PUFA NEWSLETTER

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Editorial

Finds of the Heart

The *PUFA Newsletter* welcomes two new Advisory Board members, Maria Makrides from the Child Health Research Institute, Adelaide, Australia, and Stephen Cunnane from the University of Sherbrooke, Quebec, Canada. Biographies of these scientists appear on the newsletter web site under "About Us." Drs. Makrides and Cunnane are taking over from William E. Connor of the Oregon Health Sciences University who served the *Newsletter* from its inception, and from Yasushi Saito, also a long-serving board member. The strong foundations and scientific standards of the *Newsletter* owe much to the contributions of these researchers. It has been my pleasure to have worked with them the past two years.

The first issue for 2005 presents six reviews related to heart health. Strikingly, two of the four main articles -- findings from large epidemiological studies -- reported no association between fish consumption or intake of omega-3 polyunsaturated fatty acids (PUFAs) from fish and risk of atrial fibrillation or mortality from cardiovascular disease. These reports contrast sharply with the majority of observational studies in populations and intervention trials with fish oils or omega-3 PUFAs showing a reduction in sudden cardiac death and arrhythmias. The study on atrial fibrillation in Danes who had not been hospitalized with cardiovascular disease reported omega-3 PUFA consumption greater than one gram/day in the highest fish consumption group, suggesting that dose was unlikely the concern. Whether other medications consumed by the subjects, hypertension, or possibly mercury contamination were confounding factors is unknown.

In the Iowa women's study the investigators reported an inverse association between the consumption of alpha-linolenic acid and total mortality, but no association between fish consumption and all-cause mortality, nor death from cardiovascular disease and stroke. As in much of the U.S., Iowa women consume dark fish infrequently, with two-thirds of them eating it less than once a month. This means that average daily omega-3 PUFA intake is likely to be well below the amounts associated with benefits to heart health.

Another interesting possibility would be the proportion of subjects who consume nonsteroidal anti-inflammatory medications. Regular consumption of these substances would be expected to enhance the cardioprotective effects of fish consumption. One way in which aspirin and similar agents augment the effects of omega-3 PUFAs is explained in the elegant studies on resolvin E1 by Charles Serhan and his team in the section on immune function.

This newsletter also includes a detailed animal study on where the developing rat obtains docosahexaenoic acid for its brain development. Does most come from conversion of the precursor alpha-linolenic acid, or from body stores? The answer appears in the section on maternal and infant health.

Enjoy the March issue.

Joyce Nettleton, editor
PUFA Newsletter

To be interested in the changing seasons is a happier state of mind than to be hopelessly in love with spring.
- George Santayana

Cardiovascular Health

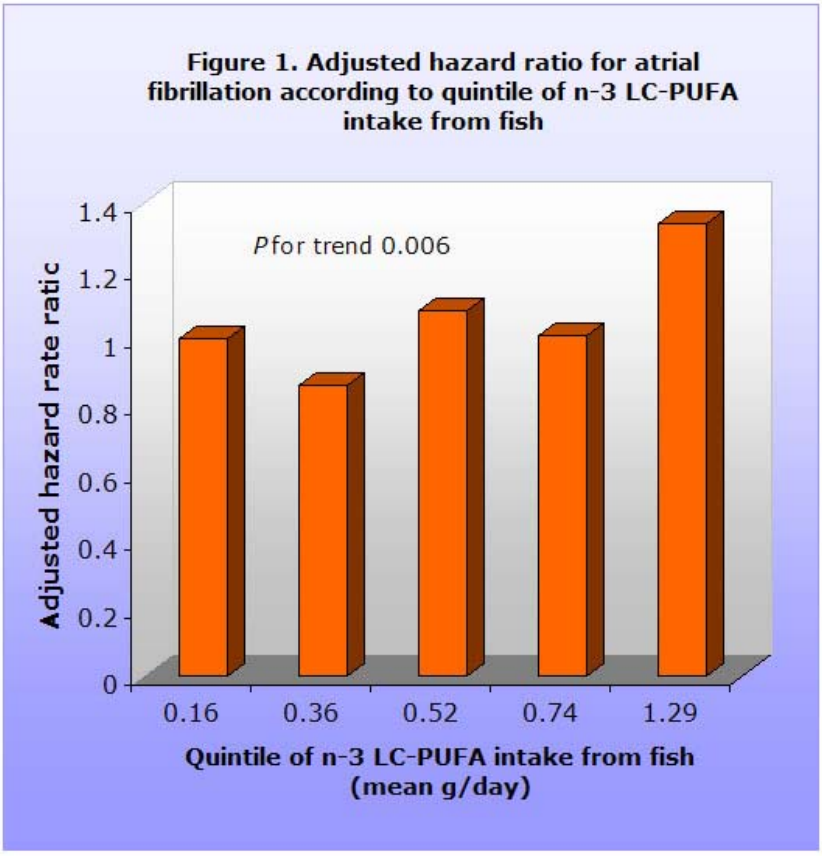
No Link Between Fish Consumption and Atrial Fibrillation in Adult Danes

It has become accepted that long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) from fish have anti-arrhythmic properties in the heart, and for this reason, may reduce the risk of developing atrial fibrillation, a condition that impairs effective blood pumping. Consistent with this thinking, a pilot study in patients with implanted defibrillators and a 12-year prospective cohort study of people 65 years or older reported reduced incidence of atrial fibrillation associated with provision of n-3 LC-PUFAs or fish consumption. In this report, two researchers from Aarhus University Hospital in Denmark examined the incidence of atrial fibrillation over six years among Danish men and women aged 50 to 64 years in relation to their fish consumption. They observed no protection from n-3 LC-PUFA intake.

Study participants were selected from the Danish Diet, Cancer, and Health Study cohort, excluding those who had endocrine diseases, ischemic heart disease other than hypertension, stroke, and diabetes, or were taking medications for these conditions. The study involved 47,949 people, whose average age was 56 years, 47% of whom were men. Fish consumption was determined by a food frequency questionnaire and used to estimate n-3 LC-PUFA intake. One hundred and sixteen cases of atrial fibrillation or flutter in people living in Aarhus county were identified from hospital discharge records for validation of their diagnosis. Ninety-seven percent (112) of the selected cases were confirmed by electrocardiogram or Holter recording.

Over an average followup of 5.7 years, 374 men (1.7% of men enrolled) and 182 women (0.7% of women) developed atrial fibrillation or flutter. Consumption of n-3 LC-PUFAs from fish by quintile ranged from an average of 0.16 g/day in the lowest quintile to 1.29 g/day in the highest intake group. The percent of those who consumed fatty fish twice or more per week ranged from 0.4% in the lowest quintile to 96.6% in the highest quintile.

Risk of atrial fibrillation was calculated using the Cox proportional hazard model. Hazard rate ratios were calculated using unadjusted and adjusted data that controlled for 10 variables such as age, sex, energy intake, serum cholesterol, and blood pressure. The adjusted hazard rate ratios by quintile of n-3 LC-PUFA intake are shown in Figure 1. Consuming n-3 LC-PUFAs from fish did not protect against the development of atrial fibrillation and was associated with increased risk at the highest level of intake.



These unexpected findings raise the question of whether protection against atrial fibrillation with fish oil, if it occurs, does so mainly in patients with established cardiovascular disease, or with levels of intake considerably greater than obtained by eating fish. The latter seems unlikely, as n-3 LC-PUFA intake may have been underestimated owing to lack of information about the use of fish oil supplements and published observations of benefit obtained among fish eaters. Is something else interfering with the response to n-3 LC-PUFAs in these patients?

Frost L, Vestergaard P. n-3 fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Clin Nutr *2005;81:50-54.*

Fish Consumption and Mortality: Evidence Against a Connection

The regular consumption of fish or long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) has been associated with significantly decreased mortality from all causes in several large diet and heart trials, including the GISSI-Prevensione study, the Multiple Risk Factor Intervention Trial and in diabetic women. Many epidemiological and clinical studies have reported reduced mortality from heart disease and sudden cardiac death with the consumption of fish, fish oils, or n-3 LC-PUFAs in patients with cardiovascular disease. However, in healthy people with no evidence of heart disease and those at low risk of heart disease, there are fewer data to indicate whether fish consumption has any effect on total mortality.

To determine whether fish consumption affects total mortality, Aaron Folsom and Zewditu Demissie at the University of Minnesota, U.S.A., examined data from 1986 to 2000 in a cohort of women aged 55 to 69 years in the Iowa Women's Health Study. Two-thirds of the women ate dark meat fish less than once per month, and consumption of n-3 LC-PUFAs among fish-eaters ranged from 53 to 188 mg/day.

Initial data analysis indicated that greater fish consumption was associated with modestly reduced mortality from all causes, heart disease, and cancer after adjustment for age and energy consumption. However, the associations were not statistically significant when adjusted for additional risks such as educational level, alcohol consumption, smoking, and other factors, nor were there significant associations between fish or n-3 LC-PUFA intake and mortality among diabetic women. Fish intake was not associated with stroke mortality or incidence of breast cancer. In contrast, alpha-linolenic acid (the plant-based n-3 PUFA) consumption was inversely associated with total mortality across tertiles of intake (1.0, 0.95, 0.35, *P* for trend = 0.01) in sub-analysis. The average alpha-linolenic acid intake was 1.1 g/day.

These findings were obtained in a population of 41,836 women who, on average, consumed fish infrequently. Even among women eating fish more than twice a week, total and cardiovascular mortality rates were unaffected by fish or n-3 LC-PUFA consumption. Likewise, similar results were observed for women with a history of heart disease. In this population, however, fish consumption was low, as revealed in the calculation of n-3 LC-PUFA consumption among the most robust fish eaters. For example, 9 percent of women consumed dark meat fish once or more a week, and 30 percent ate tuna as often.

Whether this population group was at unusually low risk for cardiovascular mortality or ate too little fish or n-3 LC-PUFAs to realize cardioprotective benefits cannot be determined from this study. The observations would be consistent with a threshold effect for n-3 LC-PUFAs in protecting against cardiovascular mortality. As the authors themselves noted, the findings "do not argue against recommending fish as part of a healthy diet." Further, they support the heart health benefits of alpha-linolenic acid.

Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. Am J Epidemiol *2004;160:1005-1010.*

Lower Risk of Heart Disease with n-3 PUFAs Not Blocked by n-6 PUFAs

An unresolved controversy about dietary intakes of omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) is the potential for dietary n-6 PUFAs to offset the beneficial potential of long-chain (LC) n-3 PUFAs to reduce heart disease and inflammation. Because most western diets are relatively high in n-6 PUFAs and low in n-3 PUFAs, it has been difficult to assess the effects of different intakes of these PUFAs in free-living populations. Recent analysis of the long-running US Health Professionals Study, begun in 1986, provides an epidemiological perspective on this question in men. The findings are likely to rekindle the debate.

Mozaffarian and colleagues at the Harvard School of Public Health in Boston, Mass., USA, examined data accumulated over 14 years on men aged 40 to 75 at enrolment who were free of heart disease at the time. Men were divided into two groups according to intakes of n-6 and n-3 PUFAs at or above the median intake (high) or below the median (low). The median n-6 PUFA intake was 11.2 g/day and for n-3 PUFAs, 250 mg/day of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA). Effects of consuming alpha-linolenic acid, the 18-carbon n-3 PUFA obtained from plants, were examined separately. Intakes of n-6 PUFAs and alpha-linolenic acid were not related to the consumption of EPA + DHA.

Relative risks of heart disease were evaluated using the Cox proportional hazards model for age-adjusted and multivariate analysis. Parameters included sudden death, nonfatal myocardial infarction, and total coronary heart disease. The relative risks for these outcomes according to both n-6 PUFA and EPA + DHA intake are shown in Table 1. Several findings were clear.

First, the consumption of 250 mg/day or more of EPA + DHA was associated with a 40 to 50 percent reduction in risk of sudden death after adjustment for multiple confounding factors, regardless of n-6 PUFA intake. This observation confirms several previous reports of significantly and substantially reduced risk of sudden death with the regular consumption of fatty fish or n-3 LC-PUFAs and supports the interpretation that these fatty acids reduce cardiac arrhythmias, the major cause of sudden death. Reduction in risk of sudden death was apparently unaffected by the level of n-6 PUFAs consumed—48% and 40% risk reduction in the low and high n-6 PUFA groups, respectively—suggesting that these fatty acids do not block the protective effects of n-3 LC-PUFAs on arrhythmias or sudden death. However, the confidence intervals around these estimates were large.

Second, nonfatal myocardial infarction and total coronary heart disease were not associated with different levels of n-6 PUFAs in the diet, nor with the consumption of EPA + DHA. Although consumption of n-6 PUFAs has long been touted for cardioprotective reasons, mainly the reduction of blood total cholesterol levels, the literature is inconsistent on the effects of these fatty acids on coronary heart disease.

The third interesting finding from this analysis was the relative importance of EPA + DHA compared with alpha-linolenic acid in reducing the risk of sudden death and heart disease. When consumption of EPA + DHA was 250 mg/day or greater, the consumption of alpha-linolenic acid was not associated with risk of heart disease. However, among men consuming less than 100 mg/day of EPA + DHA, the consumption of 1.1 g/day or more of alpha-linolenic acid was associated with a 58 percent lower risk of nonfatal myocardial infarction and a 47 percent lower risk of total heart disease. The trend toward a reduced risk of sudden death with alpha-linolenic acid consumption did not reach statistical significance. The associations with alpha-linolenic acid intake were unaffected by n-6 PUFA consumption. These observations suggest that the cardioprotective effects of alpha-linolenic acid are realized mainly, if not exclusively, in the absence of n-3 LC-PUFAs.

The authors concluded that higher n-6 PUFA intake is "unlikely to substantially reduce coronary heart disease risk in men over the range that was studied . . . and unlikely to appreciably attenuate the beneficial effects of n-3 PUFA intake on coronary heart disease risk." However, with risk of sudden death as the primary end point supporting this

Table 1. Relative risk (95% CI) of coronary heart disease parameters according to consumption of EPA + DHA and n-6 PUFAs above or below the median intake*

	Low EPA + DHA†		High EPA + DHA	
	Low n-6 PUFA†	High n-6 PUFA	Low n-6 PUFA	High n-6 PUFA
Sudden death				
Age-adjusted	1.0§	0.85 (0.60-1.20)	0.48 (0.32-0.71)	0.69 (0.48-1.01)
Multivariate	1.0	0.76 (0.52-1.11)	0.52 (0.34-0.79)	0.60 (0.39-0.93)
Nonfatal MI				
Age-adjusted	1.0	1.14 (0.99-1.32)	1.08 (0.94-1.25)	1.09 (0.94-1.27)
Multivariate	1.0	1.09 (0.93-1.28)	1.16 (0.99-1.36)	1.09 (0.91-1.29)
Total CHD				
Age-adjusted	1.0	1.01 (0.90-1.14)	0.96 (0.86-1.08)	1.02 (0.91-1.16)
Multivariate	1.0	0.97 (0.85-1.10)	1.05 (0.92-1.19)	1.02 (0.89-1.16)

*High includes median intake or greater; low is less than the median intake.
†Median EPA + DHA intake was 250 mg/d; median n-6 PUFA intake was 11.2 g/d
§Reference group was men consuming less than the median intake of EPA + DHA and n-6 PUFAs

conclusion, it remains to be established whether the many other benefits associated with n-3 LC-PUFA consumption are also unaffected by high intakes of n-6 PUFAs. Food frequency questionnaire data revealed relatively high intakes of linoleic acid, e.g., 10th percentile intake was 7.6 g/day, even in the "low" n-6 PUFA group of 11.2 g/day or less. Data on endothelial function and inflammatory responses from intervention trials would be most welcome. In the meantime, bring on the fish.

Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation *2005;111:157-164.*

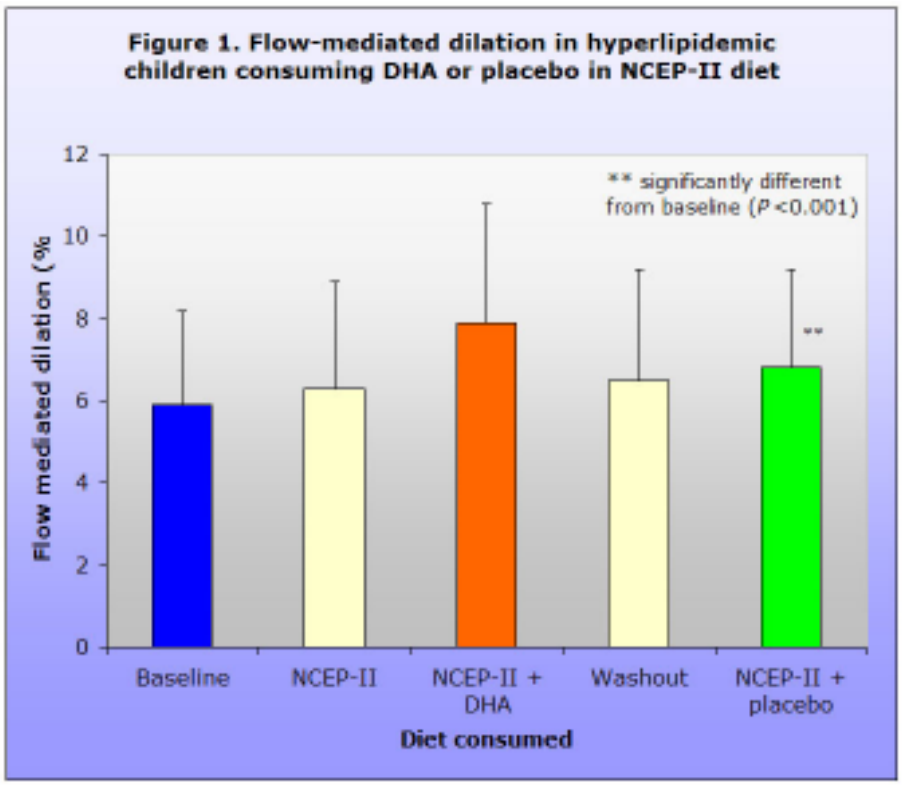
DHA Supplementation Improves Endothelial Function in High Risk Children

Some children are highly predisposed to early cardiovascular disease by virtue of inheriting genes that confer high blood cholesterol or triglyceride levels or both. In addition to their risky blood lipids, these young people have arteries with endothelial dysfunction, a characteristic that further increases their risk. Dietary fat and cholesterol modification is a key strategy in managing these cardiovascular risks. Because long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) have been associated with favorable changes in blood lipid profiles and endothelial function, Dr. Marguerite Engler and colleagues at the University of California, San Francisco, U.S.A., asked whether they might also be advantageous in improving endothelial function in these high-risk young people.

The investigators designed a randomized, double-blind, crossover study in 20 young people aged nine to 19 years, who had low-density lipoprotein (LDL) cholesterol levels greater than 130 mg/dl, or triglycerides greater than 150 mg/dL (1.7 nmol/L) or both, and a parent diagnosed with familial hypercholesterolemia or combined familial hyperlipidemia. Endothelial function was assessed by flow-mediated dilation in the brachial artery, measured by ultrasonography. After a 6-week stabilization period during which the National Cholesterol Education Program Step II (NCEP-II) diet was consumed, participants were randomized to consume the NCEP-II diet with either 1.2 g/day of docosahexaenoic acid (DHA) or a corn/soy placebo for 6 weeks. After a 6-week washout period with the NCEP-II diet, each group consumed the NCEP-II diet with the other treatment.

Consumption of the NCEP-II diet with or without supplementation had no effect on body mass index, blood pressure, or brachial artery diameter. However, consumption of the NCEP-II diet with DHA was associated with a significant increase in flow-mediated diameter compared with the placebo and washout phases of the study (Figure 1). The NCEP-II diet alone did not affect flow-mediated dilation, but the diet with placebo increased the dilation from 5.9 to 6.8% compared with baseline. Not all children responded to DHA supplementation similarly; 12 improved as compared to placebo treatment, six diminished, and one stayed the same.

DHA supplementation resulted in significant increases in total, LDL, and HDL cholesterol levels compared with the NCEP-II diet alone, but had no effect on biomarkers for oxidative stress, inflammation, or an inhibitor of nitric oxide synthesis. The authors commented that their finding of improved endothelial function, as exhibited by increased flow-mediated



dilation, is consistent with increased nitric oxide availability, but this aspect of endothelial function was not explored. With regard to changes in lipoprotein profile, the authors noted that DHA supplementation shifted the profile of lipoprotein subclasses in both LDL and HDL toward larger, more buoyant, and less atherosclerotic subtypes. Thus, increases in total cholesterol concentrations would not necessarily reflect increased risk of atherosclerosis.

The encouraging result from this study is the significant improvement in endothelial function as reflected by increased flow-mediated dilation with the consumption of 1.2 g/day of DHA. Whether the altered lipid profiles— some favorable, others not—would be favorable, as is believed, remains to be demonstrated. Long-term followup studies with larger sample sizes would provide useful information not only on the maintenance of improved endothelial function, but on the effects of DHA consumption on other risk factors and atherosclerosis development.

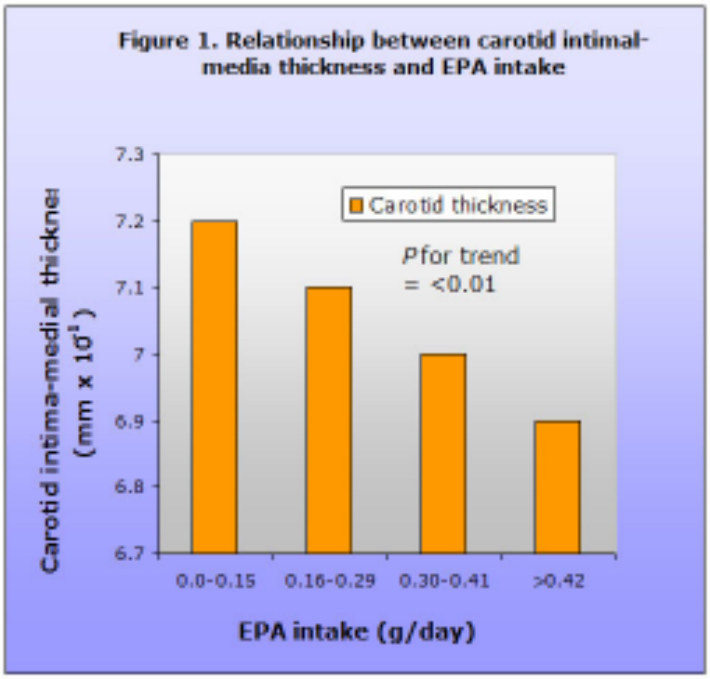
Engler MM, Engler MB, Malloy M, Chiu E, Besio D, Paul S, Stuehlinger M, Morrow J, Ridker, Rifai N, Mietus-Snyder M. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY Study. Internatl J Clin Pharmacol Therapeut *2004; 42:680-689.*

Short Takes

Omega-3 PUFA Consumption Linked to Lower Carotid Artery Thickness

The carotid arteries in the neck are the main supply routes for blood to the brain. They are a common site for the deposition of plaque, which can narrow and clog the vessel, causing stroke. Measuring the thickness of the carotid intima-media by ultrasonography has been used to evaluate atherosclerosis, although data are limited. One two-year study of patients with atherosclerosis who consumed fish oil reported no effect on the progression of atherosclerosis in carotid arteries, while a recent study reported reduced progression of artery narrowing in postmenopausal diabetic women who consumed dark fish.

Hino et al. reported the findings of a cross-sectional study of 1902 residents over 40 years of age in a farming village on Kyushu, the southwestern island of Japan. Type and frequency of fish consumption was determined by questionnaire. Carotid intimal-medial thickness was measured by duplex ultrasonography. Intake of specific long-chain n-3 polyunsaturated fatty acids (n-3 LC-PUFAs), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA), were calculated from the dietary data and related by multiple linear regression analysis to carotid intimal-medial thickness.



Average daily intakes of n-3 PUFAs were 2.2 and 2.3 g/day for men and women respectively, of which EPA+DPA+DHA supplied 0.93 g/day for men and 0.89 g/day for women. The overall diet provided an average of 24% energy from fat. Nutrient intakes of these villagers were similar to the general Japanese population. The investigators reported significant inverse trends for carotid intimal-medial thickness with increased consumption of EPA (Figure 1) and DHA ($P<0.01$) and DPA ($P<0.05$) after adjustment for age, sex, and total energy intake.

Epidemiological data have suggested that fish consumption is associated with reduced risk of stroke. The findings here are consistent with such observations and suggest that fish consumption, which provides n-3 LC-PUFAs, is also associated with reduced carotid atherosclerosis.

Hino A, Adachi H, Toyomasu K, Yoshida N, Enomoto M, Hiratsuka A, Hirai Y, Satoh A, Imaizumi T. Very long chain N-3 fatty acids intake and carotid atherosclerosis: an epidemiological study evaluated by ultrasonography. Atherosclerosis *2004;176:145-149.*

Maternal and Infant Health

Where Does the Developing Brain Obtain its DHA?

This important question has challenged fatty acid experts for years. The body requires omega-3 polyunsaturated fatty acids (n-3 PUFAs), and cannot make them from scratch or from other fatty acids. Further, it converts only tiny amounts of the 18-carbon precursor alpha-linolenic acid (ALA) to the long-chain (LC) forms needed for neural development. Thus, diet and maternal n-3 PUFA stores would appear to be the only sources of docosahexaenoic acid (DHA) for the developing fetus. What if a pregnant woman has no dietary intake of n-3 LC-PUFAs? This situation is possible if seafood and animal products are not consumed.

Feeding studies with alpha-linolenic acid and DHA have shown that humans convert some alpha-linolenic acid to DHA, but neural tissues incorporate DHA much more readily when it is supplied preformed. In addition, consuming high levels of alpha-linolenic acid reduces the amount converted to DHA. The question William Lefkowitz and colleagues at the National Institute on Alcohol Abuse and Alcoholism in Rockville, Md., USA, sought to answer was how much DHA is derived from biosynthesis (i.e., conversion of alpha-linolenic acid) and body stores in the presence and absence of dietary DHA.

To determine the amount of brain DHA obtained from the conversion of alpha-linolenic acid the investigators fed 8-day old rat pups alpha-linolenic acid labeled with the stable isotope deuterium as the sole source of n-3 PUFAs. Thus, the DHA obtained from the conversion of dietary alpha-linolenic acid would also be labeled. The investigators reasoned that unlabeled DHA in brain in the absence of dietary DHA would have to be obtained from body stores. The effect of dietary DHA on the conversion of alpha-linolenic acid could also be assessed by changes in the level of deuterated (labeled) DHA in brain.

Rat pups were hand fed experimental formulas with labeled alpha-linolenic acid with or without DHA from 8 to 28 days of age. This interval covers the majority of rat brain growth. The artificial milk with only alpha-linolenic acid contained 1 percent of total fatty acids as deuterium-labeled alpha-linolenic acid, and the DHA-supplemented formula contained 2 percent DHA plus 1 percent deuterated alpha-linolenic acid. One group of rat pups was sacrificed at eight days to obtain baseline data and a fourth group was reared by rat mothers as a reference group.

After 28 days, the body weights of the dam-reared reference rats were slightly and significantly greater than those in the experimental groups (reference 97 ± 5 g vs. 85 ± 4 and 88 ± 2 g, alpha-linolenic and DHA-supplemented groups, respectively). Brain weights of the reference group were significantly greater than both experimental groups (Table 1). There was no statistically significant difference in liver weights among the three groups at 28 days.

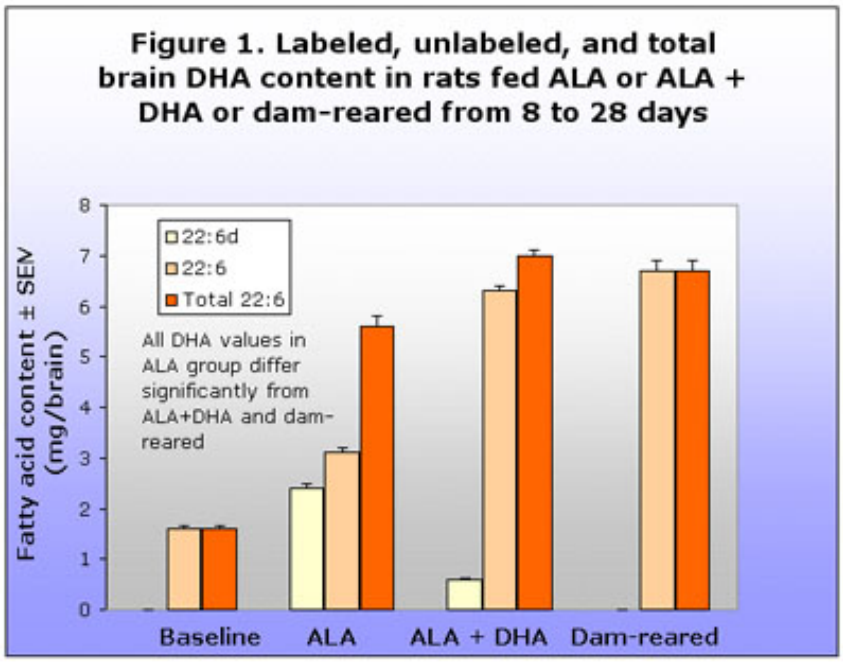
Table 1. Brain weights (g)* of rats fed formula with alpha-linolenic acid or DHA plus alpha-linolenic acid from day 8 (baseline) to 28 after birth

	Baseline	Reference	ALA only	ALA + DHA	P†
Brain wt (g)	0.73 ± 0.02	1.59 ± 0.07	1.48 ± 0.04	1.47 ± 0.01	0.05

*Values are means of 7 animals/group ± SEM
†One-way ANOVA

Quantification of the labeled and unlabeled fatty acids was determined from the peak areas of various fatty acids on the gas chromatograms of brain and liver extracts. Deuterated fatty acids had distinctly different retention times from the equivalent unlabeled fatty acid so that peaks of labeled and unlabeled fatty acids could be measured separately. The method was validated using gas chromatography/mass spectrophotometry.

From day 8 to 28, whole brain DHA content increased in all groups from 1.6 mg at baseline to 5.6, 7.0, and 6.7 mg in the alpha-linolenic acid, ALA + DHA, and reference groups, respectively (Figure 1). Total DHA content in the alpha-linolenic acid group was significantly lower than in either the ALA + DHA or reference groups confirming previous reports of lower brain DHA content when alpha-linolenic acid is the sole source of n-3 PUFAs.



the EPA was labeled, suggesting fatty acid turnover and conversion of dietary alpha-linolenic acid. In the animals fed ALA + DHA, EPA accumulation reached 0.016 mg, about three times the amount in the alpha-linolenic acid group. About 75 percent of the EPA was unlabeled, suggesting retroconversion from DHA. EPA content was less than 1 percent of the DHA content confirming the preference of brain for DHA over EPA.

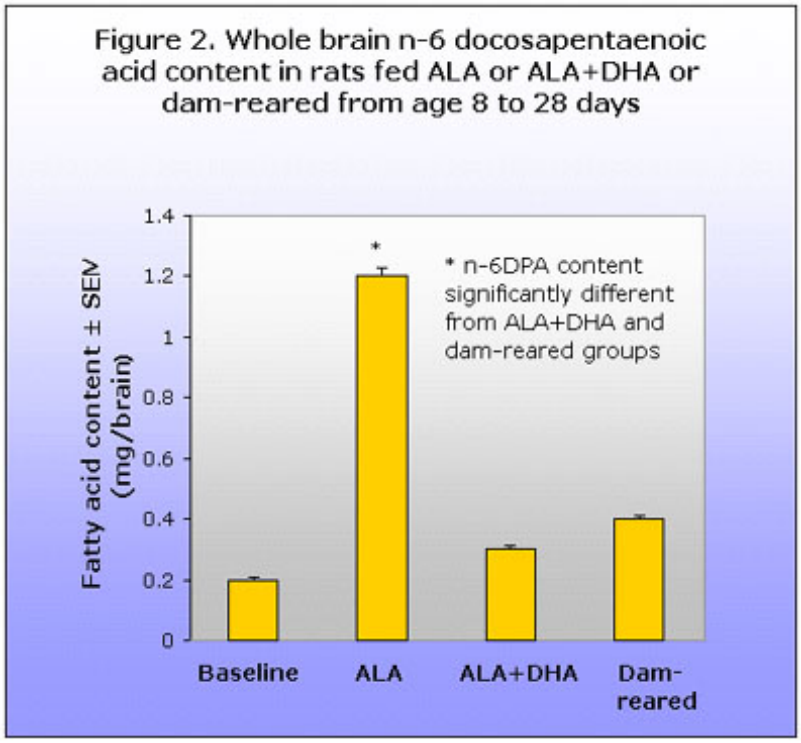
Arachidonic acid increased in both formula-fed groups from baseline (1.8 mg/whole brain) to 5.0 mg/brain for the alpha-linolenic acid group and 4.7 mg/brain for the ALA +DHA groups at 28 days. Reference animals had significantly higher levels (5.4 mg/brain) compared with the ALA + DHA group.

Of note is the finding that 60 percent of the additional brain DHA accumulated in the alpha-linolenic acid group was deuterium labeled, that is, derived from dietary alpha-linolenic acid. Forty percent, however, was unlabeled, indicating that this DHA must have come from body stores. In these animals, the content of n-6 docosapentaenoic acid (1.2 mg/brain) was four times the amount in animals fed ALA + DHA (0.3 mg/brain) and three times that in the reference group (0.4 mg/brain) (Figure 2). The accumulation of 1 mg n-6 docosapentaenoic acid represents substantial biosynthesis and is interpreted as a compensatory response to insufficient DHA.

By comparison, brains of rats fed ALA + DHA accumulated 90 percent of their DHA in unlabeled form. Labeled DHA in these animals was 0.6 mg, or about 12% of the total accumulated above the baseline level. This finding indicates that most of the brain DHA was obtained from diet, not conversion of labeled alpha-linolenic acid. The amount of n-6 docosapentaenoic acid at the end of the dietary period was unchanged from baseline, suggesting no need for biosynthesis of this fatty acid (Figure 2).

Accumulation of eicosapentaenoic acid (EPA) and arachidonic acid also differed between treatment groups. Animals fed the alpha-linolenic acid formula accumulated only 0.003 mg/brain of EPA, not different from the baseline amount. Two-thirds of

Several key findings emerge from this study. One is that a significant amount of body stores contribute DHA for brain development when dietary DHA is lacking. In this study, 40 percent of brain DHA was unlabeled, derived from body stores. The study also confirmed that in the absence of dietary DHA, total brain DHA content is significantly reduced. However, when DHA is consumed, about 88 percent of brain DHA comes from the diet. These observations show



clearly that preformed dietary DHA is the preferred source during brain growth and development. They also imply that body stores obtained from the mother can be an important, possibly critical, source of this necessary fatty acid.

The study also reported a two-fold increase in liver n-3 LC-PUFAs when the ALA + DHA diet was fed compared with the alpha-linolenic acid formula. Further, consumption of ALA + DHA suppressed liver synthesis of labeled DHA compared with the alpha-linolenic acid diet (9.9 mg/liver vs. 40 mg/liver). This observation also confirms previous reports of reduced DHA synthesis when DHA is consumed.

The authors noted that the level of two percent DHA in the diet is relatively high compared with most human milk, except among mothers consuming high fish diets. The relative contribution of body stores to brain DHA might be expected to vary with the availability of dietary DHA. The authors also suggested that low body stores could contribute to the responsiveness of preterm infants to supplemental DHA. The implications for human nutrition from this work buttress the importance of DHA in maternal and infant diets. Although the study was conducted in rats, the similarities in brain growth and development, fatty acid pathways, and neurodevelopment between humans and rats put these findings in the spotlight. They add further support to the recent regulatory decision to supplement human infant formula with DHA and arachidonic acid. Isn't it time maternal dietary DHA received similar emphasis?

Lefkowitz W, Lim SY, Lin Y, Salem N Jr. Where does the developing brain obtain its docosahexaenoic acid? Relative contributions of dietary alpha-linolenic acid, docosahexaenoic acid, and body stores in the developing rat. Pediatr Res *2005;57:157-165.*

Weaning Foods with DHA Improve Visual Acuity in Older Breast-Fed Infants

Improved visual acuity and retinal function in breast-fed infants compared with those fed formula lacking omega-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) has been amply demonstrated. As the proportion of breast milk in the infant's diet diminishes, exposure to n-3 LC-PUFAs falls, because replacement foods seldom provide these fatty acids. The infant's blood docosahexaenoic acid (DHA) level also declines. Few infant weaning foods contain these fatty acids, with the exception of n-3 PUFA-enriched egg yolk and DHA-supplemented infant formula. Once solid foods become the mainstay, canned fish and egg yolk could provide these PUFAs, but that is unlikely to occur much before one year of age.

Dennis Hoffman and colleagues at the Retina Foundation in Dallas, Texas, USA, were curious about the interval between 6 months of age and one year and whether exposure to DHA, a key n-3 LC-PUFA involved in retinal function, might affect visual function. Two groups of 6-month old, healthy, term infants exclusively breast-fed for at least four months were randomly assigned to consume one jar of baby food per day for six months. Mothers intended to continue breast-feeding. Fifty-one (out of 55) infants completed the study. Test baby food was enriched with DHA-containing egg yolk and provided approximately 10 times more linoleic acid, 80 times more arachidonic acid, 30 times more alpha-linolenic acid, and 115 times more DHA than the control baby food. The test and control baby foods contained 6.5 and 0.8 g fat/100 g, respectively. One jar of the test baby food contained about 130 mg DHA.

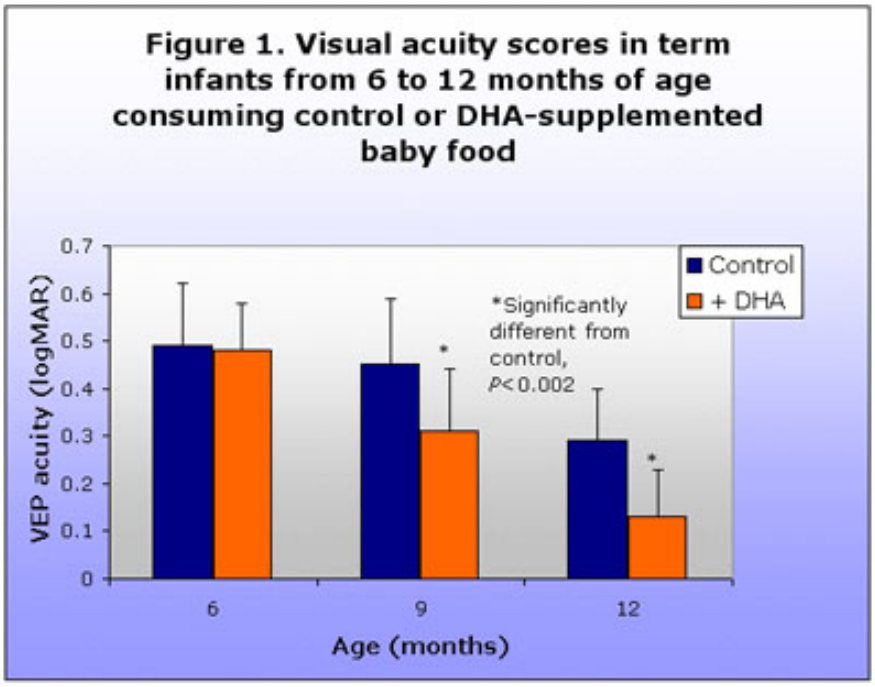
Infant visual development was assessed at six, nine, and 12 months by sweep visual evoked potential (VEP) expressed as log minimum angle of resolution. Stereoacuity was evaluated by forced-choice preferential looking using the Infant Randot Stereoacuity cards. The investigators also measured blood lipids, total antioxidant capacity, and growth.

At the end of the study, 65 percent of control and 80 percent of DHA-supplemented infants were weaned from human milk to formula before 12 months of age. Only four infants consumed DHA-enriched formula at weaning. On average, both groups of infants consumed between two-thirds and three-quarters of a jar of baby food daily (84 and 72 g/day in control and test groups, respectively). Estimated daily intakes of DHA from breast milk and food for control and test groups were about 37 and 111 mg/day, respectively.

From six to 12 months of age, red blood cell DHA concentration in control infants declined significantly from 3.8 to 3.0 percent (P=0.01) and increased significantly in the DHA-supplemented infants from 4.1 to 5.5 percent (P=0.002). These DHA responses differed significantly between groups.

Both groups of infants improved their visual acuity scores

during the six-month study, but the improvement was significantly greater, that is scores were significantly lower, for DHA-supplemented infants compared with controls (Figure 1). Visual acuity scores were significantly and inversely correlated with red blood cell DHA levels. Stereoacuity scores improved in both groups, but scores at 12 months did not differ between the two groups. In spite of the greater energy and fat content of the test food, groups did not differ in any growth measures.



Many studies on n-3 LC-PUFA supplementation in infancy have focused on the first six months of life and preterm infants. Effects of n-3 LC-PUFA supplementation have been more difficult to demonstrate in healthy term infants whose fatty acid stores and nutritional status at birth are in the "healthy" range. Maturation of visual function, however, depends critically on the availability of DHA. This study demonstrates that the continued availability of DHA throughout the entire first year of life can benefit infant visual maturation and function. The magnitude of the visual improvement reported here is equivalent to about one and a half lines on an eye chart. Subsequently (2005) Hoffman's team concluded that benefits to visual acuity of n-3 LC-PUFA supplementation that included the addition of arachidonic acid continue through the first year of life.

From the time of weaning, nearly all solid infant foods with the exception of egg yolks and fatty fish, contain only negligible amounts of n-3 LC-PUFAs. This study provides firm evidence that improving the nutritional quality of weaning foods by the addition of n-3 LC-PUFAs or at least DHA, along with educating mothers about the food sources of DHA for their infants, could provide measurable functional benefits in infant development. As this and the preceding article illustrate, outreach to mothers and by extension all women of child-bearing age about the nutritional value of dietary n-3 LC-PUFAs is long overdue.

Hoffman DR, Theuer RC, Castaneda YS, Wheaton DH, Bosworth RG, O'Connor AR, Morale SE, Wiedemann LE, Birch EE. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. J Nutr *2004;134:2307-2313.*

Immune Function

Resolvin E1: Potent Anti-inflammatory Agent Derived from EPA

It is now recognized that long-chain polyunsaturated fatty acids (LC-PUFAs) of both the omega-6 (n-6) and omega-3 (n-3) types can be converted by various enzymes to substances that have pro and anti-inflammatory properties, and sometimes both. In general, substances derived from n-3 LC-PUFAs, particularly eicosapentaenoic acid (EPA), counteract the inflammatory substances derived from arachidonic acid. However, they also decrease the production of other inflammatory substances such as cytokines, cellular adhesion molecules and leukotrienes. EPA, in the presence of aspirin, can be oxygenated by an enzyme, COX-2, to form a series of anti-inflammatory substances known as E-series resolvins. Resolvins were first identified by Charles Serhan and colleagues at the Harvard Medical School, Boston, Mass., USA, during the spontaneous resolution phase following acute inflammation. Initial conversion of EPA takes place in vascular endothelial cells in conjunction with aspirin, acetaminophen, or indomethacin, with final production of resolvin E1 occurring in polymorphonuclear leukocytes associated with the vascular endothelium.

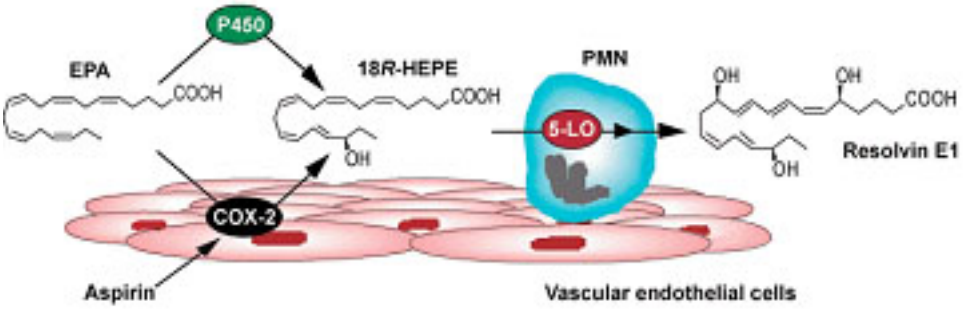


Figure 1. Proposed scheme for the generation of resolvin E1 from EPA in endothelial cells in the presence of aspirin and polymorphonuclear leukocytes. Reproduced from *The Journal of Experimental Medicine* 2005;201:713-722 by copyright permission of Rockefeller University Press.

In this paper, Serhan's team reports the detection of EPA-derived resolvin E1 in the plasma of healthy human subjects given EPA (1 g) and aspirin (160 mg). The appearance of resolvin E1 occurred within five minutes. The study extends previous observations in mice and human endothelial cells on the production of resolvin E1 and characterizes its anti-inflammatory and stereochemical properties. By synthesizing resolvin E1 from precursors, the investigators positively identified the active substance isolated from human plasma. This research provides additional evidence that resolvin E1 is produced in endothelial cells exposed to aspirin through the activity of the enzyme cyclooxygenase-2 that converts EPA to 18R-hydroxyeicosapentaenoic acid (18R-HEPE). Upon interaction with leukocytes and exposure to the enzyme 5-lipoxygenase, 18R-HEPE is converted to resolvin E1 (Figure 1). The authors suggest that cytochrome P450 monooxygenase could also convert EPA to 18R-HEPE.

To assess the anti-inflammatory properties of resolvin E1 in skin, the investigators used the mouse dorsal air pouch, a cavity lined with macrophage-like cells. These types of cells are also associated with atherosclerotic lesions. Inflammatory responses in this tissue are stimulated by the cytokine TNF-alpha, which stimulates the release of a variety of chemical mediators and cellular attractants through the activation of specific nuclear transcription factors. The result of these activities is the recruitment and infiltration of leukocytes (white blood cells) into the tissue.

When mouse air pouch was stimulated by TNF-alpha in the presence of synthetic or biologically produced resolvin E1 at a dose of 100 ng/mouse, leukocyte infiltration was reduced by 50 to 70 percent. For comparison, the equivalent inhibition required 10µg dexamethasone or 1.0 mg aspirin per mouse, indicating that resolvin E1 is several orders of magnitude more potent than these anti-inflammatory drugs.

This paper reports several series of studies to elucidate the mechanism(s) by which resolvin E1 counteracts inflammatory responses. The findings indicate that resolvin E1 in conjunction with aspirin acts during the resolution phase of inflammation by inhibiting the activation of a specific nuclear transcription factor (NF-kappa B) responsible for the production of inflammatory cytokines and mediators that stimulate the attraction of leukocytes. The investigators provided detailed evidence that helps explain the beneficial effects of EPA in diminishing inflammatory responses in a variety of tissues and clinical conditions. Further, their findings indicate that aspirin facilitates the generation of anti-inflammatory lipids, another means by which it combats inflammation.

In the accompanying editorial, Flower and Perretti suggest the need for a clinical trial to determine whether aspirin and other nonsteroidal anti-inflammatory agents have additive effects with EPA in such clinical conditions such as rheumatoid arthritis and cardiovascular disease. The potential effectiveness of such substances as therapeutic agents is apparent and Serhan's team is currently evaluating this prospect. From the perspective of wellbeing, having EPA on hand in one's tissues seems a reasonable precaution.

Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, Yang R, Petasis NA, Serhan CN. Sterochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. J Exp Med *2005;201:713-722.*

Flower RJ, Perretti M. Controlling inflammation: a fat chance? [Editorial] J Exp Med *2005;201:671-674.*

Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med *2000;192:1197-1204.*

Morale SE, Hoffman DR, Castaneda YS, Wheaton DH, Burns RA, Birch EE. Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity. Early Hum Dev *2005;81:197-203.*

Some Cellular Adhesion Molecules in Healthy People Reduced with Consumption of n-3 PUFAs

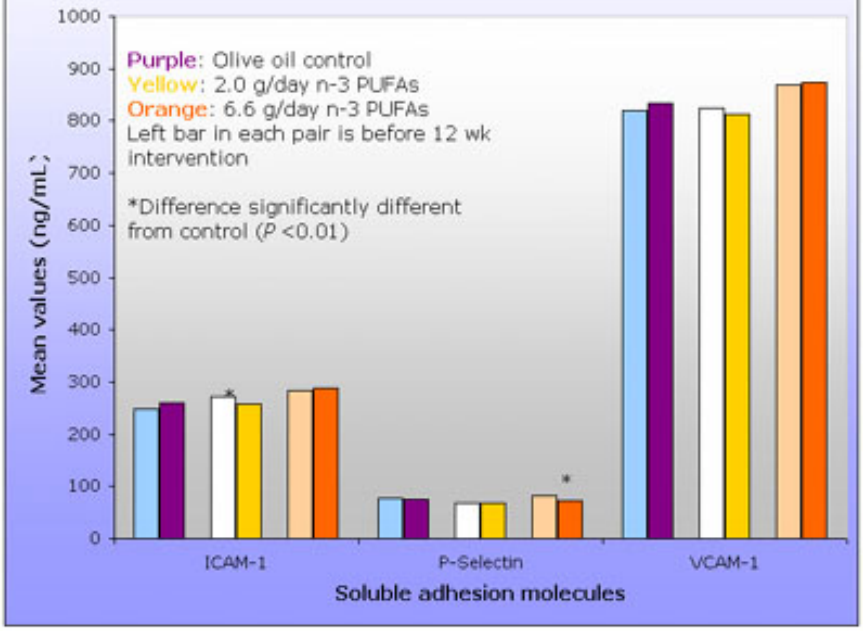
The development of atherosclerosis is accompanied by inflammation which exacerbates the condition. The inflammatory process entails in part the interaction of different types of white cells (e.g. monocytes, polymorphonuclear leukocytes) with the endothelial cells lining the blood vessels and the atherosclerotic lesions themselves. Various adhesion molecules found in endothelial cells, platelets, and the circulation, known collectively as soluble cellular adhesion molecules or sCAMs, facilitate these interactions, enabling the white cells to infiltrate the endothelium and atherosclerotic lesions. Patients with atherosclerosis and abnormal blood lipids have increased levels of adhesion molecules and inflammatory mediators, which are decreased with the consumption of fish oil.

In the randomized, double-blind, placebo-controlled study described here, Eschen and colleagues at the Aalborg Hospital in Aalborg, Denmark, examined the effects of moderate and high intakes of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) on three types of adhesion molecules in healthy subjects. Sixty healthy subjects aged 38 years on average were randomly assigned to consume 10 g/day of oil supplements containing 6.6, 2.0, or 0 g/day of EPA + DHA for 12 weeks. Those consuming 0 and 2 g/day n-3 LC-PUFAs consumed 10 and 8 g/day of olive oil, respectively. Serum lipids, granulocyte (a family of white blood cells) fatty acids, and soluble cellular adhesion molecules were measured at baseline and after 12 weeks. The three types of adhesion molecules measured were intercellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM), and P-selectin, a molecule expressed in activated platelets and granules of endothelial cells.

At baseline, it was noted that intercellular adhesion molecule levels were positively associated with total and low-density lipoprotein cholesterol levels and inversely with granulocyte docosahexaenoic acid (DHA) levels. Men had significantly higher levels of P-selectin and vascular cell adhesion molecule-1 than women. After 12 weeks, serum triglyceride levels decreased with increasing consumption of n-3 LC-PUFAs, but cholesterol levels were unaffected.

In the analysis of all subjects, intercellular adhesion molecule-1 levels were significantly reduced compared with controls in participants consuming 2 g/day n-3 LC-PUFAs, but not in those consuming 6.6 g/day (Figure 1). Levels of P-selectin were significantly reduced compared with controls only in people consuming the highest dose of n-3 LC-PUFAs. Levels of vascular cell adhesion molecules were unaffected by dietary treatment.

Figure 1. Changes in cellular adhesion molecules in healthy subjects consuming olive oil, 2.0 or 6.6 g/d n-3 PUFAs for 12 weeks



When the data were analyzed by gender, there was a significant reduction in P-selectin compared in men who consumed 6.6 g/day of n-3 PUFAs compared with those who consumed olive oil (-11 ± 10 vs. 1 ± 5 ng/mL), but not in those consuming 2.0 g/day n-3 LC-PUFAs. At the outset, men had significantly higher levels of P-selectin than women (83 ± 20 vs. 69 ± 18 ng/mL). No other cellular adhesion molecules were affected by the consumption of n-3 PUFAs in men.

In women, both P-selectin and intercellular cell adhesion molecule-1 levels were significantly reduced compared with

baseline values with the consumption of 6.6 g/day and 2.0 g/day n-3 PUFAs, respectively. In women consuming 6.6 g/day n-3 PUFAs, vascular adhesion molecule-1 levels were significantly increased by 57 ± 66 ng/mL compared with baseline and control values.

What do these responses mean? The findings provide some evidence that n-3 LC-PUFAs reduce cellular adhesion molecules and may reduce endothelial activation and inflammatory activity in blood vessels. Granulocyte DHA content was inversely associated with intercellular adhesion molecule-1 levels at baseline. A relatively high dose of n-3 LC-PUFAs (6.6 g/day), but not the lower dose (2.0 g/day) significantly lowered P-selectin levels by about 10 percent, but whether this reduction is clinically relevant in healthy subjects is unknown.

In healthy women, the lower dose of n-3 LC-PUFAs reduced intercellular adhesion molecule-1 levels by about 10 percent, but higher amounts of n-3 LC-PUFAs did not change the level of this adhesion molecule differently from placebo. Similar responses have been reported in elderly subjects and those with heart disease.

These findings indicate that n-3 LC-PUFAs may reduce levels of various cellular adhesion molecules, but that gender, health status, and dose are all important factors in the inflammatory response to these fatty acids. They provide some evidence for contrasting effects with the consumption of low and high doses of n-3 LC-PUFAs, perhaps reflecting the complexity of inflammatory responses.

Eschen O, Christensen JH, De Caterina R, Schmidt EB. Soluble adhesion molecules in healthy subjects: a dose-response study using n-3 fatty acids. Nutr Metab Cardiovasc Dis *2004;14:180-185.*

Mental Health

Fish Oil and Vitamins May Boost Brain Power Later in Life

Long-chain n-3 polyunsaturated fatty acids (n-3 LC-PUFAs) have been positively associated with cognitive function in infants, young children, and adults in middle and late life. Fish consumption has also been linked to reduced risk of developing Alzheimer's Disease. There are many unanswered questions about the importance and duration of the reported effects of n-3 LC-PUFAs in brain function, and data from longitudinal studies are limited. Fortunately, a large database providing cognitive information on people born in 1921 and 1936 exists at the University of Aberdeen, U.K. People from the original cohort, aged 64 years, formed the basis for a nested case-control study on the use of food supplements and the relationship between red blood cell n-3 LC-PUFA concentration and cognitive aging. Findings were reported by Lawrence Whalley and colleagues and described here.

Of 957 men and women who could be exactly matched to the original cohort, 567 were randomly selected for contact, and 350 completed all assessments. Red blood cell membrane fatty acid content was determined in 60 participants who consumed fish oil supplements regularly for longer than the preceding six months, and 60 people who did not use any food supplements. Participants in the two groups were matched by sex and intelligence quotient (IQ) score at age 11. Fish oil supplements in the U.K. contain vitamins A, D, and E to retard peroxidation.

Cognitive assessment at age 11 was determined by scores on the Moray House Test no. 12, an omnibus group-administered standard test. At age 64, the Mini-Mental State Examination was used to detect dementia. Non-verbal reasoning was assessed using Raven's Standard Progressive Matrices and verbal memory scored using the Rey Auditory Verbal Learning Test. The revised Wechsler Adult Intelligence Scale was also administered to assess speed of information processing, psychomotor performance, and constructional ability.

Of the 350 participants, 65% or 229 did not use any food supplements. Seventy-two (20%) participants consumed fish oil, 29 (8%) took vitamins, and 20 (6%) took other supplements. Participants did not differ by supplement use in education, blood pressure, body mass index, ratio of triglycerides to high-density lipoproteins, and IQ at age 11. Triglyceride concentration was significantly higher in people who took vitamins compared with all other participants. Those who consumed fish oil supplements also consumed significantly higher amounts of vitamin C and vegetable fiber.

At age 64, users of any type of food supplement had

Table 1. Cognitive test scores in adults by use of food supplements for 6 mos. or longer*

	Supplement consumed				
Cognitive test	**None** *n* =229	**Fish oil** *n* =72	**Vitamins** *n* =29	**Other** *n* =20	***P*** (Anova)
IQ at age 11	99.6 ± 15.1	103.9 ± 14.4	106.1 ± 13.9	101.6 ± 11.9	NS
IQ at age 64	98.4 ± 14.9	104.1 ± 14.9†	107.2 ± 17.2†	105.2 ± 11.7†	<0.01
Auditory verbal learning	56.9 ± 12.0	58.7 ± 12.4	62.1 ± 14.1	60.8 ± 9.8	NS
Digit symbol subtest	42.0 ± 11.7	47.5 ± 11.0§	50.6 ± 12.5§	51.2 ± 9.9§	<0.001

* Mean ± SD
† Significantly greater than nonusers $P<0.02$
§ Significantly greater than nonusers before and after adjustment for IQ at age 11, $P<0.02$

significantly higher IQ scores than those not using food supplements (Table 1). Of the five cognitive function tests, scores on the digit symbol subtest of the Wechsler test were the only measure that was significantly higher among all food supplement users compared with nonusers before and after adjustment for IQ at age 11. There were no significant differences among the groups according to type of supplement.

Data on the LC-PUFA content of red cell membranes were log-transformed to improve nomality of distribution and correlation coefficients were calculated between cognitive test scores and various LC-PUFA concentrations. Total n-3 PUFAs, eicosapentaenoic acid, and docosahexaenoic acid (DHA) concentrations were positively associated with IQ in childhood and at age 64 (Table 2), whereas the ratio of n-6 to n-3 PUFAs was inversely associated with both IQ scores. When the analysis was controlled for childhood IQ, two significant correlations emerged. The ratio of DHA to arachidonic acid (AA) was positively associated with IQ at age 64 (P <0.02) and block design subtest scores (P <0.01). These findings suggest that at least some aspects of cognitive performance in later life are independent of cognitive ability in childhood and that fish oil and vitamin supplements may benefit cognitive performance.

While these results are encouraging, the potential confounding by other food supplements and vitamins, and healthier food habits among fish oil consumers, complicate the interpretation. The same is true for the lack of significant differences in cognitive performance between fish oil consumers and matched nonusers. The findings related to red cell membrane n-3 LC-PUFA concentrations and cognitive tests gave more consistent results, but do not explain why cognitive performance of those consuming fish oil were similar to those of matched subjects who were nonusers. Use of biomarkers would appear to be a more reliable measure of n-3 LC-PUFA intake than questionnaires. The potential value of n-3 LC-PUFA consumption in maintaining brain function later in life would be an extraordinary addition to the established benefits of these fatty acids in heart health. However, it will take randomized, controlled, intervention trials to establish such an outcome.

Whalley LJ, Fox HC, Wahle KW, Starr JM, Deary IJ. Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. Am J Clin Nutr *2004;80:1650-1657.*

Depression Less Frequent in Young Finnish Adults Who Consume Fish Weekly

Among the factors associated with the occurrence of depression are low tissue levels of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) and infrequent fish consumption. Plasma and red cell concentrations of the two major n-3 LC-PUFAs in fish, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are lower in depressed patients than subjects without depression, and the prevalence of depression is higher among populations with low fish consumption compared with those having higher fish intake. Most data describing these relationships have come from cross-cultural studies, patient-control comparisons, or observations in small groups of people. In this investigation, Markku Timonen and colleagues at the University of Oulu in Finland report the prevalence of depression in a birth cohort of Finnish adults aged 31 years.

Table 1. Rates of depression per 100 persons and odds ratios for developing depression by frequency of fish consumption in a Finnish cohort aged 31 years

Diagnosis	Cases	Frequency of fish consumption		Odds Ratio (95% CI)*
		Rarely	Regularly	
	← — —	*Number (%)*	— — — →	
Women				
Doctor†	236 (5.3)	96 (6.1)	140 (4.9)	1.3 (0.9-1.9)
Questionnaire score >2.0	312 (7.1)	136 (8.7)	176 (6.1)	1.4 (1.1-1.9)
Doctor + score > 2.0	66 (1.6)	36 (2.5)	30 (1.1)	2.6 (1.4-5.1)
Men				
Doctor†	146 (3.6)	58 (3.9)	88 (3.5)	0.8 (0.5-1.3)
Questionnaire score > 2.0	171 (4.3)	64 (4.3)	107 (4.3)	0.8 (0.5-1.2)
Doctor + score > 2.0	41 (1.0)	14 (1.0)	27 (1.1)	0.4 (0.1-1.2)

*Odds ratios calculated with adjustment for body mass index, serum total cholesterol, and socioeconomic situation

†No self-reported doctor-diagnosed depression

Data on the occurrence of depression was determined by doctor diagnosis and scores above 2.0 on the Hopkins Symptom Checklist-25 questionnaire in 5689 of the total 8463 subjects (67%). Fish consumption was assessed by food frequency questionnaire. People were defined as rare fish eaters if they consumed fish monthly or less and regular fish eaters if they ate fish weekly or more. Odds ratios for rates of depression were calculated by logistic regression analyses using two different models, one controlling for body mass index, serum total cholesterol and socioeconomic situation, and the other adjusted for alcohol intake, smoking, physical inactivity, and marital status.

As is reflected in the prevalence of depression worldwide, depression was more common among women than men regardless of how the condition was assessed, i.e., doctor-diagnosed, depression rating scale score, or a combination of the two (Table 1). Depression was more frequent among those women eating fish rarely compared with frequent fish eaters and this was reflected in the odds ratios. For the most stringent assessment, rating scores plus doctor diagnosis, the odds of depression in women were about two and a half times greater for those who ate fish rarely, in both adjusted models. In men, fish consumption was unrelated to prevalence of depression.

The beneficial association between regular fish consumption and reduced prevalence of depression in these young adults provides no indication whether the association might be attributed to n-3 LC-PUFA intake, healthier lifestyle, or other factors associated with frequent fish consumption. Nevertheless, these data are consistent with previous reports on depression in the general Finnish population, with emerging findings on the use of n-3 LC-PUFAs in the treatment of depression, and with the expanding literature documenting an association between low fish consumption and higher rates of depression and other mental conditions.

Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Rasanen P. Fish consumption and depression: the Northern Finland 1966 birth cohort study. J Affect Disord *2004;82:447-452.*

Table 2. Pearson's correlation coefficients between cognitive test scores and selected log-transformed red blood cell n-3 PUFA measures in 120 matched users and nonusers of fish oil supplements.

Cognitive test	Total n-3 PUFAs	DHA:AA
IQ at age 11	0.211*	0.148
IQ at age 64	0.211*	0.269†
Auditory verbal learning test	0.147	0.105
Block design test	0.213*	0.291†
Digit symbol subtest	0.181	0.215*
Uses of objects test	-0.070	0.049
Raven's progressive matrices	0.195*	0.197*

*$P<0.05$

†$P<0.01$