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In the Direction You Choose

The year's close invites serious reflection, 2009 having conferred a plethora issues to ponder. Few have been spared the ironies and cruelties of war, just or otherwise, the hardships of economic shrinkage and job losses, and continued injustices of all varieties. We extend our sympathies to those who are struggling against uninvited tides and wish them the best in reversing them.

Cartoon © John O'Brien/Condé Nast Publications/ www.cartoonbank.com

On a more positive note, advances in the understanding of polyunsaturated fatty acids (PUFAs) and how they might be harnessed to improve wellbeing continue to suggest useful applications. Improved outcomes or lower risks in age-related macular degeneration, chronic kidney disease and heart health have been reported in those with higher intakes of long-chain omega-3 PUFAs (n-3 LC-PUFAs) or fatty fish as described in this issue of the *PUFA Newsletter.*

In contrast, two epidemiological reports cast doubt on the usefulness of n-3 LC-PUFAs in deterring type 2 diabetes. Clemens von Schacky discusses these studies in this issue's guest article. Might these reports encourage people at risk of diabetes to dismiss these fatty acids? Uncertain scientific findings confuse consumers and provide an excuse to ignore results that rest on solid ground. Those with the disease can lower their chances of heart problems by increasing their intake of n-3 LC-PUFAs. With soaring rates of obesity and diabetes, we can ill afford to confuse the recommendations for reducing the risk of heart disease and mortality in diabetics with uncertainties about these fatty acids and the chance of developing diabetes. Controlling obesity and adopting healthier lifestyles can mitigate the severity of this affliction.

I wish you, our readers, good health and pleasure for 2010 and hope you enjoy the wonderfully ironic cartoon by John O'Brien. These determined salmon cope creatively with winter, even as those of us who love skiing head in the opposite direction. May you ski happily in the direction you choose and encounter many salmon.

I believe there is a time for meditation in cathedrals of our own.

– Billy Joel

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Type 2 Diabetes: Do Omega-3 LC-PUFAs Make a Difference?

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Obesity is a major, if not the most important, risk factor for development of diabetes.[1] Obesity is the consequence of a positive caloric balance, i.e., consuming more calories than are expended. The evidence for any component of a diet being related to diabetes risk—positively or negatively—is much weaker. Therefore, the European Society for Cardiology and other societies recommend weight management with a target body mass index of 25 kg/m^2 or less for the prevention of diabetes.[1] Weight management may very well be the most important measure to prevent type 2 diabetes. A negative caloric balance is the cornerstone of weight loss. According to the results of two recent intervention studies, reducing caloric intake is more important than diet composition diet for weight loss.[2,3] Nevertheless, the idea appeals to many that eating a specific source of calories, in this case fish containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), might prevent type 2 diabetes.

Two recent epidemiologic studies found no evidence to support the idea that a higher consumption of fish, specifically fish rich in EPA and DHA, is associated with reduced risk for developing type 2 diabetes.[4,5] The study by Kaushik et al. was embedded in the Nurses´ Health Study in the United States and based on 195,204 adults without pre-existing chronic disease at baseline, who were followed for 14 to 18 years. The authors observed 9,380 new cases of type 2 diabetes. Data were adjusted for several confounding factors (including caloric intake and energy expenditure by physical activity). The study by Woudenbergh et al. included 4,472 Dutch participants aged more than 55 years without diabetes at baseline, who were followed for 15 years. The authors observed 463 new cases of type 2 diabetes. Data were adjusted for multiple confounding factors (including energy expenditure, but not caloric intake). Failure to adjust for caloric intake might have affected the overall results. Intake of lean fish tended to be associated positively with type 2 diabetes (relative risk for the highest group: 1.30 (95%CI 1.01, 1.68), *P* for trend= 0.06), but fatty fish was not. Both studies concluded that there was no favorable effect of fish intake, specifically fish containing EPA and DHA on the risk of developing type 2 diabetes. The results are in line with the results of previous studies based on dietary questionnaires or plasma fatty acid concentrations.[6,7]

So far, most epidemiologic studies on a relation between fish or EPA+DHA and development of a disease have been based on assessment of dietary intake. Conventionally, intake of fish and other dietary components is assessed by dietary questionnaires, which have been criticized for being inaccurate and for leading to systematic errors.[8] Originally, the dietary questionnaire of the Nurses' Health Study contained only one question relating to fish intake. The attempt to quantify intake of fish focused on portion size and frequency. Frequency of intake was assessed in 9 steps from "almost never" to "6 or more times per day."[5] Later, the questionnaire was refined, asking for different species of fish and grouping fish into categories, with the range of serving sizes shown in parentheses:[5] (a) dark-meat fish such as mackerel, salmon, sardines, bluefish, or swordfish (84 to 140 g); (b) canned tuna (84 to 112 g); (c) other fish (84 to 140 g); and (d) shrimp, lobster, or scallops (98 g). Within the categories mentioned, EPA+DHA content can vary, depending on species, season and provenance.[9] Also, differences in the concentrations of EPA+DHA in a given species exist, depending on whether the fish had been wild-caught or farmed, canned or fresh and other factors.[9] The fatty acid composition of farmed fish can also vary, because it partially depends on the composition of the fish feed. For these and other reasons, calculating a daily intake of EPA+DHA based on dietary questionnaires is less than precise. As an alternative, blood levels of EPA+DHA can be measured in epidemiologic studies.[7] If these levels are measured in red blood cells with a standardized methodology (e.g., the omega-3 index), they reflect levels in the heart and can discriminate risk better. For example, the chance of sudden cardiac death with an omega-3 index of 3.3% is 10 times the risk of sudden death with an omega-3 index of about 7%.[10]

In spite of the methodological shortcomings mentioned, the evidence is quite compelling that fish and EPA+DHA are not related to the risk of type 2 diabetes. Although type 2 diabetes is a disorder of glucose metabolism, the hallmarks of the disease are macrovascular and microvascular complications. Macrovascular complications are myocardial infarction, stroke and peripheral vascular disease, whereas microvascular complications comprise renal, ophthalmologic and similar diseases. The vascular complications are the most important limiting factors for life expectancy and quality of life for type 2 diabetics.[1] In randomized intervention studies in people with or at risk for coronary artery disease, EPA+DHA have already proven their effectiveness in reducing total mortality, sudden cardiac death, fatal and non-fatal myocardial infarctions.[10] In type 2 diabetics, EPA and DHA have been shown to exert antiatherogenic and antithrombotic effects like lowering blood pressure and heart rate, improving dyslipidemia, reducing inflammation, and enhancing vascular and platelet function.[11] Thus, the essential evidence necessary to justify large-scale clinical trials with clinical endpoints in type 2 diabetics is available. Fortunately, two large randomized intervention studies are ongoing, seeking to define the value of EPA+DHA in reducing cardiovascular death, myocardial infarction and stroke in type 2 diabetics[12] (see also www.clinicaltrials.gov, number NCT00135226). Although the results of these trials are pending, some optimism is in order that EPA and DHA will be established as an option to reduce vascular complications and prolong the lives of people with type 2 diabetes.

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CARDIOVASCULAR HEALTH

Fish or Long-Chain Omega-3 Intake Not Associated With Heart Failure in Older Adults

Recent reviews of the cardioprotective properties of fish oils, or the long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) they contain, have concluded almost unanimously that consumption of these fatty acids can lower the chance of dying from heart disease by about 35% to 50% in individuals without heart disease. Added to the epidemiological findings are those from randomized controlled trials, which reported significantly lower occurrence of coronary heart disease events (e.g., myocardial infarction) and cardiovascular mortality. It is tempting extend the findings for specific heart disease or mortality outcomes to all types of heart disease, but doing so invites trouble. Little wonder the public shakes its head when the media reports that the n-3 LC-PUFAs in fish oil "may not be as effective as people have been led to believe." Many do not appreciate the distinctions between heart failure and heart disease nor the limitations of a single study.

Heart failure, the inability to pump enough blood through the body, increases the risk of sudden death 5-fold. Does eating fish regularly or consuming long-chain omega-3 fatty acids reduce the chance of developing heart failure? The jury requests more data.

Some confusion arises from similar and confusing nomenclature for the different types of cardiovascular disease. Heart disease and cardiovascular disease are umbrella terms used interchangeably to describe diseases of the heart and blood vessels, respectively. Coronary heart disease and coronary artery disease both refer to damaged or narrowed arteries supplying the heart. Many different types of heart disease exist, of which heart failure, also called congestive heart failure, is one example. In this condition, the heart cannot pump enough blood to meet the body's needs. Patients with heart failure are 5 times more likely to succumb to sudden death. The condition develops equally in men and women. Does fish or n-3 LC-PUFA consumption reduce the chance of developing heart failure?

One observational study in US adults 65 years of age or older reported that eating tuna or other broiled or baked fish was associated with a 20% to 32% lower chance of developing heart failure, depending on the frequency of fish consumption. Another study reported a lower risk of heart failure with fish or n-3 LC-PUFA intake, but the relationship was not dose-related or statistically significant. Finally, the GISSI-Heart Failure study reported that chronic heart failure patients who consumed 1 g/day of n-3 LC-PUFAs for nearly 4 years had a small, but significant (14%), reduction in their risk of cardiovascular mortality. Thus, some evidence suggests that fish or n-3 LC-PUFA consumption might benefit patients with heart failure.

In this study, Coosje Dijkstra and colleagues from Erasmus University, the Netherlands, examined the relationship between n-3 LC-PUFA or fish consumption and the chance of developing heart failure in the general population aged 55 years or older. Participants were part of the ongoing Rotterdam Study, a prospective investigation of cardiovascular, neurological, ophthalmological and endocrine diseases in adults 45 years of age or more. Of the more than 10,000 eligible participants, 7,983 agreed to enroll. After exclusions for existing heart failure or incomplete data, the analysis included 5,299 participants with a mean age of 68 years. Participants were followed for an average of 11 years.

The investigators estimated fish consumption at baseline from a food checklist and semi-quantitative food frequency questionnaire from which they calculated the consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the principal n-3 LC-PUFAs in fish. Consumption of fish was divided into 3 categories: 0, 1 to 19 g/day, and 20 or more g/day. EPA and DHA consumption was divided into quintiles ranging from less than 28 mg/day to more than 212 mg/day . The associations between EPA plus DHA or fish consumption and heart failure were estimated from Cox proportional hazards models and relative risks estimated from them. Analyses were adjusted for age, sex and energy intake, with body mass index, education, consumption of alcohol, total and saturated fat, *trans* fatty acids and meat intake added to the models as additional confounding variables.

Heart failure was defined according to the criteria of the European Society of Cardiology. A diagnosis of heart failure during followup was classified as definite, probable, possible or unlikely.

Interestingly, 30% of the participants did not eat fish. The mean fish intake was 16 g/day (~ 0.5 oz), with a median daily intake of EPA plus DHA of 88 mg. During followup, 669 participants developed heart failure and 1,182 died.

Intakes of EPA plus DHA or fish were not significantly related to the occurrence of heart failure in adjusted

Table. Risk* of incident heart failure with increasing consumption of EPA plus DHA in 5,299 Dutch men and women aged 68 years, on average, by diabetes status

		Quartiles of EPA plus DHA intake, mg/day				
	No.	<34	34 - 89	90 – 183	>183	*P* for trend
Diabetes +	479	1.00	0.90 (0.52 – 1.54)	1.02 (0.60 – 1.75)	0.58 (0.32 – 1.06)	0.08
Diabetes -	4,820	1.00	0.99 (0.79 – 1.24)	0.84 (0.66 – 1.07)	0.96 (0.75 – 1.22)	0.62

*Risks are hazard ratios (95% confidence intervals) adjusted for age, sex, energy intake, smoking, body mass index, education and intake of alcohol, total fat, saturated fat, *trans* fat and meat.

Neither the consumption of fish nor EPA plus DHA was related to the chance of developing heart failure in 68-year-old men and women. However, those with diabetes tended to be less likely to develop the condition as omega-3 intake increased.

analysis. Those who ate ≥ 20 g of fish per day were just as likely to develop heart failure (Hazard Ratio = 0.96, 95% CI = 0.78-1.18, *P* = 0.39) as participants who did not eat fish (Hazard Ratio = 1). When the participants were separated according to age, sex, presence of diabetes or body mass index, risk of incident heart failure in diabetic participants was inversely associated with EPA plus DHA consumption (Table). The trend for decreased risk reached borderline significance (*P* = 0.08). Chance of heart failure was not related to n-3 LC-PUFA intake in any other sub-group.

These findings contrast with those in a somewhat older US population sample in whom fish or EPA plus DHA was associated with a lower chance of developing heart failure. In both studies, the average fish and EPA plus DHA intakes were similarly low. With inconsistent findings from only a few studies, the existing data are insufficient to answer the question whether fish or n-3 LC-PUFA consumption reduces the chance of heart failure.

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Low Long-Chain Omega-3 in Carotid Plaque Associated with Neurologic Symptoms

The rupture of atherosclerotic plaque in the coronary arteries leads to myocardial infarction; in the carotid arteries, plaque rupture results in cerebrovascular or ocular events. Strategies to reduce the risks for plaque rupture include diet or statin drugs to increase plaque stability and surgical removal of the lesions. Each has varying degrees of success. One strategy with the possible potential to improve plaque stability has been widely overlooked: consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs).

Limited evidence suggests that long-chain omega-3 PUFAs may increase the stability of arterial plaque. In this study, low plaque omega-3 content was associated with neurologic symptoms in patients with carotid stenosis.

Six years ago, researchers at the University of Southampton, U. K., reported that patients awaiting carotid endarterectomy (surgical removal of plaque from the carotid arteries) readily incorporated dietary n-3 LC-PUFAs into these plaques. Moreover, the had no signs of inflammation and thicker fibrous caps compared with those in control patients, suggesting that the n-3-enriched plaques were more stable. But until now, there have been virtually no followup studies to the original report on the effect of n-3 LC-PUFAs on atherosclerotic plaque stability.

Hernan Bazan and colleagues at the New Orleans School of Medicine, USA, addressed the question of carotid plaque stability relative to their n-3 LC-PUFA content in patients with at least 50% stenosis (artery narrowing) undergoing carotid endarterectomy. The investigators estimated carotid stenosis using ultrasound imaging and assessed plaque stability from clinical criteria. Symptoms included transient ischemic attack, established stroke with good neurologic recovery in the previous 6 months or temporary or partial complete loss of sight.

The study involved 41 patients ranging in age from 44 to 84 years, with a mean age of 62. Twenty-four (59%) participants were considered asymptomatic,

but carried a similar atherosclerotic burden as those with symptoms. Samples of plaque underwent immunohistochemical, lipid and lipidomic analysis.

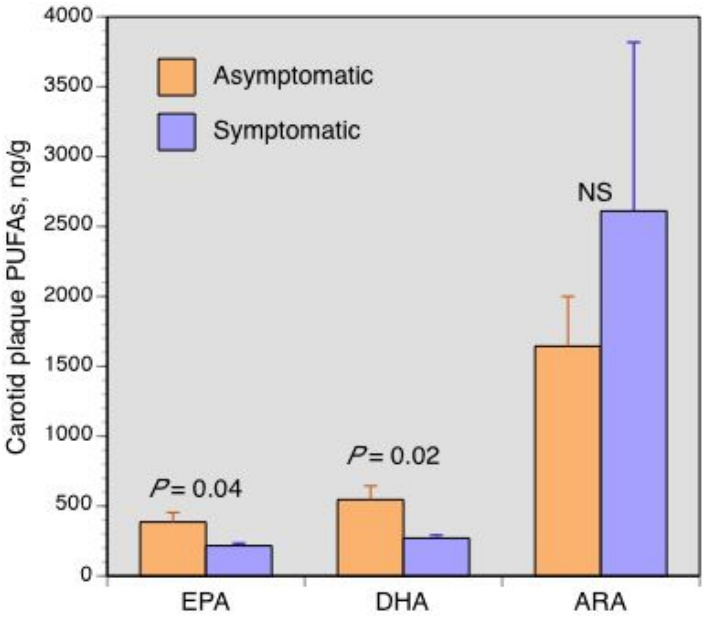

Figure. Concentrations of EPA, DHA and ARA in carotid artery plaques from patient with carotid artery stenosis with or without neurologic symptoms.

Comparing symptomatic with asymptomatic patients, the investigators observed that plaque from the former exhibited increased staining for CD68, a transmembrane protein marker for macrophages. The mean positive area for the staining of CD68 and its antibody was also significantly increased in the symptomatic patients. No other inflammatory markers were measured. The observations on CD68 indicate increased inflammatory cells in the plaques of symptomatic patients. In addition, carotid plaques from symptomatic patients were structurally distorted compared with those in asymptomatic patients.

Asymptomatic patients with carotid artery stenosis had significantly higher long-chain omega-3 levels and fewer inflammatory cells in their plaque compared with patients having neurologic symptoms.

With regard to n-3 LC-PUFAs, plaques from symptomatic patients contained significantly lower concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) compared with asymptomatic patients. The content of arachidonic acid was higher, but did not differ significantly between the two groups. These observations suggest a relationship between increased inflammation and decreased n-3 LC-PUFAs in the carotid arterial plaque of neurologically symptomatic patients. However, it remains to be demonstrated that higher concentrations of n-3 LC-PUFAs in arterial plaque improve plaque stability.

Findings from this small study are consistent with the earlier study on n-3 LC-PUFAs and plaque stability, but leave unanswered the question of whether these fatty acids affect plaque stability or contribute to the absence of neurological symptoms by diminishing plaque inflammation.

Bazan HA, Lu Y, Thoppil D, Fitzgerald TN, Hong S, Dardik A. Diminished omega-3 fatty acids are associated with carotid plaques from neurologically symptomatic patients: Implications for carotid interventions. **Vascular Pharmacol** *2009;51:331-336.*

High Fish Consumption and Lower Cardiac Risks in Acute Coronary Syndrome Survivors

Acute coronary syndrome is an umbrella term for acute myocardial ischemia, the chest pain that results from insufficient blood supply to the heart, owing to myocardial infarction or unstable angina. Observational studies and clinical trials have reported that fish consumption is associated with a significantly lower risk of myocardial infarction and coronary heart disease mortality.

In patients with angina or implantable cardioverter defibrillators the consumption of fish or fish oil has been associated with a higher risk of cardiovascular mortality in some studies, but not others. Certain types of coronary heart disease patients may not benefit from the consumption of fish oils, although clinical trials of secondary prevention following a myocardial infarction have reported significant reductions in the risk of a subsequent myocardial infarction or death.

Whether fish consumption is associated with lower cardiovascular risks in the 30 days after a myocardial infarction or hospitalization for unstable angina

is uncertain. The greatest likelihood of a recurrent cardiac event is during the first 30 days after a precipitous occurrence. A recent report suggested that high levels of long-chain omega-3 polyunsaturated fatty acids in patients with acute coronary syndrome were not associated with a lower risk of cardiac events or death. This small study from Athens, Greece, reported the cardiovascular outcomes in 293 patients discharged from the hospital with acute coronary syndrome. Data were available for 193 patients at the end of the 30-day followup.

Greek survivors of an acute coronary syndrome hospitalization were 83% less likely to have another cardiac event in the first 30 days thereafter if they consumed large amounts of fish—120 g or just over 4 oz per day. Risks were significantly reduced in both myocardial infarction and angina patients.

Diet and fish consumption were assessed 48 hours after hospitalization using a semi-quantitative food frequency questionnaire with questions about fish consumption. Within 30 days of admission, 23% of patients experienced cardiovascular events, 2.0% died and 18% underwent revascularization. In multiple logistic regression analysis adjusted for age, sex, body mass index, physical activity, smoking, prior cardiovascular disease, diabetes and others, survivors who consumed more than 7 portions of fish per week (120 g or about 4 oz/day) had an 83% lower chance of a recurrent event within 30 days of their initial event (odds ratio = 0.17, 95% CI, 0.04 to 0.80). Fish intake was not related to the patient's type of clinical syndrome. In addition, high intakes of omega-3 (8.8 g/week or 1.25 g/day) and omega-6 (13.2 g/week or 1.9 g/day) polyunsaturated fatty acids were associated with greatly reduced risks of a subsequent cardiac event, 83% and 79%, respectively.

Although this is a small study, it is one of the few reporting a significant beneficial association between high fish intakes and a lower chance of subsequent cardiac events in acute coronary syndrome survivors with angina. The findings are also consistent with previous observations of reduced cardiac events in myocardial infarct survivors.

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MATERNAL AND INFANT HEALTH

Long-Chain PUFAs in Early Infancy Linked to Improved Problem-Solving at 9 Months

Inconsistencies in findings on the relationship between long-chain PUFAs in healthy term infants and cognitive development led to studies in infants initially breastfed for different periods. Infants exposed to LC-PUFAs had an advantage in solving problems at 9 months of age compared with infants not receiving these fatty acids.

It is widely agreed that long-chain polyunsaturated fatty acids (LC-PUFAs) are essential during fetal and infant life for optimal brain growth and function. Breastfeeding or infant formula containing LC-PUFAs has been associated with improved cognitive development compared with the results obtained in healthy term infants fed unsupplemented formula. However, some studies have failed to observe cognitive differences in infants fed LC-PUFA-enriched formula or standard formula. Some reviews have concluded that studies on LC-PUFAs and cognitive development in healthy term infants remain promising, but inconclusive. A meta-analysis of randomized controlled trials of LC-PUFA supplementation of term infants reported a lack of beneficial effects on the physical, visual and neurodevelopmental outcomes in the LC-PUFA-supplemented infants.

Some reasons for these inconsistencies may be attributable to differences in the level of LC-PUFA supplementation, measures used to assess cognition and the age when infants are tested. These issues were kept consistent in this report of 3 randomized controlled trials to evaluate the effects of LC-PUFA supplementation on cognition in 9-month-old infants. Rather than assessing cognition using the Bayley Scales of Infant Development, which provides indices of perceptual and motor skills, the investigators used a means-end, 2-step problem-solving approach, which is correlated with vocabulary and intelligence quotient. The studies were led by James Drover and colleagues at the University of Texas Southwestern Medical Center, USA.

A total of 229 healthy, full-term, singleton infants—56% male and 83% Caucasian—from 3 randomized trials participated in the cognitive assessments in this study. All infants were born at 37 to 40 weeks postmenstrual age, had birthweights appropriate for their

gestational age, had no family history of milk protein allergy or eye disease, and were free of complicating perinatal events, such as jaundice or infection. At enrolment, infants were randomly assigned to consume either a control formula without LC-PUFAs or the same formula enriched with 0.36% docosahexaenoic acid (DHA) and 0.72% arachidonic acid (ARA). In 2 trials, the infants breastfed initially for 6 weeks or 4 to 6 months, then consumed the assigned formula until 12 months of age. The third trial was a 12-month feeding study with the 2 formulas from birth, without breastfeeding.

To assess the infant's ability to solve a problem—retrieve a rattle following 2 steps—the investigators gave each infant a pretest to assess his or her ability to complete each step. Infants who could not perform the pretest after 3 attempts were included in the analysis, but assigned a score of -1 on both the number of intentional solutions and average intention score. The actual test consisted of placing a rattle on a cloth beyond the child's reach, then covering the toy. The child had to pull the cloth toward him or her self, then remove the cover to find the rattle. These steps were included in the pretest. Each test was divided into 6 components, which were assessed individually according to intention on a scale from 0 to 2. Each child participated in 3 test trials to determine their average intention scores.

During the course of these studies, 27 infants were lost to followup, mainly because of sensitivity to lactose or cow's milk protein. The diet groups differed only in the number of both parents having education beyond high school.

Results among infants breastfed for 4 to 6 months prior to receiving infant formula did not differ in any outcome measure between those fed the LC-PUFA-enriched formula or the standard formula. These infants would have received LC-PUFAs from breast milk for the first 4 to 6 months.

In infants fed either LC-PUFA-enriched or standard formula for 12 months from birth, the average intention scores and the percent success on all 3 trials were significantly lower in the standard formula group (Table). Similar differences were observed between the LC-PUFA and standard formula groups in the 6-week weaning study (followed by formula feeding), with the addition that significantly fewer infants achieved a perfect intention score in the unsupplemented formula group. Infants fed the two formulas after 4 to 6 months of breastfeeding did not differ in their problem-solving scores (Table). However, the LC-PUFA levels in the weaning studies were not reported, so one cannot compare the LC-PUFA exposures with the other groups.

It may be of interest that the highest percent of infants failing to complete the pretest occurred in both formula groups in the 6-week weaning group. This group also

Table. Problem-solving results from 3 trials in 9-month-old infants fed LC-PUFA-enriched or standard infant formula after 0, 1.5 or 4 to 6 months of breastfeeding

	12-mo feeding study		6-wk weaning study		4-6 mo weaning study	
	LC-PUFA	Standard	LC-PUFA	Standard	LC-PUFA	Standard
Participants, no.	43	45	26	30	29	29
Mean intention score†	8.6 ± 3.7	6.9 ± 4.0*	6.8 ± 5.2	4.3 ± 3.8*	6.6 ± 4.0	6.7 ± 4.4
Success on all trials, %	51	29*	46	13**	28	28
Perfect score, %	26	16	35	7**	7	7
Incomplete pretest, %	2	2	12	13	7	7

*Significantly different from LC-PUFA group, $P = 0.05$
** Significantly different from LC-PUFA group, $P = 0.01$
†Mean ± SD; based on component scores for each trial, maximum score = 12 for each trial

had the greatest difference between infants fed the LC-PUFA-enriched formula (35%) and receiving the standard formula (7%) in achieving a perfect score. This observation is difficult to interpret because the infants fed the standard formula would have had LC-PUFAs from breastfeeding for the first 6 weeks.

These studies reported that infants fed an LC-PUFA-enriched formula for 9 months from birth or after 6 weeks of breastfeeding had significantly greater success in several aspects of 2-step problem-solving. In contrast, infants weaned after 4 to 6 months did not differ in their problem-solving scores regardless of the formula they consumed after weaning. The findings in infants breastfed for the longest time might be attributable to a similar exposure to LC-PUFAs in the two groups through breast milk or a shorter exposure time LC-PUFAs from formula. Unfortunately, this exposure could not be compared with the amount of LC-PUFAs provided by the supplemented formula. The table also shows that infants in the 4- to 6-month weaning group had a lower success rate in all trials and substantially fewer infants achieving a perfect score.

The 6-week weaning and 12-month studies show the advantage of exposure to LC-PUFAs early in life, shortly after birth or after 6 weeks of breastfeeding, in this means-end problem-solving evaluation. These findings are consistent with an earlier study on infant problem-solving, but contrast with a Danish study in which infants of breastfeeding mothers supplemented with fish oil or olive oil in the first 4 months of lactation did not differ in their problem-solving ability. The Danish results may have been negative because the high levels of breast milk LC-PUFAs in the unsupplemented mothers may have provided sufficient LC-PUFAs to reduce the need for supplementation.

Infants receiving LC-PUFAs from enriched formula or breast milk from birth or after 6 weeks of breastfeeding had significantly higher scores on several aspects of a problem-solving test compared to infants without LC-PUFA supplementation.

It has been suggested that better problem-solving ability may be linked to faster information processing related to increased nervous system membrane content of LC-PUFAs. Others have suggested that LC-PUFAs enhance attention control, thereby improving problem-solving, possibly by facilitating the development of the prefrontal cortex. These studies suggest that an adequate supply of LC-PUFAs in early infancy, either from breastfeeding or LC-PUFA-supplemented formula, is associated with improved cognitive function at 9 months of age. Improved infant cognition may extend into later childhood, but only a few studies have examined this possibility.

Drover J, Hoffman DR, Castaneda YS, Morale SE, Birch EE. Three randomized controlled trials of early long-chain polyunsaturated fatty acid supplementation on means-end problem solving in 9-month-olds. Child Dev *2009;80:1376-1384.*

VISUAL FUNCTION

Long-Chain Omega-3s Reduce the Risk of Advanced Age-Related Macular Degeneration

Antioxidant vitamins, zinc, lutein and zeaxanthin reduce the progression of age-related macular degeneration to its advanced forms. Long-chain omega-3s might also be protective nutrients.

The Age-Related Eye Disease Study (AREDS), an ongoing trial conducted by the National Eye Institute, Bethesda, USA, seeks to identify the risk factors and nutrient-based treatments associated with the development and progression of age-related macular degeneration (AMD). AREDS has been evaluating the effectiveness of different targeted dietary supplements, including antioxidant vitamins plus zinc, lutein and zeaxanthin and long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). High doses of antioxidant vitamins plus zinc were associated with significantly reduced progression of AMD and loss of visual acuity, but not with prevention of the condition. Dietary lutein and zeaxanthin, carotenoids in dark green leafy vegetables and egg yolk, were also associated with a significantly lower chance of developing neovascular AMD or geographic atrophy, advanced forms of the disease. Further, n-3 LC-PUFA intakes were linked to reduced progression of AMD to central geographic atrophy. AMD is the leading cause of irreversible blindness and affects about 5 million people in Europe and the U.S.

Data from the Blue Mountains Eye Study in Australia indicated that weekly fish consumption was associated with a 30% lower risk of developing early AMD, especially in people with intakes of linoleic acid below the median. Because n-3 LC-PUFAs are critical for retinal function, it is reasonable to think they might

be involved in the development or progression of AMD as the AREDS study reported. Here, the AREDS investigators report on the relationship between n-3 LC-PUFA consumption and the 12-year incidence of neovascular AMD in AREDS participants classified as having moderate- to high-risk AMD. The study involved 1,837 participants with any of the following: large drusen (yellow deposits in the macula or center of the retina), geographic atrophy (severe loss of central vision in the dry form of AMD) in one or both eyes or unilateral neovascular AMD, the wet form of the disease. These participants were considered at moderate-to-high risk of advanced AMD in the affected eye(s).

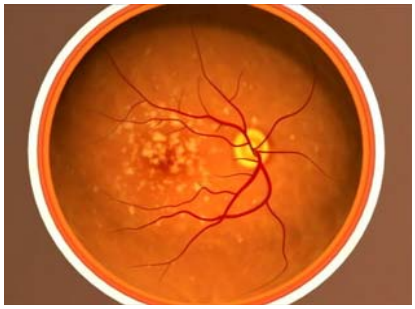


Figure. Image of the retina showing the macula (dark yellow spot) and yellow drusen deposits. *Image from the National Eye Institute.*

Trained graders assessed the participants' AMD status from stereoscopic images obtained in the year prior to enrolment and annually thereafter. AREDS-certified photographers took retinal images according to a standardized protocol and the investigators assessed dietary intakes prior to enrolment using a validated food frequency questionnaire. They expressed the consumption of LC-PUFAs in quintiles of nutrient density as a percent of total energy intake. The researchers estimated the risks of progression to central geographic atrophy or neovascular AMD from odds ratios determined from logistic regression analysis adjusted for age, sex and total energy intake. Additional statistical models included smoking, the presence of advanced AMD in one eye, baseline AMD severity and AREDS treatment assignment (antioxidants, zinc, antioxidants plus zinc and placebo).

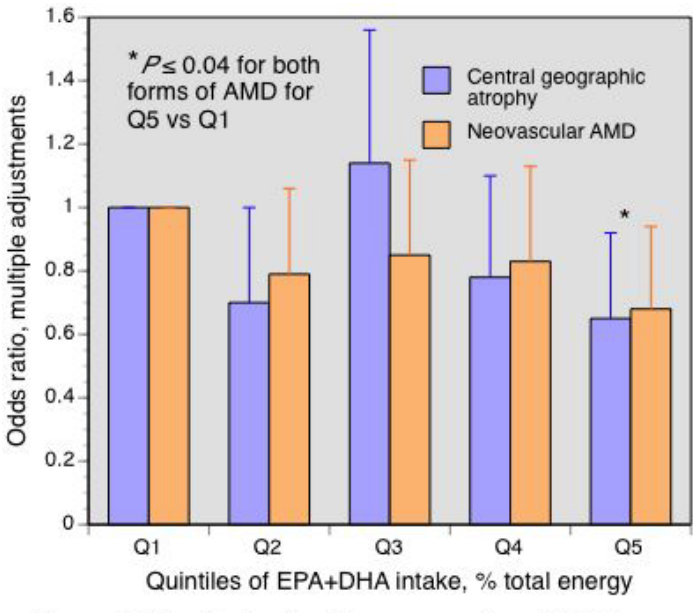


Figure. Odds ratios for the 12-yr progression of AMD to central geographic atrophy or neovascular AMD in AREDS participants at moderate to high risk of disease progression.

Over the 12-year followup, 20% of participants advanced to central geographic atrophy (364 individuals) and 32% progressed to neovascular AMD (583 participants). Those who developed neovascular atrophy were more likely to be older, female and without advanced AMD at enrolment.

Participants in the highest quintiles of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or both were approximately 30% less likely to progress to either type of advanced AMD compared with those having the lowest intakes (Figure). Smoking history was significantly related to progression of advanced AMD, with current smokers less likely to have the highest n-3 LC-PUFA consumption. The trends for reduced likelihood of progression to central geographic atrophy or neovascular AMD with increased intakes of EPA plus DHA were significant for both conditions, $P = 0.03$ and 0.04, respectively. For individual n-3 LC-PUFAs, higher intakes of EPA were associated with a lower chance of geographic atrophy (P for trend, 0.02) and of DHA with less risk of neovascular AMD (P for trend, 0.03).

Over 12 years, participants with the highest intakes of EPA, DHA or both were about 30% less likely to progress to either central geographic atrophy or neovascular AMD, advanced forms of the disease.

These findings support other lines of evidence elucidating the function of n-3 LC-PUFAs in maintaining retinal function, reducing pathological retinal angiogenesis and protecting retinal pigment epithelial cells. These fatty acids, especially DHA in retina and brain, are the precursors of resolvins and protectins, which reduce inflammatory responses and promote cell survival. DHA was reported to enhance photoreceptor survival and reduce inflammatory gene expression in an animal model of retinal degeneration. Inflammation is increasingly recognized as a key factor in the development of AMD. Because of their ability to reduce inflammatory processes in various ways and their importance in retinal function, n-3 LC-PUFAs are strong candidates to join the clutch of nutrients with strong potential for reducing the risk of advanced AMD and blindness. The potential

benefits of these nutrients to individuals and public health from reductions in blindness and visual impairment may soon be seen.

SanGiovanni JP, Agrón E, Meleth AD, Reed GF, Sperduto RD, Clemons TE, Chew EY. ω-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: a prospective cohort study from the Age-Related Eye Disease Study. **Am J Clin Nutr** *2009; 90:1601-1607.*

Dietary Fat, Age and AMD in Older Women: Murky Interactions

Higher intakes of long-chain omega-3 fatty acids have been associated with a lower risk of advanced AMD. Data from the Women's Health Initiative suggest that both omega-6 and omega-3 fatty acids interact to affect the risk of intermediate AMD in women younger than 75.

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the U.S., affecting 8% of adults over the age of 65. Many variables contribute to this condition and its progression to more advanced forms. These include genetics, smoking, cardiovascular disease and specific dietary components: antioxidant vitamins, zinc, lutein and zeaxanthin, and probably long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) and fish consumption. Dietary and lifestyle contributors to AMD are amenable to change and have the potential to substantially lower the incidence of this condition.

The literature describing the association between n-3 LC-PUFAs and AMD focuses mainly on slowing the progression of mild or moderate AMD to its advanced forms that threaten vision. Fewer studies are available on the factors affecting the development of early AMD. One large epidemiology study in Australia reported a 30% reduction in the 10-year incidence of AMD in elderly participants who ate fish once a week. Results were most pronounced in participants whose linoleic acid consumption was below the median. Another Australian study reported that higher n-3 PUFA consumption was associated with a lower risk of early AMD. A meta-analysis of 9 studies reported that consumption of fish and foods rich in n-3 PUFAs (mostly n-3 LC-PUFAs) was associated with about a 25% lower risk of early and late AMD.

Using data available from a large cohort of women (Women's Health Initiative), Niyati Parekh and colleagues at New York University and collaborating universities in the U.S. examined the relationships between different types of dietary fat and carotenoids with the occurrence of intermediate AMD in 1,787 women whose mean age was 70 years. Women were enrolled in the study if their intake of lutein and zeaxanthin (plant carotenoids that concentrate in the macula) was above or below the 78th and 28th percentiles, respectively. Participants consumed significantly less fat compared with the whole Women's Health Initiative cohort (31% vs 37% of energy). Food consumption was estimated from food frequency questionnaires administered 4 to 7 years before the photographic determination of AMD. Criteria for the grading of stereoscopic fundus photographs were the same as those used in the Age-Related Eye Disease Study. Risk of intermediate AMD was evaluated from age-adjusted odds ratios with additional adjustments for multiple confounding factors.

It is well recognized in studies of fat and fatty acid consumption that the intakes of different classes of fat are highly correlated, as they were in this study. Total fat intake was significantly related to the consumption of saturated, monounsaturated, omega-6 (n-6) and n-3 fatty acids. Intakes of n-6 PUFAs are highly correlated with intakes of n-3 PUFAs and monounsaturated fat consumption is correlated with saturated fat intake.

Total fat intake was unrelated to the occurrence of intermediate AMD in multivariate analysis of the whole sample (Table). However, when the participants were stratified by age, younger or older than 75 years, the younger group had an 80% higher likelihood of developing intermediate AMD, but the association did not reach statistical significance in multivariate analysis. In women 75 and older, the odds of AMD were 50% lower in the highest quintile of total fat intake (*P* for trend = 0.02). Discordant results by age group also appeared for saturated fat intake, with higher intakes associated with a higher prevalence of AMD in age-adjusted analysis, but only in women younger than 75. Higher consumption of monounsaturates was associated with a lower prevalence of AMD in the whole sample, but not in analysis adjusted for multiple variables.

For polyunsaturated fat consumption, higher intakes of n-6 PUFAs appeared to be associated with greater odds of AMD in women younger than 75 compared with participants having low intakes (Table). However, this association was not statistically significant in multivariate analysis. Greater consumption of total n-3 PUFAs, which included both alpha-linolenic acid and n-3 LC-PUFAs, was also associated with a greater risk of AMD and the trend for this association remained significant in multivariate analysis. When the effects of short- and long-chain n-3 PUFAs were analyzed separately, the odds ratios for AMD were 2.7 for short-chain

Table. Odds ratios (95% CI) for intermediate AMD by quintiles of fat intake in women aged 50 to 79 years

Type of fat	Quintiles of median fat intake, % energy 1	2	3	4	5	*P* for trend
Total Median intake Multivariate OR	21 1	26 1.1 (0.7 – 1.6)	31 0.8 (0.6 – 1.3)	36 0.9 (0.6 – 1.3)	43 1.0 (0.7 – 1.5)	0.79
Saturated* Median intake Multivariate OR†	7 1	9 1.2 (0.7 – 2.2)	10 1.2 (0.6 – 2.3)	12 1.6 (0.8 – 3.3)	15 1.6 (0.7 – 3.6)	0.23
Monounsaturated* Median intake Multivariate OR†	8 1	10 0.9 (0.5 – 1.7)	11 0.8 (0.4 – 1.7)	13 0.6 (0.3 – 1.5)	16 0.8 (0.3 – 2.1)	0.67
N-6 PUFA* Median intake Multivariate OR†	3 1	4 1.5 (0.8 – 2.6)	5 1.5 (0.7 -2.7)	6 1.5 (0.8 -2.9)	8 1.7 (0.8 – 3.4)	0.07
N-3 PUFA* (total) Median intake, mg/1,000 kcal	50	634	748	880	1,106	**<0.001**
Multivariate OR	1	1.5 (0.9 – 2.6)	1.2 (0.7 – 2.1)	1.6 (0.9 – 2.7)	2.6 (1.6 – 4.4)	

*Restricted to women younger than 75 years
†Models contained monounsaturates, polyunsaturates, saturates, age and lutein intake group

n-3 PUFAs ($P < 0.001$) and 1.3 for n-3 LC-PUFAs (NS) in the highest compared with the lowest quintiles of consumption. This suggests that high levels of alpha-linolenic acid (short-chain n-3 PUFA) might be harmful, whereas n-3 LC-PUFAs have no apparent effect. When the analysis was further stratified by n-6 PUFA intake above or below the median, the highest consumption of n-3 LC-PUFAs in women below the median for n-6 PUFA consumption had no effect on the risk of AMD (odds ratio = 1.0), but women in the lowest quintile of n-3 LC-PUFA consumption and above the median for n-6 PUFA consumption were nearly 3 times more likely to develop AMD (odds ratio = 2.7). Neither total nor dark fish consumption were significantly associated with AMD risk.

The observations in this study suggest that total fat intake in women 50 to 79 years of age is not associated with the risk of intermediate AMD, but that in women 75 or older, higher fat intake is linked with a 50% lower chance of AMD. It is possible that this observation relates more to other characteristics of these older women than diet or that they had lifelong healthy diets and lifestyles. Higher intakes of n-6 PUFAs appeared to be associated with a greater risk of AMD, but the association did not achieve statistical significance (odds ratio for highest vs. lowest intakes = 1.7, $P = 0.07$) once multiple variables were taken into account.

In older women, higher intakes of n-3 LC-PUFAs had no effect on the risk of intermediate AMD when the consumption of omega-6 PUFAs was below the median. When alpha-linolenic acid was included in the n-3 intake, higher total n-3 PUFAs was associated with a nearly 3-fold higher chance of intermediate AMD.

In contrast with the prevailing literature, the consumption of total n-3 PUFAs was significantly associated with a nearly 3-fold higher risk of AMD in multivariate analysis. However, when alpha-linolenic acid was removed from the estimated n-3 PUFA intake, the highest intakes of n-3 LC-PUFAs (odds ratio = 1.0) had no significant effect on the risk of AMD (odds ratio = 1.0) compared with the increased risk of AMD in women with the lowest n-3 LC-PUFA intakes (odds ratio = 2.7). When the analysis was stratified by median intake of n-6 PUFAs, the odds ratio for AMD for women in the highest quintile of n-3 LC-PUFA consumption and n-6 PUFA intake below the median was 1.0. However, women in the lowest category of n-3 LC-PUFA consumption whose n-6 PUFA intakes were above the median had an odds ratio of 2.7 for developing AMD.

In discussing these findings, the authors appeared to rely on the associations reflected in age-adjusted analyses. This could be misleading because adjustment for multiple confounding factors often resulted in nonsignificant associations. In this study, as in others, including alpha-linolenic acid with n-3 LC-PUFAs appeared to exaggerate the association between n-3 PUFAs and increased risk of AMD. The analysis of n-3 LC-PUFAs alone suggested that these fatty acids were not associated with risk of intermediate AMD. Thus, it appears misleading to suggest that the consumption of n-3 LC-PUFAs had a "direct (adverse) association" with the risk of AMD. Nevertheless, this study raises further questions about the effect of high intakes of n-6 PUFAs or alpha-linolenic acid on the risk of AMD in women. As the investigators themselves wondered, might diets high in n-6 PUFAs mask the potentially counter-balancing effects of n-3 LC-PUFAs?

Parekh N, Voland RP, Moeller SM, Blodi BA, Ritenbaugh C, Chappell RJ, Wallace RB, Mares JA; CAREDS Research Study Group. Association between dietary fat intake and age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS): an ancillary study of the Women's Health Initiative. Arch Ophthalmol *2009;127:1483-1493.*

MENTAL HEALTH

Omega-3s Do Not Boost Effectiveness of Antidepressant Drug in Heart Disease Patients

Patients with coronary heart disease who have depressive symptoms face a greater risk of mortality and a lower quality of life. Whether long-chain omega-3 fatty acids, which may be effective in both conditions independently, improve the wellbeing of such patients was explored in this study.

In matters of mind and heart, evidence suggests that having depressive symptoms substantially increases the risk of developing and dying from coronary heart disease. Individuals with one condition are more likely to develop the other, undermining their prognosis and quality of life. For example, patients with acute coronary syndrome have poorer outcomes if they are also depressed. Those with either condition are also more likely to have low levels of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) in their red blood cells. These fatty acids are associated with a significantly lower risk of cardiac death and may be useful in reducing depressive symptoms as well. Some studies have reported that adding n-3 LC-PUFAs to antidepressant medications compared with adding a placebo improves symptoms above that seen with antidepressants alone.

In the trial described here, Robert Carney and colleagues at the Washington University School of Medicine, St. Louis, USA, evaluated the effectiveness of adding 2 g/day of n-3 LC-PUFAs to antidepressant treatment with sertraline in patients with major depression and coronary heart disease. Patients with at least 50% stenosis, a history of revascularization or hospitalization for acute coronary syndrome were recruited from cardiology practices in the St. Louis area and screened for depressive symptoms using a Patient Health Questionnaire. Those scoring 10 or higher received a structured clinical interview and were further assessed for scores of 16 or higher on the Beck Depression Inventory-II. Those who met these criteria were placed on 50 mg/day of sertraline and then randomized to receive plus 2 g/day of n-3 LC-PUFAs (930 mg eicosapentaenoic acid, EPA; 750 mg/day docosahexaenoic acid, DHA) or corn oil placebo for 10 weeks.

The study used a 2-week run-in period to evaluate participant compliance with the medications and sustained Beck Depression Inventory scores of 16 or more. Those having at least 85% compliance were invited to remain in the study. Of the 178 patients who entered the pre-study phase, 122 were randomized to the treatments and 115 remained in the complete analysis. The study investigators monitored the participants' depressive symptoms and obtained weekly Beck scores as the primary outcome. Scores on the Hamilton Rating Scale for Depression provided a secondary outcome assessment. Participants were contacted by telephone weekly to encourage compliance and identify new symptoms, adverse events and medical status.

At baseline, treatment and placebo participants differed only in their use of aspirin (higher in placebo participants) and most had a history of depression (63% and 74%, respectively). Although the Beck Depression scores did not differ between the groups at baseline, the Hamilton Depression scores were higher in the n-3 LC-PUFA group compared with the placebo participants (21 vs 19). After 10 weeks, the Beck and Hamilton scores improved to a similar extent in both groups. The groups did not differ in rates of remission, treatment response or reported side effects. Most participants tolerated 2 g/day of n-3 LC-PUFAs well. There were 4 cardiac and 4 non-cardiac hospitalizations per group.

Unlike the findings in two previous studies, these results do not support improved efficacy of antidepressant medication with the addition of n-3 LC-PUFAs to the treatment of patients with depressive symptoms and coronary heart disease. There is still some question about what an effective dose of n-3 LC-PUFAs or EPA might be and the dose used here, about a gram of EPA, was reported to be effective. It is also possible that 10 weeks was too little time to achieve an effect or that other antidepressant medications might respond differently.

The addition of long-chain omega-3s to sertraline, an antidepressant medication used to treat heart disease patients with depressive symptoms, did not enhance the effectiveness of the medication. Depressive symptoms in both omega-3- and placebo-treated patients improved similarly.

The addition of n-3 LC-PUFAs to the treatment of patients with depressive symptoms and coronary heart disease did not improve the patients' depressive symptoms above that observed with the antidepressant alone. However, it increased the n-3 LC-PUFA concentration in these participants' red blood cells and would be expected to reduce their long-term risk of cardiovascular events and mortality.

Closely related to this study is a report on the relationship between n-3 LC-PUFA status and depressive symptoms in a cross-sectional study of 987 adults with stable coronary heart disease. Researchers at the University of California, San Francisco, USA, screened the participants for depressive symptoms using the Patient Health Questionnaire, as in the Carney study.

The prevalence of depressive symptoms ranged from 23% for patients in the lowest tertile of n-3 LC-PUFAs (< 3% of total blood fatty acids) to 13% in patients having red blood cell n-3 LC-PUFAs greater than 4.3% of total blood fatty acids. As the concentration of n-3 LC-PUFAs fell, the odds of having depressive symptoms increased. However, when the analysis was adjusted for age, sex, ethnicity, income and education, the relationship between low n-3 LC-PUFA status and depressive symptoms no longer achieved statistical significance. The same results were obtained in analyses for eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) alone. The authors noted that participants in the lowest tertile of n-3 LC-PUFAs were less likely than those in the highest tertile to be married, have a college degree or household income above $20,000. They were more likely to be Hispanic or black; have hypertension, myocardial infarction or diabetes; and to smoke and be physically inactive. For these reasons, the authors suggested that the differences in socioeconomic variables between the n-3 LC-PUFA tertiles likely explains the lack of significant association between n-3 LC-PUFA status and depressive symptoms. These studies indicate that both the heart and mind require attention when it comes to depression.

Carney RM, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Harris WS. Omega 3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. JAMA *2009;302:1651-1657.*

Ali S, Garg SK, Cohen BE, Bhave P, Harris WS, Whooley MA. Association between omega-3 fatty acids and depressive symptoms among patients with established coronary artery disease: data from the Heart and Soul Study. Psychother Psychosom *2009;78:125-127.*

Fatty Fish Consumption Unrelated to Cognitive Changes in Aging Men

The literature is divided on the question of whether fatty fish consumption or long-chain omega-3 intakes affect cognitive change in aging. This 6-year study in older men suggests there is no relationship between different types of cognition and eating fatty fish.

Whether long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) protect against loss of mental function in aging remains an unresolved question. Much as one hopes that scientific studies can provide a clear answer, the findings to date are inconsistent. Several studies have reported better cognition among the elderly who have high dietary intakes or blood levels of n-3 LC-PUFAs, but other studies, both cross-sectional and prospective, reported either no association or poorer cognition. The Zutphen Elderly Study reported that 70- to 80-year old fish consumers had significantly less cognitive decline than those who did not eat fish. Another complicating factor is that cognitive function declines in different areas of the brain at different rates. Existing diseases such as diabetes also affect changes in cognition. One study reported cognitive differences in prospective and retrospective memory tasks in various age groups. Of the 3 studies that examined the association between cognitive

performance and slower sensorimotor and complex speed, 2 reported that a higher intake of fatty fish or n-3 LC-PUFAs reduced the chance of impaired speed and one reported a lower risk of declining verbal fluency. To detect variations in different aspects of cognitive function, specific rather than global cognitive assessments are necessary. It would be useful to know which, if any, aspects of cognitive function may be better protected from decline with greater exposure to n-3 LC-PUFAs or eating fatty fish.

The Normative Aging Study, a longitudinal study of US men free of heart disease or other major health problems, began in 1963 with the goal of identifying the risk factors for cognitive decline in aging and assessing the various components of cognitive change. Findings from this study previously reported that low B vitamin levels and elevated homocysteine concentrations were associated with greater cognitive decline over 3 years. In the Cardiovascular Health Cognition Study, the consumption of fatty fish was associated with a lower risk of dementia and Alzheimer disease in individuals without the APOE ε4 allele, a known risk factor for Alzheimer disease.

Participants received a health examination every 3 to 5 years with cognitive tests given every 3 years. These tests included the Mini-Mental State Examination, a global measure of cognitive function, memory tests, a backward digit span test, language tests, assessments of perceptual speed and attention, continuous performance and a spatial copying task. Dietary consumption information was assessed for the preceding year by a food frequency questionnaire. Fish consumption was assessed in 4 categories: dark-meat fish, canned tuna, other fish, and shrimp, lobster or scallops. In the 6-year analysis, there were 451 men with baseline scores and all included tests. Participants averaged 68 years of age at the time of baseline cognitive measurements. Average total fish consumption was 2.4 servings/week and 1.3 servings for fatty fish (tuna and dark-meat fish). These intakes provided an average of 280 mg/day of n-3 LC-PUFAs, nearly 3 times the US average.

The investigators derived 3 factors for cognition: memory/language, visuospatial/attention and speed. They evaluated the relationship between fatty fish or n-3 LC-PUFA intakes by quartile median values and composite test outcomes using linear models adjusted for different numbers of confounding factors. Additional analysis examined the effect of the main contributing cognitive test on the relationship with fatty fish consumption.

In adjusted analysis, increased consumption of fatty fish showed no association with cognitive assessments in any of the memory/language, visuospatial or speed tests at baseline. Over the 6-year study period, neither fatty fish intake nor n-3 LC-PUFA consumption was related to changes in cognition in any dimension. Thus, in these men, none of the changes in any cognitive dimension was related to fish consumption. Although this study adds to others reporting no association between cognition and fatty fish or n-3 LC-PUFAs, these findings provide no plausible explanation for why they differ from other reports of a beneficial effect of fish consumption on cognition later in life.

In spite of eating an average of 2 fish meals per week, aging US men exhibited no differences in cognitive change over 6 years compared with men who ate little or no fish.

Van de Rest O, Spiro III A, Krall-Kaye E, Geleijnse JM, de Groot LCPGM, Tucker KL. Intakes of (n-3) fatty acid and fatty fish intake are not associated with cognitive performance and 6 y cognitive change in men participating in the Veterans Affairs Normative Aging Study. J Nutr *2009;139:2329-2336.*

Case-Control Study Reports No Link Between Long-Chain Omega-3s and Depression

Several lines of evidence suggest that low fish consumption or low concentrations of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) in blood or red blood cells is associated with a higher prevalence of depression or an increased risk of developing the condition. Some studies also reported improvements in depressive symptoms when the consumption of n-3 LC-PUFAs, especially eicosapentaenoic acid (EPA) is increased. As is often the case, not all studies have observed these associations or effects and many studies were conducted in only a small number of participants.

Many, but not all, studies have reported a link between higher consumption of long-chain omega-3 fatty acids and a lower chance of developing depressive symptoms. This report contradicts that literature and earlier findings in the same participants. The involvement of long-chain fatty acids is likely highly complex.

This French study, led by Pierre Astorg and colleagues at the Université Paris, reports additional findings

from a large, randomized, placebo-controlled primary prevention trial in middle-aged men and women. The study was designed to evaluate the effect of multiple antioxidants on the incidence of ischemic heart disease and cancer. Data on food and fish consumption were used to explore the relationship between eating fish and depression. The study previously reported that participants who consumed more than 0.1% of energy from n-3 LC-PUFAs were significantly less likely to have any or recurrent depressive episodes during an 8-year followup period. In this report, the investigators conducted a nested case-control to examine the relationship between serum phospholipid fatty acids in participants with at least 2 depressive episodes paired with participants who did not have depressive symptoms. The investigators used the completion of prescriptions for antidepressant medications as a marker of depressive episodes.

At study enrolment, there were 13,017 men and women. Men were aged 45 to 60 years and women 35 to 60 with an overall mean age of 48. Baseline information queried health and disease events and existence of a history of depressive episodes. Thereafter, monthly monitoring tracked health events, consultations with a health professional and drugs prescribed. Initially, there were 232 participants (cases) with or without a history of depression and at least 2 occurrences of antidepressant or lithium prescriptions. Control participants (232) were matched to the cases except for absence of depression history and no declarations of antidepressant or lithium prescriptions. The study matched control participants to cases by sex, age (5-year strata) and intervention group (placebo or treatment). Investigators obtained blood samples at baseline for the analysis of plasma phospholipid fatty acids. The association between fatty acids was tested using unconditional logistic regression so that data from participants without a history of depressive episodes could be analyzed similarly. Additional adjustment variables included marital status, education, socioprofessional status and tobacco use. Final analyses included 222 complete case-control pairs, of which 80% were women.

Table. Odds ratios for the association between 8-year followup occurrence of depressive episodes and baseline plasma phospholipid fatty acids

Fatty acid	Odds ratio (95% CI)*	*P*
Palmitic acid, 16:0	1.15 (1.01 – 1.32)	**0.032**
Linoleic acid, 18:2n-6	0.90 (0.83 – 0.96)	**0.002**
Eicosatrienoic acid, 20:3n-9 or Mead acid	1.38 (1.08 – 1.76)	**0.010**
Eicosapentaenoic acid, 20:5n-3 or EPA	1.12 (0.88 – 1.43)	0.34
Docosahexaenoic acid, 22:6n-3 or DHA	1.06 (0.87 – 1.30)	0.56

*Calculated for case-control pairs (n=222)

The plasma phospholipid fatty acid values revealed no significant differences in the concentration of any n-3 LC-PUFAs between participants with depressive symptoms during followup and matched controls. Linoleic acid concentrations were significantly lower in cases than controls, but not in analyses where participants had no history of depression or symptoms at baseline. On the basis of continuous odds ratios in case-control pairs, palmitic acid and eicosatrienoic acid (20:3n-9 or Mead acid) were significantly associated with an increased depression risk, whereas linoleic acid was linked to a lower risk (Table). Mead acid is considered a marker for essential fatty acid deficiency and is normally present only in trace amounts. These associations were not significant in participants without a depression history or depressive symptoms at baseline.

In an 8-year followup of middle-aged adults with depressive episodes, baseline long-chain omega-3 fatty acids were unrelated to the chance of recurrent depressive events. Patients had significantly lower plasma phospholipid concentrations of linoleic acid and higher levels of Mead acid, an indicator of essential fatty acid deficiency.

Overall, the authors concluded that there was no consistent association between risk of depressive symptoms and any fatty acid, despite significantly lower concentrations of linoleic acid in case participants. These findings stand in contrast to previous observations in this study population and other reports, which found a lower risk of depressive episodes with higher intakes of n-3 LC-PUFAs. One drawback to the study is the lack of validated diagnoses of major depressive disorder. Antidepressant medications are also prescribed for a range of anxiety disorders and pain. The study provides some evidence for marginal essential fatty acid status or deficiency in patients with depressive episodes, as shown by the lower linoleic acid and higher Mead acid concentrations in cases compared with controls. These observations are in general agreement with other studies reporting a lower concentration of PUFAs in

patients with depressive symptoms, but they offer no support for the involvement of n-3 LC-PUFAs in this condition. Contradictory data are to be expected in clinical studies, but this study begs a good explanation.

Astorg P, Bertrais S, Alessandri JM, Guesnet P, Kesse-Guyot E, Linard A, Lallemand MS, Galan P, Hercberg S. Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: A nested case-control study within a cohort of middle-aged French men and women. Prostaglandins Leukot Essent Fatty Acids *2009;81:265-271.*

CLINICAL CONDITIONS

Type 2 Diabetes

Do Omega-3 PUFAs Increase the Risk of Type 2 Diabetes?

Long-chain omega-3 PUFAs are beneficial in reducing the risk of cardiovascular disease and improving some clinical abnormalities associated with diabetes. Whether omega-3 PUFAs are associated with the chance of developing diabetes is less clear. This study says they might increase the risk.

Diet and lifestyle are key factors in the development of type 2 diabetes (diabetes) and are important for its prevention. The dietary management of diabetes has shifted away from simple sugars and carbohydrates to the importance of the type and quality of dietary fat. Limiting the consumption of saturated fatty acids and substituting mono- and polyunsaturated fatty acids (PUFAs) instead is a key dietary strategy. Because the development of diabetes is closely linked to obesity, weight loss is another critical factor in lowering the chance of developing this disease and in slowing its progression.

Among dietary fats, PUFAs of the omega-6 (n-6) and omega-3 (n-3) families are important. N-6 PUFAs and monounsaturated fatty acids can replace a large portion of dietary saturated fatty acids, while long-chain n-3 PUFAs (n-3 LC-PUFAs) may correct the abnormalities in lipid profiles that occur in diabetes. As reviewed by de Caterina and colleagues, n-3 LC-PUFAs are associated with a dose-dependent decrease in low-density lipoprotein cholesterol and triglycerides and only slight changes in high-density (HDL) lipoprotein cholesterol. Reduced consumption of fat and energy also lower the chance of developing diabetes. In addition, n-3 LC-PUFAs are associated with a lower risk of cardiovascular disease through their antithrombotic, anti-inflammatory and anti-arrhythmic effects. The complexity of these effects has been reviewed recently.

The consumption of n-3 LC-PUFAs by diabetic patients generally reduces the risk of cardiovascular disease, which is significantly elevated in these patients. Results from a large secondary prevention trial concluded that concomitant disease states in survivors of a myocardial infarction did not alter the therapeutic benefits of n-3 LC-PUFAs. N-3 LC-PUFAs reduce triglycerides, thrombogenesis and inflammatory mediators in type 2 diabetic patients, while improving dyslipidemia. In an open study in Spain, diabetic patients with elevated triglycerides who consumed 1.7 g/day of n-3 LC-PUFAs for 12 weeks had significant reductions in triglycerides, non-HDL-cholesterol, C-reactive protein and TNF-alpha levels, with significant increases in HDL-cholesterol concentrations. Oddly enough, epidemiological studies with fish consumption have reported mixed findings.

Contention arises partly from inconsistencies in findings and lingering concerns about glucose control and glycated hemoglobin. Although some earlier studies reported deterioration in glucose control, more recent studies and a meta-analysis have demonstrated no adverse effects. In a large intervention study, the consumption of 1.7 g/day of n-3 LC-PUFAs for 1 year showed no worsening of glucose control. The possibility remains, however, that in a minority of patients, consumption of n-3 LC-PUFAs might adversely affect glucose metabolism. Other studies have reported no effect of n-3 LC-PUFA consumption on glycated hemoglobin, although glucose increased in this particular study. In addition, n-3 LC-PUFAs improve insulin sensitivity, although well designed studies are not abundant.

In this article, Boston epidemiologists examined the relationships between n-3 LC-PUFAs, fish consumption and the risk of diabetes in 3 large cohort studies, the Nurses' Health Studies (original and Study 2) and the Health Professionals Follow-up Study. The combined studies included 195,204 participants, with the nurses' ages at enrolment ranging from 26 to 55 and the health professionals ranging from 39 to 78. Followup ranged from 14 to 18 years. Seafood consumption by type of fish and frequency was assessed by a semi-quantitative food frequency questionnaire administered every 4 years and n-3 LC-PUFA intakes calculated from those data. Five categories of fish consumption were less than once a month, 1 to 3 times a month, once a week, 2 to 4 times a week and 5 or more times a week. Self-reported cases of diabetes were validated according to the National Diabetes Data Group criteria.

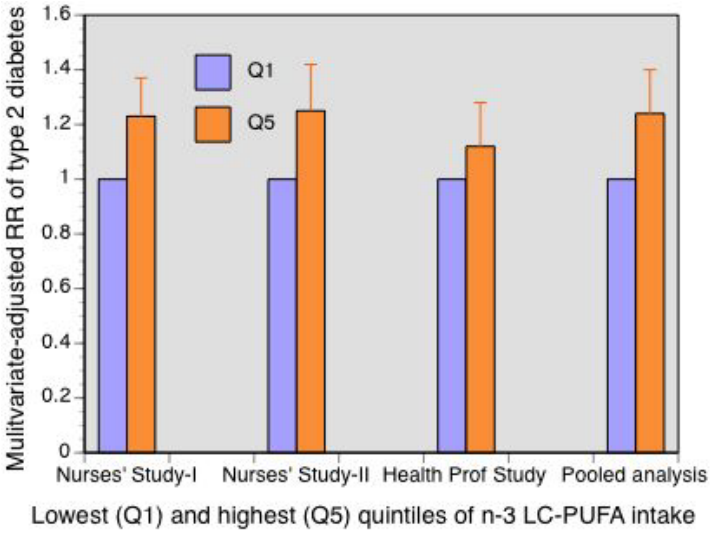


Figure. Multivariate-adusted risk of type 2 diabetes by cumulative average n-3 LC-PUFA intake in 3 cohorts of professionals. *P* for trend in both Nurses' studies and pooled analysis <0.001; for the Health Professionals study, *P*=0.03.

In age-adjusted models using Cox proportional hazards, the relative risks of diabetes in the second Nurses' Study and the Health Professionals Study were not associated with the consumption of n-3 LC-PUFAs and only weakly associated with diabetes risk in the original Nurses' Study. With additional adjustment for lifestyle habits, body mass index and dietary factors, such as cereal fiber and glycemic index, higher intakes of n-3 LC-PUFAs were associated with significantly increased risk of diabetes in each cohort (Figure). The relative risks of diabetes in the highest n-3 LC-PUFA consumption quintiles compared with the lowest ranged from 12% to 25% in the three cohorts. In pooled analysis, multivariate-adjusted risk was elevated in the highest intake group by 24%.

The investigators also analyzed the risk of diabetes with n-3 LC-PUFAs treated as a cumulative variable. The pooled analysis yielded an 18% greater risk in the highest intake category compared with the lowest. There was a modest dose-response relationship with increasing n-3 LC-PUFA or fish consumption up to an intake of 300 to 350 mg/day, with the highest risk estimated at 22% greater compared with the lowest intake.

The investigators also noted that the consumption of different types of fish (canned tuna, dark fish or shellfish) was associated with only modest increases in the risk of diabetes when compared with consumption of less than once a month. Relative risks ranged from 14% for canned tuna, 9% for dark fish to 6% for shellfish consumed more than once a month.

These observations raise the possibility that considerable sensitivity may be lost when n-3 LC-PUFA intakes are estimated or fish consumption and cohorts are pooled. They are also a reminder that estimating intakes of small amounts of substances from dietary questionnaires is limited by the difficulties inherent in food frequency questionnaires.

Statistically significant associations between fish or n-3 LC-PUFA intakes and risk of type 2 diabetes were observed in 3 large cohort studies, but the clinical significance of these observations is unclear.

These findings agree with the modest increase (11%) in diabetes risk reported in the Iowa Women's Study, but are at odds with other epidemiological studies reporting either no relationship between diabetes risk and n-3 LC-PUFA consumption or a modest reduction in risk. In spite of the benefits of fish and n-3 LC-PUFA consumption on many cardiovascular risk factors and inflammation, questions about their effects on glucose control remain. However, concerns about this possibility have usually been considered clinically minimal, as suggested by the American Diabetes Association's recommendation of fish consumption twice a week or more. The meaning of these associations is difficult to discern.

Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willet WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. **Am J Clin Nutr** *2009;90:613-620.*

Fish Consumption Linked to Higher Diabetes Risk, But Not Among Fatty Fish Eaters

Long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) have well recognized benefits in reducing the risk of dying from heart disease. Several studies suggest they may reduce the likelihood of cardiovascular events as well. Because the majority of individuals with type 2 diabetes eventually die from heart disease, managing cardiovascular risks in diabetic patients is a high priority.

Some evidence suggests that diabetics with higher intakes of fish or n-3 LC-PUFAs have a lower incidence of coronary heart disease and mortality. Several studies have shown, for example, that the consumption of n-3 LC-PUFAs in the 1 to 2 g/day range or higher by patients with diabetes and hypertriglyceridemia improves lipid profiles and inflammatory markers. Similar patients without

Eating fatty fish or long-chain omega-3 fatty acids improves several risk factors for cardiovascular disease in individuals with type 2 diabetes. However, a greater risk of developing diabetes with higher fish consumption in older Dutch adults was reported in this study. Higher intakes of long-chain omega-3s were unrelated to diabetes risk. How puzzling.

hypertriglyceridemia who consumed 30 g/day of walnuts as part of a 30% fat diet rich in polyunsaturates showed significant improvements in their fasting insulin levels, but it is not known whether the alpha-linolenic acid content of the walnuts contributed to their response. Another study reported that the addition of 4 g/day of n-3 LC-PUFAs to the statin medication taken by type 2 diabetic patients significantly enhanced the reduction of apolipoprotein B48 above that achieved with the statin alone. Thus, some cardiovascular benefits of increased n-3 LC-PUFA consumption have been demonstrated in individuals with type 2 diabetes.

Possible effects of n-3 LC-PUFAs on improving insulin sensitivity are less clear. One review concluded that design flaws in most of the existing studies limit possible conclusions. Another concluded that these fatty acids had no significant effect on glucose control or fasting insulin. However, other reports suggest that n-3 LC-PUFAs may lower insulin responses without affecting glucose control in diabetic patients.

Whether high fish or n-3 LC-PUFA consumption affects the risk of developing type 2 diabetes is unclear. This is an important question because of the soaring increase in this disease, in addition to obesity and the metabolic syndrome with which diabetes is closely associated. The preceding study reported an increased risk of developing diabetes in adults with the highest fish consumption. In contrast, 3 other studies reported either reduced risk or no association between fish intake and type 2 diabetes. In the study described here, investigators at Wageningen University, the Netherlands, monitored 4,472 participants aged 55 years or older (mean age 67 years) to identify the risk factors for developing the disease. Participants did not have diabetes at enrolment and were monitored for 15 years (median 12 years).

Baseline demographic information, dietary intake and clinical assessments were obtained at enrolment along with detailed information about the type and frequency of eating fish. The investigators obtained information about major medical events, including the development of diabetes, from general practitioners and pharmacies throughout the study. The relationships between baseline characteristics and types and amounts of fish consumed were determined by analysis of variance and the chance of developing type 2 diabetes assessed from hazard ratios based on these associations. Risks were adjusted for age, sex, smoking and education level, with additional models including dietary factors. Further analyses added more potential confounders, such as family history of diabetes, body mass index, hypertension and others.

During followup, there were 463 incident cases of type 2 diabetes (10%) with onset at an average age of 74. Nearly 30 % of participants did not eat fish and those who did consumed little—an average of 10 g/day. The median intake of participants eating the most fish was 36 g/day or more. Lean and fatty fish accounted for about 80% and 18% of the fish consumed, respectively. The median intake of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) was 89 mg/day.

Unexpectedly, the risk of developing type 2 diabetes increased with total fish consumption in analysis adjusted for age, sex, smoking, education and dietary variables (Figure). Compared with the reference group who ate no fish, fish eaters with the highest intakes of total or lean fish had a 30% greater chance of developing diabetes. The trend for greater risk was significant only for total fish consumption, $P = 0.04$. However, no trend for increased risk was observed among those who ate

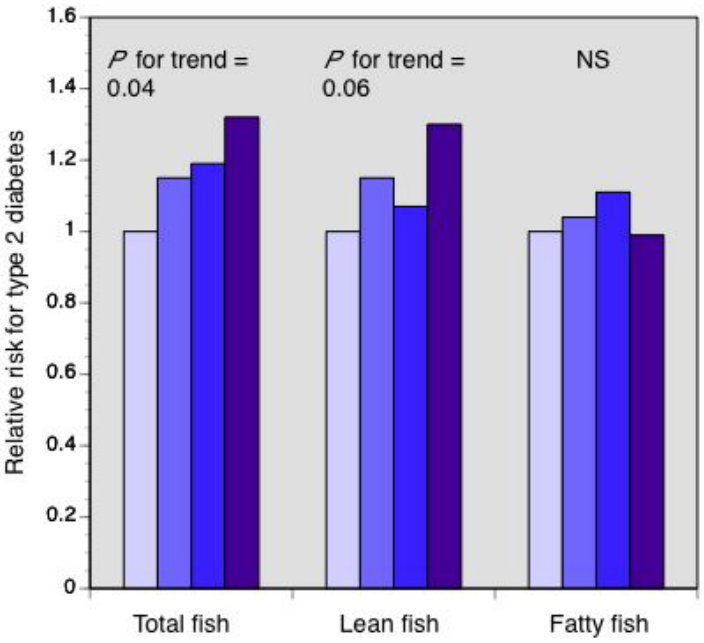
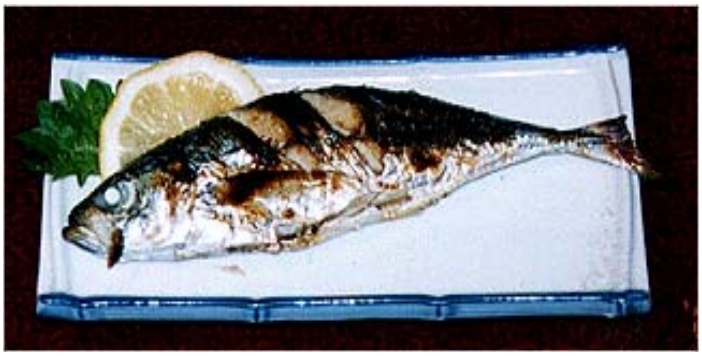


Figure. Relative risks for type 2 diabetes with increasing intakes of different types of fish. Bars from left to right represent median fish intakes of zero (reference), low, moderate and high amounts for each type of fish.

fatty fish (Figure) or had moderate or high consumption of EPA plus DHA. When the relationship between the highest intake of EPA plus DHA was further adjusted for selenium, vitamin D and cholesterol, the relative risk of diabetes fell from 1.22 to 1.05. Identifying and accounting for confounding variables can have a large influence on the analysis.

In older Dutch adults, greater consumption of total or lean fish was associated with a 30% higher chance of developing type 2 diabetes. But those who ate fatty fish were not more likely to develop diabetes.

These findings relate mainly to the consumption of lean fish, which accounted for about 80% of the fish eaten. Those who ate fatty fish did not experience a greater diabetes risk, even though they ate only 25% to 50% as much fish as those eating lean fish. This observation suggests that n-3 LC-PUFAs might have mitigated the risk for type 2 diabetes, even though the analysis found no correlation between EPA plus DHA intake and diabetes risk.



These findings are in partial agreement with the preceding study, but do not support the positive association between greater EPA plus DHA intakes and diabetes risk observed in the former. It is likely that the US participants in the studies analyzed by Kaushik *et al*. consumed mainly lean fish, although the estimated median n-3 LC-PUFA intakes were larger in the moderate and highest intake groups compared with the Dutch study. This study shows that consideration of the type of fish consumed may outweigh or even contrast with observations based on total fish consumption. Given the many other health benefits associated with fish consumption, especially of fatty fish, and the numerous other factors associated with the chance of developing type 2 diabetes, these observational studies provide insufficient basis for limiting or restricting one's fish consumption in order to avoid type 2 diabetes.

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Chronic Kidney Disease

Long-Chain Omega-3s Improve Blood Pressure and Heart Rate in Chronic Kidney Disease

Patients with chronic kidney disease, often as a result of diabetes or hypertension, face a 2- to 50-fold higher risk of cardiovascular disease and mortality. Whether long-chain omega-3 fatty acids and coenzyme Q10 can reduce these risks has received little inquiry until this study.

One of the potential consequences of diabetes or hypertension is kidney damage that can lead to chronic kidney disease and eventually kidney failure. The prevalence of this condition increased in the U.S. from 10% in 1988 to 13% in 2004, largely as a result of the increased incidence of diabetes and hypertension. Chronic kidney disease increases the risk of cardiovascular disease by 2 to 50 times, with kidney dialysis patients having a 50% chance of dying from cardiovascular disease. Control of blood pressure and cardiovascular risk factors is especially important in these patients and can slow disease progression and reduce the risks of cardiovascular events. In addition to blood pressure control, management of lipid abnormalities, endothelial dysfunction, inflammation and insulin resistance contribute to patient health and risk reduction. Because so many clinical issues are involved in patients with chronic kidney disease, multiple medications may be prescribed. Research suggests that long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) may be effective in reducing some of the clinical risks of chronic kidney disease and could be added to the treatment list.

Fish oil or n-3 LC-PUFA supplementation lowers C-reactive protein, inflammatory markers and triglycerides in patients with chronic kidney disease. Other improvements include increased high-density lipoprotein levels, better dialysis access patency, lower protein excretion and reduced oxidative stress. Effects of these fatty acids on glomerular filtration appear mixed. Overall, n-3 LC-PUFAs appear to offer many benefits to kidney disease patients.

Less is known about the health effects of coenzyme Q10 (CoQ10), also known as ubiquinone. This coenzyme is

Table. Mean 24-h awake and asleep blood pressure (mean ± SEM) at baseline and after 8 weeks' intervention

Blood Pressure	Control	n-3 LC-PUFA	CoQ10	n-3 LC-PUFA + CoQ10	Main effects* n-3 LC-PUFA	(*P*-value) CoQ10
24-h Systolic						
Baseline	117.2 ± 1.9	120.4 ± 2.1	119.0 ± 2.3	119.2 ± 2.1	NS	
8-wk	118.6 ± 0.8	116.9 ± 0.7	120.8 ± 0.7§	115.9 ± 0.7†	-3.3 (<0.0001)	0.6 (NS)
24-h Diastolic						
Baseline	122.1 ± 2.1	74.8 ± 1.7	73.7 ± 1.5	69.5 ± 2.0	NS	
8-wk	122.8 ± 1.0	71.7 ± 0.5	74.2 ± 0.5§	69.4 ± 0.5‡	-2.9 (<0.0001)	-0.5 (NS)
Asleep SBP						
Baseline	108.7 ± 2.3	108.8 ± 2.3	111.0 ± 3.4	112.9 ± 3.2	NS	
8-wk	110.1 ± 1.3	109.5 ± 1.2	113.2 ± 1.1§	105.2 ± 1.2†	-4.3 (<0.0003)	-0.6 (NS)
Asleep DBP						
Baseline	64.4 ± 2.0	64.5 ± 1.7	66.4 ± 1.6	63.3 ± 2.2	NS	
8-wk	65.3 ± 0.9	64.1 ± 0.8	67.9 ± 0.8§	60.6 ± 0.8‡	-4.3 (<0.0001)	-0.5 (NS)

*Main effects from linear analysis adjusted for baseline values. Significance levels were adjusted for multiple comparisons. §$P < 0.05$ compared with n-3 LC-PUFA group and $P < 0.001$ compared with n-3 LC-PUFA + CoQ10 group; †$P < 0.05$ and ‡$P < 0.0001$ compared with control.

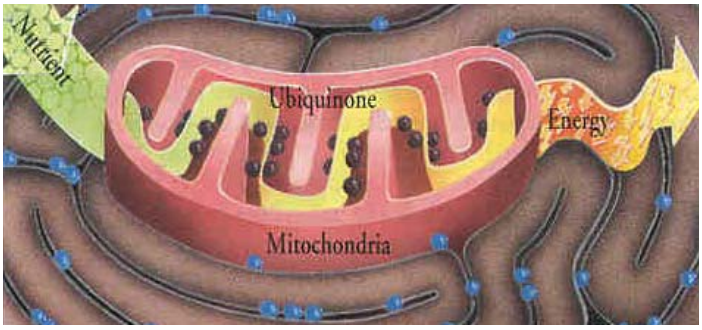

Figure. Site of action for CoQ10 (ubiquinone) in mitochondrial energy production.

found in nearly all human cells, especially those rich in mitochondria or with high energy demands such as the brain, liver and heart. There is some evidence that its concentration is reduced in patients with heart failure, but researchers disagree about its usefulness in cardiovascular conditions. In hemodialysis patients, CoQ10 was reported to suppress oxidative and antioxidative markers. Its levels were significantly lower than normal in one study of kidney patients, a finding with potential implications for oxidative stress. Further, CoQ10 was associated with improved blood pressure and endothelial function in type 2 diabetic patients.

Thinking creatively, Trevor Mori and colleagues at the University of Western Australia investigated the independent and additive effects of n-3 LC-PUFAs and CoQ10 on blood pressure, vascular function and dyslipidemia in nondiabetic patients with moderate to severe chronic kidney disease. Patients were excluded if they had angina pectoris, major surgery, a cardiovascular event within the past 3 months, blood pressure above 170/100 mm Hg, liver disease or nephrotic syndrome. Patients were ineligible if they consumed fish more than once a week, took fish oil capsules, inflammatory or immunosuppressant drugs or nitrates.

Eighty-eight participants aged 25 to 75 years (average age 56 years) provided baseline measurements during a 3-week familiarization period and then were stratified by age and body mass index and randomized to consume either 4 g/day of n-3 LC-PUFAs (eicosapentaenoic acid, EPA, 460 mg/capsule; docosahexaenoic acid, DHA, 380 mg/capsule), 200 mg/day of CoQ10, both n-3 LC-PUFAs and CoQ10, or a control supplement of olive oil (4 g/day). Supplementation continued for 8 weeks as part of the participants' usual diet. Both investigators and participants were unaware of which treatment the participants had. Participants' diets were monitored every 2 weeks to ensure compliance with usual eating habits. Ambulatory blood pressure (24-hour) and heart rate were assessed at baseline and after 8 weeks, as were forearm circulation, brachial artery diameter, echocardiography and blood and urine analyses.

After 8 weeks, there were no significant differences between the groups in body weight, serum or urinary metabolites. Platelet phospholipid fatty acids showed increased EPA, DHA and docosapentaenoic acid (n-3) in the groups consuming n-3 LC-PUFAs. Consumption of CoQ10 was associated with significant increases in its plasma concentration, but the increase was significantly less in the presence of n-3 LC-PUFAs compared with CoQ10 alone. Serum lipoproteins, lipids and C-reactive protein were unaffected by any treatment, except for a 24% drop in triglycerides in both groups consuming n-3 LC-PUFAs. Serum glucose and insulin, albumin and protein excretion were also unchanged after the treatments.

Consumption of n-3 LC-PUFAs, but not CoQ10, was associated with significant reductions in systolic and diastolic blood pressures. The greatest decrease occurred during sleep in patients consuming the n-3 LC-PUFAs plus CoQ10 (Table). These patients experienced the greatest drop in 24-hour systolic blood pressure during sleep, but the falls in 24-hour diastolic blood pressure resulted from changes in both awake and sleep diastolic pressure. Blood pressures in those consuming only CoQ10 were significantly higher than in the n-3 LC-PUFA groups (Table). Similarly, groups consuming n-3 LC-PUFAs experienced significantly lower heart rates at the end of 8 weeks, but those taking CoQ10 had increased heart rates. Large artery compliance improved significantly in the n-3 LC-PUFA groups compared with the controls.

Consumption of n-3 LC-PUFAs has been associated with lower blood pressure in previous studies, a finding confirmed here. Similarly, CoQ10 has been linked to lower blood pressure in 3 clinical trials, but not in this study of chronic kidney disease patients. However, the greatest reduction in blood pressure was observed in patients who consumed both n-3 LC-PUFAs and CoQ10, particularly in asleep blood pressure. The authors were at a loss to explain this observation, given that CoQ10 alone had no effect on blood pressure. The two substances also had differential effects on heart rate, with n-3 LC-PUFAs reducing and CoQ10 raising it.

Patients with chronic kidney disease who consumed 4 g/day of long-chain omega-3 fatty acids for 8 weeks had significantly lower 24-hour systolic and diastolic blood pressures compared with control patients. Consumption of CoQ10 was associated with higher blood pressure.

Increased blood pressure is one of many factors contributing to the increased risk of cardiovascular disease and mortality in chronic kidney disease. High blood pressure is more difficult to control in chronic kidney disease than in other conditions. Successful management of hypertension, particularly systolic pressure, in mild kidney disease has been associated with a 30% to 40% reduction in cardiovascular events. Consumption of 4 g/day of n-3 LC-PUFAs for 8 weeks by patients with chronic kidney disease further reduced blood pressure from what was achieved with blood pressure medications. In another study, 3 g/day of these fatty acids slowed the progression of renal disease for more than 6 years in patients with IgA nephropathy. Thus, targeting blood pressure control with medications and n-3 LC-PUFAs has substantial potential benefits. Moreover, these fatty acids apparently have cardioprotective effects in renal disease, as suggested by the reduced heart rate, improved large artery compliance and lower triglycerides observed in this study. This is good news for patients with chronic kidney disease.

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