stress may contribute to changes in cognition.

As Connor and Connor point out in their editorial, n-3 LC-PUFAs are associated with slower cognitive decline in aging in this study and the preceding one. The anti-inflammatory and anti-thrombotic effects of these fatty acids are relevant to Alzheimer's disease and dementia, as well as to membrane effects such as cell signaling. It is probably not coincidental that at least one fatty acid linked to increased risk of cardiovascular disease–palmitic acid-–and those with cardioprotective effects, n-3 LC-PUFAs, have similar associations in brain function later in life.

Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr *2007;85:1103-1111.*

Connor WE, Connor SL. The importance of fish and docosahexaenoic acid in Alzheimer disease. [Editorial] Am J Clin Nutr *2007;85:929-930.*

Long-Chain Omega-3s of Little Clinical Benefit in Alzheimer's Symptoms

Increasing longevity has resulted in a dramatic increase in the number of elderly patients with impaired cognition and inability to function independently. The worldwide prevalence of dementia has been estimated at nearly 28 million, with someone (in the U.S.) developing Alzheimer's disease every 72 seconds. Secrets for preventing this most common type of dementia remain undiscovered, although some lifestyle habits may be useful. These include being socially active, attaining higher education levels, engaging the mind and, from a dietary point of view, consuming fish regularly. Factors beyond one's control, such as age, genetic susceptibility and carrying the APOE-ε4 gene increase the chance of developing the condition later in life.

Once Alzheimer's disease is diagnosed, is it too late for n-3 LC-PUFAs to benefit the brain? This study says it may be.

Long-chain polyunsaturated fatty acids (LC-PUFAs), especially docosahexaenoic acid (DHA) and arachidonic acid are significantly decreased in the brains of Alzheimer's patients, but there is scant evidence that treatment with omega-3 (n-3) LC-PUFAs affects the course of the disease. In the early phase of the disease, increased consumption of DHA-rich n-3 LC-PUFAs may slow its insidious progress. In this second report from a randomized, double-blind, placebo-controlled trial of the effects of n-3 LC-PUFAs in early Alzheimer's disease, Yvonne Freund-Levi and colleagues at the Karolinska University Hospital in Sweden describe the neuropsychiatric effects of 6 and 12 months of supplementation. Of the original 204 participants, 174 completed the study. Patients averaged 73 years of age.

The study protocol called for supplementation with n-3 LC-PUFAs (600 mg eicosapentaenoic acid (EPA) + 1,720 mg DHA) or corn oil for 6 months, followed by open treatment of all participants with n-3 LC-PUFAs. Several outcomes were assessed at baseline, 6 and 12 months. These included the Neuropsychiatric Inventory of 12 behavioral domains, Montgomery Åsborg Depression rating scale, caregivers burden scale (3 items) and the Disability Assessment for Dementia scale, which assesses daily living activities.

Less than 10% of participants exhibited psychotic symptoms and scores for neuropsychiatric symptoms were low in both groups. Total neuropsychiatric, depression, caregivers burden and daily living scores did not differ between the two groups at 6 or 12 months. Within the neuropsychiatric domains, however, there were significant improvements in hallucinations with the consumption of n-3 LC-PUFAs and in irritation scores with the placebo. When scores were adjusted for age, APOE genotype and gender, these differences were not significant. Interestingly, in the adjusted analysis, agitation was significantly improved in participants carrying the APOE-ε4 gene. There was a significant interaction between treatment and APOE genotype with agitation and total depression score. No other outcomes were affected by treatment.

In Alzheimer's patients with the APOE-ε4 genotype, consumption of n-3 LC-PUFAs was associated with improvements in agitation. In non-carriers, it was linked with improved depression scores. Other benefits in symptoms were not observed.

Overall, these findings suggest that consuming modest amounts of n-3 LC-PUFAs in early Alzheimer's disease has only a slim benefit, which is related to the APOE genotype. Agitation improved in carriers of the APOE-ε4 gene and overall depression score improved in non-carriers. The latter observation is consistent with improved depression scores in non-Alzheimer's patients consuming n-3 LC-PUFAs.

Several factors may have clouded the possible benefits from n-3 LC-PUFAs. One is the dose of 2.3 g n-3 LC-PUFAs/day. Late in life, even higher doses may be needed to reach effectiveness.

Another consideration is the effect of Alzheimer's medications and anti-depressants. These may have shadowed the treatment effects of n-3 LC-PUFAs. Of course, it is also possible that brain function at this stage of the condition is relatively impervious to an additional supply of n-3 LC-PUFAs. DHA has been effective in suppressing the production of the abnormal beta-amyloid proteins in animal models of the disease and in human neural cells, but whether and at what stage it may be effective in people is unknown. This randomized trial is contributing useful information to the field, but shows the large gap between animal studies and what may be occurring in the seventh stage of man.

Freund-Levi Y, Basun H, Cederholm T, Faxen-Irving G, Garlind A, Grut M, Vedin I, Palmblad J, Wahlund LO, Eriksdotter-Jonhagen M. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry *2007; doi:10.1002/gps.1857*

VISUAL FUNCTION

Long-Chain Omega-3s and Their Derivatives Promote Healthy Vascular Growth in Damaged Retinas

The American Academy of Ophthalmology recently stated that age-related eye diseases are expected to increase from 28 million now afflicted to 43 million by the year 2020. Yet, few Americans see themselves as candidates for eye disease or know what puts them at risk. This dismal picture may not be unique to the United States. Seeing what is coming, several government and university research centers have focused on dietary strategies to reduce the development and progression of various eye diseases, especially those affecting the retina. In this context, long-chain polyunsaturated fatty acids (LC-PUFAs) are among the key nutrients.

Can long-chain n-3 PUFAs ensure an adequate network of healthy blood vessels after the retina is damaged from hypoxia? This report suggests not only that they can, they may do more.

The retina contains high concentrations of docosahexaenoic acid (DHA), an omega-3 (n-3) LC-PUFA and arachidonic acid (ARA), an omega-6 (n-6) LC-PUFA. It also has access to eicosapentaenoic acid (EPA), an n-3 LC-PUFA, from the retinal vascular endothelium. These LC-PUFAs can be converted to highly active derivatives, such as eicosanoids, neuroprotectins and resolvins, which may exacerbate or protect eye health. People with age-related macular degeneration who have higher DHA levels in their tissues are less likely to have their disease progress than those with little DHA.

Other types of retinopathies, such as those occurring in preterm infants and diabetic patients, are also sensitive to DHA status. In the paper discussed here, Kip Connor and colleagues at the Harvard Medical School, Boston, USA, describe the effects of dietary n-3 LC-PUFAs on the growth of new blood vessels (angiogenesis) in the retina following hypoxia. A reduction in blood (and oxygen) supply known as retinal ischemia and increased carbon dioxide that accompanies hypoxia can cause pathological neovascularization. This is the growth of new blood vessels where they don't belong or that are abnormal. This process underlies the blindness associated with various retinopathies. In contrast, angiogenesis is the growth of new blood vessels from pre-existing ones that contribute to a healthy blood supply.

The action of n-3 LC-PUFAs and their derivatives in protecting retinal pigment epithelial cells and neurons faced with oxidative stress or ischemia prompted the exploration of n-3 LC-PUFAs in an animal model of oxygen-induced retinopathy. The investigators fed 10% fat diets enriched with 2% EPA+DHA or arachidonic acid (ARA) to mice whose offspring were exposed to an atmosphere of 75% oxygen from days 7 to 12 after birth. Thereafter, animals were returned to room air for another 5 days. This last period is when the destructive neovascular response is the greatest. Mothers of the newborn mice consumed diets enriched with 2% of the total fatty acids from DHA and EPA or ARA, amounts considerably higher than those found in western or Japanese diets. Their milk reflected the fatty acid composition of their diet.

At the end of the experimental period, 17 days after birth, the retinas of mice consuming the n-3 LC-PUFA-enriched diet had significantly greater concentrations of total and individual n-3 LC-PUFAs and significantly lower n-6 LC-PUFAs compared with mice consuming the ARA-enriched diet. However, linoleic acid concentration was higher in the retinas of the EPA+DHA-fed mice. The mice consuming n-3 LC-PUFAs had significantly less retinal vaso-obliteration (loss of blood vessels) and neovascularization compared with the ARA-fed mice (Figure).

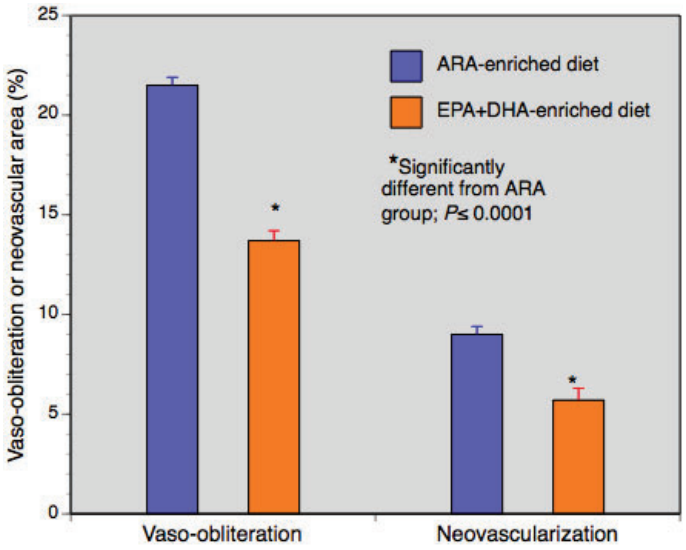

Figure. Decreased retinal vaso-obliteration and unhealthy neovascularization in mice exposed to low oxygen for days and fed an EPA + DHA-enriched diet compared with mice fed an ARA-enriched diet.

Immediately after the 5-day period of reduced atmospheric oxygen, there was no difference between the dietary groups in the percentage of vascularized area in the retinas. Thereafter, the vascularized area increased in both groups, but was significantly greater in the

EPA+DHA-fed animals. The loss of blood vessels after the first 24 hours of hypoxia did not change in either group. Thus, the increased vascularization observed in the EPA+DHA group compared with the ARA-fed animals was attributed to the development of new blood vessels rather than reduced loss of them.

Next, the investigators examined the retinas from each group for the presence of neuroprotectin D1 and resolvins E1 and E2. These derivatives of DHA and EPA, respectively, have potent cell protective properties in the retina and brain under conditions of hypoxia, oxidative stress, inflammation and other injuries. Neither resolvins nor neuroprotectins were detected in the retinas of the ARA-fed animals, but were found in the EPA+DHA-fed animals.

Increased intake of EPA + DHA promoted the growth of healthy blood vessels and reduced the vascular damage and loss in the retinas exposed to hypoxia. These effects were also observed with the EPA and DHA derivatives resolvins and neuroprotectin D1.

When very low doses of resolvin D1, E1 or neuroprotectin D1 were given to mice not fed n-3 LC-PUFAs, vasoobliteration and damaging neovascularization were significantly reduced following hypoxia. Normal vascular development and vessel loss prior to reduced oxygen did not differ between the n-3 LC-PUFA mice and those given resolvins and neuroprotectin. These observations are consistent with the interpretation that resolvins and neuroprotectin D1 enhance new blood vessel growth and are involved in mediating the effects of dietary of n-3 LC-PUFAs.

Further studies demonstrated that feeding the n-3 LC-PUFA-rich diet suppressed the expression of retinal tumor necrosis factor-α, an important mediator of inflammation, during and following hypoxia. Production of this cytokine was identified in microglial cells closely associated with retinal blood vessels. When the ARA-fed animals had this factor blocked with a chemical agent, the size of the retinal area without blood vessels was reduced to that observed in the n-3 LC-PUFA animals. Even though production of tumor necrosis factor-a was not completely suppressed, damage to the retina was significantly reduced.

The investigators also conducted parallel experiments in genetically modified mice bearing the *fat*-1 gene. These mice have reduced levels of n-6 and increased levels of n-3 LC-PUFAs. Results in this model were comparable to those obtained in the mice fed the n-6 and n-3 PUFA diets.

These detailed studies provide evidence that increased intake of n-3 LC-PUFAs promoted healthy vascularization and reduced blood vessel damage and loss in the retina exposed to hypoxia, a condition common in several retinal pathologies. The protection associated with dietary n-3 LC-PUFAs was likely to be mediated, at least in part, by resolvins and neuroprotectin D1 derived from n-3 LC-PUFAs and the suppression of tumor necrosis factor-α production. In addition to their effects on reducing inflammation, these substances and dietary n-3 LC-PUFAs increased the healthy development of new blood vessels, reduced the production of damaging blood vessel growth, and resulted in less retinal area devoid of blood vessels. The implication of these studies is that provision of n-3 LC-PUFAs may help prevent or limit the severe eye damage in such conditions as premature birth, diabetic retinopathy and age-related macular degeneration.

Connor KM, Sangiovanni JP, Lofqvist C, Aderman CM, Chen J, Higuchi A, Hong S, Pravda EA, Majchrzak S, Carper D, Hellstrom A, Kang JX, Chew EY, Salem N Jr, Serhan CN, Smith LE. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nat Med *2007;13:868-873.*

Iffy Links Between Cataracts and Omega-3 PUFAs

Some observational studies suggest the involvement of dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) in the development of cataracts, dry eye and other visual impairments outside the retina. However, reports on the associations between cataracts and alpha-linolenic acid or long-chain n-3 PUFAs are contradictory. Two recent observational studies focus on n-3 PUFAs and cataracts, but the picture remains unclear.

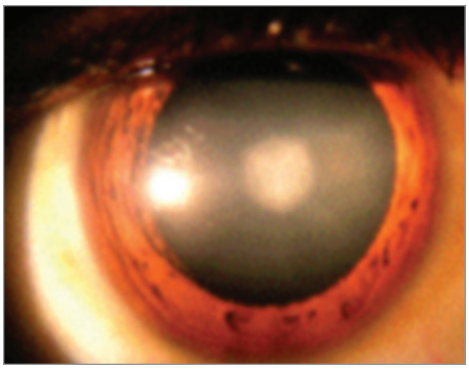

Figure. Human eye showing a cataract in the lens.

A cataract is the clouding of the lens in the eye that occurs most commonly after the age of 60. Cataracts may develop after eye injury and smoking, certain diseases (diabetes) and with some medications (corticosteroids). Untreated, they can lead to blindness, but surgical lens replacement can restore clear eyesight. First symptoms of the condition may appear as blurred or dim vision and increasingly difficult night vision.

Cataracts may affect any of 3 layers in the lens: the nuclear or inner center; the soft middle cortical layer; or the posterior subcapsular, an opaque area just under the outer layer or capsule of the lens.

In the Blue Mountains Eye study from Australia, Bradley Townend and colleagues at the Centre for Vision Research in Sydney surveyed survivors of a cohort of 3,652 residents aged 49 years or older whose visual function was originally assessed in 1992-1994. A 5-year follow-up survey was conducted from 1997 to 1999 among 2,335 of the original participants. Cataract severity of at least 5% cortical opacity was determined from eye examinations and slit-lamp photographs graded by comparison with standard photographs. Food and nutrient intakes were assessed by food frequency questionnaire modified for the Australian diet. There were 1,988 complete dietary questionnaires at baseline. Patients with previous cataract surgery or using glaucoma medications were excluded.

Using baseline photographs, the investigators estimated that 50% of participants were at risk for nuclear cataract, 81% for subcapsular cataract and 72% for the cortical type. The reported incidences of these forms were 285 (29%), 60 (4%) and 175 (12%) participants for each type, respectively.

To determine whether the consumption of different foods and nutrients was associated with the development of the 3 types of cataracts, the researchers calculated odds ratios using logistic regression models adjusted for age, gender, diabetes, corticosteroid use, smoking and other health or descriptive variables, such as myopia and dark brown iris color. Consumption was expressed as quintiles of intake in g/day based on medians.

In the Blue Mountains Eye Study, only higher intakes of protein and total n-3 PUFAs were associated with lower risk of at least one type of cataract over 5 years.

Two significant associations with dietary components were apparent. Greater consumption of protein was associated with significantly lower risk of subcapsular cataracts and higher intakes of total n-3 PUFAs were linked to lower chance of developing nuclear cataracts (Table). Neither total nor n-6 PUFAs were related to cataract risk. The inverse association with total n-3 PUFAs is at odds with a previous report from the Boston Nurses' Study, which noted an increased risk of age-related lens opacity as consumption of linoleic or alpha-linolenic acids increased. However, the likelihood of cataract extraction in the nurses was reduced with higher intakes of n-3 LC-PUFAs.

Unfortunately, the Blue Mountains Study made no distinction between the intakes of n-3 LC-PUFAs and alpha-linolenic acid. As fish and meat contributed about 22%

Table. Multivariate odds ratios (95% confidence intervals) for the associations between quintiles of energy-adjusted intakes of total n-3 and n-6 PUFAs for 5-year cataract.

Nutrient intake	Median intake g/day	Type of cataract Nuclear	Subcapsular	Cortical
n-6 PUFAs				
Q1	4	1.0	1.0	1.0
Q2	6	0.89 (0.55-1.46)	0.65 (0.28-1.49)	1.04 (0.61-1.76)
Q3	7	0.60 (0.36-0.99)	0.28 (0.09-0.86)	1.49 (0.89-2.49)
Q4	9	0.71 (0.43-1.16)	0.85 (0.38-1.89)	0.73 (0.42-1.29)
Q5	12	0.71 (0.43-1.17)	0.70 (0.30-1.62	0.80 (0.46-1.40)
P for trend		0.233	0.230	0.445
n-3 PUFAs				
Q1	0.52	1.0	1.0	1.0
Q2	0.70	0.80 (0.49-1.30)	0.81 (0.36-1.84)	2.45 (1.42-4.22)
Q3	0.85	0.72 (0.43-1.19)	0.95 (0.42-2.14)	1.60 (0.89-2.88)
Q4	1.03	0.59 (0.35-0.98)	0.44 (0.16-1.17)	1.29 (0.71-2.35)
Q5	1.42	0.58 (0.35-0.97)	0.61 (0.25-1.50)	1.48 (0.82-2.67)
P for trend		0.027	0.172	0.889

and 17% of the total n-3 PUFA intake, respectively, the majority of n-3 PUFAs consumed in Australia apparently comes from alpha-linolenic acid. If this fatty acid and n-3 LC-PUFAs have contrasting effects on the risk of cataracts, it would not be detected in this study. Lack of an association between any cataract and fish consumption suggests either that n-3 LC-PUFAs are unrelated to risk of cataracts or that intakes were too low to observe an effect. Bear in mind, too, that the number of cataract patients was relatively small.

In an update from the Boston Nurses' Study, Minyi Lu and colleagues in Boston, USA, reported observations from a 5-year follow-up of 440 women from the original cohort of 603 participants aged 52 to 73 years. The investigators assessed lens status in the women from slit-lamp images of the lens nucleus graded for opacity as a function of a standard gray scale using digital image analysis software. Dietary variables were based on the average of 4 or 5 food frequency questionnaires. Baseline data on summer sun exposure, weight and medical history and other lifestyle variables were used in the data analysis. All statistical analyses were adjusted for multiple variables including age at examination, total energy intake, physical activity, smoking, alcohol consumption, vitamin supplement use and others.

Five-year changes in nuclear density according to quartiles of total or any type of fat or fatty acid intake were significant only for alpha-linolenic acid (*P* for trend = 0.05). n-3 LC-PUFAs and linoleic acid were unrelated to changes in lens density. Women with the highest nuclear density at baseline and the highest consumption of alpha-linolenic acid experienced a 70% greater increase in nuclear density compared with women in the lowest intake category.

These findings do not support the initial observations of these participants in which the risk of cataract extraction was significantly lower with higher consumption of n-3 LC-PUFAs. Higher intakes of linoleic and alpha-linolenic acids had previously been associated with higher risk of cataract extractions in this cohort.

Neither the Blue Mountains Study nor the follow-up nurses' study provide much support for a potential effect of alpha-linolenic acid on the risk of cataract or lens density. In the Blue Mountains Study, higher intake of all n-3 PUFAs was associated with lower risk of nuclear cataracts, but had no effect on posterior subcapsular or cortical cataract. The 5-year follow-up among Boston area nurses confirmed previous observations about alpha-linolenic acid and increased lens opacity, but not about n-3 LC-PUFAs or linoleic acid.

Taken together, these reports are suggestive, but not conclusive. Associations do not mean cause and when they are inconsistent no conclusions can be drawn.

Townend BS, Townend ME, Flood V, Burlutsky G, Rochtchina E, Wang JJ, Mitchell P. Dietary macronutrient intake and five-year incident cataract: the Blue Mountains eye study. Am J. Ophthalmol *2007;143:932-939.*

Lu M, Taylor A, Chylack LT, Rogers G, Hankinson SE, Willett WC, Jacques PF. Dietary linolenic acid intake is positively associated with five-year change in eye lens nuclear density. J Am Coll Nutr *2007;26:133-140.*

CLINICAL CONDITIONS

Depression and Cardiovascular Disease: Linked Through Inflammation?

Cardiovascular disease and depression often go hand in hand, with low n-3 LC-PUFA status common in each condition. In elderly Dutch men without cardiovascular disease, higher n-3 LC-PUFA status was linked to lower chance of depression, but did not affect the risk of cardiovascular mortality.

It is now recognized that cardiovascular patients are at increased risk of depression and vice versa. A depressive state predicts long-term cardiac mortality following a myocardial infarction. Presence of both conditions doubles the chance of subsequent cardiac events. Why these two conditions should accompany each other is uncertain, but plausible hypotheses could account for some of the commonalities. For example, altered autonomic system responses, subclinical inflammation, endothelial dysfunction and enhanced platelet responsiveness are observed in both conditions. Another common characteristic is low status of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). Patients with acute coronary syndrome and depression have, on average, significantly lower levels of docosahexaenoic acid (DHA) and total n-3 PUFAs in their plasma phospholipids compared with patients without depression. Low n-3 LC-PUFA status and enhanced inflammatory responses are also characteristic of depressed patients. Three recent papers have examined the relationships among depression, cardiovascular disease and the immune system from different perspectives.

In the prospective cohort study of elderly men in Zutphen, the Netherlands, Marjolein Kamphuis and colleagues at the University of Utrecht obtained data from 332 participants aged 70 to 90 years who were

free of cardiovascular disease and diabetes. Dietary and self-administered depression assessments were administered at baseline, with mortality data collected 10 years later. Intake of n-3 PUFAs was based on eicosapentaenoic acid (EPA) and DHA, 71% of which came from consuming fish.

At baseline, 22% of the participants had mild to severe depressive symptoms. Men with the highest n-3 LC-PUFA intake had a significantly lower risk of depression compared with men in the lowest tertile of intake in multivariate adjusted analysis (Odds Ratio = 0.46, 95% CI=0.22 to 0.95). After 10 years, 51% of the participants had died, 28% from cardiovascular disease. Cardiovascular mortality was unrelated to n-3 LC-PUFA consumption. These findings suggest that n-3 LC-PUFA consumption, while associated with baseline risk of depression, could not explain the relationship between depression and cardiovascular disease. The authors did not report whether the patients who died were any more likely to have been depressed compared with the survivors.

In the second report, Annique Schins and colleagues at Maastrict University, the Netherlands, compared post-myocardial infarction patients who developed depression with those who did not in terms of their plasma levels of C-reactive protein and the ratio of arachidonic acid (ARA) to EPA. C-reactive protein and other markers of inflammatory responses are increased in patients with cardiovascular disease and in depressed patients, but not in all studies of depression and coronary heart disease. Increased C-reactive protein levels are also predictive of poorer memory in elderly women.

Fifty patients with a myocardial infarction (average age 55 years) were screened for depressive symptoms during hospitalization and 3, 6, 9, and 12 months thereafter. Twenty-one control patients had Beck depression scores of 9 or less and were classified as controls; 21 others scored 10 or higher and were considered depressive. Those considered depressed had significantly higher ratios of ARA to EPA (15.2 in depressed vs 11.2 in control patients, respectively), but did not differ from controls in their C-reactive protein levels. The lack of difference might be attributable to the statins taken by over 93% of patients in each group. What cannot be determined from this study is whether these differences in fatty acids existed prior to myocardial infarction or whether other inflammatory mediators, such as interleukin-6, were different between the two groups. As it is often with ratios, it is unclear whether changes in ratios are due to increases or decreases in the numerator or denominator. Data on individual fatty acid concentrations are needed. However, the study agrees with others that have reported altered n-6 and n-3 PUFA levels in cardiac patients with depression.

Post-myocardial infarction patients with and without depression were assessed for the inflammatory marker C-reactive protein and for the ratio of ARA to EPA in their plasma. Depressed patients had higher ARA to EPA ratios, but the groups did not differ in C-reactive protein. These observations agree with some reports, but not others.

In the third report, Nancy Frasure-Smith and colleagues at McGill University, Montreal, Canada, monitored the health of 741 acute coronary syndrome patients for 2 years after enrolment, paying special attention to the incidence of major adverse cardiac events. Patients were recruited about 2 months after hospital discharge and assessed at enrolment for depression (Beck Depression Inventory scores) and inflammatory markers (C-reactive protein, interleukin-6 and soluble intercellular adhesion molecule-1). Eighty-one percent of the participants were men, who ranged in age from 24 to 90 years (mean=60 years). Beck's Depression Inventory scores of 14 or higher were observed in 27% of the participants, with a higher proportion of cases occurring in the female participants (35% vs 25% of men).

In the 2-year followup period, 102 patients (14%) experienced at least one major cardiac event, including 10 cardiac deaths, 49 survived myocardial infarctions, 1 survived cardiac arrest and 39 revascularizations. The risk of incurring a major cardiac event was positively associated with depression in the whole sample (Hazard Ratio=1.74, 95% CI=1.17-2.59) and in men, but not in women. Diagnosis of unipolar depression was associated with an even greater risk of subsequent major cardiac events (Hazard Ratio=2.38, 95% CI=1.33-4.26). When the association between major events and baseline depression scores was adjusted for multiple confounding variables, the increased risk remained significant.

Patients with depression at enrolment differed significantly from those without it in several characteristics. They were more likely to be sedentary, to smoke, have a previous cardiac history, and higher triglyceride and glucose levels compared with non-depressed patients. The inflammatory markers C-reactive protein and soluble intercellular adhesion molecule-1 values were also higher in the depressed patients. C-reactive protein levels were higher in patients not taking statins.

Only men with lower depression scores and C-reactive protein levels less than 2 mg/L had a comparatively low risk of subsequent cardiac events after acute coronary syndrome. C-reactive protein levels and depression appeared to be related.

In terms of the inflammatory markers, C-reactive protein levels were associated with increased risk of major adverse cardiac events in multiple-adjusted analysis (Hazard Ratio=1.36, 95% CI=1.11-1.66), with the risk increasing for C-reactive protein levels of 2.0 mg/L or higher (Hazard Ratio=1.68, 95% CI=1.04-2.71). The effect of higher C-reactive protein was greatest in depressed patients compared with non-depressed, but the risk was significantly elevated above that observed in patients with the most favorable scores in both C-reactive protein and depression. The significant association with soluble intercellular adhesion molecule-1 observed in unadjusted analysis lost significance when confounders were included.

Depression scores and C-reactive protein levels of 2.0 mg/L or more were inter-related, but the effects of each were not additive in predicting the time until the first major adverse cardiac event. Only men with lower depression scores and C-reactive protein levels below 2.0 mg/L had a comparatively low risk of subsequent cardiac events. These findings suggest that the effect of depression on the increased risk of cardiac events is not mediated through inflammation, but that C-reactive protein levels and depression are related. The effects were most dramatic in men, but the sample included too few women to determine whether these variables would be different in them. The interaction between C-reactive protein and depression has been reported in another study of men without coronary artery disease, in which depression increased the power of C-reactive protein to predict myocardial infarction.

It is tempting to suggest that treatment with n-3 LC-PUFAs might ameliorate both elevated markers of inflammation and depressive symptoms, as would be suggested by their individual effects in these conditions. Such evidence is lacking, although untangling the interactions among the baseline conditions and dietary interventions would be challenging. For the patient, it would be prudent to increase consumption of n-3 LC-PUFAs long before the development of acute cardiac conditions.

Kamphuis MH, Geerlings MI, Tijhuis MAR, Kalmijn S, Grobbee DE, Kromhout D. Depression and cardiovascular mortality: a role for n–3 fatty acids? Am J Clin Nutr *2006;84:1513-1517.*

Schins A, Crijns HJ, Brummer R-Jm, Wichers M, Lousberg R, Celis S, Honig A. Altered omega-3 polyunsaturated fatty acid status in depressed post-myocardial infarction patients. Acta Psychiatr Scand *2007;115:35-40.*

Frasure-Smith N, Lesperance F, Irwin MR, Sauve C, Lesperance J, Theroux P. Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. Biol Psychiatry *2007;62:302-308.*