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Classic and Modern Ho-Hos

From this high midtown hall, undecked with boughs, unfortified with mistletoe, we send forth our tinselled greetings as of old, to friends, to readers, to strangers of many conditions in many places.

Merry Christmas to uncertified accountants, to tellers who have made a mistake in addition, to girls who have made a mistake in judgment, to grounded airline passengers, and to all those who can't eat clams! We greet with particular warmth people who wake and smell smoke. To captains of river boats on snowy mornings we send an answering toot at this holiday time.

Merry Christmas to intellectuals and other despised minorities! Merry Christmas to the musicians of Muzak and men whose shoes don't fit! Greetings of the season to unemployed actors and the blacklisted everywhere who suffer for sins uncommitted; a holly thorn in the thumb of compilers of lists! Greetings to wives who can't find their glasses and to poets who can't find their rhymes!

Merry Christmas to the unloved, the misunderstood, the overweight. Joy to the authors of books whose titles begin with the word "How" (as though they knew!). Greetings to people with a ringing in their ears; greetings to growers of gourds, to shearers of sheep, and to makers of change in the lonely underground booths! Merry Christmas to old men asleep in libraries! Merry Christmas to people who can't stay in the same room with a cat!

We greet, too, the boarders in boarding houses on 25 December, the duennas in Central Park in fair weather and foul, and young lovers who got nothing in the mail. Merry Christmas to people who plant trees in city streets; merry Christmas to people who save prairie chickens from extinction! Greetings of a purely mechanical sort to machines that think--plus a sprig of artificial holly. Joyous Yule to Cadillac owners whose conduct is unworthy of their car!

Merry Christmas to the defeated, the forgotten, the inept; joy to all dandiprats and bunglers! We send, most particularly and most hopefully, our greetings and our prayers to soldiers and guardsmen on land and sea and in the air--the young men doing the hardest things at the hardest time of life. To all such, Merry Christmas, blessings, and good luck! We greet the Secretaries-designate, the President-elect; Merry Christmas to our new leaders, peace on earth, good will, and good management!

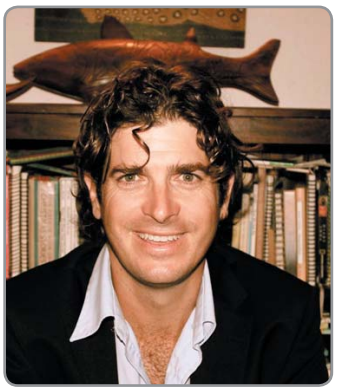
Reproduced with permission from the artist, Ray Troll, www.trollart.com.

Merry Christmas to couples unhappy in doorways! Merry Christmas to all who think they are in love but aren't sure! Greetings to people waiting for trains that will take them in the wrong direction, to people doing up a bundle and the string is too short, to children with sleds and no snow! We greet ministers who can't think of a moral, gagmen who can't think of a joke. Greetings, too, to the inhabitants of other planets; see you soon!

And last, we greet all skaters on small natural ponds at the edge of woods toward the end of afternoon. Merry Christmas, skaters! Ring, steel! Grow red, sky! Die down, wind! Merry Christmas to all and to all a good morrow!

– E.B. White, 1952

Eating with Intelligence . . .



Philippe Rouja, Department of Conservation Services, Government of Bermuda, Bermuda
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Fisheries of different species around the world have already collapsed or are in imminent danger of collapse. The demand for fish continues to increase yearly even though consumers remain confused about the risk-benefit balance of fish consumption.[1] Is it possible to maintain the benefits of fish consumption while minimizing the risks to both human health and global fisheries?

We are familiar with the image of a series of fish, each progressively larger than the other, eating the fish in front and being eaten by the larger fish behind. These kinds of cultural representations have been created by our incredible brain capacity, which arguably evolved due to the availability of marine fats.[2] Western culture has transcribed our assessment of what one could call the brain chain (with the human species posited at the top) to the food chain so that we logically believe that we are, and should eat, at the top. But this mistaken belief may be leading us to the nutritional equivalent of the Peter Principle,[3] whereby our harvesting from higher trophic levels in the marine food chain eventually leads us to make nutritionally and ecologically incompetent choices. Ironically, while seafood may have pushed us to the top of the brain chain, the way we consume seafood today may not keep us there. We are eating the wrong kinds of fish and too many of them. Fish consumers and the planet alike might be much better off were they to follow the example of many indigenous fishermen by fishing and eating with more intelligence.

The Bardi people of North Western Australia follow fishing strategies in which fish are selected for both their nutritional quality and their relative seasonal fatness, rather than their size, ease of capture and relative quantity of calories they might provide. The Bardi teach us that in temperate and tropical fisheries such a seasonal fishing strategy based on procuring seasonally fat fish enhances human health and leads to the avoidance and protection of spawning fish, many of which are not fat when reproducing.[4]

In traditional Polynesian society, pregnant women specifically avoid pelagic fish consumption, fish that we now assess as being relatively low in nutrients and high in contaminants such as mercury.[5,6] The Polynesians and many other Pacific islanders also cook fish whole with the guts, head and skin intact in order to consume the fats found therein. These parts of the fish are discarded and rarely eaten by most western consumers but are considered a delicacy in many other cultures around the globe. For many indigenous fishing cultures these parts of the fish are the prime motivating factor in choosing which fish to catch.

Our recent research in Bermuda, which measured omega-3 fatty acids, selenium and mercury in a wide range of local fish species, indicated that some of the smaller fish species have more to offer to human health with less risk than larger fish closer to the top of the food chain.7 There are several reasons for this. Fish at the top can become significant repositories for a range of contaminants—both natural and anthropogenic—and may also have unhealthy concentrations of certain nutrients that have negative impacts on human health.

The flesh of most large predator fish from warm water fisheries (big tuna, swordfish, marlin and shark) is usually lean with low omega-3s and high in mercury/selenium ratios.[7]

Small fish, however, not only provide higher levels of beneficial nutrients, but are also significantly lower in contaminants ubiquitous to the marine food chain. Small fish, such as sardines, tend to be eaten whole, whereas large fish like tuna or swordfish are treated, sold, prepared and eaten in much the same way as cattle. What we are left with is a slab of meat, that is for larger fish species, referred to (without irony) as a steak and for smaller fish, a fillet. The fillet and the steak are both divorced from the most nutritious parts of the fish: the skin, bone, brain and eye. The parts of the fish that we discard are, in fact, preferred by the brown and black bear which, during specific seasons, only consume the head and stomach of salmon, leaving the racks along the river's edge for less nutritionally discerning scavengers.[8] As people have less time to prepare fish, the fish fillet and steak have taken over from the whole fish that may have once been available from the fishmonger. Smaller fish, however, continue to be eaten whole, giving consumers access to the full warehouse of nutrients that fish can deliver.

Get off the Top of the Food Chain

Small fish have not been subject to the same over-fishing pressure that has befallen almost all of the larger fish species. Sardines, for example, have been the top pick for many fish watch organizations as they are healthy to eat and sustainably harvested.

We are selling ourselves short every time we use smaller more beneficial fish to catch or grow larger, more contaminated fish. We need to investigate how we can catch fish exclusively for the particular nutritional benefits they impart, not just for the ubiquitous meat and protein all fish can provide. Like the Bardi, we should learn that every fish has its season where both its taste and its nutritional value will be maximized. In seeking the best from their resources, they also nurture their sustainability. It has worked for them for at least 27,000 years[9]—perhaps it is not too late for us.

Think big. Eat small.

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CARDIOVASCULAR DISEASE

Subclinical Atherosclerosis

Less Subclinical Atherosclerosis with Higher Intake of Long-Chain Omega-3s

Associations between the consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs), found predominantly in fatty fish and fish oil, and reduced risks of cardiovascular mortality and disease are well documented in the scientific literature. The underlying reasons for these associations are believed to relate to the effects of these fatty acids on thrombosis, the heart's electrical activity, inflammation, blood lipids, the development and progress of atherosclerosis and other conditions. Evidence supports the involvement of each of these mechanisms, but data have been inconsistent, especially in patients with different types of cardiac disease. In addition, some clinical effects of n-3 LC-PUFA consumption, such as modest increases in low-density lipoprotein cholesterol and changes in some inflammatory markers are inconsistent with lower cardiovascular risk. Some data from patients with implantable cardioverter defibrillators suggest increased risk of cardiovascular arrhythmias with fish oil consumption.

Long-chain omega-3 fatty acids lower the risk of cardiovascular mortality in patients with heart disease. Are they involved in preventing the disease in those free of clinical symptoms? This study suggests that a higher intake of omega-3s is linked to less subclinical atherosclerosis in people without heart disease.

Patients with heart disease and those at high risk of the condition are a key target for preventive interventions that deter the onset of adverse cardiac events or mortality. However, preventing cardiovascular events in individuals free of clinical heart disease is also vital for improving quality of life and lowering the burden of the world's leading cause of death. Whether n-3 LC-PUFAs are involved in preventing cardiovascular disease is hotly debated. If they are, what are the mechanisms?

Assessment of heart disease risk rests mainly on the evaluation of a patient's risk factors, including circumstances such as age, family history, blood lipids, etc. that affect the chances of serious cardiac events. Increasingly, measurements of risk may include scanning the coronary arteries for calcium and evaluating the thickness of the intimal and medial layers of the common carotid arteries (carotid intima-media thickness, CIMT) using ultrasound technology. These assessments featured in a recent study comparing the arterial health, an indirect measure of cardiovascular risk, of Japanese and white men.

This cross-sectional observational study describes the relationship between coronary artery calcium, CIMT measurements and fish or n-3 LC-PUFA consumption in a population-based study of atherosclerosis in the U.S. The goal was to determine to what extent fish or n-3 LC-PUFA consumption might explain measures of subclinical atherosclerosis in middle-aged or older adults. The multi-ethnic participants included 6,814 men and women aged 45 to 84 years, recruited from 6 US communities, who were without clinical cardiovascular disease at baseline. Those who enrolled provided information about sociodemographic and psychosocial factors, diet, lifestyle and cardiovascular risk factors. All participants were assessed for coronary artery calcium, CIMT and ankle-brachial index at baseline. Positive assessments of subclinical atherosclerosis were predefined for coronary artery calcium as Agatston score > 0, common CIMT > 80th percentile values and an ankle-brachial index value < 0.9. After exclusions for incomplete data and extremes of energy intake, data were available from 5,488 participants.

The study gave particular attention to the frequency, type and preparation of the seafoods consumed. Fish consumption was divided into fried fish (including shellfish), non-fried fish (broiled, steamed, baked or raw) and non-fried fish plus shellfish. Nearly half of the participants reported eating no shellfish. Mixed seafood dishes, such as stir-fried fish, were excluded from the main analysis, but added to the secondary analysis by weighted adjustment of the serving size, type of seafood, and age- and sex-specific serving size. Fish and n-3 LC-PUFA consumption were grouped in quartiles and the relationships between dietary intake and subclinical measurements were analyzed using logistic regression, adjusted for multiple demographic and lifestyle factors added to the model in a hierarchical manner.

Median n-3 LC-PUFA intakes ranged from 40 to 220 mg/day across the quartiles. Those in the highest quartile were more highly educated, affluent, physically active and less likely to smoke. As illustrated in the Figure, participants with the highest n-3 LC-PUFA consumption were 31% less likely to have adverse thickening of the lining of their carotid arteries compared with those in the lowest intake group (odds ratio: 0.69, 95% CI 0.55 to 0.86, P= 0.05). No significant relationship was observed for n-3 LC-PUFA or fish consumption and coronary calcium evaluations. Those with higher intakes of non-fried fish were 20% more likely to have a lower carotid CIMT score (P= 0.05), but the inclusion of shellfish weakened

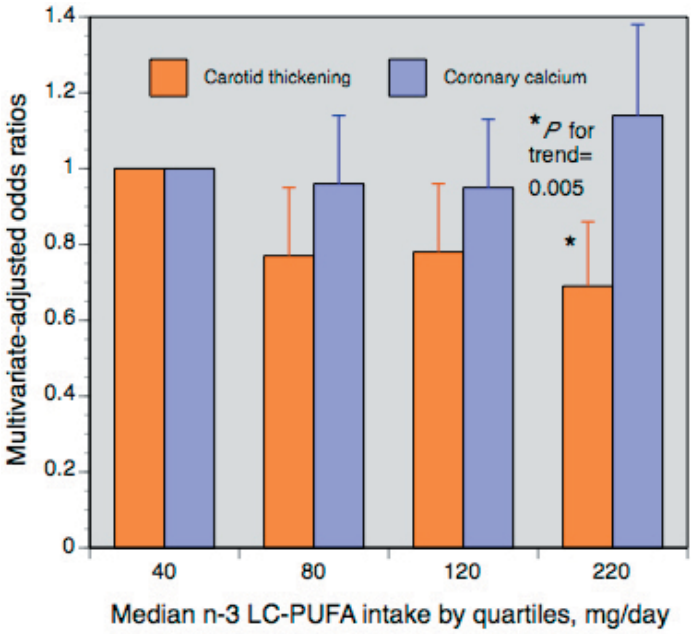

Figure. Multivariate adjusted odds ratios (+95% CI) of subclinical atherosclerosis with increasing intake of n-3 LC-PUFAs in multiethnic US adults aged 45 to 84.

this association. The frequencies of eating fried fish, non-fried fish or the combination were not associated with n-3 LC-PUFA intake.

Other significantly favorable associations were reported between the highest category of n-3 LC-PUFA—but not fish—consumption and lower blood triglycerides and higher high-density lipoprotein cholesterol concentrations. Intake of n-3 LC-PUFAs was unrelated to low-density lipoprotein or total cholesterol concentrations. None of the other assessments of subclinical atherosclerosis were related n-3 LC-PUFA intake.

High consumption of long-chain omega-3s was associated with significantly less carotid artery intima-media thickening and thus less subclinical atherosclerosis. Those eating non-fried fish were more likely to have less carotid artery thickening.

The primary observation that high consumption of n-3 LC-PUFAs is associated with a significantly lower chance of having a CIMT score indicative of subclinical atherosclerosis supports previous studies linking high n-3 LC-PUFA consumption with less arterial plaque or atherosclerosis progression. For example, fish consumption was associated with significantly less progression of coronary atherosclerosis in postmenopausal women. Another study reported a significant association existed between high serum n-3 LC-PUFA concentrations and the reduced occurrence of carotid plaques in Japanese villagers. In contrast, findings from two randomized controlled trials of n-3 LC-PUFAs in patients with documented coronary heart disease observed no effect of high-dose n-3 LC-PUFA consumption on the diameter of atherosclerotic coronary arteries or the progression of carotid atherosclerosis. Thus, the data remain inconsistent.

The present findings confirm previous reports that eating fried fish confers no detectable heart health protection and may be linked to greater risk of heart disease. Those participants with higher intakes of non-fried fish were less likely to have higher CIMT values and a positive assessment of subclinical atherosclerosis. This observation was less robust than the association between n-3 LC-PUFA intake, but reinforces many reports that eating fish rich in n-3 LC-PUFAs is protective of heart health. The study also demonstrates differences in associations according to the method used to assess subclinical atherosclerosis. Notwithstanding the limitations of cross-sectional observational data, this report is consistent with the suggestion that consuming higher amounts n-3 LC-PUFAs discourages the accumulation of arterial plaque.

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High Intakes of Long-Chain Omega-3s Unrelated to Carotid Artery Plaque

Do high intakes of n-3 LC-PUFAs protect against carotid artery plaque and thickening of the carotid artery lining? The answers may be no and yes.

The odds that an individual will incur an adverse cardiac event, such as a myocardial infarction or sudden death, are usually evaluated clinically according to the classic risk factors for cardiovascular disease. Many of these characteristics can be kept in check by not smoking, eating a healthful diet, exercising regularly and maintaining a desirable body weight. With aging, however, the risk of cardiovascular disease increases, and may become life-threatening. To improve the assessment of heart health risks and implement preventive interventions earlier, clinicians may determine whether and to what extent a patient has developed atherosclerosis. With ultrasound imaging technology, it is possible to detect arterial plaque in the carotid arteries and measure how much the lining of these vessels has thickened. These arterial changes indicate the presence of subclinical atherosclerosis.

A promising intervention to reduce atherosclerotic plaque and slow or halt the thickening of the lining of the blood vessels is to increase the patient's consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). The dietary consumption of about 2 g/day of eicosapentaenoic acid (EPA), an n-3 LC-PUFA, for 2 years was associated with a reduction in the carotid intima-media thickness (CIMT) in Japanese patients with type 2 diabetes and with a slower rate of CIMT thickening in elderly men with hyperlipidemia.

Given that subclinical atherosclerosis develops less extensively among Japanese men with high fish intakes compared with their compatriots in Hawaii or Caucasians in the U.S., one may ask whether other populations with very high n-3 LC-PUFA intakes, such as the Alaska Inuit (Eskimos), have less subclinical atherosclerosis. This question was addressed in a longitudinal study of the genetics of coronary artery disease among Alaska natives whose high consumption (>3 g/day) of n-3 LC-PUFAs was associated with more favorable markers of cardiovascular disease and the metabolic syndrome. Nevertheless, coronary heart disease is highly prevalent among the Alaska Inuit (15% of adults 45 years old or more) and heart disease mortality rates are 30% to 40% greater than in US caucasians. The present situation in Alaska contrasts sharply with the low prevalence of heart disease among the Greenland Inuit in the 1970s, but these Inuit now exhibit a high prevalence of heart disease.

Inuit participants ranging in age from 17 to 92 years were recruited from coastal villages in northwest Alaska and assessed for atherosclerosis risk factors by physical examination, questionnaire and blood sampling. The investigators used ultrasonic imaging to detect and measure arterial plaque in 8 segments of both carotid arteries and calculated a plaque score based on the number of plaque-containing segments. They measured CIMT in the arterial wall where no plaque was present. Associations between risk factors and CIMT or plaque scores were assessed by linear regression of log-transformed scores. The associations were adjusted for age, sex, body mass index, high- and low-density lipoprotein cholesterol, smoking, diabetes and hypertension. The investigators compared the prevalence of plaque in these Inuit with previously published data from the general US population in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study in individuals 65 years or older. In addition, they assessed the relationship between dietary fatty acid consumption and the prevalence and extent of plaque and CIMT scores.

The sample in the prevalence study presented here (Cutchins *et al.*) consisted of 1,214 men and women who averaged 42 years of age, with a mean body mass index of 27 and 29 kg/m^2 for men and women, respectively. There were about 100 fewer participants in the Ebbesson report. Nearly a quarter of the participants had hypertension, but the prevalence of diabetes was low (2% for men, 5% for women), low-density lipoprotein cholesterol levels near optimal and high-density lipoprotein levels high. About 60% of participants smoked.

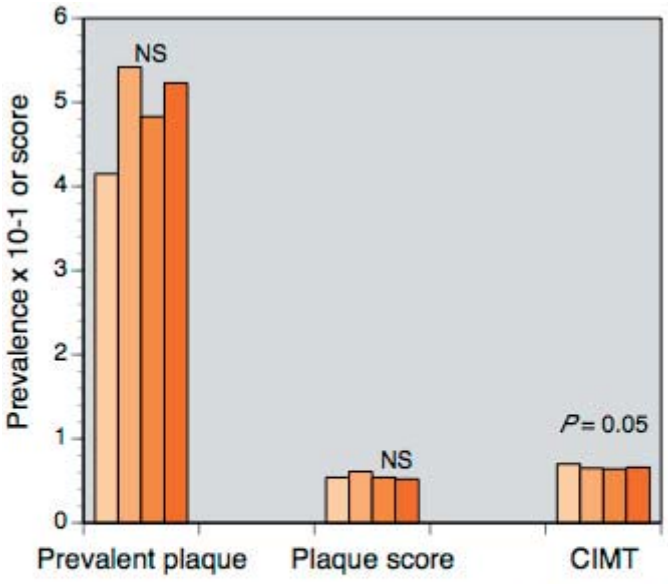

Figure. Prevalence of carotid plaque x 10^{-1}, extent of plaque (score) and mean carotid intima-media thickness (mm) by increasing quartiles of n-3 LC-PUFA consumption in Alaska Inuit aged 35 yr or more. Source: Ebbesson et al., *Atherosclerosis* 2008;199:346-353.

The presence and extent of atherosclerosis (plaque score) were significantly associated with each decade of increasing age and the presence of hypertension. Smokers were more likely to have carotid plaque. Other factors significantly associated with greater CIMT and more extensive atherosclerosis included male sex and diabetes.

Intakes of n-3 LC-PUFAs were high, regardless of plaque status, ranging from a mean of 5 to 6 g/day in both studies, but consumption was unrelated to the presence or extent of carotid artery plaque (Figure). Others have reported no association between the consumption of n-3 LC-PUFAs and carotid artery disease. However, n-3 LC-PUFA intakes were inversely associated with CIMT scores, suggesting a protective effect on carotid artery thickening (Figure). In contrast, the intakes of palmitic and stearic acids were significantly linked to plaque occurrence, with increasing palmitic acid consumption also associated with more extensive lesions in multivariate analysis.

High intakes of n-3 LC-PUFAs were unrelated to the presence or extent of carotid artery plaque, but were associated with less thickening of the carotid artery lining.

When the prevalence of carotid artery plaque was compared with the findings from two other US population studies, the prevalence of carotid plaque in the Alaska Inuit was markedly higher—sometimes twice as great—at all ages from 45 to 74 years and in both men and women.

This study singles out several familiar cardiovascular risk factors, particularly male sex, smoking, hypertension and diabetes as key harbingers of more severe subclinical atherosclerosis in coastal Alaska Inuit. The participants displayed little to no advantage in atherosclerosis status from their high consumption of n-3 LC-PUFAs, except for being less likely to have high CIMT scores. In spite of this presumed advantage, the average CIMT scores were similar to values reported in two comparison populations. The dramatically higher smoking rate in this population (60% compared with 20% in the reference studies) and perhaps less favorable dietary changes may have abrogated the cardiovascular benefits from the high exposure to n-3 LC-PUFAs. It seems a cruel irony that the traditional diet of Arctic natives, the characteristic first associated with the cardioprotective properties of n-3 LC-PUFAs, may have given way to lifestyle habits that promote the disease once unknown to these people.

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Chronic Heart Failures

Long-Chain Omega-3s Modestly Improve Lifespan in Chronic Heart Failure

In one of the largest, randomized, intervention trials with long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) to date, the Italian investigative team of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, better known as the GISSI investigators, have previously reported a 45% reduction in the risk of sudden death among more than 11,000 survivors of a myocardial infarction who were assigned to consume 850 mg/day of n-3 LC-PUFAs for about 3 years. The chance of dying from cardiovascular disease was 30% lower. This landmark study ensured that the cardioprotective effects of n-3 LC-PUFAs would not go unnoticed and drew attention to factors affecting cardiovascular mortality other than blood lipid concentrations which were unchanged in this study.

New results from heart failure patients who consumed long-chain omega-3 fatty acids suggest modest benefits among older individuals receiving standard care.

The GISSI investigators now report the results of the first randomized, double-blind, placebo-controlled trial with clinically relevant endpoints and n-3 LC-PUFA treatment. Study participants were patients with class II-IV chronic heart failure as defined by the New York Heart Association. Chronic or congestive heart failure is characterized by the heart's inability to pump sufficient blood to the rest of the body. The condition is complex, often resulting from acute or chronic cardiac injury. As described in a recent scientific statement from the American Heart Association, its development is largely independent of myocardial infarction, but is strongly linked to high blood pressure. Because of the increasing number of people over the age of 65, the incidence of heart failure is expected to increase dramatically in the next 20 years. From public health and individual quality of life perspectives, interventions that might discourage the condition and its morbidity and mortality would be especially welcome.

The GISSI investigators recruited 7,046 eligible men and women aged 18 or older from more than 300 cardiology centers in Italy and obtained data from 6,975 participants. Patients were excluded if they had other serious conditions, such as cancer or liver disease, had acute coronary syndrome or revascularization procedures within the preceding month or had forthcoming cardiac surgery. Participants were randomly assigned to consume 850 to 880 mg/day of n-3 LC-PUFAs as ethyl esters or placebo for at least 3 years and continued their prescribed medications. In addition, a subgroup of patients who were not on statin drugs were randomly assigned to consume 10 mg/day of rosuvastatin (a cholesterol-lowering drug) or placebo. Compliance was pre-established as the administration of treatment for 80% of the days of observation. At the end of the study, about 70% of participants achieved compliance, defined as taking at least 80%

of their prescribed drugs, whether placebo, statin or n-3 LC-PUFAs.

The mean age of the patients was 67 years, with 42% over age 70. The median duration of the followup was 3.9 years and ranged from 3 to 4.5 years.

There were two primary endpoints: time to death and time to death or hospital admission for cardiovascular reasons. Several secondary cardiovascular endpoints were assessed, including sudden cardiac death, admissions for heart failure, fatal and nonfatal myocardial infarction, and stroke.

To determine whether the intervention was related to the observed outcomes, the investigators calculated the Cox proportional hazards at 6-month intervals for the intervention and placebo groups. The analysis adjusted for variables that were uneven between the groups at baseline, a statistical practice the investigators' did because of a lack of an agreed set of prognostic factors for patients with this type of heart failure.

Older patients with chronic heart failure who consumed about 1 g/day of n-3 LC-PUFAs for 3 years were slightly, but significantly, less likely to die compared with the placebo group. They were also less likely to be hospitalized for cardiovascular reasons.

In the adjusted intention-to-treat analysis of the time to all-cause mortality, participants taking n-3 LC-PUFAs were slightly, but significantly, less likely to die compared with the placebo group, 27% vs. 29% over 3 years (Table). Similarly, the n-3 LC-PUFA patients were less likely to die or be hospitalized for cardiovascular reasons (57% vs. 59%). In absolute terms, the chance of dying from any cause was 1.8% lower with the consumption of n-3 LC-PUFAs and the frequency of the combined endpoint was 2.3% lower. In relative terms, the risk for death was reduced by 9% and cardiovascular hospitalization or death b 8%. Differences between the treatment and placebo groups appeared after 2 years. In the per protocol analysis, which included all participants who were compliant with their medications, the relative risk reductions were 14% for total mortality and 9% for the combined endpoint, both statistically significant.

For the secondary cardiovascular outcomes, small but significant differences favoring n-3 LC-PUFA consumption were observed for cardiovascular mortality and hospital admission for any or heart health reasons in adjusted analysis. The authors noted that almost half the risk reduction for the first cardiovascular hospital admission was due to fewer ventricular arrhythmias, the main cause of sudden cardiac death. However, the number of such deaths did not differ between the groups. There were no significant treatment effects on blood pressure, heart rate, hemorrhagic events or blood lipids and little benefit on myocardial infarction or stroke.

Although the GISSI investigators had hoped for a larger effect from n-3 LC-PUFAs, readers should note that the treatment was safe and effective. These participants were older, already receiving recommended therapies for their conditions and sustained no adverse effects other than mild gastrointestinal discomfort. The ability to reduce the risk for death in heart failure patients using a completely harmless agent, n-3 LC-PUFAs, that does not adversely interact with any current cardiac medications opens the door to greater use of these nutrients in this expanding patient population.

GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet *2008;372:1223-1230.*

Table. Primary and secondary outcomes in heart failure patients who consumed ~ 1 g/day n-3 LC-PUFAs for 3 years

Outcomes	n-3 LC-PUFAs %	Placebo %	*P**
Total mortality	27	29	0.041
All-cause mortality or hospital admission for CVD	57	59	0.009
CVD mortality	20	22	0.045
Hospital admission, any	57	58	0.049
Hospital admission, CVD	47	48	0.026
CVD mortality or any hospital admission	62	63	0.043

*Based on adjusted Hazard Ratios and 95% confidence intervals

Cardiovascular Disease Mortality and Heart Failure Reduced with High Fish Intakes

Data from Asian populations suggest that high fish intakes reduce mortality from heart disease, but whether eating fish reduces the mortality from specific types of heart condition, such as heart failure, is not known.

Data from Asia, particularly among Japanese individuals, have consistently described significantly lower mortality from and incidence of cardiovascular disease that has been linked to the high consumption of fish and long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). While fish and n-3 LC-PUFA intakes are not the only differences between Asian and western populations, these dietary features are plausible candidates to account for much of the better heart health among Asians. Both cohort and randomized controlled intervention studies support this interpretation. Data suggesting an association between n-3 LC-PUFA intakes and reduced risk of stroke or heart failure are less plentiful. A recent Japanese study reported that the consumption of about 2 g/day of eicosapentaenoic acid was associated with a 20% lower chance of having a recurrent stroke, but not a first one.

Health and mortality data from a community-based sample of nearly 111,000 individuals in 45 Japanese districts were available for investigators to examine the possible relationships between fish and n-3 LC-PUFA intakes and the chance of dying from ischemic heart disease, cardiac arrest or failure, stroke and cardiovascular disease incidence. Participants in the study aged 40 to 79 years were monitored for 13 years. Cause of death, coded by the International Statistical Classification of Diseases, was ascertained from death certificates. Investigators from several Japanese universities and the University of Minnesota, USA, conducted the study.

Fish consumption was assigned to one of 4 categories: fresh fish, kamaboko (steamed fish paste), dried or salted fish, and deep-fried fish or shellfish. Total fish intake was calculated from the frequency and portion size data for each type of fish. Consumption of total n-3 PUFAs was estimated from Japanese food tables for each category of fish. The correlation coefficient between energy-adjusted fish and n-3 PUFA intakes was 0.84.

Over the course of the study, there were 2,045 total cardiovascular deaths. Principal causes were 972 due to stroke (319 from ischemic stroke), 419 from ischemic heart disease, 307 from heart failure and 107 from cardiac arrest. Participants with the highest fish intake were more likely to be older, have diabetes, smoke and drink less alcohol. Fish-eaters consumed less total energy, but ate more cholesterol and all types of fatty acids, fruits and vegetables. There were no interactions between fish or n-3 PUFA intake and sex, so data from men and women were combined.

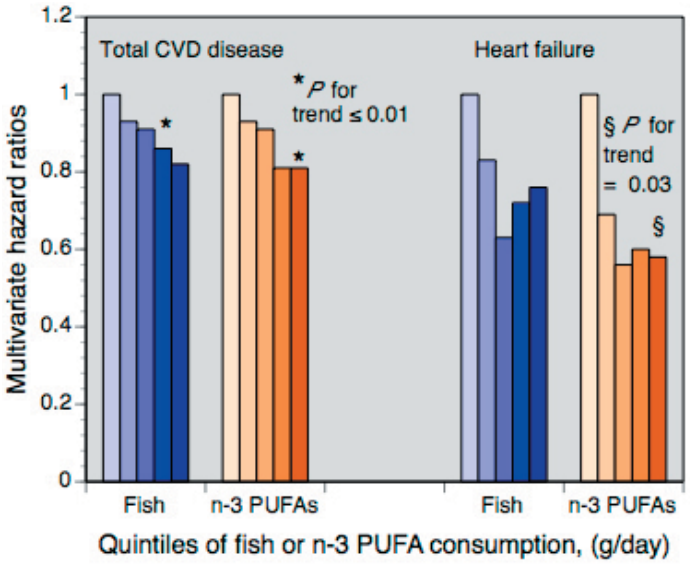

Figure. Multivariate hazard ratios for mortality from total cardiovascular disease (left panel) or heart failure (right panel) according to quintiles of fish or n-3 PUFA consumption in 57,972 Japanese men and women aged 40 to 79.

When the investigators calculated the hazard ratios—a way of assessing the chance that an event (e.g., death) will occur—for dying from any cause or specific cardiovascular reasons, they observed a significantly lower chance (18%) of total cardiovascular disease mortality as fish intake increased and a 19% reduced chance with higher n-3 PUFA consumption. The analyses accounted for 17 confounding variables. No other specific causes of cardiovascular disease mortality were significantly associated with high fish consumption, but the trends for mortality from ischemic heart disease, myocardial infarction and heart failure tended to improve with greater intakes of fish or n-3 PUFAs. For heart failure, the multivariate mortality risk was 42% lower in the highest compared with the lowest quintile of n-3 PUFA intake (*P* for trend = 0.03). There were no associations between fish or n-3 PUFA intakes and fatal stroke. This observation agrees with three previous observational studies in Asian populations.

The main conclusion that high fish or n-3 PUFA consumption is associated with a lower chance of cardiovascular mortality agrees with many other observational studies describing lower total cardiovascular mortality rates among individuals who consume greater amounts of fish or n-3 PUFAs. In this large

High intakes of n-3 PUFAs were linked to significantly lower chances of cardiovascular and heart failure mortality in Japanese adults aged 40 to 79.

study, all types of cardiovascular disease, but especially heart failure, were significantly lower in those eating the most n-3 PUFAs. Many studies have focused on the consumption of n-3 LC-PUFAs, whereas this study included all types of n-3 PUFAs, not just the long-chain ones. However, the high correlation between fish and n-3 PUFA intakes and the similarity of findings when the analysis included only n-3 LC-PUFAs suggest that the relationships may be largely attributed to the long-chain forms. This report provides welcome confirmation that high fish consumption is linked to a significantly lower mortality from cardiovascular disease and heart failure and confirms other studies where stroke mortality is unaffected by n-3 LC-PUFA intake.

Yamagishi K, Iso H, Date C, Fukui M, Wakai K, Kikuchi S, Inaba Y, Tanabe N, Tamakoshi A; Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study Group. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. J Am Coll Cardiol *2008;52:988-996.*

MATERNAL AND INFANT HEALTH

High Prenatal Fish Intake and Long Breastfeeding Time Favor Developmental Scores

The importance of mothers' consumption of sufficient amounts of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) during pregnancy and lactation has become more widely appreciated, as confirmed by the expert recommendation that women consume at least 200 mg of docosahexaenoic acid (DHA)/day during pregnancy and lactation. Higher maternal consumption of DHA has been associated with beneficial infant outcomes, such as improved cognition, intelligence and problem-solving; better visual acuity; improved quality of movement; and more mature sleep patterns. DHA is most safely obtained by eating fatty fish low in contaminants, such as salmon, rainbow trout, sardines, herring and mackerel, and from fish oil or n-3 LC-PUFA supplements.

In spite of the fact that higher maternal fish or DHA intake is consistently associated with beneficial infant outcomes, fish and DHA intakes in many western countries fail, sometimes spectacularly, to meet current recommendations of 200 mg of DHA/day.

Nevertheless, fish and DHA intakes in many western countries are lower than optimal, and fall short—sometimes spectacularly so—of meeting these recommendations. Pregnant women in New England, USA, where fish consumption is common, consumed an average of 150 mg/day of eicosapentaenoic acid (EPA) and DHA. Women who did not eat fish consumed about 20 mg/day. There are many reasons for this dietary inadequacy, including misleading and false information and communications and misperceptions about the amount and dangers of methylmercury in fish. Overly cautious government advisories about fish consumption, confusion in the literature about real and potential risks, and the understandable aversion to risk characteristic of pregnant and nursing women all contribute to low seafood intakes in the U.S.

Scientific reviews of the benefits and risks of eating seafood during pregnancy and lactation have consistently concluded that the benefits to child development outweigh the potential risks of exposure to methylmercury. There is general agreement that provision of DHA, and perhaps arachidonic acid (ARA), during fetal development bears a stronger relationship to infant outcomes than supplying these fatty acids after birth. That said, infants fed breast milk, which contains these LC-PUFAs, or formula containing DHA and ARA have better neurodevelopmental outcomes compared with those fed unsupplemented formula.

The investigators in the study described here examined a novel aspect of maternal fish consumption during pregnancy, the possible association with the duration of breastfeeding. They wished to determine whether any such association might further be linked to the infant's achievement of developmental milestones at 6 and 18 months of age. The multinational investigative team analyzed data from the Danish National Birth Cohort, a large population-based study of pregnant women and their offspring.

Enrollees in the study, about 30% of all deliveries in Denmark, completed computer-assisted telephone interviews at 12 and 30 weeks' gestation and again at 6 and 18 months after delivery. Of the more than 92,000 mothers with live singleton births, 50,276 completed the first interview and food frequency questionnaire. There were 28,958 and 25,446 women who completed the 6- and 18-month postpartum interview, respectively, and had complete data for all covariates. Enrollees not

included were similar in age, parity and fish consumption to the participants, but had somewhat shorter breastfeeding times and were more likely to be single and smokers. The children of the included mothers had slightly longer gestation times and higher birthweights than those who were excluded.

Fish consumption was determined from a detailed food frequency questionnaire given to the participants at 25 weeks' gestation. Daily fish intake was divided into quintiles as well as serving frequencies of 0, 1 to 2 (1 to 340 g/week) or 3 or more servings/week (>340 g/wk). The 340 g (12 oz) level is the maximum weekly fish intake recommended in the 2004 US fish consumption advisory.

Developmental milestones were assessed from the mothers' responses to 9 questions about the child's functional abilities at 18 months of age, e.g., climb stairs, drink from a cup, fetch an object, etc. From these answers, the researchers constructed a "total development" score and subscales for motor and social or cognitive milestones. Similarly, for 6-month infant development, the investigators scored the mothers' responses to a different set of age-appropriate questions, creating a total development score with motor and social or cognitive subscales. Because low scores were infrequent, scores in the lowest developmental category were included in the next category for each assessment age.

Data from the 25,000 women who completed the 18-month interviews revealed a mean fish consumption of 27 g/day, ranging from none to 494 g/day. The mean intakes by quintile of consumption ranged from about 5 g/day in the lowest quintile to 59 g/day in the highest. In terms of weekly fish servings, the lowest quintile of fish consumption was <1 serving, the middle quintile was about 1.5 servings and the most frequent fish-eaters ate approximately 3.5 servings/week. About 86% of mothers ate fish once or twice/week. Only 3% of women reported never consuming fish.

In these mothers, the frequency of eating fish was significantly associated with a longer time breastfeeding. In the overall sample, mothers breastfed their infants for an average of 8 months, with no distinction made between exclusive or supplemented breastfeeding. This comparatively long period of breastfeeding contrasts markedly with breastfeeding times in the U.S., which peaks at 3 months for mothers who nurse. Recent results from the Infant Feeding Practices Study II, a longitudinal study of the infant feeding habits of 4,900 women who were followed from prenatal enrolment through their infant's first year of life, indicate that 83% of mothers begin breastfeeding in the hospital, with or without additional infant formula. The percentage drops to 50% at 6 months and 24% by 12 months. Another US study reported that 37% of selected Boston mothers were still breastfeeding at 6 months.

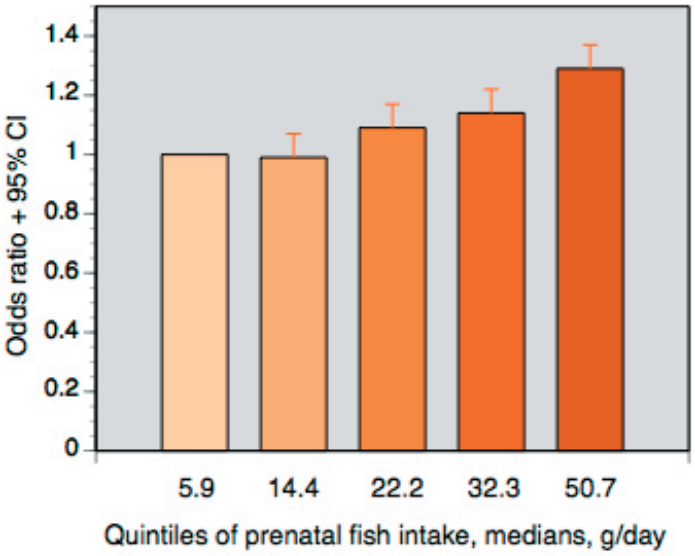

Figure. Odds ratios for higher total development scores at 18 mo. with increasing prenatal maternal fish intake.

Primary developmental outcomes at 18 months showed significant trends favoring the infants of mothers in the three highest fish-consumption quintiles by median intake (Figure). These infants were least likely to have the lowest scores for motor, social or total development in multivariate analysis compared with the infants whose mothers ate fish infrequently. Others have reported that fish intakes of about 15 g/day or more, which is close to the second quartile in this study, were associated with a significantly lower likelihood of preterm delivery, suggesting a benefit for infant outcomes of even this modest intake. The trends for the 6-month assessments followed the same pattern as those at 18 months. The investigators also reported an association between longer breastfeeding and better development at 18 months.

In a cohort of more than 25,000 Danish women, those who breastfed 8 months or longer and consumed 3.5 fish meals/week had children with higher total developmental scores at 18 months of age compared with children whose mothers breastfed one month or less and ate less than 340 g of fish/week.

The investigators also analyzed the fish consumption data in terms of current US recommendations that pregnant and lactating women limit their intake of fish and shellfish to no more than 340 g (12 oz)/week. Eating up to 12 oz of fish/week was not associated with higher total development

scores, but intakes greater than that were associated with a 20% greater likelihood of higher total development scores at 18 months. The odds for higher development scores more than doubled to 49% for each additional weekly serving of fish when the analysis treated fish consumption as a continuous variable. Thus, these findings confirm those from the Avon Longitudinal Study in which greater childhood benefits were observed when maternal fish intakes were greater than 340 g/week.

The investigative team acknowledged that confounding by unmeasured variables, such as parental intelligence, might have biased their findings. This consideration is always a worry in such studies. They noted that they were unable to control for exposure to potential toxicants in fish, but that the key species with high mercury content are infrequently consumed in Denmark. On average, the most commonly consumed fish contain about 0.03 to 0.04 ppm of mercury—very small amounts.

In this study, breastfeeding longer than 7 months, with or without additional food, and greater maternal fish consumption before delivery—3.5 fish servings/wk—were associated with higher attainment of three types of developmental milestones. These findings strengthen the evidence that fish consumption during pregnancy is associated with better childhood developmental outcomes and suggest that undue fear of seafood contaminants that discourages fish consumption may be detrimental to childhood development.

Oken E, Østerdal ML, Gillman MW, Knudsen VK, Halldorsson TI, Strøm M, Bellinger DC, Hadders-Algra M, Michaelsen KF, Olsen SF. Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. Am J Clin Nutr *2008;88:789-796.*

Supplementation Increases Arachidonic Acid in Breast Milk Without Reducing DHA

There has been almost no examination of the effect of arachidonic acid supplementation on breast milk fatty acid composition in lactating women. Here, investigators studied the effects on breast milk composition of adding long-chain omega-3 fatty acids, with or without arachidonic acid, to nursing women.

Pregnancy and lactation have marked effects on maternal essential fatty acids, especially the long-chainpolyunsaturated fatty acids (LC-PUFAs) docosahexaenoic acid (DHA) and arachidonic acid (ARA). These LC-PUFAs accumulate by about 40% over the course of pregnancy, but functionally speaking, these increases may not keep pace with the demands of the fetus, especially in the last trimester. DHA increases more than twice as much as ARA (52% vs. 23%). After delivery, a nursing mother continues to transfer these fatty acids to the infant, further risking her own LC-PUFA levels. This is particularly true for DHA, which declines after delivery more markedly in lactating than non-lactating women. In contrast, a non-lactating woman gradually replenishes her stores. Maternal plasma phospholipid LC-PUFAs return to pre-pregnancy values in about 6 to 8 months. Once lactation ends, maternal DHA status increases quickly. The depletion of maternal DHA during pregnancy and a slow restoration of DHA status after delivery have been linked to a greater risk of perinatal depression.

Although many studies have examined the relationships between maternal LC-PUFA intake or status and the mother's health, for example in perinatal depression, pregnancy outcomes, and LC-PUFA status after multiple pregnancies, the emphasis has been on the infant's brain function and development. There have been comparatively few studies on the changes in maternal LC-PUFA status after delivery relative to the mother's LC-PUFA intake. However, recognition that the mother's DHA concentrations during and after pregnancy are important considerations along with the infant's need for sufficient DHA, an international working group of perinatal experts recommended that pregnant and lactating women consume at least 200 mg of DHA/day. The experts concluded that maternal tissue and plasma ARA concentrations are relatively stable, even with DHA supplementation, and are relatively unaffected by dietary ARA. There are some reports, however, of lower concentrations of ARA when large amounts of n-3 LC-PUFAs (2.7 g/day) were consumed during pregnancy. The expert group concluded that additional dietary ARA was not needed during pregnancy.

Maternal supplementation with DHA during pregnancy, with or without continued supplementation in lactation, results in a strong correlation between the mother's n-3 LC-PUFA status in late pregnancy and the content of these fatty acids in breast milk during the first 6 weeks of lactation. DHA supplementation was without significant effect on breast milk ARA concentrations. An earlier study of cod-liver-oil-supplemented lactating women also reported no effect of n-3 LC-PUFAs on breast milk ARA concentrations, even with 10 ml of cod liver oil/day. A recent survey of breast milk DHA and ARA concentrations from women around the world concluded that ARA concentrations were higher and less variable than for DHA and that the two LC-PUFAs were poorly correlated.

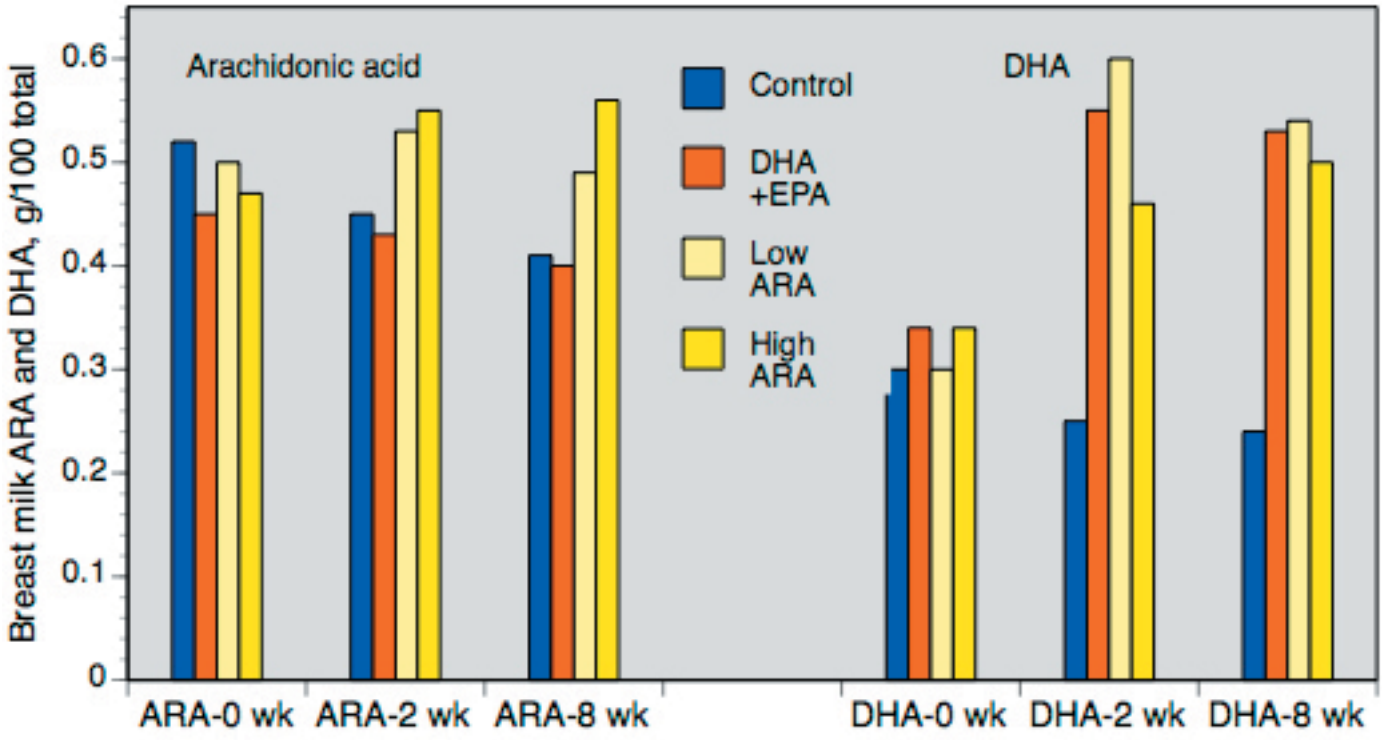

Figure. Mean breast milk ARA and DHA concentrations in lactating women at baseline and after 2 and 8 wk of supplementation with DHA+EPA alone or with ARA in low or high doses. Decline in control ARA (left panel, blue), P=0.0004 at 8 wk; decline in ARA with DHA+EPA (orange), NS. Increase in ARA with ARA supplementation, P<0.05. Change in DHA (right panel) in controls, NS. Increase in DHA with DHA+EPA supplementation, P=0.05, with no significant effect of ARA at either dose.

The investigation reported here examined the effect on breast milk LC-PUFA composition of maternal supplementation from 3 to 11 weeks postpartum with n-3 LC-PUFAs alone (320 mg DHA and 80 mg eicosapentaenoic acid (EPA)/day, DHA + EPA + 200 mg ARA/day, or DHA + EPA + 400 mg ARA/day. A control group of mothers received a test beverage without added LC-PUFAs. All mothers received vitamins and minerals. Fifty-two mothers were randomly assigned to one of the 4 treatment groups and 34 women completed the 8 weeks of supplementation. Baseline characteristics of the participants and their breast milk fatty acid concentrations did not differ among the groups, except that the DHA + EPA group was significantly younger.

Lactation in the unsupplemented mothers was associated with a significant reduction in ARA at 2 and 8 weeks after the study began, the equivalent of 5 and 11 weeks after delivery (Figure). There was also a significant reduction in total n-6 LC-PUFAs in the control mothers, but DHA and total n-3 LC-PUFAs were not significantly reduced at these times. The consumption of DHA + EPA increased breast milk DHA concentration after 2 and 8 weeks of supplementation, without affecting ARA concentrations (Figure). However, total n-6 LC-PUFAs were significantly lower in this group after 8 weeks of supplementation, but the decrease did not differ from that observed in the control mothers.

The consumption of either low or high levels of ARA resulted in significantly higher breast milk ARA concentrations after 2 and 8 weeks of supplementation, with the greatest increase observed in the high (400 mg/day) compared with the low dose (200 mg/day) group after 8 weeks. Thus, both levels of ARA supplementation (given with DHA + EPA) counteracted the loss in this LC-PUFA seen in the unsupplemented women. In addition, ARA supplementation at both levels had no effect on the increased DHA levels observed with only DHA + EPA supplementation. Similar results were observed with the total n-3 LC-PUFAs.

In contrast with the changes in breast milk LC-PUFAs, maternal red blood cell DHA concentrations showed a strong decline after 2 and 8 weeks of unsupplemented lactation. Red cell ARA concentrations, however, were slightly increased after 8 weeks. Supplementation with DHA + EPA abolished the loss in red blood cell DHA without affecting ARA concentrations, though total n-6 LC-PUFAs declined significantly. When the mothers consumed ARA (given with DHA + EPA), red cell ARA concentrations increased significantly, but DHA concentrations were mostly unchanged from baseline values. The high dose of ARA reduced the increase in DHA and total n-3 LC-PUFA concentrations observed with DHA + EPA supplementation alone.

As might be expected, changes in the fatty acid concentrations in breast milk were correlated with changes in maternal red cell concentrations after 2 and 8 weeks of supplementation. Linear regression analysis showed that breast milk ARA and DHA increased as the concentrations of these LC-PUFAs went up in red blood cells. The consumption of 400 mg of DHA + EPA was accompanied by higher concentrations of these fatty acids in breast milk that were apparent within 2 weeks. Breast milk ARA and total n-6 LC-PUFA concentrations were unaffected by n-3 LC-PUFA supplementation. When ARA was added to the fatty acid supplementation, ARA and total n-6 LC-PUFA concentrations increased significantly in breast milk after more than 2 weeks.

Supplementation with DHA+EPA in lactation increased the breast milk concentration of these fatty acids. Adding low or high doses of ARA to the n-3 LC-PUFA supplementation increased ARA concentrations without affecting DHA levels.

In summary, the consumption of DHA + EPA (400 mg/day) in amounts greater than current recommended intakes for DHA in pregnancy and lactation, significantly increased the breast milk and maternal red blood cell concentrations of these LC-PUFAs, without altering the concentration of ARA. The addition of ARA to the n-3 LC-PUFA supplementation also increased ARA concentrations in breast milk and red blood cells, but the effect took longer to achieve than with DHA + EPA.

ARA supplementation during lactation has received little attention, save for one study in which consumption of 300 mg ARA for one week had no significant effect on breast milk LC-PUFAs. In this study, the results for maternal red cell LC-PUFA concentrations were similar to those for breast milk, with the exception that supplemental ARA reduced red cell DHA concentrations. The investigators suggested that DHA and ARA might compete for uptake into red cell phospholipids. Increased intake of ARA in amounts equivalent to DHA consumption can raise breast milk and maternal red blood cell ARA concentrations, without jeopardizing breast milk DHA, but with some reduction in maternal red cell DHA concentration. As the availability of ARA in maternal diets and breast milk apparently present no problems, this study would support the conclusion of the expert working group that lactating mothers do not need additional ARA.

Weseler AR, Dirix CE, Bruins MJ, Hornstra G. Dietary arachidonic acid dose-dependently increases the arachidonic acid concentration in human milk. J Nutr *2008 138:2190-2197.*

IMMUNE FUNCTION

Introducing Fish to a Child's Diet Before Age One May Reduce Chance of Eczema

What effect fish or omega-3 fatty acid consumption during pregnancy or early childhood might have on the development of childhood eczema has been controversial. Data support both sides of the issue. In this study, children who ate fish before the age of 1 year were significantly less likely to develop eczema.

The prevalence of childhood allergies, chiefly asthma, allergic rhinoconjunctivitis and eczema has been increasing worldwide for at least the past decade. Variations in the occurrence of these conditions range from 20- to 60-fold in different parts of the world. For example, the prevalence of eczema in children aged 6 to 7 years ranged from less than 2% in Iran to more than 16% in Japan and Sweden and a similar spread in prevalence occurred in 13 to 14-year old children. Although heredity influences the incidence of these conditions, other factors associated with increased risk include parental tobacco smoking and environmental allergens. Lower occurrence of eczema has been associated with earlier introduction of potential allergens, longer duration of breastfeeding in infants of non-allergic mothers, modification of intestinal microflora with probiotics, maternal fish consumption during pregnancy and children's intake of fish and fruity vegetables.

The potential protective effect of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs), found predominantly in fish and shellfish, derives from the ability of these fatty acids to modify immune responses. Although some studies have reported that maternal fish consumption during pregnancy is associated with lower risk of certain allergies, such as allergic rhinitis, others have reported that modification of dietary PUFAs, including increased consumption of n-3 LC-PUFAs, does not help prevent atopy and asthma. During childhood, parents often avoid or delay the introduction of potentially allergenic foods from concern that such foods will promote allergic responses. However, some epidemiologic evidence suggests that introducing potentially allergenic foods, such as fish, in the first year of life is associated with a lower risk of allergic disease and food sensitization by age 4.

In this study from western Sweden, investigators examined the relationships between the prevalence of eczema in 1-year-old children and a family history of allergic diseases and environmental factors, including the children's consumption of fish. The prevalence of eczema in Sweden

is high, over 16% in children 6 to 7 years of age. The sample was obtained by systematic random selection of 50% of births in the western region identified in the country's national birth cohort. Of the 8,176 families invited to participate, 4,941 completed questionnaires when the children were 6 and 12 months old and medical birth register data were available for 4,921 families. The presence of infant eczema and doctor-diagnosed food allergy was assessed from the parental responses. Food intakes were determined from food frequency questionnaire data.

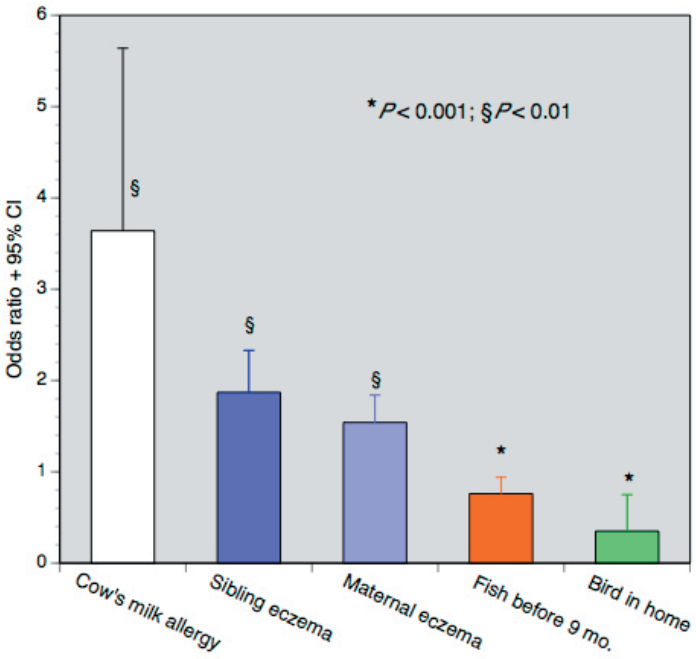

Figure. Odds ratios for developing eczema at 1 year of age according to various risk factors. Eating fish before 9 months of age and having a bird in the home were associated with significantly reduced risk of eczema.

The cumulative prevalence of infant eczema at 6 and 12 months was 14% and 21%, respectively, with a median age of onset of 4 months. The presence of any food allergy was reported by 5% of participants, with the predominant allergies being cow's milk and eggs. Fish allergy was reported by fewer than 0.3% (14) of participants. Sixty percent of families reported fish consumption 1 to 3 times/week by the time the child was 1 year of age, with 26% reporting fish consumption 1 to 3 times/month. Only about 8% of children ate fish a few times/year or not at all. Nearly 80% of the fish consumed were lean species, such as cod and haddock. Salmon or fatty fish were consumed by 18% of children.

In multivariate analysis, cow's milk allergy and maternal or sibling eczema were the most significant risk factors for the child's developing eczema (Figure). The two most protective factors were having a bird in the home and eating fish before the age of 9 months. Breastfeeding and smoking were not significant risk factors (P >0.01) in univariate or multivariate analysis.

Whether the presence of furry pets and animals in the home affects or increases risk of allergic disease is controversial. There is evidence that feathers from bedding are not associated with risk of allergic rhinitis or asthma, and that having a bird in the home has no effect on atopic diseases in early childhood. On the other hand, pet ownership in general has been associated with a significantly higher risk of any of the three major childhood allergies. In univariate analysis, having a dog or a bird in the home was associated with higher prevalence of eczema, but in multivariate analysis, only bird ownership remained significant. The authors of this study commented that it is possible that non-atopic families were more likely to keep birds.

Introducing fish in a child's diet before the age of 9 months was associated with a significant 25% lower risk of eczema at 1 year of age.

Including fish in the child's diet before the age of 9 months was associated with a significant 25% lower risk of eczema at 1 year of age. Because the main type of fish consumed in western Sweden is lean white fish, it is difficult to argue that the observed association might be attributable to n-3 LC-PUFAs. Nonetheless, this study supports others in suggesting that earlier rather than later introduction of potentially allergenic foods, including fish, is likely to reduce not promote the development of childhood eczema.

Alm B, Abaerg N, Erdes L, Möllborg P, Pettersson R, Norvenius G, Goksör E. Wennergren G. Early introduction of fish decreases the risk of eczema in infants. Arch Dis Child *2008; Epub Sept. 25.*

Consumers with Fish Allergies Show No Sensitivity to Two Fish Oil Supplements

Occasionally, the question arises whether individuals allergic to eating finfish (excluding shellfish) should also avoid fish oil supplements because of the small chance that trace amounts of fish allergens might be present. Apart from the gel capsule, fish oil supplements are entirely composed of lipids, whereas specific proteins are nearly always the culprits behind food allergies. Fish oil supplements are rigorously refined and purified to remove impurities, organic and heavy metal contaminants and non-lipid substances, but concern about a possible risk of allergens lingers.

Sensitivity to fish allergens in children tends to be higher for those with multiple food sensitivities and higher levels of food-specific immunoglobulin E levels. However, sensitivity to fish is more common in adults. In a study on the prevalence of seafood allergy in the U.S., investigators reported a prevalence of 2% for shellfish and 0.4% for fish allergy.

The major fish allergens are the alpha and beta parvalbumins, proteins found mainly in cod and carp species, but also predominant in tropical fish species. Patients with fish allergies are highly likely to react to both cod and carp parvalbumins, as reported recently. Allergies to fish appear to depend on the amount of fish consumed, with the highest childhood prevalences reported in Scandinavia, Spain and Portugal.

Even though the introduction of fish to a child's diet before the age of 9 months has been associated with a lower likelihood of developing eczema in childhood (see preceding article), families with a history of fish allergy may prefer to consume fish oil supplements rather than fish. A recent pilot study examined the safety of fish oil consumption in 6 individuals with a clinical history of finfish allergy. Participants were evaluated for skin prick sensitivity to allergen extracts from cod, catfish, mackerel, salmon, sardines, tuna and 2 commercial fish oil products. Each participant exhibited at least 3 positive skin prick tests to the 6 finfish allergen extracts, but none had a positive test to either of the fish oils. Each participant then received an oral challenge to one softgel capsule of each supplement given one hour apart. None experienced any adverse response to the oral challenge.

Fish oil supplements have been used in many clinical trials without serious adverse effects or allergic responses. Most participant complaints relate to gastrointestinal distress or difficulty in swallowing large capsules. A fishy aftertaste is often reported. In a 4-year, placebo-controlled study of docosahexaenoic acid supplementation at 400 mg/day in 44 patients with retinitis pigmentosa, no identifiable safety risks were observed. Another short-term study reported that healthy adults consuming up to 5 g of eicosapentaenoic acid/day for 14 days tolerated the supplements well. A report of 18 psoriasis patients who consumed fish oil capsules for 15 weeks also noted a lack of safety issues. Although such studies cannot prove safety, they document the absence of adverse events and clinical harm. Even among patients with allergic conditions, but not fish allergies, the consumption of fish oil has not been associated with adverse outcomes.

This pilot report provides some reassurance that people with fish allergies can likely consume fish oil supplements without adverse effects. The study evaluated only 2 fish oil products in a small number of individuals with documented allergic reactions to fish. While there is no reason to expect different results from other fish oil supplements, it would be useful to have the supporting evidence for that assumption. For wary US consumers, foods, not dietary supplements, are required to identify the presence of allergenic proteins from any of the top 8 allergenic foods, including fish. Until dietary supplements are required to meet the same testing and labeling standard, consumers with fish allergies are left to trust fish oil supplement manufacturers about the quality of their products. To date, their trust appears to be well-placed.

Mark BJ, Beaty AD, Slavin RG. Are fish oil supplements safe in finned fish-allergic patients? Allergy Asthma Proc *2008;29:528-529.*

VISUAL FUNCTION

Age-Related Macular Degeneration

Twice Weekly Fatty Fish Linked to Half the Chance of Advanced Macular Degeneration

Seeing your way to eating fatty fish at least once a week may ensure that you see clearly for a long time. Long considered "brain food," fish may be "eye food" as well. The long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) provided by fish are essential constituents of brain membranes, interlocutors in the communication between brain cells and critical components of the retina of the eye. As noted by vision specialist Helga Kolb, the retina is "essentially a piece of brain tissue" that is stimulated by light. Its function depends on having sufficient docosahexaenoic acid (DHA) in the outer rod segments.

Age-related macular degeneration (AMD) is a degenerative condition of the retina that is the leading cause of adult blindness. The chances of developing neovascular AMD, an advanced form, may be halved by eating fatty fish twice a week.

When the macula, the center of the retina, is impaired, vision is threatened by a condition called age-related macular degeneration or AMD. This is the major cause of adult blindness and afflicts more than 1.7 million people in the U.S. It develops with advancing age and is more common in women than men. The condition begins with the formation of yellow deposits or drusen under the retina and progresses to blurriness in the center of the visual field. Unchecked, AMD leads to blindness.

AMD occurs in two forms, a dry form and a wet or neovascular form (Illustration). The latter is much less common than dry AMD, but accounts for about 85% of the severe vision loss associated with the condition. In neovascular AMD, fibrovascular tissue develops, retinal capillaries proliferate, leakage and hemorrhage may occur and vision deteriorates rapidly. Treatment options are limited, though substances that inhibit angiogenesis (the growth of new blood vessels) have been promising.

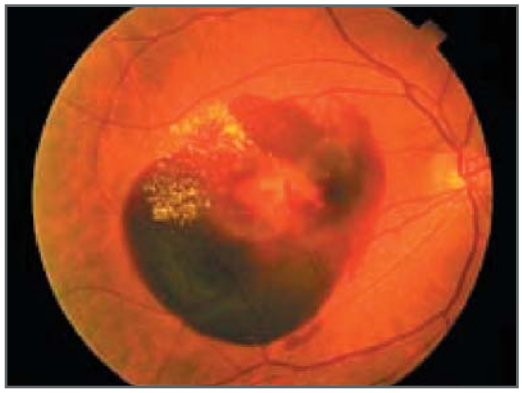

Illustration of neovascular AMD. Image reproduced courtesy of the Macula Foundation.

Recent strategies to halt or retard the progress of AMD, especially in its advanced stages, have examined the effect of n-3 LC-PUFAs and other nutrient-related substances, such as lutein, zeaxanthin and antioxidant vitamins on the occurrence and progression of AMD. Previous epidemiological studies reported that n-3 PUFA and fish consumption were associated with significantly lower risk of AMD, but the limited data from prospective and intervention trials have supported a cautious approach to recommending increased consumption of these substances. However, a large cross-sectional study (AREDS) on the relationships between these nutrients and others in individuals with AMD reported that dietary n-3 LC-PUFAs and fish consumption were significantly associated with a 40% lower chance of having neovascular AMD. A subsequent report from this trial describes the relationship between n-3 LC-PUFA consumption and the progression of mild to moderate drusen in both eyes to advanced AMD.

The current article describes the findings from the EUREYE study, a randomized population-based survey in 7 European countries of nearly 5,000 people 65 years and older. The study's goal was to assess the prevalence of AMD and its relationship to the intake of DHA and eicosapentaenoic acid (EPA), fatty fish, vitamin D and other dietary and medical variables. Participants were interviewed and had the back of their eyes photographed. The images were graded according to the International Classification System of Age-Related Maculopathy, with 5 mutually exclusive grades varying from no maculopathy to neovascular AMD or geographic atrophy (retinal pigment atrophy). A semiquantitative food frequency questionnaire, as used in the UK European Prospective Investigation into Cancer and Nutrition study and modified for local foods, was used to assess dietary intakes. Of the 4,753 participants, 158 (3%) had late AMD, 109 (2%) had neovascular AMD, 49 (1%) geographic atrophy and 2,262 (48%) no AMD.

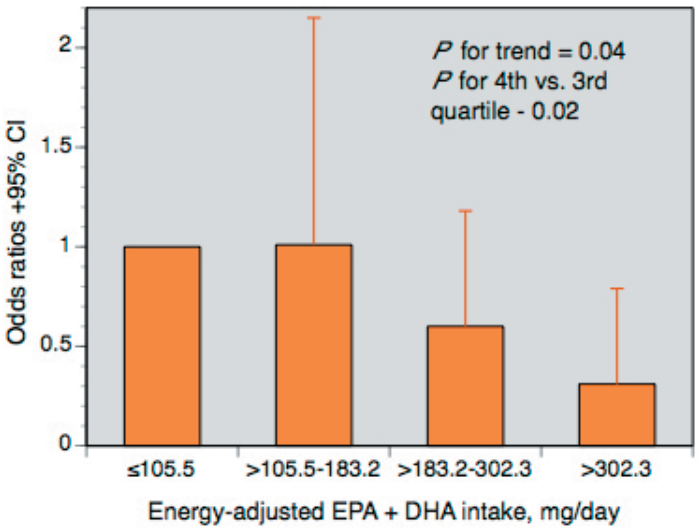

Figure. Odds ratios for the risk of developing neovascular AMD in adults 65 years and older by increasing quaratiles of EPA + DHA intake.

The primary outcome was the prevalence of neovascular AMD. Fish consumption was classified into less than once/week, once/week, twice/week or more. Significant confounding variables, defined as those that changed the odds ratios by 5% or more, were age, sex, smoking status, diabetes and use of aspirin. All models were adjusted for energy consumption.

In countries ranging from Norway and Estonia to Italy and Spain, the average frequency of eating fatty fish varied from 64% eating such fish less than once/week to 25% eating oily fish weekly and 12% eating them two or more times/week. Dietary EPA and DHA were strongly associated with fish intake, as were vitamin D, zinc, vitamin E and protein intakes. About 8% of participants in this study used fish oil supplements.

The key observation was a 50% reduction in the chance of having neovascular AMD associated with eating fatty fish once/week compared with eating these fish less often. Higher fish consumption of twice/week or more showed a continued trend toward further reduced odds of neovascular AMD (42%), but the results were not statistically significant, possibly because of the small number of participants eating fish that often. Similarly, intakes of DHA + EPA greater than 300 mg/day were significantly associated with a 70% lower risk of developing neovascular AMD (Figure). In contrast, eating white fish once a week or more compared with less than weekly was not associated with the risk of neovascular AMD.

As the consumption of fatty fish increased, so did vitamin D intakes, but the association between vitamin D and neovascular AMD was weak. Including DHA and EPA consumption in the model abolished this association.

Eating fatty fish twice a week or consuming 300 g/day of EPA + DHA was associated with a 60% to 70% lower chance of developing neovascular AMD.

These findings support several other epidemiological studies (e.g., the Blue Mountain Eye Study and the AREDS Study) that have reported significantly lower risk of any or neovascular AMD with increasing EPA + DHA intakes. The growing evidence that eating fatty fish weekly helps keep AMD away appears to be an insightful option as we age. For any individual, of course, many factors affect the susceptibility to AMD, but eating fatty fish may see you with a significantly lower likelihood of developing advanced AMD.

Augood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR, Fletcher AE. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr *2008;88:398-406.*

Higher Long-Chain Omega-3s Linked to Half the Chance of Geographic Atrophy in AMD

The Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute, Bethesda, USA, is a large multi-center trial on the natural history of and risk factors for age-related macular degeneration (AMD) and cataract. Participants in the study aged 50 to 85 years with or without AMD were randomized to receive antioxidant vitamins, zinc and copper or placebo. They were evaluated at baseline and annually for 5 years. Those who consumed the combination of supplements had a 25% lower risk of progression to advanced disease.

The Age-Related Eye Disease Study reported that fish or long-chain omega-3 consumption was linked to half the chance of developing neovascular age-related macular degeneration (AMD). This study now reports on the relationship of long-chain omega-3s to the progression of AMD.

A second AREDS trial with about 4,000 participants is currently underway to examine the effects of supplementation with lutein and zeaxanthin with or without long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) on the progression of AMD to advanced disease. The study had previously reported that higher intakes of these xanthophylls and of fish or n-3 LC-PUFAs were associated with decreased likelihood of

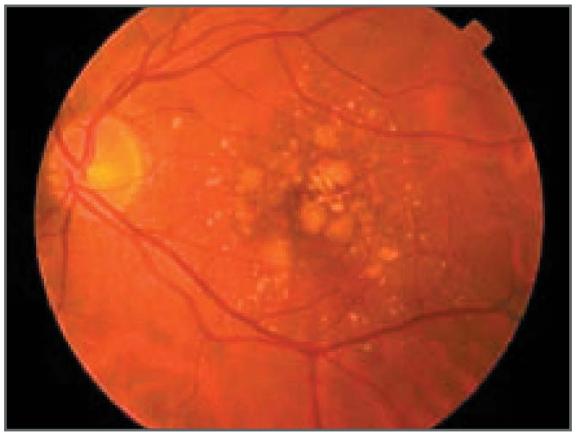

Illustration of geographic atrophy in AMD. ***Image reproduced courtesy of the Macula Foundation.***

neovascular AMD. In the case of n-3 LC-PUFAs, those with the highest intake were 40% to 50% less likely to develop neovascular AMD compared with participants in the lowest consumption group. Participants in AREDS2 will be offered the combined vitamin and mineral supplement used in the first AREDS trial, now the standard of care for those at risk of AMD.

This AREDS report describes the relationship between n-3 LC-PUFA consumption and the chances of developing either neovascular or central geographic atrophy or for progression of bilateral drusen to either of these forms of advanced AMD. There were 2,132 participants in the study who were monitored annually for a median of 6.3 years. Progression to neovascular AMD was evaluated by photodocumentation of one of several criteria for the condition. Assessment of central geographic atrophy was based on the deterioration of the center of the macula, except when subretinal fibrosis occurred at the same visit. The data analysis was performed without regard to progression of the other form or whether one or two eyes were involved. Although the study included participants from 50 to 85 years of age, most participants in this report were 70 years or older, largely female and nearly all Caucasian.

The investigators analyzed the data using repeated-measures logistic regression, adjusted for age, sex, AREDS treatment, smoking history and antacid use. Median intakes of the major n-3 LC-PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were adjusted for total daily energy intake. Additional confounding variables were included according to whether each factor yielded a significant effect on the fit of the model. The effects of EPA and DHA were analyzed separately because each contributes to eye function on a different physiological basis.

Central geographic atrophy developed in 113 participants (5%). Individuals with the highest levels of DHA intake, median 130 mg/day, were half as likely to progress to central geographic atrophy as those with the lowest intake (median 22 mg/day). However, the odds ratio for DHA consumption did not reach statistical significance. Individuals with the highest EPA consumption or EPA + DHA intakes were 60% less likely to advance to geographic atrophy, and these odds were statistically significant compared with the lowest quintile (Figure).

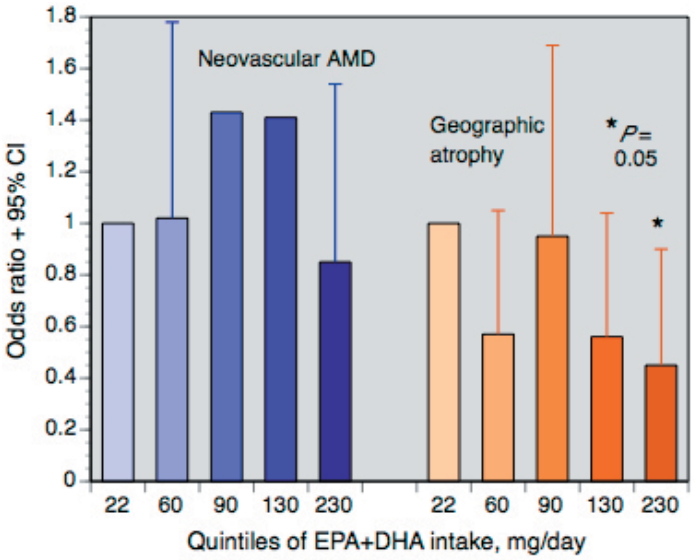

Figure. Odds ratios for progression to neovascular AMD (blue) or geographic atrophy (orange) with increasing consumption of EPA+DHA in adults with early age-related macular degeneration.

For the occurrence of neovascular AMD (198 cases or 9%), there were, unexpectedly, no relationships with the consumption of DHA, EPA or EPA + DHA. In spite of these observations, participants who had the highest intake of tuna, 1 to 2 servings/week, had half the chance of progressing to neovascular AMD compared with those who ate tuna least often, 1 to 3 times/month. There were no other significant associations with total fish, baked or broiled fish, or fried fish consumption. The investigators commented that tuna consumption may be a proxy for a healthy lifestyle, as there were no relationships for neovascular AMD and n-3 LC-PUFAs.

This report is unique in documenting a significant association between the consumption of EPA or EPA + DHA and a 50% lower chance of progressing from early AMD to central geographic atrophy. Previous studies on the relationship between n-3 LC-PUFAs and the progression of AMD have grouped both geographic atrophy and neovascular AMD as outcomes, without separating the two conditions. It remains for the AREDS2 study to provide additional evidence for whether n-3 LC-PUFAs affect the development of neovascular AMD.

This report is unique in documenting a 50% lower chance of progressing from early AMD to central geographic atrophy with the highest intake of EPA+DHA.

SanGiovanni JP, Chew EY, Agron E, Clemons TE, Ferris FL III, Gensler G, Lindblad AS, Milton RC, Seddon JM, Klein R, Sperduto RD, for the Age-Related Eye Disease Study Research Group. The relationship of dietary ω-3 long-chain polyunsaturated fatty acid intake with incident age-related macular degeneration. Arch Ophthalmol *2009;126:1274-1279.*

MENTAL HEALTH

Bipolar Disorder

Less DHA and Arachidonic Acid in Frontal Cortex of Patients with Bipolar Disorder

The number of neurodegenerative conditions and psychiatric disorders with abnormal polyunsaturated fatty acids, especially DHA, is growing. In Alzheimer disease, depression and now bipolar disorder, there is too little DHA to go around.

It has now been documented in at least three mental health conditions that patients have less docosahexaenoic acid (DHA) in their frontal cortex compared with individuals without these conditions. The disorders identified thus far include with Alzheimer disease, major depressive disorder and schizophrenia. Further, with advancing age, the content of long-chain polyunsaturated fatty acids (LC-PUFAs) declines, especially for arachidonic acid and DHA. At the other end of the age spectrum, infants and young children receiving insufficient DHA also have less DHA in their brain, whereas those whose mothers consume fish or fish oil supplements during pregnancy have higher brain DHA levels. The importance of brain omega-3 (n-3) LC-PUFA concentrations is further reinforced by their usefulness in the treatment of various mood disorders, although data are inconsistent.

Patients with unipolar or bipolar disorder have lower concentrations of DHA in their red blood cells compared with controls, and the DHA content of the orbitofrontal cortex in unipolar patients is significantly reduced. In this report, Robert McNamara and colleagues at the University of Cincinnati College

of Medicine, USA, describe fatty acid deficits in the orbitofrontal cortex of patients with bipolar disorder. Imaging studies have suggested that this region of the brain, along with the right hippocampus and left cingulate, exhibit significantly lower task-related activation in patients with mania, a component of bipolar disorder.

In this study, the investigators examined postmortem brain tissue samples from Brodmann area 10 of the orbitofrontal cortex in 19 normal males and females without psychiatric disease and 18 age- and sex-matched patients with bipolar disorder. Fifteen of the patients with bipolar disorder were taking at least one mood stabilizer and various antipsychotic medications. The average age at death was 42 and 40 years for the control and patients with bipolar disorder, respectively. Suicide (11/18) was the main cause of death in patients with bipolar disorder, whereas cardiopulmonary disease accounted for the majority of deaths in the control group (15/19).

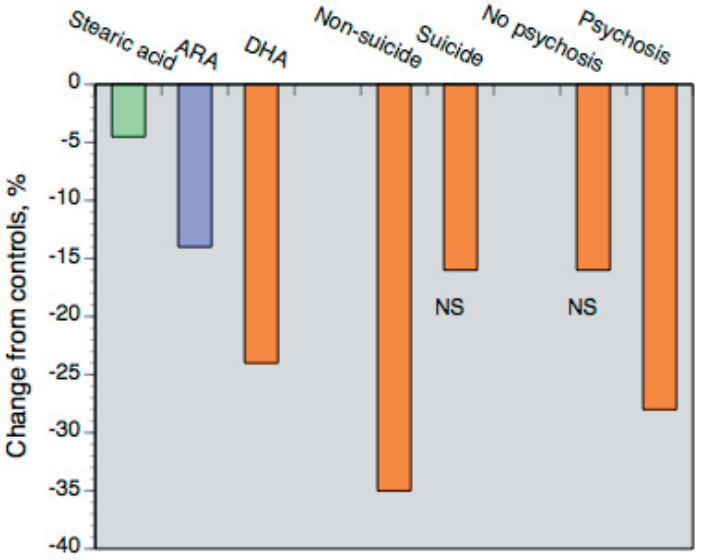

Figure. Changes (%) in fatty acid concentrations in the orbitofrontal cortex of postmortem bipolar patients compared with normals. All deficits statistically significant compared with controls, but cause of death and history of psychosis were not significant. Green, stearic acid; purple, arachidonic acid; orange, DHA.

Fatty acid composition results revealed significantly lower total LC-PUFAs (-15%) and saturates (-7%) in the patients with bipolar disorder compared with the age-matched controls. After correcting for multiple comparisons, the deficits in DHA (-24%), arachidonic acid (-14%) and stearic acid (-4.5%) in the patients with bipolar disorder were all statistically significant at $P < 0.003$ (Figure). Neither sex nor age at death affected these observations. Eicosapentaenoic and alpha-linolenic acid concentrations were not detected, a finding consistent with other data indicating that these fatty acids, unlike DHA, do not concentrate in brain tissue. In the analysis of variance, the interaction between illness and fatty acids was highly significant, as were the main effects of these variables. Significant interaction means that the effects of illness and fatty acid depended on each other.

The investigators conducted subgroup analysis to determine whether death from suicide, a diagnosis of psychosis and alcohol or substance abuse influenced the results. Compared with control patients who took their own lives, those with bipolar disorder who died by suicide had a significantly greater DHA deficit in (-16%, $P = 0.03$), the only fatty acid differing between the two groups. A diagnosis of psychosis had no effect on any fatty acid in these patients, but relative to the controls, patients with bipolar disorder and a history of psychosis had significantly greater deficits in DHA (-28%) compared with those not having psychosis (-16%). This difference was borderline statistically significant ($P = 0.04$).

For patients with bipolar disorder, low or high abuse of alcohol did not affect orbitofrontal cortex DHA or arachidonic acid. However, in the combined sample of patients with bipolar disorder and controls, those with more severe alcohol abuse had significantly less DHA (-42%) and arachidonic acid (-17%) compared with those with low severity of alcohol abuse. This observation confirms a previous report that rhesus monkeys chronically exposed to alcohol have significantly lower DHA in their brains and retinas. In contrast, substance abuse did not affect cortex fatty acid content.

Patients with bipolar disorder had significantly less total LC-PUFAs, DHA, arachidonic acid and stearic acid in their frontal cortex compared with controls. The greatest deficit (-24%) was in DHA.

With this report, these investigators have added bipolar disorder to the psychiatric conditions in which lower DHA concentrations in the orbitofrontal cortex have been observed. Previously reported disorders included unipolar depression (especially women) and schizophrenia in men, but not adolescent suicide victims. Notable differences besides sex are that patients with schizophrenia or bipolar disorder also have less cortex arachidonic acid, but those with unipolar depression do not. In this study, suicides had lower cortex DHA compared with controls, but in adolescent suicides, DHA concentrations were not reduced.

Readers should note that these investigators discuss possible abnormalities in the metabolism of n-6 LC-PUFAs in patients with bipolar disorder, as suggested by the decrease in arachidonic acid and the increased concentration of adrenic acid, a 22-carbon metabolite of arachidonic acid that competes with it for conversion by cyclooxygenase enzymes. The fatty acid abnormalities reported in this study, including those affecting stearic, oleic and palmitoleic acids, present a more complex view of the alterations in fatty acid metabolism associated with bipolar and other mental disorders than only reductions in DHA might suggest. Lower DHA might signal diverse fatty acid derangements in these conditions, but when corrected, might herald effective treatments.

McNamara RK, Jandacek R, Rider T, Tso P, Stanford KE, Hahn CG, Richtand NM. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. Psychiatry Res *2008;160:285-299.*

Dementia

Low EPA and Depression Associated with Greater Risk of Dementia

The most common form of dementia in the elderly is Alzheimer disease, a progressive neurodegenerative condition that affects the cerebral cortex and certain subcortical regions of the brain. Key characteristics of the disease include the accumulation of insoluble amyloid plaques outside the neuron, the build-up of neurofibrillary tangles inside neurons and the loss of neurons themselves. It remains controversial whether the abnormal beta amyloid proteins in the plaques cause the disease. What is clear, however, is that the chances of developing the late-onset form of the disease are partly genetic, with the presence of the ε4 allele of the apolipoprotein E gene significantly increasing the likelihood of developing the condition.

Higher fish consumption is associated with a lower risk of developing Alzheimer disease. This study examined whether individual long-chain omega-3 fatty acids or other fatty acids were linked to Alzheimer risk. Higher plasma EPA appeared to be protective.

Nutrition may also influence the chances of developing Alzheimer disease, with regular fish consumption significantly reducing the risk by as much as 60%. In the Framingham heart study, older adults in the highest 25% of plasma phospholipid docosahexaenoic acid (DHA) concentrations were 40% less likely to develop any type of dementia. However, not all prospective studies have observed a protective effect of eating fish on Alzheimer disease or dementia.

Eating fish at least once a week or more significantly reduced the rate of cognitive decline in adults 65 years old or more. The benefits associated with fish intake are believed attributable to the consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs), found mainly in fish. Several studies have reported lower rates of cognitive decline in elderly adults who consumed about 400 mg/day of these fatty acids.

Data from the longitudinal study of the vascular risk factors for dementia, currently taking place in Dijon, Bordeaux and Montpellier, France, were examined for a possible relationship between plasma eicosapentaenoic acid (EPA) concentrations and the development of depression or dementia. The 9,200 participants in the study were at least 65 years old, living independently and free of dementia at enrolment. Of the 1,518 individuals in the Bordeaux sample, blood samples and data from at least one followup examination were available for 1,214 nondemented participants.

Assessment of dementia consisted of a 3-step process of baseline neurological examination, several neuropsychological tests and followup neurological examination if dementia were suspected. An independent committee of neurologists reviewed all prevalent and incident cases to obtain consensus on the diagnosis. Depressive symptoms were determined according to scores on the Center for Epidemiologic Studies-Depression scale, an assessment tool considered appropriate for studies of the elderly. Participants were also screened for apolipoprotein E genotype.

Over the 4-year study, there were 65 incident cases of dementia. Those with dementia were significantly more likely to develop the condition if they had the apolipoprotein E 4 allele, were diagnosed with depression or type 2 diabetes, or had higher plasma triglyceride levels. The only plasma fatty acid significantly associated with a greater chance of developing dementia in age-adjusted analysis was palmitoleic acid. In multivariate analysis, taking into consideration education, apolipoprotein E allele status, diabetes, plasma triglycerides and vitamin E levels, the risk of dementia in the absence of depression was 9% greater for each standard deviation increase in palmitoleic acid. Among depressed individuals, however, the risk of dementia with increasing palmitoleic acid was 2-fold higher.

In multivariate analysis, only EPA was significantly associated with a lower likelihood of dementia—30% less—in participants without depression. There were significant inverse associations, i.e., a lower risk of dementia,

for the sum of n-3 PUFAs, EPA and DHA in age-adjusted analysis, but the significance for total n-3 PUFAs and DHA was not attained when additional confounders were considered.

In multivariate analysis, only EPA was significantly associated with a lower likelihood of dementia—30% less—in participants without depression. Higher ratios of arachidonic acid to DHA were linked to greater risk of dementia, especially in depressed individuals.

No n-6 PUFAs were associated with dementia risk, but higher ratios of arachidonic acid to DHA and total n-6 PUFAs to n-3 PUFAs were associated with greater risk. These ratios will be greater in people whose intake of n-3 LC-PUFAs is low, which would explain these associations. When the data were analyzed according to depressive symptoms, a higher ratio of arachidonic acid to DHA in depressed individuals was associated with a more than 2-fold increase in risk of dementia for each unit of the ratio ($P = 0.03$). In participants without depression, an increased arachidonic acid to DHA ratio was significantly associated with a 10% greater chance of dementia ($P = 0.002$).

The investigators put forward several plausible ways in which EPA might be protective of developing dementia. These include neuroprotection independent of DHA, stimulation of ketogenesis to compensate for impaired brain glucose uptake, anti-inflammatory effects and effects on cerebrovascular function. The observation that participants with depressive symptoms were more than twice as likely to develop dementia is consistent with a previous report that patients with a lifetime history of depression have more severe Alzheimer lesions in their hippocampus compared with nondepressed patients.

This study is a reminder that both EPA and DHA have important functions in the brain and several of its neuropathologies, although each may influence brain function in different ways. The study also reinforces the importance of confounding variables and co-existing conditions, especially depression, in the development of neurodegenerative diseases. As the investigators observed, randomized controlled intervention trials will be needed to determine whether EPA supplementation before the onset of dementia can delay or prevent its onset.

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Childhood Hyperactivity and Intelligence

Fish Consumption in Pregnancy Linked to Less Hyperactivity and Higher Verbal IQ

Several epidemiological studies have reported improved behavioral and cognitive outcomes in the children of mothers who consumed generous amounts of fish during their pregnancy. In the Avon Longitudinal Study of Parents and Children (ALSPAC), children whose mothers ate more fish than what is currently recommended in the U.S., i.e., more than 340 g (12 oz)/week were less likely to have suboptimal scores for verbal intelligence, prosocial behavior, fine motor skills, communication and social development compared with children whose mothers did not eat seafood. In the U.S., children of mothers who ate 2 or more servings of fish/week had better cognitive test scores compared with children whose mothers did not eat fish. In a study from Norway, children's mental processing scores at 4 years of age were significantly higher in those whose mothers took cod liver oil during pregnancy compared with those whose mothers took corn oil. A variety of mechanisms have been suggested that might contribute to these observations, many of which are based on the involvement of docosahexaenoic acid (DHA), a long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) in the structure and function of the brain.

A growing number of epidemiological studies have reported improved cognitive and behavioral outcomes in children whose mothers frequently consume fish, especially fatty fish, during pregnancy. In this report, the children of mothers who ate fatty fish during pregnancy were less likely to develop hyperactivity and had higher verbal intelligence scores.

A persistent question in these studies is how long-lasting the observed effects may be. In the ALSPAC study, differences were observed when the children were 8 years old. However, in the Norwegian cohort, maternal concentration of n-3 LC-PUFAs during pregnancy was not related to their children's global intelligence scores at age 7, but was correlated with sequential processing. In a Dutch study, there was no correlation between the availability of DHA at birth and motor function at age 7.

In a new report from the U.K., Catherine Gale and colleagues at the University of Southampton examined the relationships between maternal fish consumption in early and late pregnancy and their children's intelligence scores, maladaptive behaviors (e.g., hyperactivity, emotional difficulties or conduct problems)

and their prosocial behavior when the children were 9 years of age. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence and maladaptive behavior ratings according to the Strengths and Difficulties Questionnaire. From the original 559 participants, 226 agreed to participate. Complete data on behavioral and cognitive outcomes were available for 217 children.

Maternal fish consumption at 15 and 32 weeks' gestation was assessed according to all types of fish consumed and the frequency of eating fatty fish. There were no differences in the frequencies of fish consumption between early and late pregnancy. Mothers who ate fish more frequently during pregnancy differed from those who never ate fish, especially regarding fatty fish consumption. Those who ate fatty fish more often in late pregnancy tended to have higher education and intelligence scores (IQ), were older, and less likely to come from a manual labor social class. These mothers smoked less, but were more likely to drink alcohol during pregnancy. Their babies were heavier and they were more likely to breastfeed longer.

In multivariate analysis of the associations between the frequency of eating all types of fish and the chances of childhood hyperactivity, conduct or emotional problems, the differences favoring more frequent fish consumption did not reach statistical significance, although they were significant in unadjusted analysis.

The children of mothers who ate fatty fish less than weekly in early or late pregnancy were significantly less likely to exhibit hyperactivity compared with children whose mothers never ate fatty fish (Table). If the mothers ate fatty fish at all in early pregnancy, their children were significantly less likely to become hyperactive (odds ratio = 0.34, 95% CI, 0.15 to 0.78). The trend was similar, but not statistically significant for eating fatty fish late in pregnancy. In multivariate analysis, no significant associations with maternal fish consumption were observed for other childhood behavioral outcomes, including peer or emotional problems, total difficulties scores or conduct disorders (Table).

In terms of the children's IQ, eating fatty fish in early pregnancy was not significantly associated with full-scale IQ scores in adjusted analysis. In contrast, mothers who ate fish once or twice/week or less in late pregnancy had children with significantly higher full-scale IQ scores compared with children whose mothers never ate fish. Greater maternal fish consumption in late pregnancy was significantly associated with higher verbal IQ scores, but not with performance IQ. Compared with mothers who did not eat fish, verbal IQ scores were 7.7 points higher (95% CI, -0.1 to 15.4) in the children of fish-eating mothers. Scores of children whose mothers ate fish 3 or more times/week were 8.1 points higher. This finding supports the observation in the ALSPAC study where children of mothers with higher fish consumption were more likely to have

Table. Adjusted odds ratios (95% CI) for children's behavioral outcomes at 9 years of age with frequency of maternal fatty fish intake in early or late pregnancy

Outcome/Time of maternal fish intake	Frequency of maternal fish consumption		
	Never	Less than 1x/wk	More than 1x/wk
Hyperactivity			
Early	1.0	0.30 (0.12 – 0.75)	0.41 (0.15 – 1.12)
Late	1.0	0.40 (0.16 – 0.98)	0.72 (0.26 – 1.98)
Conduct problems			
Early	1.0	0.58 (0.22 – 1.53)	0.36 (0.11 – 1.21)
Late	1.0	0.46 (0.18 – 1.17)	0.31 (0.08 – 1.10)
Peer problems			
Early	1.0	0.79 (0.27 – 2.32)	1.44 (0.47 – 4.80)
Late	1.0	0.68 (0.25 – 1.82)	0.82 (0.27 – 2.57)
Emotional symptoms			
Early	1.0	0.63 (0.19 – 2.06)	0.79 (0.20 – 3.08)
Late	1.0	2,32 (0.73 – 7.43)	0.82 (0.27 – 2.57)
Total difficulties			
Early	1.0	1.23 (0.41 – 3.66)	0.83 (0.22 – 3.04)
Late	1.0	1.25 (0.43 – 3.60)	1.20 (0.32 – 4.49)

Children whose mothers ate fatty fish in pregnancy were significantly less likely to exhibit hyperactivity compared with children whose mothers did not eat fish. Maternal fish consumption was also linked to higher verbal IQ scores in their children.

higher verbal intelligence scores. Eating fatty fish, rather than just eating fish, was not associated with the children's intelligence scores.

This study increases the knowledge base documenting beneficial effects in children's development with higher maternal consumption of fish or fatty fish during pregnancy. It is noteworthy that the study found no evidence of any adverse effects in the children from maternal fish consumption at least once/week. As in all studies describing associations, this one does not establish a causal relationship, but it bears a strong resemblance to one. Without information about the children's fish consumption during childhood, the study cannot rule out the possibility that children's fish consumption was linked to more desirable outcomes. Unidentified or unmeasured confounding variables could influence these results, as could the demographic differences between mothers who ate fish and those who did not. Nonetheless, this study makes it more difficult to argue that fish consumption during pregnancy should be restricted.

Gale CR, Robinson SM, Godfrey KM, Law CM, Schlotz W, O'Callaghan FJ. Oily fish intake during pregnancy - association with lower hyperactivity but not with higher full-scale IQ in offspring. J Child Psychol Psychiatry *2008;49:1061-1068.*