PUFA NEWSLETTER

Volume 12 • Issue 1

March 2007 Contents

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

Long-Term Benefits from Higher Maternal Intake of Marine Omega-3s

Recent evidence about the effects of long-chain omega-3 polyunsaturated fatty acids (marine omega-3s) in young children and people with certain cancers adds useful information to the limited evidence previously available in these areas. Overall, they point to suboptimal health outcomes at different stages of life when marine omega-3s are insufficient.

Many studies have documented improved visual function in infancy associated with the consumption of marine omega-3s in pregnancy and infancy, but evidence of more long-lasting effects has been scarce. In this issue of the *PUFA Newsletter*, results from 4 studies suggest that seafood consumption or intake of n-3 LC-PUFAs during pregnancy is beneficially associated with several neurodevelopmental outcomes in children. Associations with higher marine omega-3 or docosahexaenoic acid status included enhanced eye and hand coordination at 3 years, better social development and improved visual acuity at age 4, higher verbal IQ and lower likelihood of internalized problem behavior at 7 years of age. Differences may sometimes be small and subtle, but they strengthen the evidence suggesting that higher exposure to marine omega-3s during fetal and infant life could have positive long-term advantages.

Links between marine omega-3s and risk of various cancers have been reported for several cancers, including colorectal, prostate, renal cell carcinoma and non-Hodgkin's lymphoma, but data are inconclusive. Associations have not been established for cancers of the breast, pancreas, ovary and bladder, except in some populations with habitually high fish intakes. A systematic review published last year in the *Journal of the American Medical Association* concluded that a "large body of literature . . . does not provide evidence to suggest a significant association between omega-3 fatty acids and cancer incidence." However, 2 new studies in patients with prostate cancer provide more evidence of the involvement of polyunsaturated fatty acids (PUFAs) in this disease. In one study, fish consumption was associated with significantly lower risk of the disease, and in another, higher total PUFAs and monounsaturates were linked with lower risk of disease recurrence. In a third study, high consumption of fatty fish and marine omega-3s was linked to a 40% to 50% lower chance of developing non-Hodgkin's lymphoma. These findings illustrate why investigations into the function of various PUFAs in different cancers will continue.

The newsletter also reports strong findings that topical application of resolvin E1 inhibits bone destruction in periodontitis, even though the bacteria contributing to the disease flourish. Resolvin E1 is synthesized from eicosapentaenoic acid and is a key mediator halting inflammation.

Evidence continues to accumulate describing the benefits of marine omega-3s in different aspects of cardiovascular disease, including the progression of atherosclerosis and cardiovascular homeostasis in heart failure.

We appreciate readers' comments.

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

CARDIOVASCULAR HEALTH

Long-Chain Omega-3s Enhance Cardiovascular Homeostasis in Heart Failure

Long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) contribute to reduced risk of cardiovascular mortality, especially in secondary prevention. Various mechanisms are implicated, including anti-arrhythmic, anti-thrombotic and anti-inflammatory effects; reduced circulating triglycerides; improved heart rate and heart rate variability; and others. Impaired cardiovascular reflex mechanisms–principally baroreceptor control of blood pressure–also contribute to increased cardiovascular mortality in heart failure. Little is known whether baroreceptor reflexes are sensitive to dietary PUFAs in cardiovascular disease. In one report, baroreceptor sensitivity and heart rate variability were unaffected by the consumption of 3.5 g/day of fish oil for 12 weeks in healthy people aged 50 to 70 years.

Little is known whether baroreceptor reflexes are sensitive to dietary PUFAs in cardiovascular disease, but improvements in heart rate and heart rate variability with n-3 LC-PUFAs would be consistent with improved baroreceptor sensitivity.

Others have reported reduced heart rate and increased heart rate variability in response to n-3 LC-PUFAs that would be consistent with improved baroreceptor sensitivity. In this study, Alberto Radaelli and colleagues at the University of Milano-Bicocca, Milan, Italy, evaluated the baroreflex responses in 25 patients (24 men) with chronic post-myocardial infarction heart failure (ejection fraction <40%), who were clinically stable with optimized drug treatment that included beta-blockers, angiotensin-converting enzyme inhibitors and diuretics. Twenty-three of the 25 patients also received statin medications. To exclude hemodynamic instability, patients underwent a clinical evaluation, electrocardiogram, assessment of heart failure functional class, exercise test and complete echocardiographic evaluation. The patients' average age was 60 years.

Patients were randomized to receive 2 g/day PUFAs containing no less than 85% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or a placebo control for 4 months. Patients were not blinded or informed of the treatment they received. Patients were evaluated for arterial baroreflex and cardiovascular variability before randomization and during the final week of treatment. All measurements were taken with the patient resting supine and 3 to 5 minutes rest after each stimulus period. Coffee and tea were excluded for 24 hours before measurements. During baroreflex testing, finger pulse blood pressure, electrocardiogram and ventilatory activity were measured.

Baroreflex testing consisted of neck suction stimulus applied by a pneumatic chamber around the individual's neck, with a user-controlled adaptor to obtain the desired suction. Test periods consisted of alternate periods of rest and suction at 1 of 2 levels (-20 and -40 mm Hg), each preceded by a pre-determined pre-stimulus period using the tested pressure. Test periods were administered in random sequence. Systolic, diastolic and mean arterial blood pressure was derived beat by beat from the recorded blood pressure and electrocardiogram recordings.

Peak bradycardic and depressor responses observed within 15 seconds of neck suction were calculated by averaging the 2 consecutive beats showing the greatest and smallest R-R interval (two consecutive R waves on the electrocardiogram) and mean arterial pressure, respectively. Peak reflex responses to different neck pressures were analyzed by regression analysis.

After 4 months of n-3 LC-PUFA or placebo consumption, left ventricular function, heart failure classification, body weight and blood pressure were unaffected by treatment. R-R interval increased in the n-3 LC-PUFA group, but the change did not reach statistical significance. However, the variability in the R-R interval (heart rate variability) was markedly and significantly increased with n-3 LC-PUFA consumption, but not with placebo (Figure).

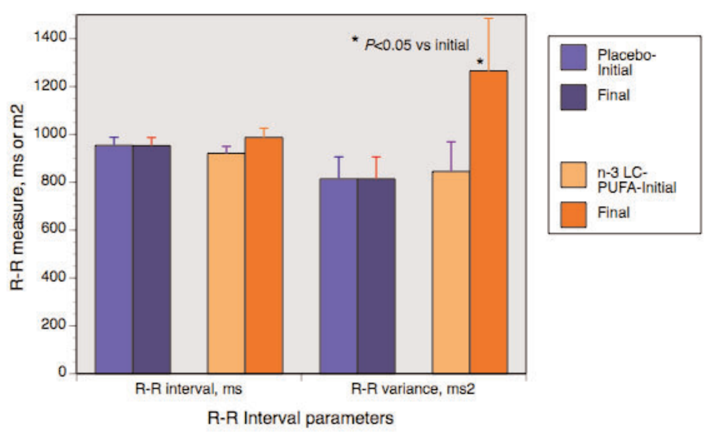

Figure. Electrocardiogram R-R interval and variance in heart failure patients consuming n-3 PUFAs or placebo for 4 months

Changes in heart rate variability were observed on the electrocardiograms and analyzed by regression of the R-R interval versus changes in baroreceptor stimulation (negative neck suction pressure) for both groups. There were no observed changes in either electrocardiograms or regression slopes in the placebo group. In the n-3 LC-PUFA patients, regression slopes for heart rate variability were significantly increased (1.25 before vs 1.75 after 4 months, $P<0.01$). Similarly, mean arterial pressure regression slopes decreased significantly in the n-3 LC-PUFA patients (-0.09 before vs -0.16 after, $P<0.01$), but were unchanged in the placebo group.

Consumption of 2 g/day n-3 LC-PUFAs for 4 months in patients with chronic heart failure significantly improved heart rate, heart rate variability and peripheral vasculature.

This study demonstrated significant improvements in baroreceptor regulation of heart function with the consumption of 2 g/day n-3 LC-PUFA for 4 months in patients with chronic heart failure. Baroreceptor control of heart rate, heart rate variability and peripheral vasculature were significantly improved. The slopes of the regression responses of heart rate variability and mean arterial blood pressure were, according to the investigators, "only slightly less steep in the n-3 LC-PUFA-treated heart failure patients compared with age-matched healthy patients," as had been reported in a previous study.

The investigators commented that these substantial improvements with n-3 LC-PUFA treatment occurred in addition to concurrent medications known to affect the vagal and sympathetic systems involved in baroreceptor regulation. Improved cardiovascular homeostasis would be expected to facilitate a patient's adjustment to exercise, digestion and other life activities, as well as patient prognosis. Nevertheless, the authors noted that despite the beneficial changes in neurophysiological factors, there were no detectable changes in the severity of the heart failure itself. Whether the effects of n-3 LC-PUFAs would translate into long-term clinical improvements remains to be evaluated.

Radaelli A, Cazzaniga M, Viola A, Balestri G, Janetti MB, Signorini MG, Castiglioni P, Azzellino A, Mancia G, Ferrari AU. Enhanced baroreceptor control of the cardiovascular system by polyunsaturated fatty acids in heart failure patients. J Am Coll Cardiol *2006;48:1600-1606.*

Dietary Counseling and Fish Oil Modestly Affect Atherosclerosis Severity in Older Men

It is encouraging that positive lifestyle changes (diet, exercise, fish consumption) can improve the course of cardiovascular disease, as most people in rich countries already have some atherosclerosis in childhood. Measures of atherosclerosis progress are not usually made until later in life, when risk becomes dangerous.

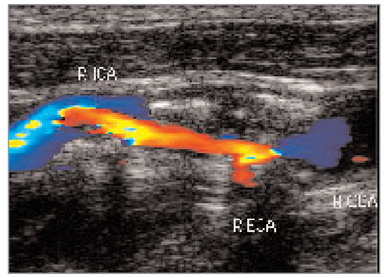

Figure 1. Ultrasound image of carotid plaque (red) and narrow artery. *Image courtesy of Tristram Clinic, Hamilton, NZ.*

One of the ways to determine whether treatment interventions in cardiovascular disease slow disease progression is to measure the changes in arterial plaque in an accessible artery. This can be done without invading the artery itself by using ultrasound imaging (Figure 1). This technology captures images of plaque that can be measured and replicated. The carotid artery is often used for this purpose because it is close to the surface.

Atherosclerosis includes more than growth of deleterious plaque. Blood vessels change, losing elasticity and functionality. Stiffness of the artery can be measured using pulse wave velocity. This technique provides an index of blood vessel distention with each heart beat and the tension in the vessel walls, based on the physics of blood flow following a heart contraction. Pulse wave velocity is calculated according to the time for a pulse to travel from the heart to the site of pulse detection, such as a finger.

Ultrasound imaging and pulse wave propagation time were used to assess the progress of atherosclerosis in 70-year-old men at high risk of cardiovascular disease. Men with or without dietary counseling consumed n-3 LC-PUFAs or placebo for 3 years.

Dr. Elsa Hjerkinn and colleagues at the Ullevaal University Hospital, Oslo, Norway, used these techniques to assess the progress of atherosclerosis in men at high risk of cardiovascular disease, who had participated in the Oslo diet and smoking study, begun in 1972. This study was conducted among 910 survivors of the original study, who participated in a 3-year study of the effects of dietary counseling, with or without long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) supplementation. Of the 655 participants screened for eligibility, 563 men, aged 65 to 75 years (mean 70 years), participated in the study.

Participants were randomly assigned to 1 of 4 groups receiving either placebo or n-3 LC-PUFA capsules: 1) placebo capsules (corn oil), without dietary counseling; 2) placebo capsules plus individualized dietary counseling to limit fat intake to 30% of total energy, dietary cholesterol to no more than 300 mg/day and to substitute mono- and polyunsaturated fatty acids for saturated ones; 3) 2.4 g/day n-3 LC-PUFAs without dietary counseling; and 4) dietary counseling and 2.4 g/day n-3 LC-PUFAs. All participants given dietary counseling were provided with vegetable oils and soft margarines containing, respectively: 62% and 36% oleic acid, 20% and 38% linoleic acid and 9% and 5% alpha-linolenic acid. Dietary counseling was given at the time of randomization and after 3 months. Thereafter, participants visited or contacted a nutritionist every 6 months, with additional follow-up provided to participants with poor adherence. A food frequency questionnaire was given at baseline and at the final visit of all participants after 36 months.

Fasting blood samples were collected at baseline and at 36 months. Measurements of carotid intima media thickness (CIMT) and plaque were obtained by ultrasound from the position of the thickest part of the far wall of the common carotid and analyzed blindly. CIMT measures the thickness of the intima and media, the two inner layers of the vessel wall. The mean CIMT in a 10 mm long segment in the common carotid artery was used for statistical analysis. CIMT is a strong predictor of future vascular events and risk assumptions based on CIMT measurements of single carotid artery segments are affected by factors such as blood glucose, history of diabetes, smoking and others.

Pulse wave propagation to assess arterial elasticity was measured in the left third finger in fasting participants, using the time from the beginning of the QRS complex in the electrocardiogram to digital pulse initiation in the finger. The shorter the pulse wave propagation time, the stiffer the blood vessels. Investigators used the mean of 3 pulse wave registrations obtained at baseline and after 36 months.

At the end of 3 years, 487 participants (86%) remained in the study. There were 38 deaths and 37 people not available for follow-up. Regardless of dietary counseling, participants experienced a statistically significant decrease in energy and fat intake. However, total n-3 PUFA intake fell significantly in those without counseling, but remained unchanged in those with dietary guidance. Dietary counseling was associated with a significantly greater reduction in saturated fat consumption compared with participants not receiving counseling, but intake fell significantly in both groups compared with baseline values.

As expected, the two groups consuming n-3 LC-PUFAs had increases in all serum n-3 LC-PUFAs, whereas those in the control and placebo groups did not. Triglycerides decreased significantly within each of the four groups. High-density lipoprotein cholesterol increased significantly from baseline within both n-3 LC-PUFA and placebo groups, but the increase was only significantly different from the control group in participants receiving both n-3 LC-PUFAs and counseling.

With regard to CIMT, all groups exhibited increased thickening, with the placebo participants who received dietary counseling having a significantly smaller increase compared with the control group. The consumption of n-3 LC-PUFAs had no significant effect on reducing CIMT. The score for arterial plaque increased significantly in all groups, with no differences between groups.

Pulse wave propagation time decreased significantly in the control group, suggesting reduced arterial elasticity. Pulse wave propagation time did not change significantly from baseline in any of the n-3 LC-PUFA treatment groups or the placebo group receiving dietary counseling. However, in the absence of dietary counseling, the pulse wave propagation time in the n-3 LC-PUFA group barely changed (0.36 ± 21 ms) compared with a decreased propagation time (reflecting greater arterial stiffness) in the placebo control group (-7.83 ± 21 ms). This observation suggests that n-3 LC-PUFAs help slow the decline in arterial elasticity.

Univariate and multivariate analyses adjusted for age and diastolic blood pressure both revealed significant inverse associations between changes in CIMT and increases in HDL-cholesterol and between changes in pulse wave propagation time and serum EPA concentrations.

This study examined the effects of two main interventions on the progress of atherosclerosis, dietary counseling and n-3 LC-PUFA supplementation in a population of older men. Dietary counseling by itself had a significant and positive effect on reducing the increase in CIMT in the placebo group, but not in the n-3 LC-PUFA group. It had no significant additive effect on pulse wave propagation time in either placebo or n-3 LC-PUFA groups. The authors suggested that counseling was likely beneficial in reducing total energy, fat and saturated fat consumption and in increasing the intake of other healthful foods, such as fruits and vegetables and fiber-rich bread. Some of these changes were statistically significant (e.g., reduced saturated fat intake).

Consumption of n-3 LC-PUFAs was more effective than placebo in s lowing the decrease in pulse wave propagation, and hence, in retarding arterial stiffness, but the effect was significant only in the group with n-3 LC-PUFAs without dietary counseling. Unexpectedly, these findings were not associated with the observations on CIMT. More than half the participants (55%) had previously consumed n-3 LC-PUFA supplements, which they discontinued at least 1 month prior to enrolment. One month may have been insufficient to provide washout of n-3 LC-PUFAs from arterial vessels. It is possible, if not likely, that long-term consumption of n-3 LC-PUFAs in this population would have already had some benefit in slowing atherosclerosis in these 70-year-old men. In a different study of the progression of coronary artery disease over 3 years in 65-year old women, which measured more segments (9 vs 1) in different blood vessels (epicardial vs carotid) by coronary angiography, higher concentrations of plasma phospholipid DHA were associated with significantly reduced disease progression.

Modest as these outcomes may be, they demonstrated that it really is never too late to improve one's dietary habits and that supplementary n-3 LC-PUFAs may modestly slow the deterioration in blood vessel characteristics and function.

Hjerkinn EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen I, Seljeflot I, Aase O, Klemsdal OT, Hjermann I, Arensen H. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. Eur J Cardiovasc Prev Rehabil *2006:13:325-333.*

MATERNAL & INFANT HEALTH

Greater Seafood Intake in Pregnancy Associated with Better Neurodevelopmental Outcomes in Offspring

Findings from a long-term study of environmental factors and health outcomes in infants and children in the United Kingdom challenge the assumptions of US government advice for pregnant women to "eat up to 12 ounces a week of a variety of fish and shellfish," which implies a limit on their consumption of seafood. Women in the U.S. currently eat less than 3 ounces/wk.

In the UK study, children of mothers who consumed more than 12 ounces (340 g) of seafood/wk scored significantly higher on tests of verbal IQ, social behavior, development and communication compared with children whose mothers ate no seafood. After adjustment for 28 potentially confounding social and dietary factors, the positive association with seafood consumption remained. The authors further noted that the British population has a higher average mercury consumption than the US population, suggesting that mercury in seafood, as commonly consumed in the U.K., poses no measurable risk to the development of children whose mothers consumed more than 340 g (12 ounces) of seafood per week during pregnancy.

Fear of the potential danger of mercury in fish has led to consumer scares and government advisories recommending that pregnant women and young children consume no more than 12 ounces (340 g) of seafood per week.

The consumption of seafood, especially fatty fish, during pregnancy has several unique nutritional advantages. These include long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) necessary for optimum fetal neurodevelopment and selenium, a mineral that offsets–at least partially–the potentially toxic effects of methylmercury. Some fatty species are also rich in vitamin D. In the U.S., fear of the potential danger of mercury in fish has led to consumer scares and government advisories recommending that pregnant women and young children eat up to 12 ounces (340 g) of seafood per week. Some pregnant women viewed these advisories as warnings and reduced their fish consumption. There is concern that reduced fish consumption in populations with low intakes, such as the U.S., might increase health risks in the offspring from inadequate maternal intake of n-3 LC-PUFAs.

Whether the fish intakes recommended by US and Canadian government agencies for pregnant and nursing women meet fetal developmental needs has not been evaluated. This question is being addressed in the Avon Longitudinal Study of Parents and Children (ALSPAC), a long-term examination of various environmental factors during and after pregnancy on health outcomes in the offspring. To assess the effect of government-recommended fish consumption, Dr. Joseph Hibbeln of the U.S. National Institutes of Health and colleagues at the University of Bristol, U.K., examined selected neurodevelopmental outcomes in the children of women enrolled in the ALSPAC study in relation to maternal fish intake during pregnancy.

From the original cohort of 14,541 pregnant women, 8,801 mothers provided demographic, social and dietary data for themselves and developmental data for their children. Seafood consumption was assessed in terms of frequency and types of fish consumed, i.e., white fish, oily fish and shellfish. Consumption of total n-3 LC-PUFAs was determined from the amount and species of fish consumed. Five frequency response categories were available, ranging from never or rarely to more than once a day. For statistical analysis, frequency of eating seafood was divided into 3 groups: none, 1 to 340 g (12 ounces)/week, and more than 340 g/week.

The children's gross and fine motor skills, communication and social skills were measured by their parents using a scale developed by the ALSPAC investigators with items from the Denver Developmental Screening Test. Parents assessed their children at ages 6, 18, 30 and 42 months. Mothers completed the behavior assessment questionnaires when their children were 81 months (6.75 years) of age. These questionnaires had 5 subscales: prosocial (i.e., positive social interactions), hyperactivity, emotional symptoms, conduct problems and peer problems, plus a total difficulties score. At 8 years of age, 5,449 children had their Intelligence Quotient (IQ) measured by an abbreviated Wechsler Intelligence Scale for Children III.

Relationships between developmental outcomes and maternal seafood consumption during pregnancy were analyzed using multiple logistic regression analysis. Twenty-eight potentially confounding variables, identified by literature review, were considered in the analysis. These included adverse social and developmental factors (e.g., family adversity index), perinatal variables (e.g., birthweight, gestation at delivery) and categories such as sex of the child, age of the mother, parity, maternal education and 12 food groups previously noted to have a social pattern in this cohort.

Table. Multiply adjusted odds ratios for suboptimum development in children in relation to maternal seafood consumption during pregnancy in the ALSPAC longitudinal study

OUTCOME	AGE	COMPARISONS AMONG SEAFOOD INTAKES, G/WK				TREND	
		None vs >340		1-340 vs >340			
		OR*	95% CI	OR*	95% CI	*P*	n
COGNITION							
Verbal IQ	8 yr	1.48	1.16-1.90	1.09	0.92-1.29	0.004	5407
Performance IQ	8 yr	0.98	0.76-1.27	0.99	0.84-1.18	0.902	5042
Full scale IQ	8 yr	1.29	0.99-1.69	1.19	0.99-1.42	0.039	5000
BEHAVIOR							
Prosocial	7 yr	1.44	1.05-1.97	1.16	0.93-1.44	0.025	6582
Hyperactivity	7 yr	1.13	0.84-1.53	0.91	0.73-1.12	0.629	6575
Emotional	7 yr	1.09	0.83-1.44	0.96	0.80-1.17	0.681	6582
Conduct	7 yr	1.21	0.89-1.64	1.01	0.81-1.25	0.287	6586
Peer problems	7 yr	1.25	0.96-1.62	0.97	0.80-1.16	0.175	6581
Total score	7 yr	1.17	0.86-1.60	0.98	0.79-1.22	0.383	6570
CHILD DEVELOPMENT							
Gross motor skills	06 mo	1.10	0.90-1.34	1.06	0.92-1.21	0.326	8764
	18 mo	1.02	0.85-1.22	1.01	0.89-1.13	0.842	8227
	42 mo	0.96	0.78-1.18	0.99	0.87-1.13	0.716	7603
Fine motor skills	06 mo	1.01	0.83-1.23	1.12	0.99-1.28	0.519	8746
	18 mo	1.25	1.04-1.51	1.09	0.96-1.23	0.022	8228
	42 mo	1.35	1.09-1.66	1.14	0.98-1.31	0.005	7596
Social development	06 mo	1.15	0.95-1.40	1.01	0.89-1.16	0.217	8743
	18 mo	1.01	0.83-1.24	1.01	0.88-1.15	0.894	8226
	42 mo	1.21	0.98-1.50	1.17	0.01-1.35	0.038	7592
Communication	06 mo	1.30	1.04-1.63	1.15	0.98-1.35	0.018	8745
	18 mo	1.26	1.03-1.53	1.02	0.90-1.17	0.048	8237

*OR=Odds Ratio determined by logistic regression analyses adjusted for 28 variables

Analysis of the children's development at 42 months, 7 and 8 years of age revealed significantly more suboptimal scores for IQ, positive social behavior and fine motor skills in children whose mothers did not eat fish compared with children whose mothers consumed more than 340 g (12 ounces) of fish/week (Table). Children of mothers who consumed between 1 and 340 g fish/week, had developmental risks intermediate between children whose mothers did not eat any fish and those whose mothers ate more than 340 g/week. However, there was no trend toward benefit in any developmental outcome with seafood consumption less than 340 g/week. Most developmental differences did not appear before 42 months.

When the fish consumption data were expressed as the percent of energy from n-3 LC-PUFAs, greater maternal intake was associated in a curvilinear way with lower chance of suboptimal verbal IQ at 8 years of age. Similar relationships were observed for other developmental outcomes, but the data were not presented.

Mothers in the ALSPAC study consumed an average of 235 g of seafood/week or about 34 g/day (equivalent to 1.2 ounces). Seafood consumption by US women aged 15 to 44 years averages a third of that at 11.3 g/day (less than half an ounce/day or 2.8 ounces/wk). British women's intake of methylmercury from seafood is correspondingly higher, 0.05 µg/kg bodyweight, than in US women (0.02 µg/kg bodyweight). In spite of these differences, children of mothers consuming the highest amounts of seafood, more than 340 g/week, had higher neurological function than children whose mothers ate little or no seafood. For example, the odds for suboptimal verbal IQ in children whose mothers did not eat seafood were 50% greater (OR = 1.48, CI 1.16-1.90) than for children whose mothers consumed more than 340 g/week.

Mothers who heed US, Canadian and Australian advice to limit seafood consumption during pregnancy do not protect their children from adverse neurodevelopmental outcomes, and may increase their likelihood of suboptimal neurodevelopment instead.

From the perspective of current US, Canadian and Australian advice to limit seafood consumption during pregnancy, these findings suggest that mothers who heed the advice and consume less than 340 g seafood/week do not protect their children from adverse neurodevelopmental outcomes, and may increase their likelihood of suboptimal neurodevelopment instead. It is doubtful that women of child-bearing age would knowingly choose this option.

In their accompanying editorial, Drs. Myers and Davidson, leaders of the longitudinal study of maternal fish consumption and childhood neurodevelopmental outcomes in the Seychelles Islands, point out that "there has never been even one child with prenatal mercury poisoning from consuming fish," outside of Japan, where there was massive industrial pollution of Minamata Bay in the 1950s and 1960s. Populations with fish consumption 10 times that in the U.S. exhibit no clinical signs of toxicity or impaired function. It is time North American women learned that seafood contains several nutrients critical to optimum fetal brain development and that consuming too little fish could put their offspring at neurodevelopmental risk. Following FDA's advice to eat up to 12 ounces/wk of fish low in mercury would be a step in the right direction. Be brainy: avoid highly contaminated fish species, of which there are few, but feast on the others, if only for the baby's brain.

Hibbeln JR, Davis, JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet *2007;369:578-585.*

Myers GJ, Davidson PW. Maternal fish consumption benefits children's development. Editorial. Lancet *2007;369:537-538.*

Fish Oil in Pregnancy Linked to Enhanced Toddler Eye and Hand Coordination

The high concentration of docosahexaenoic acid (DHA) a long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) in the brain and its involvement in neurotransmission, visual acuity and cognitive development in the infant have focused attention on the nutritional adequacy of maternal and infant diets as a source of this fatty acid. In the fetal period, DHA is furnished from the mother's diet and stores. Western diets are often low in fish, so pregnant and nursing women may have insufficient intake of n-3 LC-PUFAs to meet their own needs and those of their infants. After birth, the infant obtains n-3 LC-PUFAs from breast milk or DHA-supplemented infant formula. Term infants have some LC-PUFAs available from their body fat stores.

Several studies have reported improved scores for visual acuity and various neurodevelopmental outcomes in DHA-supplemented term infants, but there are few reports of long-term benefits from n-3 LC-PUFA supplementation during pregnancy or early infancy. Thus, questions of long-term and transient benefits remain.

Supplementation with n-3 LC-PUFAs typically reduces the content of the n-6 LC-PUFA arachidonic acid (ARA) in cell membranes. To ensure that DHA supplementation would have no adverse effect on ARA metabolism, infant formula is often supplemented with both DHA and ARA.

Dunstan and colleagues examined the effects on toddler development of taking large amounts of fish oil in pregnancy.

Dr. Jan Dunstan and colleagues at the University of Western Australia in Perth investigated the long-term effects of maternal consumption of 4 g/day of fish oil or olive oil during pregnancy from the 20th week of gestation until delivery. The fish oil capsules provided 1.1 and 2.2 g/day of eicosapentaenoic acid (EPA) and DHA, respectively. This level of n-3 LC-PUFA consumption would be about 3 times the amount in a single serving of salmon.

Eighty-three of 98 participating mothers completed the study and 72 healthy children, born after at least 36 weeks' gestation, were available for assessment at 2½ years of age. Outcome measures included mental development (Griffiths Mental Development Scales), receptive language (Peabody Picture Vocabulary Test) and behavior (Child Behavior Checklist). The Griffiths test includes 6 individual subscales and a quotient of the mean subscale measurements. The Peabody test evaluates listening comprehension of standard English vocabulary. The Child Behavior Checklist measures parental perception of the child's competencies and behaviors. The investigators measured phospholipid fatty acids in the red blood cells of cord blood of infants who completed the cognitive assessments. Mothers consuming fish oil were similar to those taking olive oil, except they were slightly younger (30.9 vs 32.6 years, P= 0.05).

Children from both groups of mothers did not differ in height, weight or head circumference. As expected, red cell phospholipid fatty acids in the fish oil group had increased n-3 LC-PUFA and reduced ARA concentrations compared with the controls (Table 1).

Table 1. Red cell fatty acids in cord blodd from neonates whose mothers consumed fish or olive oil from 20 wk gestation until delivery

Fatty acid	Fish oil	Control	P
20:4 n-6, ARA	14.9 ± 1.4	17.6 ± 1.0	<0.001
20.5 n-5, EPA	1.3 ± 0.5	0.4 ± 0.3	<0.001
22.5 n-3, DPA	6.3 ± 0.8	6.0 ± 0.5	0.037
22.6 n-3, DHA	10.3 ± 1.1	7.4 ± 0.9	<0.001

Scores from the Griffiths Mental Development assessment revealed no differences in the overall scores between the fish oil and control groups, nor in 5 of the 6 subscales (Table 2). However, scores for eye and hand coordination were significantly higher in the children of fish oil mothers compared with controls (114.0 ± 10.2 vs. 108.0 ± 11.3, P=0.02). When the scores were compared taking into consideration potentially confounding variables, this difference remained statistically significant. Scores from the Peabody test for language and the behavior checklist indicated no significant differences between the two groups.

Table 2. Mean subscale scores on the Griffiths Mental Development Scales in children aged 34 months whose mothers consumed fish or olive oil from 20 weeks gestation until delivery

Griffiths Mental Dev't Subscales	Fish oil	Control	P
General score	114.2 ± 9.8	110.5 ± 10.6	0.13
Locomotor	112.5 ± 12.2	107.9 ± 12.6	0.13
Personal social	112.4 ± 11.9	109.4 ± 11.5	0.28
Speech & hearing	112.0 ± 15.0	109.6 ± 14.9	0.50
Eye & hand coordination	114.0 ± 10.2	108.0 ± 11.3	0.02
Performance	120.9 ± 12.7	115.8 ± 13.7	0.11
Practical reasoning	114.3 ± 14.5	113.6 ± 15.0	0.84

The authors examined the relationship between individual red cell fatty acids in cord blood and cognitive outcomes for the whole sample. They observed a significant relationship between EPA, DHA and the ratio of n-3 to n-6 PUFAs and eye and hand coordination (P=0.01). There was a significant inverse relationship with ARA at age 34 months. The correlations were independent of potentially confounding factors, such as maternal education and duration of breastfeeding.

Of the 72 children in this study, 91% from the fish oil group and 95% from the control mothers were breast fed for an average of 8.8 and 7.5 months, respectively. These differences were not statistically significant. The enhanced eye and hand coordination of children of fish oil-fed mothers was positively associated with cord red blood cell EPA and DHA concentrations. No other cognitive scores were significantly associated with red cell fatty acids. Improved eye and hand coordination would be consistent with improved visual function in infants fed n-3 LC-PUFA-supplemented infant formula and increased mental processing in children whose mothers consumed DHA during pregnancy as reported by others.

Two comments are pertinent. One is the relatively high dose: 4 g/day total n-3 LC-PUFAs. Other studies using smaller amounts of n-3 LC-PUFAs have reported positive outcomes associated with the consumption of these fatty acids, suggesting that these findings may not have depended on the high dose. The other comment is that Griffiths mental development scores in all tests for the children whose mothers consumed fish oil were consistently, but not statistically significantly, higher than in control children (Table 2). A larger sample might have provided the statistical power needed to determine whether n-3 LC-PUFAs consumed during pregnancy would have affected other developmental outcomes. The authors also noted that the relatively high dose was not associated with any adverse effects or interference with n-3 PUFA metabolism. These findings are good news for those worried about consuming too much of a good thing.

Dunstan JA, Simmer K, Dixon G, Prescott SL. Cognitive assessment at age 2½ years after maternal fish oil supplementation in pregnancy: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed *2006; doi: 10.1136/adc.2006.099085*

Low DHA Status at Birth May Affect Some Problem Behavior in Childhood

The high concentration of long-chain polyunsaturated fatty acids (LC-PUFAs) in the brain, their involvement in neurotransmission and cell signaling, and their rapid accumulation in fetal brain during the last trimester of pregnancy underscore their potential importance in brain growth and function. Nevertheless, studies designed to evaluate the relationships between LC-PUFA status in the mother or infant and neurodevelopmental outcomes have produced mixed results. Composite assessments have generally concluded that better or higher LC-PUFA status, especially for omega-3 (n-3) LC-PUFAs, is associated with more favorable outcomes. Cognitive effects observed in the early months of life have been sustained at 4 years of age in some studies, but not in others. The fact that infants fed formula without LC-PUFAs have less DHA in their brains than breast-fed infants suggests the importance of maternal LC-PUFA status during pregnancy for adequate transfer to the fetus, and the value of LC-PUFAs from breast milk or LC-PUFA-supplemented formula after birth.

Cognitive effects related to LC-PUFA status observed in the early months of life have been sustained at 4 years of age in some studies, but not in others. However, some differences in development may be consistent or long-lasting.

Some of the reasons for inconsistent and transient findings relate to differences in study populations, dose of LC-PUFAs, confounding factors, sensitivity of assessment measures, and healthy changes in neurodevelopment with time. Thus, not all outcomes that differ in the first few months of life would be expected to persist for several years. Some differences in development may be consistent or long-lasting, if they can be appropriately assessed over time. For example, motor coordination disorders, learning skills, aggressive or hostile behavior and depression have all been reported in young children and linked to LC-PUFA status. Many persist into adulthood. Children with developmental coordination disorder, who had difficulties in learning, behavior and psychosocial adjustment, showed improvements in some behaviors with LC-PUFA supplementation for 3 months.

The study reported a significant negative association between scores for internalized problem behavior, e.g., withdrawal, anxiety, in 7-year-olds and DHA concentrations in cord blood at birth.

In this report from the Maastricht Essential Fatty Acid Birth cohort in the Netherlands, Dr. Lydia Krabbendam and colleagues observed a relationship between low docosahexaenoic acid (DHA) status at birth and certain problem behaviors in 7-year-old children. Of the original cohort of 750 children, 393 parent-rated behavior assessments were obtained and 292 children gave blood samples for plasma fatty acid analysis. The children's mean age was 7.0 years and 54.5% (214) were boys. Behavior was assessed using the Dutch version of the Child Behavior Checklist. This instrument provides a score for internalizing behavior, such as anxious/depressed, withdrawn/depressed and externalizing behavior, which includes aggression and breaking the rules. Fatty acids had been determined in umbilical venous plasma phospholipids. The investigators noted whether the infants received human milk or unsupplemented infant formula after birth.

The study reported a significant negative association between the overall scores for internalizing problem behavior at age 7 years and the DHA concentration in cord plasma phospholipids at birth. The interaction between type of feeding after birth and DHA concentration was statistically significant for infants fed infant formula, but not for breast-fed infants. When the authors analyzed the behavior scores according to whether the cord plasma phospholipid DHA concentration was above or below the median, they found higher scores, i.e., more problematic behavior, in children fed infant formula and lower scores in children whose DHA concentrations were above the median (6.4 ± 6.0

vs 5.2 ± 4.7), suggesting an adverse effect on behavior of lower DHA concentrations at birth. Adjustment of DHA values for current DHA at age 7, sex, birth weight, maternal smoking and drinking during pregnancy, parental education and parenting skills increased the strength of the association with DHA in the total group and those who had consumed infant formula.

There were no significant associations with externalizing behaviors (e.g., aggression) or between either types of behavior and arachidonic acid concentrations. Thus, less problematic internalized behavior was related to having greater DHA, but was not related to arachidonic acid concentrations. The investigators found no associations with any problematic behaviors and current LC-PUFA concentrations.

Although association studies linking distant outcomes with previous clinical measurements do not show causation, the idea is plausible. Reduced DHA availability at birth and in early infancy have been linked to several behavioral disorders, including depression, in children and adults. Lower brain content and red cell concentrations of DHA were associated with reduced dopamine and serotonin neurotransmission and attention deficit hyperactivity disorder. Treatment of childhood depression with n-3 LC-PUFAs recently gave promising results. This study provides support for the expanding literature suggesting a beneficial effect of n-3 LC-PUFAs on behavior.

Krabbendam L, Bakker E, Hornstra G, van Os J. Relationship between DHA status at birth and child problem behaviour at 7 years of age. Prostaglandins, Leukot Essent Fatty Acids *2006;74:29-34.*

Long-Chain PUFAs in Early Infancy Improve Visual Acuity and IQ at Age 4

One of the earliest and most consistently observed effects of insufficient long-chain polyunsaturated fatty acids (LC-PUFAs) in human infants is suboptimal visual acuity. Compared with infants fed infant formula lacking LC-PUFAs, breast-fed infants and those consuming infant formula supplemented with docosahexaenoic acid (DHA), an omega-3 (n-3) LC-PUFA, and arachidonic acid (ARA), an omega-6 (n-6) LC-PUFA, have improved visual acuity scores up to 4 months of age. These findings are especially true in preterm infants. Eileen Birch and colleagues at the Retina Foundation in Dallas, Texas, USA, have reported differences in visual acuity between supplemented and unsupplemented infants up to 12 months of age, but others have reported no differences beyond 6 or 12 months of age. Differences in methods of measuring visual acuity, levels of LC-PUFA supplementation, duration of supplementation and other study design factors may account for some of these discrepancies. However, it is important to know how persistent the effects of insufficient LC-PUFAs in early infancy may be, even if they are subtle.

Visual acuity develops rapidly in the first 6 months of life and continues gradually thereafter until 4 to 6 years of age. This suggests the possibility that the effects of LC-PUFAs on visual acuity might persist longer than previously observed. A second question relates to the involvement of ARA in retinal function, about which less is known than for DHA. Insufficient DHA is associated with abnormal retinal structure and function. There is some indication that infants supplemented with DHA and not ARA may have suboptimal vocabulary scores at 14 months of age compared with infants receiving both LC-PUFAs, but the effect may be transitory. These two questions along with cognitive development were investigated in a follow-up study of a cohort of 79 healthy term infants randomly assigned to consume exclusively one of the following iron-supplemented infant formulas for 17 weeks: control without added LC-PUFAs, control plus 0.35% DHA (of total fatty acids), or control plus 0.35% DHA and 0.72% ARA. At age 4, there were 52 of the original 79 infants available for evaluation. In addition, 32 of 40 healthy breast-fed infants originally enrolled in the study for comparison purposes were available for follow-up evaluation at 4 years of age.

Visual acuity was assessed in the 4-year-old children using HOTV testing in the Electronic Visual Acuity system developed by Moke and colleagues. In this test, the letters H, O, T and V, framed with crowding bars spaced around the letter, are presented on the electronic display according to a predetermined protocol. Acuity in each eye is evaluated individually. The investigators assessed intelligence (IQ) using the revised Wechsler Preschool and Primary Scale of Intelligence, which has two scales, performance and verbal IQ. Full scale IQ is computed from both the performance and verbal scores standardized for the child's age and time of testing.

Results from the visual acuity testing and IQ assessments are presented in below. Visual acuity in the right eye was significantly poorer in the children fed unsupplemented formula (control) compared with the breast-fed children and those fed DHA-supplemented formula. There were no significant differences in left eye acuity among the groups in spite of a 7-fold difference between the control and breast-fed children.

Table. Visual acuity* and IQ scores at 4 years of age (mean ± SE) in children fed different formulas for the first 17 weeks after birth

Outcome	Treatment			
	Control-no LC-PUFAs n=19	DHA n=16	DHA + ARA n=17	Breast-fed n=32
Acuity, right eye	0.076 ± 0.022†◊	0.023 ± 0.019	0.034 ± 0.017	0.017 ± 0.013
Acuity, left eye	0.052 ± 0.016	0.016 ± 0.018	0.026 ± 0.017	0.007 ± 0.013
Performance IQ	104.2 ± 2.7	108.1 ± 3.8	108.6 ± 3.3	108.4 ± 2.5
Verbal IQ	98.8 ± 2.6†	102.7 ± 4.1†	104.5 ± 2.9	112.6 ± 2.3
Full scale IQ	101.0 ± 2.6	105.9 ± 3.9	107.5 ± 3.1	111.2 ± 2.3

*Log of the minimum angle of resolution in minutes of arc; higher positive values reflect loss of acuity
†Significantly poorer than breast-fed children, ($p<0.03$)
◊Significantly poorer than DHA group, ($p<0.03$)

Full scale and performance IQ did not differ among the groups of children. Verbal IQ, however, was significantly lower in the control (unsupplemented) and DHA-supplemented children compared with the breast-fed children (Table). The authors noted that the prevalence of above average full scale IQ scores in the control group was significantly lower than in the breast-fed group and that neither of the LC-PUFA supplemented groups differed significantly from the breast-fed group. However, the numbers of children in each group was small.

The investigators compared the evaluations of visual acuity assessed with sweep visual evoked potentials when the children were 17 and 52 weeks of age with visual acuity and IQ measurements at age 4. They found no significant associations. This finding was unexpected, as they had previously reported an association between visual acuity at 17 weeks and Bayley mental development scores at 18 months. In contrast with the visual acuity findings, Bayley mental development scores at 18 months were significantly and inversely correlated with HOTV acuity and positively with all three IQ scores at age 4. In other words, higher Bayley scores at 18 months were associated with better visual acuity and higher IQ at age 4. Bayley scores for psychomotor development were not associated with visual acuity or IQ.

Without LC-PUFA supplementation in early infancy, formula-fed children had significantly poorer visual acuity and verbal IQ scores compared with breast-fed children at age 4. This observation suggests that the effects of insufficient DHA+ARA on visual function persist long past infancy. Children supplemented with DHA and ARA for the first 17 weeks of life did not differ significantly from breast-fed children in visual acuity or IQ. For those who received only DHA in early life, verbal IQ was significantly lower than in breast-fed infants, but did not differ from infants provided DHA and ARA. This question warrants additional investigation with a larger sample, as the study was likely underpowered to detect a significant difference between DHA alone or DHA plus ARA. Although breast-feeding is the optimum course for infant feeding, breast-fed children differ from formula fed infants in other ways than milk composition that could affect neurodevelopmental outcomes.

The authors noted that the differences in visual acuity as reflected in the HOTV assessment are subtle, a little less than one line on an eye chart. All scores in this study were in the normal range for 4-year-olds. Likewise, for the mean IQ scores, none of the groups had borderline or intellectually deficient mean scores. Nevertheless, verbal IQ scores were significantly lower in children not provided LC-PUFAs in early infancy. These findings are consistent with the observations from the Avon Longitudinal Study in the U.K., which reported suboptimal verbal IQ scores in children whose mothers ate no seafood during pregnancy.

Birch EE, Garfield S, Castaneda Y, Hughbanks-Wheaton D, Uauy R, Hoffman D. Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. Early Hum Dev *2007; doi:10.1016/j.earlhumdev.2006.11.0003*

MENTAL HEALTH

Omega-3 PUFAs Improve Outlook in Patients Who Intentionally Harm Themselves

Low red blood cell or plasma concentrations of long-chain polyunsaturated fatty acids (LC-PUFAs) are characteristic of several mental pathologies. Both the omega-6 (n-6) and omega-3 (n-3) families are affected, *Patients who harm themselves are at high risk of suicide and have higher scores on depression and impulsivity assessments than controls. They also have lower cholesterol, n-6 and n-3 PUFAs compared with controls without psychosocial symptoms.*

but n-3 LC-PUFAs may be more so. These fatty acid abnormalities have been documented in patients with depression, bipolar disorder, alcoholism, violent and addictive disorders and suicidal tendencies. Worldwide prevalence of several of these disorders has been associated with low consumption of seafood, the primary dietary source of n-3 LC-PUFAs. Reduced concentrations of cholesterol and serotonin have also been linked to increased risk of suicide. The orbitofrontal cortex of the brains of people who took their lives violently were reported to have significantly lower cholesterol content compared with non-violent suicides. Other diet-related factors associated with suicide thoughts or attempts include low high-density (HDL) cholesterol, triglycerides, polyunsaturated fats, fiber and body mass index.

Individuals attempting suicide may exhibit diverse pathological behaviors including aggression, irritability, hospital admission for psychiatric illness, depression and self-harm. The condition is more prevalent in women, whites and smokers.

In the observational study described here, Malcolm Garland and colleagues at St. Ita's Hospital, Dublin, Ireland, investigated the lipid, fatty acid and demographic status of 40 patients who were admitted to the Galway University Hospital, Ireland, with evidence of self-inflicted harm. Patients were without serious medical complications, psychiatric diagnoses or psychotic disorders, current or recent psychotropic medication or any illness known to affect plasma cholesterol, including cardiovascular or lipid disorders. Participants were excluded if they consumed fish more than once a week, were younger than 16 or older than 65 years. A group of patients recruited from the medical day ward and matched for age and sex served as controls.

Psychometric assessments included the Suicide Intent Scale, Beck Depression Inventory and the Barratt Impulsivity Scale-II, which has 3 subscales reflecting attention, motor and unplanned types of impulsivity.

Compared with control patients, patients who harmed themselves were more likely to be women, to smoke and drink alcohol excessively, be unemployed, have lower social class and exercise less frequently. Scores on the Beck depression scale and for all components of the Barratt Impulsivity Scale were significantly higher in self-harm patients than in controls. Six of the 40 self-harm patients and none of the controls were diagnosed with depressive (2) or adjustment disorder (4).

As has been reported previously for patients at high risk of suicide, these self-harm patients had significantly lower plasma total (4.18 ± 0.93 vs 4.87 ± 0.83 mmol/L) and low-density lipoprotein (LDL) (2.03 ± 2.79 ± 0.79

Table. Plasma fatty acid concentrations in self-harm patients and controls

Plasma fatty acids µg/ml	Controls Mean (95% CI)	Self-harm patients Mean (95% CI)	*P**
Total fatty acids	267.2 (247.0-287.4)	243.9 (225.9-261.9)	0.233
Total saturates	87.6 (79.5-95.7)	79.5 (73.1-86.0)	0.206
Total monounsaturates	74.0 (66.0-82.0)	76.6 (68.9-84.3)	<0.001
Total n-6 fatty acids	93.8 (88.2-99.4)	79.5 (74.3-84.6)	0.003
Linoleic acid, 18:2n-6	71.4 (67.0-75.7)	59.7 (55.4-63.9)	0.019
Arachidonic acid, 20:4n-6	16.1 (14.6-17.6)	14.4 (13.2-15.6)	0.295
Total n-3 fatty acids	11.8 (10.3-13.3)	8.3 (7.4-9.1)	0.011
a-Linolenic acid, 18:3n-3	1.9 (1.7-2.2)	1.7 (1.5-1.9)	0.676
Eicosapentaenoic acid, 20:5n-3	3.2 (2.4-4.0)	1.7 (1.3-2.1)	0.015
Docosahexaenoic acid, 22:6n-3	5.1 (4.4-5.8)	3.7 (3.2-4.2)	0.016

*Ordered logistic regression adjusted for alcohol, smoking, social class and total fatty acids level mmol/L) cholesterol concentrations (s<0.001). There were no significant differences in triglyceride or HDL concentrations between self-harm patients and controls. None of the lipid measurements was associated with any psychopathology.

Fatty acid concentrations differed significantly between the two groups, especially in n-3 LC-PUFAs, as shown below. After controlling for social class, smoking, alcohol and total fatty acids, self-harm patients had significantly lower concentrations of total n-6 and n-3 PUFAs. Interestingly, arachidonic acid did not differ between the two groups, but linoleic acid, which accounted for 75% of the total n-6 PUFAs, was significantly lower in the patients. Reduced concentrations of total n-6 and n-3 PUFAs were significantly associated with greater depression and impulsivity scores.

As the authors commented, the relatively small sample size limited the ability to control for other possible confounding factors, but alcohol consumption, a known confounder, was considered.
Thus, increased risk of self-harm was associated with reduced plasma concentrations of cholesterol (total and LDL) and low n-6 and n-3 PUFAs. Particular attention may be given to low EPA and DHA levels because of their function in neurotransmission and the previously reported association between attempted suicide and reduced red blood cell EPA, but not n-6 PUFAs. Arachidonic acid was not different in patients and controls.

In a related study led by Dr. Brian Hallahan, Beaumont Hospital, Dublin, Ireland, 49 patients with recurrent self-inflicted harm were recruited from the hospital for participation in a double-blind, randomized, controlled trial to assess the effects of daily supplementation with n-3 LC-PUFAs. Patients aged 16 to 64 years, without substance abuse, addiction or psychosis, psychotherapy or treatment for illness known to interfere with lipid or n-3 PUFA metabolism, who did not take n-3 PUFA supplements or eat fish more than once a week were eligible to participate. More than 80% of the participants had personality disorders, with equal proportions in the treatment and placebo groups. In the analysis of covariance, presence or absence of these disorders did not affect any treatment outcome.

The trial consisted of randomized assignment to consume 4 capsules once daily providing a total dose of 2.1 g of EPA (1.2 g) plus DHA (0.9 g) or corn oil placebo containing 1% EPA+DHA to mimic fishiness. The intervention continued for 12 weeks. Supplements were provided in addition to usual treatment and care. Psychometric evaluations were performed to assess depression, aggression, perceived stress and daily ups and downs. Patients completed assessments at baseline and every 4 weeks thereafter. Clinician-administered assessments were conducted every 6 weeks. The evaluations included: the Beck Depression Inventory and the Hamilton Rating Scale for Depression; Overt Aggression Scale (modified version), a clinician-administered assessment with subscales for aggression, irritability and suicidality; Immediate and Delayed Memory Tasks test, which includes impulsivity; Perceived Stress Scale; and the Daily Hassles and Uplifts Scale. Thirty-nine patients completed the trial, with 20 of 27 in the placebo group and 19 of 22 taking n-3 LC-PUFAs.

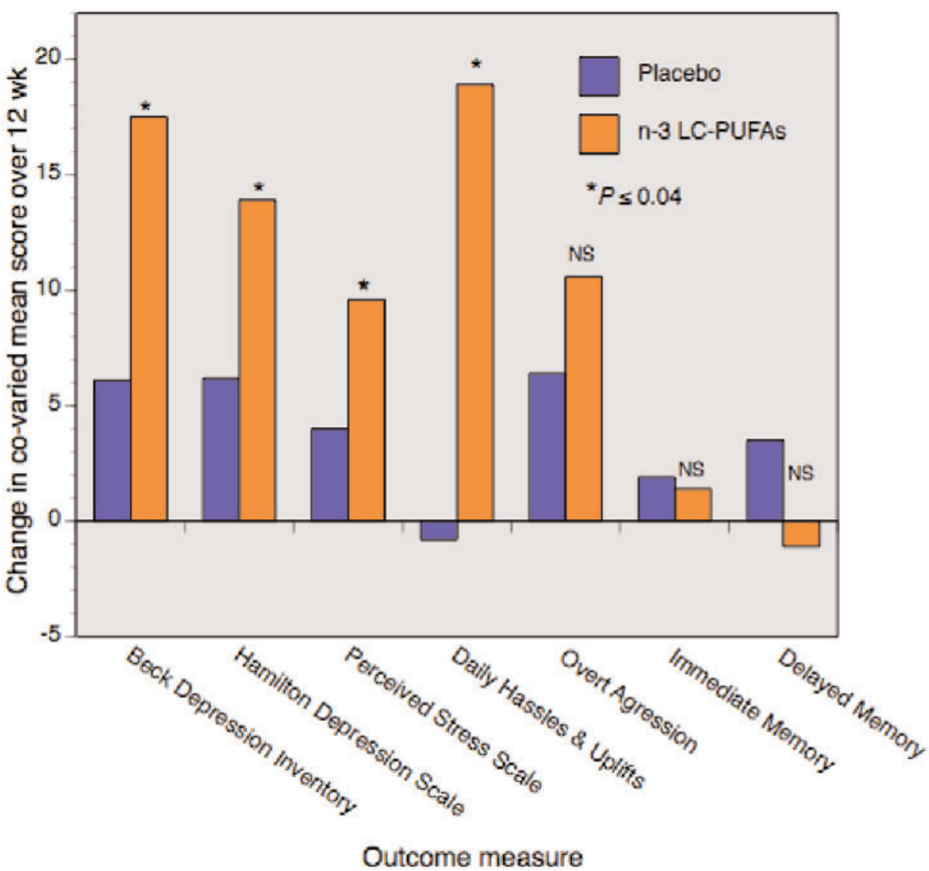

Figure. Change in outcome measures in self-harm patients consuming n-3 LC-PUFAs or placebo for 12 weeks

After 3 months, patients consuming EPA and DHA exhibited significant improvements in depression ratings evaluated by both the Beck and Hamilton assessments (Figure). Significantly more patients consuming n-3 LC-PUFAs experienced a greater than 50% reduction in depressive symptoms and a 70% reduction in remission than in the placebo group. Mean change in the Beck scores in the n-3 LC-PUFA group compared with the placebo group was 17.5 (CI=12.1-22.9) versus 6.1 (CI=24.0-33.8), *P*=0.004.

More patients consuming n-3 LC-PUFAs than placebo patients reported no suicidal ideation (14 vs 8, *P*=0.02), although differences in the actual scores did not reach statistical significance. In logistic regression analysis, irritability, aggression and depression scores did not affect the suicidality score. There were no completed suicides during the study and an equal number of self-harm incidents (7) occurred in both groups. Impulsivity, aggression and memory assessments did not differ between the two groups.

Among patients consuming n-3 LC-PUFAs, there was a significant reduction in the perception of daily stresses by both measures, Perceived Stress and Daily Hassles scales, greater prevalence of participants attaining a 50% reduction in stress scores, and a greater mean improvement in the Daily Hassles score at 12 weeks compared with patients taking the placebo (Figure). In contrast to these improvements, there were no significant differences in overt aggression or in the memory assessments (Figure). The investigators noted that the improved trends for depression, stress and daily hassles and uplifts continued to diverge from the scores in the placebo group, suggesting that with more time, differences might have been even more pronounced.

Self-harm patients who consumed 2 g/day EPA and DHA for 12 weeks improved their scores for depression, perceived stress and daily hassles and thought less about suicide compared with patients taking the placebo.

In summary, patients with a documented tendency to harm themselves had significantly lower levels of PUFAs in their plasma lipids, especially of linoleic acid, EPA and DHA, which were all associated with greater occurrence of depression and impulsivity. These findings are consistent with other reports of significantly lower n-3 LC-PUFAs in depressed patients and those at risk for suicide. In a randomized, controlled, double-blind trial among patients with recurrent self-harm, the consumption of 2 g/day of EPA and DHA for 12 weeks was associated with significant improvements in depression, suicidal thoughts and perceptions of stress, but not with aggression, impulsivity or incidents of self-harm. These observations concur with previously published reports of improved depressive symptoms in patients with various psychosocial disorders who increased their consumption of n-3 LC-PUFAs., Although limited by their small size, these studies increase the hope that modest dietary change can have a markedly positive effect on patients struggling with complex and life-threatening mental disorders.

Garland MR, Hallahan B, McNamara M, Carney PA, Grimes H, Hibbeln JR, Harkin A, Conroy RM. Lipids and essential fatty acids in patients presenting with self-harm. Br J Psychiatry *2007;190:112-117.*

Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm: Single-centre double-blind randomised controlled trial. Br J Psychiatry *2007;190:118-122.*

Red Blood Cell Omega-3 PUFAs Linked to Reading Scores with or without Dyslexia

Dyslexia involves more than just reading difficulties – it has a neurological origin. People with dyslexia process information in a different area of the brain than do non-dyslexics.

Dyslexia, as described by the International Dyslexia Association, is a "specific learning disability that is neurological in origin." The Association estimates that 15% to 20% of the population has a language-based learning disability. The characteristics of dyslexia include difficulties with accurate or fluent word recognition, poor spelling and decoding problems related to disordered phonological processing. Individuals with dyslexia process information in a different area of the brain than do non-dyslexics. The condition involves more than just reading difficulties and includes such features as abnormal visual and auditory processing, motor coordination, and problems with orientation, direction and sequencing. It has been estimated that half of dyslexic children also have attention deficit hyperactivity disorder (ADHD). Dyslexia is more common in boys than girls and can be a life-long condition.

It is becoming more widely recognized that deficiencies or imbalances in long-chain polyunsaturated fatty acids (LC-PUFAs) are involved in this disorder, but it is unclear how. Dyslexic individuals are more likely to exhibit symptoms typical of essential fatty acid deficiency, such as excessive thirst, dry hair and skin, soft brittle nails and follicular keratosis (scaly skin) and, if present, these symptoms may presage more severe dyslexia.

> *There is some evidence that children with reading and language difficulties significantly improved their reading and spelling skills after 3 months' supplementation with n-3 LC-PUFAs.*

Low blood concentrations of LC-PUFAs have been reported in children with dyslexia and related conditions with impaired reading skills, such as ADHD and developmental coordination disorder. Although few well controlled, randomized intervention trials with LC-PUFAs or n-3 LC-PUFAs have been published, some evidence indicates that reading and written language difficulties in children with developmental coordination disorder improved after 3 months' supplementation with mainly n-3 LC-PUFAs. Children with ADHD and reading problems also responded favorably to LC-PUFA supplementation, although not in all studies. Notwithstanding the progress in teaching reading skills to dyslexic individuals, the need to document and understand the effects of dietary LC-PUFAs is a priority, in part because of their therapeutic potential.

In this report, Dr. Eva Cyhlarova of Oxford University and colleagues at the University of Stirling, U.K., studied the relationship between LC-PUFA status and literacy skills in 32 dyslexic adults (mean age 35 ± 9 years) and 20 matched controls (mean age 32 ± 10 years) without reading difficulties. Participants were eligible if they had a previous history or assessment of dyslexia, a discrepancy of at least 1.5 SD between their general ability IQ and reading, impaired auditory working memory, and a score greater than 8 on the adult dyslexia screening checklist. Potential participants with low general ability IQ, major medical or psychiatric disorders, or use of fatty acid supplements were excluded. Control participants had no history of reading difficulties, normal reading and spelling tests and a score of less than 8 on the adult dyslexia screening checklist. Fasting blood samples were collected on the morning of the psychometric assessments.

Psychometric evaluations included reading and spelling by the Wide Range Achievement Test and working memory by two subscales of the Wechsler Adult Intelligence Scales, Digit Span and Digit Symbol tests. Fatty acids were measured in red blood cell membrane phospholipids.

Psychometric tests confirmed that control participants had significantly better reading, spelling and working memory than dyslexic participants. However, red blood cell fatty acid patterns did not differ between the groups. Reading, but not spelling, scores were significantly and positively associated with red blood cell total n-3 LC-PUFAs in the whole sample and each group of participants (Table). Notably, docosahexaenoic acid (DHA) was significantly associated with both reading and spelling in the whole sample and control subjects, but not in the dyslexic participants. n-3 PUFAs accounted for 9.2 mg/100 mg total phospholipids in the red cell membranes of both control and dyslexic participants. It should be noted that none of the correlations was adjusted for potentially confounding variables.

Table. Correlation coefficinets between selected red cell PUFAs and reading scores in control and dyslexic adults

FATTY ACID	ALL PARTICI-PANTS	CONTROL	DYSLEXIC
n-3 PUFAs			
ALA, 18:3	0.12	0.14	0.42*
EPA, 20:5	0.26	0.12	0.33
DHA, 22:6	0.35*	0.56*	0.33
Total n-3s	0.36**	0.49*	0.37*
n-6 PUFAs			
LA, 18:2	0.11	0.44	-0.12
ARA, 20:4	-0.26	-0.34	-0.29
Adrenic, 22:4	-0.34*	-0.14	-0.42*

*Spearman's rank correlation coefficient *$P<0.05$, ** $P<0.01$

The most intriguing finding in this observational study was the significant positive association between red blood cell membrane n-3 LC-PUFAs and better reading performance in both control and dyslexic participants. The involvement of n-6 LC-PUFAs in dyslexia was less clear, although a negative trend with increased total n-6 PUFA red cell concentrations was suggested. More conclusive results must rely on clear differences between treatment and control groups.

The implications of n-3 LC-PUFA involvement in dyslexia and reading performance in the absence of dyslexia suggest that these fatty acids may be involved in common neural pathways that, when impaired, result in altered n-3 LC-PUFA utilization or metabolism. Dietary intake in these groups was not evaluated in detail, but the study did exclude those with high fish consumption. Results from a larger randomized controlled trial of highly unsaturated PUFAs in dyslexia, currently underway, may ease the reading of these research runes.

Cyhlarova E, Bell JG, Dick JR, MacKinlay EE, Stein JF, Richardson AJ. Membrane fatty acids, reading and spelling in dyslexic and non-dyslexic adults. Eur Neuropsychopharmacol *2007;17:116-121.*

IMMUNE FUNCTION

EPA-Derived Resolvin E1 Inhibits Bone Loss in Periodontitis

The involvement of inflammation in the pathology of many chronic diseases is now recognized. For example, cardiovascular disease, digestive diseases, anemia, cancer, and Alzheimer's disease all have chronic inflammation as part of their underlying pathology. Autoimmune

Periodontitis – an inflammatory condition that destroys the supporting structures of the teeth – can destroy bone and have serious consequences for therosclerotic vascular disease.

diseases such as rheumatoid arthritis, asthma, psoriasis and allergies also have exaggerated inflammatory responses that contribute to their symptoms. Periodontitis – an inflammatory condition that destroys the supporting structures of the teeth – can destroy bone and may have serious consequences for atherosclerotic vascular disease. Others have linked endodontic disease to increased risk of coronary heart disease in men under the age of 40. Bacteria from patients with serious periodontitis have been detected in their atherosclerotic plaques. For these reasons, control of periodontitis has implications beyond bone and dental health.

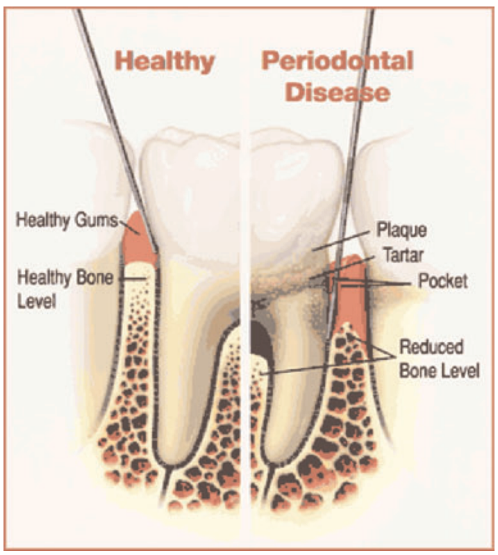

Figure. Healthy tooth and gum structure (left) and erosion of gum and bone from periodontal disease (right). Reproduced courtesy of the American Academy of Periodontology.

Long-chain polyunsaturated fatty acids (LC-PUFAs) have regulatory effects in immune and inflammatory conditions that may exacerbate or suppress symptoms associated with excess inflammation. LC-PUFAs of the omega-3 (n-3) family generally have inhibitory effects on inflammation and are precursors of oxygenated derivatives, resolvins and protectins, with potent anti-inflammatory effects. Similar substances derived from arachidonic acid include lipoxins and aspirin-triggered lipoxins, produced in response to aspirin. Lipoxins and resolvins reduce neutrophil infiltration and trigger the resolution of inflammation.

In this study, Dr. Hatice Hasturk of Boston University and colleagues at Harvard Medical School, Boston, USA, compared the effects of eicosapentaenoic acid- (EPA) derived resolvin E1 with aspirin-triggered lipoxin in human neutrophils from patients with localized aggressive periodontitis. Patients with this condition have excessive neutrophil-mediated tissue and bone loss. Results from the topical application of resolvin E1 are also reported.

To compare the effects of resolvin E1 and aspirin-triggered lipoxin, the investigators measured the respiratory burst of neutrophils from periodontitis patients and healthy controls. Neutrophils exhibit respiratory burst under appropriate stimulation (e.g., infection) by releasing reactive oxygen products, such as superoxide, which can damage tissues. Healthy neutrophils respond to lipoxins with suppressed respiratory burst.

Neutrophils from infected patients were resistant to the anti-inflammatory effects of aspirin-triggered lipoxins, but were susceptible to resolvin E1.

In these experiments, the production of superoxide by neutrophils from healthy participants was significantly suppressed by about 90% in response to aspirin-triggered lipoxin, but superoxide production by neutrophils from periodontitis patients was reduced by less than 5%. When increasing doses of the lipoxin were tested, the responses of the 2 groups remained significantly different, 80% vs 30% inhibition for healthy and periodontitis neutrophils, respectively (P<0.05).

In contrast, exposure to resolvin E1 suppressed neutrophil superoxide generation by more than 90% in both patients and controls. Thus, neutrophils from infected patients were resistant to the anti-inflammatory effects of aspirin-triggered lipoxins, but were susceptible to resolvin E1.

The investigators examined the effect of topical treatment with resolvin E1 in experimental animals (rabbits) with experimentally induced periodontitis. Disease was established by ligature of the second premolar for 6 weeks and topical application of the bacterial pathogen *Porphyromonas gingivalis*. One group of infected animals received resolvin E1 (~4µg/tooth) topically every other day for 6 weeks. Another received a bacterial inhibitor and the third group an ethanol placebo. Negative controls included animals treated only by ligature and another group receiving no treatment.

The combination of ligature and topical bacteria led to the development of periodontitis that affected exposed tissue and bone. The bacterial inhibitor suppressed infection and disease did not develop in the untreated

The most striking observation was a 95% inhibition of tissue and bone damage in the animals treated with resolvin E1, in spite of the growth of the applied bacteria.

animals. The most striking observation was a 95% inhibition of tissue and bone damage in the animals treated with resolvin E1, in spite of the growth of the applied bacteria. Radiographic evaluation of the bone loss in animals with periodontitis indicated a 4-fold protection against loss with resolvin E1 treatment compared with animals not treated with resolvin E1. Histologic examination showed no tissue damage or neutrophil infiltration in the resolvin-treated animals in contrast to the extensive bone loss in the untreated animals. Osteoclasts, bone cells that degrade bone structure, were present in large numbers in the infected animals, but scarce in the resolvin-treated animals, suggesting that resolvin E1 suppressed the activity of these cells. Osteoclasts are involved in other inflammatory diseases of tissue degradation, such as rheumatoid arthritis.

These results showed that resolvin E1 directly curtails neutrophil activity and suppresses osteoclast activity in experimental periodontitis, thereby preventing tissue and bone loss. These observations were obtained in the presence of robust bacterial activity, suggesting that anti-bacterial treatments alone do not spare tissue damage. Topical applications of n-6 or n-3 PUFAs failed to inhibit gingivitis, a forerunner of periodontitis, whereas the oxygenated derivative of EPA, resolvin E1 was highly effective in arresting tissue damage. With these promising results, studies in people appear warranted. A further question is whether resolvin E1 will have tissue-sparing effects in other inflammatory diseases of tissue degradation and, if so, can it be delivered to the site?

Hasturk H, Kantarci A, Ohira T, Arita M, Ebrahimi N, Chiang N, Petasis NA, Levy BD, Serhan CN, Van Dyke TE. RvE1 protects from local inflammation and osteoclast-mediated bone destruction in periodontitis. FASEB J *2006;20:401-403.*

CLINICAL CONDITIONS

Cancer

Marine Omega-3 PUFAs and Other Nutrients Lower Risk of Non-Hodgkin's Lymphoma

Environmental factors are implicated in the development of various cancers, but the strength and nature of the links between diet, viruses, chemicals and pollutants, lifestyle and other influences are poorly understood in most instances. In general, high consumption of fruits, vegetables and fish are protective against several cancers, whereas high intakes of dairy products, saturated fats, red and processed meats appear to increase risk. Still, exceptions to these generalizations are common.

In general, high consumption of fruits, vegetables and fish has been found protective for several cancers, whereas high intakes of dairy products, saturated fats, red and processed meats appear to increase risk.

In a previous study of non-Hodgkin's lymphoma and diet, Ellen Chang at the Northern California Cancer Center, Freemont, USA, and colleagues reported that high consumption of dairy products and fried red meat was associated with increased risk of the disease, whereas fruit and vegetable intake was inversely linked to risk. Other epidemiological studies have reported conflicting observations for dietary variables and non-Hodgkin's lymphoma, an immune system cancer.

To clarify the relationships between specific dietary variables and the different types of non-Hodgkin's lymphomas, Chang and colleagues extended their dietary analysis among patients with the disease and controls in a study of residents of 7 counties in Sweden and Denmark. Patients were newly diagnosed with malignant lymphoma identified from a nationwide cancer registry and classified by histopathology according to World Health Organization criteria. Control participants were selected randomly from the same counties as the patients. Of the 811 cases and 718 control participants eligible for the study, 591 cases and 460 controls satisfactorily completed the semi-quantitative food frequency questionnaire and personal telephone interview.

Cases of non-Hodgkin's lymphoma were separated into the following subtypes: diffuse large B-cell lymphoma (147), chronic lymphocytic leukemia (148), follicular lymphoma (108) and T-cell lymphoma (41). Dietary fat consumption was divided into major fatty acid class, total and marine n-3 PUFAs, n-6 PUFAs, animal and vegetable fatty acids. Data were analyzed by unconditional logistic regression analysis, adjusted for 5-year age group, sex, total energy intake and other potential confounders. Odds ratios were calculated for the associations between nutrient intake and risk for non-Hodgkin's lymphoma case status. Nutrient intakes were divided into quartiles, with the lowest quartile as the reference group. Categories of fish consumption for total and fatty fish were: <1.5, 1.5 to <3.0 and ≥ 3.0 servings/week*. Associations for type of fat consumed were adjusted for the other fat types.

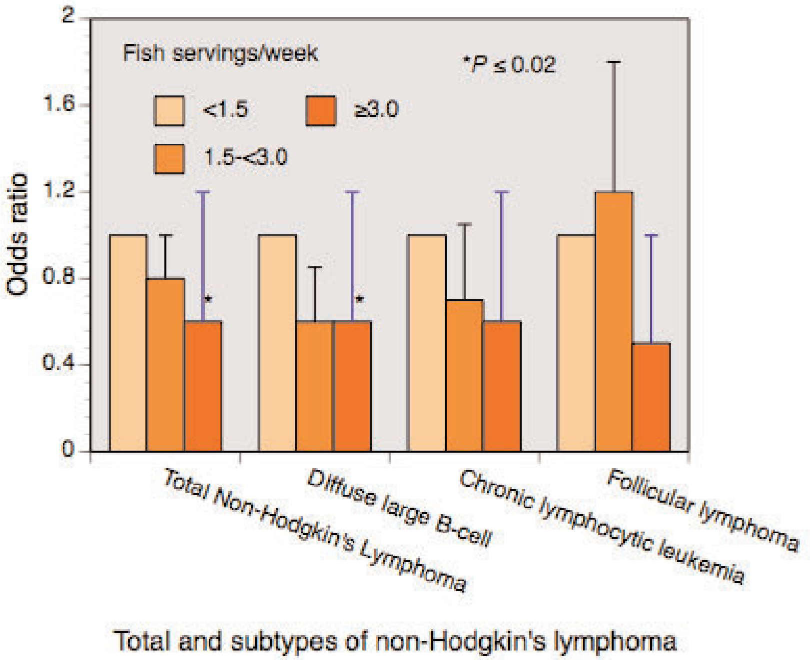

Figure. Odds ratios for assoications between categories of fish consumption (serving/week) and risk of non-Hodgkin's lymphoma

Total fat consumption and intake of saturated, polyunsaturated, animal and vegetable fat were not associated with risk of non-Hodgkin's lymphoma or any of its subtypes. High consumption of marine n-3 LC-PUFAs, all fish and fatty fish were significantly associated with lower risk of total non-Hodgkin's lymphoma (Figure). In addition, consumption of all fish and fatty fish were both associated with lower risk of all subtypes of lymphoma, except T-cell, for which there were only 51 cases. For calculated marine n-3 LC-PUFAs, only the relationship with total non-Hodgkin's lymphoma was significant. When alpha-linolenic acid was included in the n-3 PUFA intake, only chronic lymphocytic leukemia was significantly and inversely associated with risk. n-6 PUFAs were significantly and inversely associated only with risk of follicular lymphoma. Dietary fiber was associated with significantly lower risk of all non-Hodgkin's lymphoma and all major subtypes except T-cell lymphoma.

The 40% to 50% lower risk of non-Hodgkin's lymphoma with increased consumption of fatty fish and marine n-3 LC-PUFAs confirms an earlier report by these investigators related to seafood consumption. Lower risk of all lymph and blood cancers with fish intake was reported in another study. Other nutrients associated with lower risk in this investigation included dietary fiber, beta-carotene, vitamins C and E, folate and iron – all pointing to the benefits of eating plenty of fruits and vegetables with fish.

The investigators noted that marine n-3 LC-PUFAs suppress inflammation, a risk factor for non-Hodgkin's lymphoma. Other nutrients that prevent oxidation, mediate normal DNA methylation (e.g., folic acid) or enhance vitamin D activity (e.g., exposure to ultraviolet light) appear to reduce risk of the condition as well.

As with all observational reports, epidemiological associations only direct the gaze. Seeing more clearly how LC-PUFAs affect cancer through well designed intervention studies will determine if these observations can be supported. Until such time, these studies suggest that it matters to fish for good health by good eating.

*Corrected from the original servings/day per the author

Chang ET, Bälter KM, Torrång A, Ekström Smedby K, Melbye M, C Sundström C, Glimelius B Adami H-O. Nutrient intake and risk of non-Hodgkin's lymphoma. Am J Epidemiol *2006;164:1222-1232.*

Lower Risk of Prostate Cancer with Fatty Fish Intake is Enhanced by COX-2 Gene Variant

> *The association between omega-3 PUFAs and prostate cancer continues to be contentious. Long-chain omega-3 PUFAs found in fatty fish have been linked to lower risk of prostate cancer and alpha-linolenic acid, found in plants, has been associated with greater risk of the disease.*

The association between omega-3 polyunsaturated fatty acids (n-3 PUFAs) and prostate cancer continues to be contentious. There are reports that men who consumed fish regularly had significantly lower risk of developing the disease. Other reports observed increased risk of the disease with the consumption of alpha-linolenic acid, the plant-based n-3 PUFA, an observation that defied most thinking about the way these fatty acids behave. Both long-chain n-3 PUFAs (n-3 LC-PUFAs) found in fatty fish and arachidonic acid, an n-6 LC-PUFA, were linked to lower risk of advanced prostate cancer in another study. More recently, British investigators reported *in vitro* evidence that arachidonic acid may enhance the invasiveness of prostate cancer cells, while n-3 LC-PUFAs may inhibit it.

Although doubts have been aired about the link between alpha-linolenic acid and risk of prostate cancer, a recent study expressed concerns. The study examined prostate fatty acid levels and prostate-specific antigen (a marker for the disease) in men with prostate cancer and benign prostatic hyperplasia. It reported higher concentrations of alpha-linolenic acid in the prostate tissue of men with the disease compared with those having benign hyperplasia. Alpha-linolenic acid levels, but not n-3 LC-PUFAs, were positively associated with prostate-specific antigen. Thus, these investigators concluded that their findings supported a deleterious involvement of alpha-linolenic acid in this disease. To add to the confusion, another recent prospective study of alpha-linolenic acid intake and prostate cancer risk concluded that its consumption was unrelated to risk of total or advanced disease. Someone seeking to sort out the effects of these PUFAs in prostate cancer could justifiably abandon the task.

One approach to understanding how n-3 PUFAs affect prostate cancer has been to examine the expression of enzymes in the pathways that convert n-6 and n-3 PUFAs to eicosanoids. It has been shown in several studies that the enzyme cyclooxygenase-2 (COX-2) is over-expressed in prostate cancer and that inhibition of its activity by non-steroidal anti-inflammatory agents, such as aspirin, reduces the risk of incurring the disease. Prostaglandin E2, an eicosanoid product of COX-2 acting on arachidonic acid, is produced at 10 times the rate in prostate cancer tissue as in healthy tissue. The importance of COX-2 activity in this disease was further underscored by the discovery that genetic variation in the COX-2 gene affects the risk of prostate cancer.

To better understand the effects of these genetic variants and fish intake, Maria Hedelin and colleagues at the Karolinska Institute in Sweden examined the consumption of various types of fish and the risk of prostate cancer in a large Swedish case-control population. They also explored potential interactions between fish consumption and COX-2 gene variants.

Patients with pathologically verified prostate adenocarcinoma were recruited from the Swedish Prostate Cancer Registry and matched for age and geographic residence with control participants selected from the Swedish Population Registry. Patients aged 35 to 79 years were asked to complete a questionnaire about risk factors and food intake and to donate a blood sample. Of the 1499 patients who completed the questionnaire, 1,400 donated blood and 1,352 did both. Among control participants, 1,130 completed the questionnaire, 879 gave a blood sample and 858 did both.

The investigators reviewed public databases of the COX-2 gene for single nucleotide polymorphisms (SNPs) occurring at a frequency of 1/kilobase or per known missense mutation. These 16 SNPs were genotyped in 94 randomly selected control participants to assess allele frequency and 5 such SNPs occurred at a frequency of more than 5%. These 5 SNPs were then genotyped in all cases and controls (1,378 and 782 participants, respectively). All 5 SNPs were in strong linkage disequilibrium, indicating that their occurrence was not random.

The relationship between fish consumption and prostate cancer was evaluated by unconditional logistic regression, adjusted for age, intake of energy, alcohol, saturated fat, type of fish consumed and 6 other nutrients. The relationships were expressed as odds ratios. Seafood consumption data were divided into 3 frequencies: none, 1 to 3 times/month and 1 or more times/week. Intake of salmon plus herring/mackerel was grouped into none, ≤≤2 times/week, 3-4 times/week and ≥5 times/week.

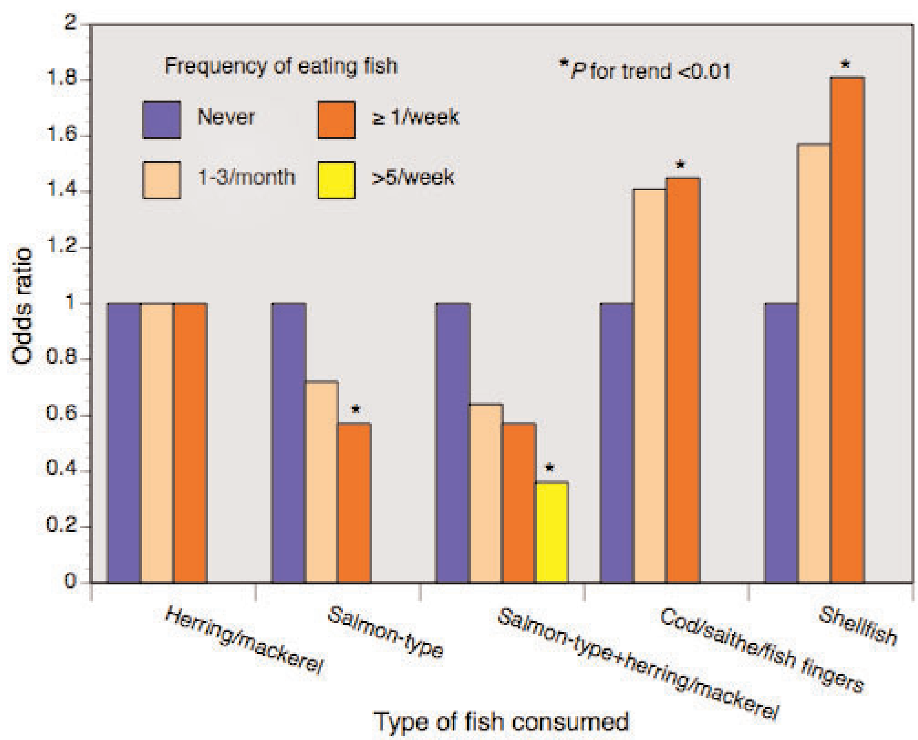

Figure 1. Odds ratios for prostate cancer with frequency and type of fish consumed, adjusted for age, intake of energy, alchol, and multiple nuutrients including type of fish consumed. Frequnecies of eating salmon-type + herring/mackerell are never, ≤2/week, 3-4/week and >5/week.

Interactions between COX-2 SNPs and fish intake were assessed statistically for additive and multiplicative effects using age and energy-adjusted models. Medium and high fish consumers were compared with non-consumers and SNPs were designated as variant or not.

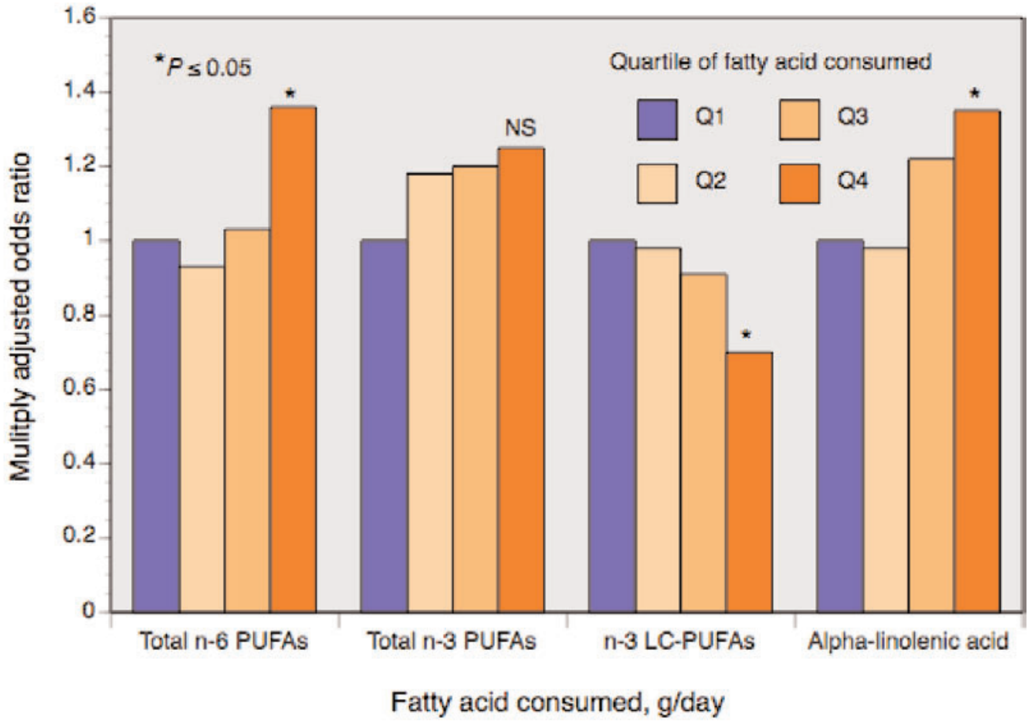

Figure 2. Multiply adjusted odds ratios for risk of prostate cancer by type and amount of fatty acid consumed

Case and control participants did not differ in body mass index, smoking history, education or intake of most macronutrients and food groups. Cases had significantly higher energy intake than controls. Fish consumption and marine fatty acids were similar in both groups. When risk of prostate cancer was analyzed by the frequency and type of fish consumed, there was a strong and significant inverse trend for disease risk with the consumption of salmon-type fish and with salmon-type fish plus herring and mackerel (Figure 1). Risk was not associated with intake of herring and mackerel without salmon. Prostate cancer risk in men who consumed more than 5 servings of fatty fish/week was reduced by 64%. Additional adjustments for several other nutrients and type of fish consumed modestly strengthened these relationships.

In contrast, the risk of prostate cancer increased significantly with higher consumption of cod, saithe and fish fingers and with higher shellfish intake (Figure 1). After multiple adjustments, the increased risk with frequent consumption of lean/fried fish was 45% and for shellfish, 81%. The authors suggested that the findings with lean fish and shellfish might be attributable to their low content of n-3 LC-PUFAs. However, it is more likely that another factor associated with these diets was related to the increased risk. It has been reported previously that the cardiovascular benefits associated with eating fatty fish were not observed in people who ate fried lean fish.

When the risk of prostate cancer was examined in terms of the consumption of fatty acids, the intakes of n-6 PUFAs (linoleic and arachidonic acids) and alpha-linolenic acid were associated with significantly higher risk (35%) after multiple adjustments (Figure 2). In a separate analysis of linoleic and arachidonic acids, the risk associated with n-6 PUFAs was attributable solely to linoleic acid.

Consumption of total n-3 PUFAs, which included alpha-linolenic acid, was not significantly associated with risk. When the sum of all n-3 LC-PUFAs was evaluated, frequency of consumption was significantly associated with a 30% risk reduction (Figure 2). The investigators repeated the analyses for cases of localized or advanced prostate cancer and found no differences in risk across disease stages.

The investigators analyzed the relationship between intake of salmon-type fish and each of the 5 SNPs, analyzing separately individuals who were heterozygous and homozygous for the common and variant alleles. The interaction between one SNP (+6365 T/C) and the consumption of salmon-type or combined salmon-herring type fish was significant on both the multiplicative and additive scales. Those who had at least one variant allele of this SNP and who ate salmon-type fish once a week or more had a significant 72% reduction in relative risk of prostate cancer compared with men carrying the same variant who never ate salmon. No relationship was found among men homozygous for the more common allele. Risk was unrelated to disease stage.

This study confirms the relationship between alpha-linolenic acid intake and prostate cancer risk and previous reports that a high intake of fatty fish is associated with a lower risk of prostate cancer. Risk was 43% lower with high fish intake after adjustment for multiple variables. The association with fish consumption

This study confirms the link between high intake of fatty fish and lower risk of prostate cancer and the positive association between alpha-linolenic acid and increased risk. High fatty fish consumption was linked to even lower risk of the disease in men with certain gene variant for the COX-2 enzyme.

was further modified by a specific polymorphism in the COX-2 gene in men carrying the gene variant. In men consuming fatty fish, those having the variant allele had a 72% lower risk of prostate cancer compared with men carrying the common allele. A protective potential of high fish intake and a SNP variant in the COX-2 gene and in the PPAR gamma genotype has been reported in colorectal adenoma, but this is the first report in prostate cancer. These investigators have also reported that genetic variation in several inflammatory genes is associated with greater risk of prostate cancer.

Although this report linked high intake of linoleic acid to increased risk of the disease, other reports have observed a reduced risk with prostate cancer. These findings confirm the positive association between prostate cancer risk and consumption of alpha-linolenic acid, although not all studies have confirmed this association (see following report). Eating fatty fish frequently, which will improve the dietary balance of n-6 and n-3 PUFAs, may reduce risk of prostate cancer risk and may give added protection to individuals with genetic mutations in their eicosanoid enzymes.

Hedelin M, Chang ET, Wiklund F, Bellocco R, Klint A, Adolfsson J, Shahedi K, Xu J, Adami HO, Gronberg H, Balter KA. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. Int J Cancer *2007;120:398-405.*

Total PUFAs in Surgical Tissue Linked to Lower Chance of Prostate Cancer Recurrence

Obesity and lack of exercise increase risk of prostate cancer recurrence, but consumption of processed tomato products and fish lower it.

Prostate cancer is the most common newly diagnosed cancer among men in the U.S., accounting for one third of all cancers in men each year. If detected while the disease is still confined to the prostate, a cure is possible, but recurrence develops within 5 years in about 10% to 15% of cases. Conditions that influence risk of recurrence include the type of pathology, level of prostate-specific antigen (PSA, a marker for the disease) at the time of diagnosis, and several diet and lifestyle factors. These include obesity and lack of exercise, which increase risk of recurrence, and consumption of processed tomato products and fish, which lower it.

Prostatic tissue concentrations of polyunsaturated fatty acids (PUFAs) from non-malignant tissue have been associated with lower risk of metastasis, particularly to the seminal vesicle. Long-chain omega-3 (n-3 LC) PUFAs and arachidonic acid are associated with lower risk. The investigators who reported these findings now describe the associations between prostatic fatty acid concentrations and the likelihood of disease recurrence in men with organ-confined disease who underwent radical prostatectomy.

Participating patients were 50 years of age and older (mean age 62 years) with stable weight and dietary habits, who did not receive therapy for the primary tumor prior to surgery. Tissue samples from non-cancerous prostate tissue were obtained from 184 of the 290 study participants. PSA was measured prior to surgery and at 3, 6, 9 and 12 months thereafter and then annually. Biochemical recurrence was defined as serum-detectable PSA increasing after a biochemical disease-free interval of at least 6 months. Date of recurrence was the date of the test result that marked the onset of rising PSA.

The average follow-up time was 49 months (median 47), ranging from 25 to 74 months. During this period, 14 men experienced biochemical recurrence.

Men with biochemical recurrence had higher PSA concentrations at the time of diagnosis, greater likelihood of seminal vesicle metastasis and a tendency toward obesity. Those with recurrence had significantly lower concentrations of total PUFAs, n-3 LC-PUFAs and arachidonic acid in their prostatic tissue compared with men without detectable disease. Patients with recurrence also had significantly higher levels of total monounsaturates, oleic and palmitoleic acids. When the relative risks (expressed as hazards ratios) of developing biochemical recurrence in relation to tissue fatty acid concentrations were determined, including multiple adjustments, several inverse associations were observed.

Risk of recurrence, after multiple adjustments for confounders, was significantly less likely with higher concentrations of total PUFAs and stearic acid, and more likely with higher total monounsaturates and oleic acid (Table). Risks were not significantly associated with n-3 LC-PUFAs, arachidonic acid or alpha-linolenic acid. Interestingly, the inverse associations previously observed for n-3 LC-PUFAs and arachidonic acid and risk of metastasis to the seminal vesicle did not persist after accounting for total PUFAs.

Table. Risk of biochemical recurrance of prostate cancer (hazard rastio) with prostate tissue fatty acids in 184 men treated by radical prostatecotomy

Fatty acid (%)	Hazard ratio (95% CI)	*P*
Total PUFAs	0.51 (0.29-0.90)	0.021
EPA+DHA	0.37 (0.09-1.56)	0.175
Alpha-linolenic acid	1.17 (0.72-1.90)	0.52
Arachidonic acid	0.61 (0.34-1.09)	0.096
Total Monounsaturates	2.04 (1.24-3.35)	0.005
Oleic acid	1.93 (1.18-3.14)	0.009
Total saturates	0.76 (0.51-1.14)	0.184
Stearic acid	0.53 (0.33-0.85)	0.009

Instead, total monounsaturates and oleic acid were associated with greater risk of recurrence, while stearic acid was associated with lower risk. Increased red blood cell oleic acid content has been observed in a small number of patients with and has been linked to increased risk of in some studies, but not . The authors speculate that these fatty acids may relate to the activity of stearoyl-CoA desaturase, an enzyme that converts stearic and palmitic acids to oleic and palmitoleic acids, respectively. Similarly, lower concentrations of arachidonic acid in patients with recurrence could be attributable to higher cyclooxygenase-2 activity, which greatly increased in prostate cancer.

The authors caution readers about the small number of cases and the preliminary nature of their report. To that must be added the complexity of interpreting "total PUFAs." Evidence suggests that the effects of individual PUFAs may be contradictory. The association between oleic and palmitoleic acids and risk of disease recurrence warrants attention in future studies. This report suggests that monitoring prostate tissue fatty acid concentrations at the time of surgery or biopsy might have predictive value for recurrence.

Freeman VL, Flanigan RC, Meydani M. Prostatic fatty acids and cancer recurrence after radical prostatectomy for early-stage prostate cancer. Cancer Causes Control *2007;18:211-218.*