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EDITORIAL

Omega 3s Show More Cardiovascular Benefit and Reduced Risk of Preterm Delivery and Kidney Disease

While the dog days of a hot summer in the northern hemisphere bespeak beaches and backyard barbecues, the science underlying the links between polyunsaturated fatty acids and health takes no holiday. The August PUFA Newsletter reports the effects of long-chain omega-3 PUFAs on arterial stiffness and heart function in chronic heart failure. These fatty acids may have potential benefit in the immediate aftermath of a stroke as suggested by animal studies.

Another study in animals suggests that in traumatic brain injury, the administration of fish oil shortly after the injury preserves the ability of neurons to release the neurotransmitter dopamine, thus maintaining neuronal function. This work supports previous studies reporting that pretreatment with long-chain omega-3 PUFAs reduces the damage caused by traumatic brain injury.

Three reports on fish or DHA consumption in pregnancy and infancy bring good news to a field of inconsistent results. One study confirms the relationship between fish consumption and a lower chance of preterm delivery. Another reports better growth in preterm infants receiving higher than standard amounts of DHA. A third found improved mental development and language scores in infants fed DHA for 12 months.

Studies in these areas have produced many mixed findings, so these reports are welcome.

Nutrients can affect gene expression and thereby, the risk of some diseases. In patients at high risk of age-related macular degeneration (AMD) because of their genotype, those with the highest risk because they had two copies of the risky gene variant were less likely to develop early AMD if they had high intakes of EPA and DHA. Other nutrients may be involved as well.

On the clinical side, those at risk of chronic kidney disease, including individuals with type 2 diabetes, hypertension and cardiovascular disease, may reduce their risk of chronic kidney disease by consuming fish often, according to findings from a large Australian study of older adults.

We wish you enjoyable reading, delicious barbecued fish and fine health both summer and winter.

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Daily Long-Chain Omega-3 Consumption Associated with Reduced Arterial Stiffness

The familiar term “hardening of the arteries” refers to the gradual loss in blood vessel elasticity or compliance resulting from arteriosclerosis and aging. Increased arterial stiffness causes the heart to work harder, alters arterial blood pressure and affects the dynamics of blood flow. Arterial stiffness is a good predictor of cardiovascular events such as myocardial infarction and stroke, dementia, long-term increase in blood pressure and mortality.

Blood pressure is a leading contributor to arterial stiffness and a risk factor for stroke and cardiovascular disease. However, measuring arterial stiffness improves the ability to predict cardiovascular risk. Noninvasive measurement of pulse wave velocity—the difference in the rate of blood flow between the femoral and carotid arteries—is considered the gold standard for the assessment of arterial stiffness (Figure). The slower the pulse wave velocity, the more elastic the arteries. Pulse wave analysis, which measures central blood pressure and is considered a reflection of arterial stiffening throughout the arterial tree, is also widely used to assess arterial stiffness.

Nutrition, diet and lifestyle factors affect arterial stiffness through their effects on endothelial cell function, such as the production and release of vasoactive substances like nitric oxide and their influences on inflammation and oxidative stress. High consumption of fruits and vegetables over 27 years was associated with significantly lower arterial stiffness in Finnish adults. A nutritionally poor diet rich in meat and alcohol and low in micronutrients was associated with greater pulse wave velocity and arterial stiffness in a sample of middle-aged French adults. Other lifestyle factors such as smoking and physical inactivity contribute to greater arterial stiffness.

Long-chain omega-3 PUFAs (n-3 LC-PUFAs) are obvious candidates for the modification of arterial stiffness because of their ability to improve endothelial function and reduce markers of subclinical inflammation. Eicosapentaenoic acid has also been associated with improved arterial elasticity after a high-fat meal. However, results of n-3 LC-PUFA supplementation on endothelial function in healthy individuals have been inconsistent. Recently, a randomized controlled study in a small number of healthy individuals with moderate hypertriglyceridemia reported no effect of low or high doses of n-3 LC-PUFAs on endothelial function or inflammatory status after 8 weeks of supplementation. Thus, a systematic review of randomized controlled trials on the effects of n-3 LC-PUFAs on arterial stiffness is timely.

This systematic review of the effects of animal, plant and nutrient interventions on arterial stiffness found that evidence was most extensive for reduced arterial stiffness with the supplementation of long-chain omega-3 PUFAs based on randomized controlled trials.

This review selected trials with at least 15 participants per group, a nonactive control and a validated measure of arterial stiffness, such as pulse wave velocity. The authors assessed the quality of the methods in each study according to the augmented Jadad scale and calculated effect sizes for each trial based on the differences between the placebo and intervention groups. The review included 38 of the 75 randomized controlled trials considered relevant. The studies were grouped according to interventions with animal foods (11), nutrients (15) or plant foods (12).

The animal-food trials included 9 studies on n-3 LC-PUFAs and 2 on fermented milk. All but one of the n-3 PUFAs trials were long-term studies from 1.5 to 25 months. Of these 8 studies, 7 reported improved pulse wave velocity or arterial compliance with n-3 LC-PUFAs and one reported no effect. The effect sizes in the chronic n-3 LC-PUFA studies ranged from small to large. There were no trials with alpha-linolenic acid, but a recent report from the U.K. found no differences in pulse waveform analysis of arterial stiffness when results from 4 weeks of modest walnut supplementation were compared with the control group in healthy participants.
The reviewers concluded that chronic supplementation with n-3 LC-PUFAs was efficacious in reducing pulse wave velocity and increasing arterial compliance. Most of the participants in these studies were overweight, diabetic, dyslipidemic or hypertensive. In the one trial in healthy participants, n-3 LC-PUFAs did not affect arterial compliance. The authors noted that the lowest efficacious dose of n-3 LC-PUFAs was 540 mg EPA plus 360 mg DHA daily and that the effect size of the combined n-3 LC-PUFAs was greater than with EPA alone. The effects of n-3 LC-PUFAs also appear independent of changes in blood pressure. A potentially effective approach to lowering the risk of heart failure might be to increase the consumption of fish or long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) found mainly in fatty fish. Several prospective observational studies have reported a lower risk of heart failure in individuals with high fish or n-3 LC-PUFA intakes. There are no randomized controlled trials addressing this question. Middle-aged and older Swedish women who consumed fatty fish twice a week were 30% less likely to develop heart failure compared with women who did not eat fatty fish. A similar reduction in risk with a high intake of n-3 LC-PUFAs was reported in women, but not men, in the Rotterdam study. In a large cohort of Japanese men and women, those with the highest consumption of n-3 LC-PUFAs had a significantly lower risk of heart failure compared with those having the lowest intakes.

The value and timeliness of this review highlights another effect of n-3 LC-PUFAs in reducing the risks associated with cardiovascular disease—the reduction in arterial stiffness. As this condition is highly predictive of future adverse cardiovascular events, dementia and death, ensuring a moderate intake of n-3 LC-PUFAs, at least 900 mg/day would be wise dietary insurance, especially among individuals at increased risk of cardiovascular disease. Additional evidence about the association between fish or n-3 LC-PUFA consumption and the risk of heart failure was obtained from data collected in the Women’s Health Initiative Observational Study in the U.S. This report describes the findings from that study.

Participants were healthy postmenopausal women ages 50 to 79 years recruited from across the U.S. who were not randomized in the Women’s Health Initiative trial. After exclusions for baseline heart failure and missing data on fish intake or covariates, 84,493 participants remained. The average follow-up period was 10 years. The investigators divided the fish consumption data into two categories: baked or broiled fish and fried fish. The associations between baked or broiled fish, fried fish, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) intake, alpha-linolenic acid (ALA) intake and heart failure in older women according to preparation and frequency of fish consumed over 10 years.

Could a simple dietary change reduce the risk of heart failure? Growing evidence suggests that eating more fatty fish might lower the risk of heart failure in women.
and trans fatty acid intakes and incident heart failure were assessed by Cox-proportional hazards models. Data were adjusted for potential confounders, which included age, race, education, physical activity and traditional heart failure risk factors. The latter included smoking status, alcohol consumption, diabetes mellitus, atrial fibrillation, coronary artery disease, hypertension, body mass index and time-related myocardial infarction. The investigators reported analytical results based on a composite model adjusted for the confounders just mentioned plus dietary factors (fiber, fruits and vegetables, saturated fatty acids, trans fatty acids, ALA and alternate type of fish preparation).

Women who incurred heart failure, death or loss to follow-up were excluded from further analyses at the time the event occurred. The authors also calculated heart failure-free survival probabilities based on various fish and fatty acid intakes.

As shown in the Figure, the incidence of heart failure in women consuming 5 or more servings of baked or broiled fish per week was 19.4 per 10,000 person-years compared with 26.7 per 10,000 person-years in women who ate fish less than once a week (p for trend = 0.02). These data correspond to a 30% lower risk of heart failure in the highest compared with the lowest consumption groups.

In contrast, women who consumed fried fish one or more times per week experienced nearly twice the incidence of heart failure as women who ate fish less than once a month (39.4 vs 20.8 per 10,000 person-years, p for trend = 0.005). These data correspond to a 48% greater risk of heart failure in women who consumed fried fish most frequently.

The incidence of heart failure was even lower among women who consumed dark fish once a week or more compared with a consumption frequency of less than once a month (incidence per 10,000 person-years: 15.3 vs. 24.5, p = 0.012).

When the analyses were performed using estimates of DHA+EPA consumption, the association with incident heart failure did not reach statistical significance in the adjusted models. Likewise, ALA and trans fatty acid intakes were not associated with risk of heart failure.

These findings confirm the previously reported associations in describing an approximately 30% lower risk of heart failure in women with the highest intakes—5 or more servings per week—of baked or broiled fish, especially fatty fish. They also confirm earlier reports that the weekly consumption of fried fish is associated with a significantly greater risk of heart failure compared with eating fried fish less than once a month. Although this analysis did not find a significant association between n-3 LC-PUFA intakes and incident heart failure, other studies have reported that higher intakes of these fatty acids are associated with a lower risk of heart failure. The estimates of fatty acid consumption from food frequency questionnaires, especially in populations with low n-3 LC-PUFA intakes, may be too variable to achieve statistically significant associations.

Although the findings from this and two previous studies have not been confirmed by randomized clinical trials, their consistency suggests that higher consumption of fish and n-3 LC-PUFAs may reduce the risk of heart failure, especially in women. Why fish consumption would be more protective of heart failure in women than men remains to be explained.


High-Dose n-3 LC-PUFAs Associated with Increased Ventricular Ejection Fraction in Advanced Heart Failure

Individuals with chronic heart failure (CHF) may face various consequences of their disease in other tissues. These include impaired kidney function, fluid accumulation, endothelial dysfunction, chronic inflammation and other disorders resulting from insufficient blood flow to the organs. Surgical interventions and medications are widely used to improve the prognosis of patients with CHF, while...
lifestyle changes such as a low-fat, low-sodium diet may be recommended. An additional dietary strategy may be the inclusion of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). Evidence from the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI) study in Italy suggested a small but significant benefit on mortality in CHF patients who consumed approximately 1 g/day of n-3 LC-PUFAs for almost 4 years. In addition, CHF patients who consumed n-3 LC-PUFAs for 2 or 3 years had significantly increased left ventricular ejection fraction (11%) at the end of 2 and 3 years.

Several research groups have recently published findings from randomized trials with n-3 LC-PUFA supplementation in CHF patients. In this study, investigators at the Medical University of Vienna, Austria, explored the effects of 2 doses of n-3 LC-PUFAs compared with placebo in patients with severe CHF of nonischemic origin who were stable with optimum CHF treatment for at least 3 months. On average, participants had left ventricular ejection fractions of 25% or less. From 57 eligible patients, 49 were randomized to the treatment groups and 43 completed the study.

The participants were randomized to receive approximately 1 or 4 g/day of n-3 LC-PUFAs or placebo for 12 weeks. The n-3 LC-PUFA capsules each contained at least 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA) as ethyl esters and the placebo capsules contained gelatin.

The physiological parameters measured at baseline and after 3 months included flow-mediated vasodilation as a marker of endothelial function, left ventricular ejection fraction assessed using radionuclide ventriculography, inflammatory markers (IL-6 and TNF-α) and peak exercise oxygen consumption assessed using symptom-limited maximal incremental cycle exercise testing with gas exchange measurements (Figure 1).

After 3 months’ treatment, left ventricular ejection fraction increased significantly from baseline in both n-3 LC-PUFA treatment groups, with no change in the placebo group. Treatment and dose effects were statistically significant (Figure 2). Flow-mediated dilation increased significantly only in patients consuming 4 g/day of n-3 LC-PUFAs, increasing from 8.4% at baseline to 11.6% after 3 months of treatment. Interleukin-6 decreased significantly in the high n-3 LC-PUFA group only, but the reduction in TNF-α in this group did not reach statistical significance. The investigators noted that these patients had low concentrations of these inflammatory markers at baseline, which suggests that further reduction might be difficult to achieve.

Of those who completed the study, 26 performed the exercise test. Peak oxygen volume increased significantly only in the highest n-3 LC-PUFA group, but was unchanged in the placebo patients. Changes in exercise capacity were not significant. It has been reported previously that exercise capacity in CHF does not correlate with left ventricular ejection fraction, but is related to peripheral blood and nutrient flow.

The key finding in this report is the dose-dependent effect of n-3 LC-PUFAs on increasing left ventricular ejection fraction in patients with advanced CHF. The study suggests that high doses—about 4 g/day—of n-3 LC-PUFAs also decrease inflammatory cytokine production, improve endothelial function and modestly increase exercise capacity. Larger trials are required to confirm these observations.
Am Heart J
Sopravvivenza nell’Insufficienza Cardiaca (GISSI-HF) trial. A substudy of the Gruppo Italiano per lo Studio della chronic heart failure and implantable cardioverter-defibril-
acids on malignant ventricular arrhythmias in patients with
ted cardiomyopathy. Am Heart J 2011;161:915.e1-9

Worth Noting


Stroke

Neuroprotection From DHA Infused Up to 5 Hours After Experimental Stroke

Stroke exacts a merciless toll in death and disability from about 15 million people worldwide each year. The occurrence of stroke is rising in low- to middle-income countries, but decreasing in high-income countries, largely as a result of better health care in the latter. Over 80% of all strokes are the ischemic type where blood flow to the brain is blocked, either as a result of a blood clot or obstruction in a cerebral artery. The only approved treatment, intravenous thrombolysis, must be administered within 3 hours of onset to be effective. Thus, few patients benefit from this therapy.

Research on stroke has led to new concepts of the underlying events in the affected tissues. There is a greater appreciation that stroke involves destruction, repair and protection of the tissues exposed to the injury. Understanding the underlying processes opens new avenues for treatments and prevention. Consistent with these advances is the potential for docosahexaenoic acid (DHA) and its derivatives to limit the damage associated with stroke.

DHA, a long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA), and its derivative neuroprotectin D1 have neuroprotective effects in brain in cerebral ischemia, oxidative stress and Alzheimer’s disease. Neuroprotectin D1 has potent anti-inflammatory, anti-apoptotic and cell survival properties in the brain. Recently, DHA was shown to improve neurological and histological outcomes in experimental focal cerebral ischemia. Low and medium doses of DHA ranging from 3.5 to 35 mg/kg bodyweight given 3 hours after stroke induction were associated with significantly improved neurological scores, dramatically reduced infarct size (up to 72%) and induced extensive neuroprotection of the neocortex and subcortical tissue—up to 61%. Higher doses of DHA were without significant neuroprotective effects.

These promising findings prompted Ludmila Belayev and colleagues at Louisiana State University, USA, to examine the time frame for the effectiveness of DHA following ischemic stroke in animals and to see whether DHA treatment in mice would restore the peripheral tissue surrounding the core site of stroke injury, the penumbra, after damage. It has been suggested that the penumbra might be salvageable, thereby limiting the damage from a stroke and providing an additional target for therapeutic intervention.

Using transient right middle cerebral artery occlusion to mimic stroke, the investigators examined the therapeutic window for DHA treatment by infusing DHA at 3, 4, 5 or 6 hours after the onset of stroke in male Sprague-Dawley rats. Animal behavior was assessed 1, 2, 3 and 7 days after the stroke procedure. Behavioral tests included the postural reflex test and the forelimb-placing test to visual, tactile and propriocep-
tive stimuli. Neurological function tests were described previously. Magnetic resonance imaging (MRI) was used to assess the size and location of the infarcts. Lipidomic

Few treatments and only a 3-hour time frame limit the most effective therapy for stroke. DHA, a long-chain omega-3 PUFA, may extend that window and offer neuroprotection.
analysis was performed to determine the production of neuroprotectin D1 and 17-HDHA, a precursor of neuroprotectin D1.

DHA administration at 3, 4 and 5 hours after artery occlusion resulted in reduced cerebral cortex infarct volumes 49, 77 and 71% of the control values, respectively (Figure 1). Infarct volume did not differ significantly from the control when DHA was given after 6 hours. Infarct volumes in the subcortex were unaffected by DHA infusion. The greatest reductions in total infarct volume corrected for brain swelling were 66% and 59%, following DHA administration 4 and 5 hours after occlusion, respectively.

Neurological deficits were also significantly reduced by the administration of DHA up to 5 hours after artery occlusion as shown in Figure 2. Improved neurological performance was significant as early as 24 hours after artery occlusion and continued to improve gradually through 7 days.

Histological and immunostaining studies revealed that artery occlusion led to a significant loss of neurons and astrocytes and a substantial influx of macrophages at day 7. These changes were substantially counteracted in the cortex and striatum by the administration of DHA after 3 hours, with cell counts for each type significantly different from the saline controls (data not shown).

Finally, the investigators analyzed the penumbra 3 days after artery occlusion for the presence of neuroprotectin D1 and 17-HDHA, a precursor of neuroprotectin D1. In the DHA-infused animals, neuroprotectin D1 and 17-HDHA were approximately 15- and 8-fold greater, respectively, compared with the saline-treated control animals. The production of neuroprotectin was approximately 15 times greater than in the controls.

This series of experiments demonstrated in an animal model of ischemic stroke that the administration of DHA within 5 hours of arterial occlusion is associated with significantly fewer neurological deficits, smaller infarct volumes, greater...

![Figure 1. Infarct volumes in the cortex, subcortex and total area 7 days after cerebral artery occlusion in rats infused with saline or DHA 3 to 6 hours after occlusion. Image from Belayev et al, Transl Stroke Res 2011;2:33-41. Reproduced under Creative Commons Attribution Noncommercial License.](image1)

![Figure 2. Neurological scores at 60 min to 7 days following right middle cerebral artery occlusion in rats infused with saline (control) or DHA 3 to 6 hours after occlusion. Image from Belayev et al, Transl Stroke Res 2011;2:33-41. Reproduced under Creative Commons Attribution Noncommercial License.](image2)
preservation of neurons, reduced infiltration of macrophages—which are associated with inflammation—and the production of neuroprotectin D1 in the penumbra surrounding the infarct site. These observations suggest that DHA may be an effective treatment for reducing the neurological and behavioral damage incurred by a stroke and preserving neuronal cell function. Further, the available time frame for improving the neurological outcomes with DHA treatment after a stroke may be as long as 5 hours. The observations are consistent with the view that DHA may limit the loss of neuronal tissue in the penumbra around the stroke site through the neuroprotective effects of neuroprotectin D1.


# MATERNAL AND INFANT HEALTH

**Moderate Fish Consumption Associated with Lower Risk of Recurrent Preterm Delivery**

The relationship between the frequency of fish consumption and the chance of preterm birth remains controversial because research findings are inconsistent. It has been suggested that fish consumption or higher long-chain omega-3 PUFA (n-3 LC-PUFA) intakes may prolong gestation only in women with habitually low fish intakes. This might imply a threshold effect for n-3 LC-PUFAs in pregnancy. Low fish or n-3 LC-PUFA intakes in early pregnancy or before conception might also affect embryonic development. Increased n-3 LC-PUFA intake prior to conception was reported to improve embryo morphology.

In a recent report the authors determined whether the fish or n-3 LC-PUFA intakes of the women early in pregnancy might affect their risk of recurrent preterm delivery, defined as birth at less than 37 completed weeks of gestation.

Women with a history of at least one previous preterm birth were recruited from 13 centers in the U.S. At randomization to treatment, 852 participants were interviewed about their frequency of consuming 4 different types of fish from the time of their last menstrual period. Participants consuming fish oil or n-3 PUFA supplements were excluded. Data on fish consumption were grouped into one category because of small numbers in some categories. Participants also had their gestational age confirmed by ultrasonography. All women were given weekly injections of 17-alpha-hydroxy-progesterone caproate to reduce the risk of preterm delivery.

Fish consumption patterns within the sample varied with ethnicity, with African-American and Hispanic women eating fish significantly more often than non-African-American or non-Hispanic women. Overall, 30% of women reported eating fish less than once per month or never, while 9% ate fish more than 3 times per week.

Preterm birth occurred significantly ($P < 0.001$) more often in women who ate fish once per month or less (49%) compared with women who ate fish more often (36%). As fish consumption increased to approximately 3 fish meals per week, the probability of preterm birth declined, but risk was not reduced with more frequent fish consumption (Table). When the probability of preterm birth was calculated on the basis of red blood cell EPA plus DHA as a percent of total fatty acids at

<table>
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<th>Servings of fish per week</th>
<th>Odds ratios for preterm birth</th>
<th>$P$</th>
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<tr>
<td>&lt; 1/mo</td>
<td>1</td>
<td>0.01</td>
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<tr>
<td>1</td>
<td>0.76 (0.61 – 0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>0.64 (0.45 – 0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>0.60 (0.38 – 0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>4</td>
<td>0.62 (0.37 – 1.04)</td>
<td>0.07</td>
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<tr>
<td>5</td>
<td>0.70 (0.40 – 1.24)</td>
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<tr>
<td>6</td>
<td>0.89 (0.46 – 1.71)</td>
<td>0.72</td>
</tr>
<tr>
<td>7</td>
<td>1.24 (0.55 – 2.82)</td>
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<tr>
<td>8</td>
<td>1.93 (0.65 – 5.69)</td>
<td>0.24</td>
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**Table. Adjusted odds ratios (95% CI) for preterm birth by frequency of fish consumption in pregnant women at high risk of preterm delivery**

Findings on whether fish or n-3 LC-PUFA consumption is associated with lower risk of preterm birth are inconsistent. This report examined the effect of fish consumption in early pregnancy on the risk of preterm birth in high-risk women.
randomization, women with the lowest n-3 LC-PUFA levels had a greater risk of preterm birth compared with women in the higher quartiles, but the overall association was of borderline statistical significance (P = 0.054).

This study suggests that fish consumption 2 to 3 times per week is associated with significantly lower risk of preterm birth in high-risk women. Interestingly, higher fish consumption was suggestive of a higher risk. Others have reported that birthweight tends to level off with 3 seafood meals per week.

In seeking a plausible explanation why preterm delivery was higher in women who ate fish once per month or less, the investigators suggested that women who do not eat fish very often might have higher intakes of n-6 PUFAs than women who eat fish. Metabolites of n-6 PUFAs, such as prostaglandins and leukotrienes, stimulate uterine contractions and parturition and these effects are counteracted by n-3 LC-PUFAs. One cannot exclude the possibility that other dietary and lifestyle factors may have contributed to the observations reported.


Greater Growth in Heavier Preterm Infants Fed 1% DHA After Birth

Preterm infants are acutely dependent upon adequate nutrition after delivery because of their lack of body stores and fat, shortage of accumulated nutrients during fetal life and their increased risk of poor developmental outcomes. They are especially vulnerable to suboptimal intakes of long-chain (LC) PUFAs because they missed some of the large transfer of these fatty acids that occurs in the last trimester. While the need for LC-PUFAs is recognized, it remains controversial whether both arachidonic acid (ARA) and docosahexaenoic acid (DHA) should be included in preterm infant formula and at what levels. Some reviews have concluded that LC-PUFA supplementation offers no clear benefits, although most studies have reported either positive or no effects on weight and length. A recent large, randomized controlled study in which the provision of 2 levels of DHA supplementation with constant ARA were evaluated in preterm infants reported no effect of higher compared with lower DHA on Bayley Mental Development Index scores in the overall sample, but did observe higher scores in girls receiving the higher level of DHA. More complete findings from that study, the DINO trial, are described here.

Infants born before 33 weeks’ gestation, free of congenital or chromosomal abnormalities, were eligible to participate. The study also included infants from a multiple birth where all live-born infants were eligible. Each multiple birth was considered one randomization unit according to the sex and weight of the first-born infant. There were 657 infants from 545 mothers randomized to treatment. At 18 months corrected age, data were available from 598 infants.

Lactating mothers were randomly allocated to consume 3 g/day of DHA-rich tuna oil capsules, an amount selected to achieve 1% of total fatty acids in breast milk as DHA. Mothers randomized to the placebo capsules consumed 3 g/day of soy oil that did not change the fat or fatty acid content of their breast milk. Infants of mothers who could not breastfeed were fed standard formula containing 0.35% DHA and 0.6% ARA. Mothers consumed the capsules until their infants reached their expected delivery date. After that time, mothers were encouraged to breastfeed and mothers of infants weaned to formula were encouraged to use formula supplemented with DHA and ARA.

Infant weight, length and head circumference were assessed at study entry and weekly until the expected delivery date. At that time the mothers donated a sample of breast milk. Infant neurodevelopment was assessed at 4, 12 and 18 months corrected age using the Mental Development Index of the Bayley Scales of Infant Development, Second Edition (BSID-II). Corrected age is the chronological age minus the number of weeks born before 40 weeks’ gestation.
In terms of absolute growth measures, infants in the higher DHA group were 0.7 cm longer than those in the standard DHA group (P = 0.02, 95% CI, 0.02 – 0.54) at 18 months of corrected age, after adjusting for sex and gestational age. There were no differences in weight or head circumference. For infants born weighing more than 1,250 g, those in the higher DHA group had a significant increase in weight and length at 12 and 18 months corrected age compared with those fed the standard level of DHA. Length was also greater in this group at 4 months corrected age. Infants weighing less than 1,250 g at birth experienced no effect of DHA level on weight or length.

Although there were no significant differences in growth measures between the treatment groups in infants weighing less than 1,250 g at birth, those in the higher DHA group had a significantly higher weekly growth rate in head circumference compared with infants fed the standard level of DHA.

In this study of preterm infants fed a standard (0.35%) or higher (1%) level of DHA during lactation or formula feeding after birth, those receiving 1% DHA were significantly longer at 18 months of age compared with infants fed 0.35% DHA. Infants fed the higher level of DHA who weighed more than 1,250 g at birth were also significantly heavier at 12 and 18 months corrected age. Infants weighing less than 1,250 g at birth showed no effect of level of DHA intake on growth, except for a greater rate of head circumference growth with the higher level of DHA. There were no obvious reasons why there was no effect of DHA level on growth in the lower birthweight infants.

The authors noted that the growth of infants weighing 1,250 g or more at birth was consistent with the World Health Organization standard, but that infants below 1,250 g were below the expected ideal growth of breastfed term infants. They further commented that although the higher level of DHA was associated with reduced plasma and red blood cell membrane phospholipid ARA concentrations, infant growth was not adversely affected as had been reported in some earlier studies. The investigators reported no adverse effects associated with the consumption of 1% DHA. This level of DHA is found in the breast milk of women in Japan.

Researchers at the University of Texas Southwestern Medical Center, Dallas, USA, conducted a randomized, controlled, double-masked trial to evaluate the effect of 4 different levels of DHA in the presence of a constant amount of ARA in infant formula on the cognitive and visual outcomes of healthy term infants who were fed formula for 12 months. The control group received formula without DHA or ARA. Results for visual acuity reported previously showed no differences among supplementation groups at 12 months of age for DHA of 0.32% or more total fatty acids. This report describes the findings for cognitive function in these infants at 18 months of age.
There were 181 healthy, singleton infants of 37 to 42 weeks’ gestation recruited from two hospitals in Dallas and two in Kansas City, USA, who were fed cow’s milk-based formula containing 0, 0.32, 0.64 or 0.96% DHA from the age of 1 to 9 days until 12 months of age. All formulas except the 0% DHA contained 0.64% ARA. Formula was the sole source of nutrition until the introduction of additional foods at 4 to 6 months of age. Formula feeding continued until the infants were 12 months of age when 141 infants remained in the study. Of these, 131 completed the cognitive assessment at 18 months with the Bayley Scales of Infant Development, 2nd edition. The Bayley Scales consist of 3 parts: mental, psychomotor and behavioral development—each with several subscales for such skills as memory, language, gross and fine motor abilities, emotional regulation and orientation and engagement. Fatty acids in red blood cells were measured at 4 and 12 months of age.

In the overall analysis, there were no significant effects of different DHA levels on the Mental Development Index, Psychomotor Development Index or Behavioral Rating Scale scores. However, when the DHA groups were combined and compared with the control (no supplemental DHA) group, infants consuming supplemental DHA had significantly higher Mental Development Index and language scores (Table). The Mental Index scores were significantly correlated with the visual acuity scores at 12 months of age.

The Behavioral Rating scores were not associated with DHA supplementation when the DHA groups were combined and compared with the control. Analysis of the individual subscales of the Behavioral Rating Scale showed that scores for emotional regulation were significantly higher in the DHA groups than in the control (mean 70.0 vs 61.5, respectively, \(P = 0.035\)).

Several subscales of the primary developmental indexes were significantly correlated with visual acuity at 12 months. These included emotional regulation, quality of movement, cognitive developmental age and language developmental age, as well as the Mental Development Index. The interpretation of these correlations is uncertain because visual acuity in the control group was sufficient for adequate test performance. Whether the correlations might imply changes in brain development that are linked to cognitive function is not known.

The present study observed significantly higher Bayley Mental Development Index scores in healthy term infants at 18 months of age who consumed DHA-supplemented formula for 12 months compared with infants fed unsupplemented formula. The data suggest that supplementation with at least 0.32% DHA is adequate to improve cognitive function in term infants and that higher levels do not confer additional benefits. Supplementation of DHA up to 0.96% was without adverse effects.


<table>
<thead>
<tr>
<th>Developmental index or subscale scores</th>
<th>Control</th>
<th>Combined DHA groups</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Development</td>
<td>98.4 ± 13.1</td>
<td>104.1 ± 10.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Psychomotor Development</td>
<td>102.0 ± 6.3</td>
<td>105.6 ± 9.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Behavioral Rating Scale</td>
<td>73.5 ± 17.5</td>
<td>77.2 ± 18.7</td>
<td>0.37</td>
</tr>
<tr>
<td>Cognitive</td>
<td>17.1 ± 1.7</td>
<td>17.9 ± 1.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Language</td>
<td>15.6 ± 2.7</td>
<td>16.9 ± 2.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Motor</td>
<td>17.7 ± 1.2</td>
<td>18.2 ± 2.1</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*Statistical analysis using Kruskal-Wallis Analysis of variance.
Worth Noting


Smithers LG, Gibson RA, Makrides M. Maternal supplementation with docosahexaenoic acid during pregnancy does not affect early visual development in the infant: a randomized controlled trial. Am J Clin Nutr 2011;93:1293-1299.


Innis SM. Metabolic programming of long-term outcomes due to fatty acid nutrition in early life. Matern Child Nutr 2011;7 Suppl 2:112-123.


BRAIN FUNCTION

Fish Oil After Traumatic Brain Injury Restores Dopamine Release in Animals

Dopamine is a key neurotransmitter—a substance that relays signals from a neuron to a target cell—that is concentrated in the substantia nigra and ventral tegmentum of the brain. It is involved in the control of movement, emotional response and the ability to experience pleasure and pain. Loss of neurons in the substantia nigra leads to dopamine deficiency and is a hallmark of Parkinson’s disease. Dopamine is also associated with susceptibility to addiction. Provision of dopamine via levodopa, a precursor of dopamine, is the primary treatment for Parkinson’s disease and a genetic movement disorder called Segawa’s disease.

The consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) affects the release of dopamine and other neurotransmitters. For example, dopamine activity was greater in the mesolimbic pathway, but lower in the mesocortical pathway of n-3-PUFA-deficient animals compared with control animals, while dopamine pools in both systems were significantly reduced (Figure). Functional links between n-3 PUFA status, neurotransmission and behavioral disorders have been proposed. In an animal model of Parkinson’s disease, DHA supplementation was associated with reduced motor deficits and protection of dopamine neurons in the substantia nigra. Recently, DHA treatment was reported to protect and enhance dopaminergic neurons in experimental Parkinson’s disease, possibly through the increased effectiveness or synthesis of the neurotrophic factors GDNF and neurturin.

Traumatic brain injury may also be accompanied by reduced striatal dopamine release. The striatum is below the cortex in the forebrain and receives input from the cerebral cortex (Figure). There is evidence in humans that striatal dopaminergic function is related to prefrontal cortex functions, such as working memory, which declines in aging. The investigators sought to determine whether treatment with fish oil after traumatic brain injury would restore dopamine release.

The study was conducted in anesthetized rats given a controlled cortical impact following craniectomy. Sham-treated animals received only the craniectomy procedure. After full recovery from the procedures, the animals were administered fish oil providing 360 mg...
EPA and 240 mg DHA by oral gavage once daily for 7 days. The placebo group received olive oil. Seven days after surgery, a microdialysis probe was implanted into the striatum, ipsilateral to the site of injury. After the animals were allowed to recover, artificial cerebrospinal fluid was infused overnight. Samples were then collected every 20 minutes and after one hour the fluid was changed to a high-potassium solution for 40 minutes in order to elicit dopamine release. After restoring the infusion with the original fluid, the animals were sacrificed and the location of the microdialysis probe verified. Dopamine concentrations in the microdialysate samples were measured using high performance liquid chromatography. Area-under-the-curve values were calculated for each group of animals from plots of the dopamine concentrations during the potassium infusion. The highest concentrations of dopamine were observed in the injured animals fed fish oil. These levels were approximately 3-fold higher than those observed in the injured animals treated with olive oil. There was no difference between treatments in the sham-operated animals, which had dopamine levels similar to those in the fish oil-treated, injured animals. There were also no differences among the groups in the concentrations of 2 major metabolites of dopamine, suggesting that the enzymes metabolizing dopamine were unaffected by the treatments. Thus, the administration of fish oil following traumatic brain injury restored dopamine release, whereas olive oil treatment was devoid of effects.

Other investigators have reported that pretreatment with n-3 LC-PUFAs prior to traumatic brain injury prevents the loss of brain-derived neurotrophic factor, synapsin I and cAMP response element-binding protein. In addition, n-3 LC-PUFA pretreatment reduced oxidative damage and counteracted learning deficits. These studies and others indicate that n-3 LC-PUFAs likely exert their neuroprotective effects in brain injury via mechanisms affecting neurotransmission, inflammation, oxidation, apoptosis, cell survival and gene expression. These mechanisms are directly relevant to Alzheimer’s and Parkinson’s diseases, stroke, aging and traumatic brain injury. This study suggests that damage to key functions, such as behavior, emotion and motor control, in brain injury may be reduced with the timely provision of n-3 LC-PUFAs.


Worth Noting

■ MENTAL HEALTH

Long-Chain Omega-3 PUFAs Not Associated with Cognitive Decline in Older Adults

The question of whether long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) can prevent or slow the onset of cognitive decline in aging cannot be answered definitively. Some studies suggest that if provided before the loss of mental function sets in, n-3 LC-PUFAs might delay its onset. Observational studies have suggested some benefit of higher n-3 LC-PUFA status in reducing some aspects of cognitive decline, such as verbal fluency and self-reported cognitive difficulties. Others have reported that n-3 LC-PUFA supplementation provided to patients in the early stages of impaired cognition or early Alzheimer’s disease may slow the rate of decline. Yet other studies have reported no benefit in patients with early Alzheimer’s disease and no association with fatty fish or n-3 PUFA intake in early cognitive decline. The potential effectiveness of n-3 LC-PUFAs in maintaining cognitive function may also depend on other factors, such as apolipoprotein E genotype. Some reasons for the inconsistencies in the literature have been discussed in a recent review.

Cognitive function was assessed in a cohort of men and women aged 45 to 80 years of age (mean age 61 years) who were enrolled in a study of the effects of supplementation with B vitamins, n-3 LC-PUFAs, both vitamins and n-3 LC-PUFAs or a placebo for 4 years. The B vitamins...
included 0.56 mg 5-methyltetrahydrofolate, 3 mg vitamin B₆, and 0.02 mg vitamin B₁₂. The n-3 LC-PUFAs included 600 mg EPA plus DHA in a ratio of 2:1. All participants had cardiovascular disease, including recent myocardial infarction, unstable angina or ischemic stroke. Of the 2,501 eligible participants randomly assigned to treatment, 1,881 completed 4 years in the study and 1,748 completed the cognitive assessment and data collection.

The main outcome was cognitive function at 4 years assessed using a modified and validated version of the Telephone Interview for Cognitive Status. Baseline cognition was evaluated with the Isaacs Set Test because the validated version of the former test was not available at the time. The Isaacs Test is based on verbal fluency. Cognitive performance at baseline was similar across all treatment groups. Statistical models were adjusted for variations in age, EPA and vitamin B₁₂ concentrations at baseline. Participants in this study with those who were not included indicated that these participants had slightly higher vitamin B₆, folate, EPA and DHA status, slightly higher baseline cognitive scores, a slightly lower mean body mass index and were slightly younger than the non-participants.

There were no significant effects of treatment on cognitive function or the follow-up cognitive scores (Table).

Plasma homocysteine levels were unrelated to cognitive outcomes. In subgroup analysis, the type of cardiovascular disease was significantly related to the final cognitive scores and memory subscores when the 4 treatment groups were analyzed individually. Those with a history of myocardial infarction or unstable angina had higher total cognition scores than stroke participants (28.9 ± 4.6 vs 27.1 ± 5.4, P < 0.0001). The myocardial infarction or unstable angina group who consumed B vitamins alone also had lower semantic memory scores than those receiving n-3 LC-PUFAs or the placebo. However, B vitamin supplementation was associated with higher temporal orientation scores in ischemic stroke participants compared with the placebo or n-3 LC-PUFA groups. Thus, the effect of B vitamins, but not of n-3 LC-PUFAs, varied with the type of cardiovascular disease. Participants aged 65 years or older who took the B vitamin supplement had lower total cognitive scores than those taking the placebo.

The two most important variables related to cognition in this study were type of cardiovascular disease and age. Stroke patients and older participants had lower

---

### Table. Cognitive performance in older adults with cardiovascular disease by treatment group after 4 years’ supplementation*

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B vit + n-3 LC-PUFA</td>
</tr>
<tr>
<td>Phone interview score</td>
<td>28.5 ± 4.7</td>
</tr>
<tr>
<td>Temporal orientation, %</td>
<td>83</td>
</tr>
<tr>
<td>Spatial orientation, %</td>
<td>94</td>
</tr>
<tr>
<td>Memory</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>Attention/calculation, %</td>
<td>48</td>
</tr>
<tr>
<td>Semantic memory, %</td>
<td>71</td>
</tr>
<tr>
<td>Recall</td>
<td>3.3 ± 1.8</td>
</tr>
<tr>
<td>Repetition, %</td>
<td>40</td>
</tr>
</tbody>
</table>

*Scores are means ± SD; percentages are proportions of patients scoring above the established cut-off. B vitamins include folate, B₆, and B₁₂. Phone interview score based on French Telephone Interview for Cognitive Status. No significant main effects were observed.
overall scores than patients with myocardial infarction or unstable angina. It was unexpected that vitamin B supplementation was associated with significantly lower scores on semantic memory tests in patients with myocardial infarction or unstable angina, but not in patients with ischemic stroke. One possible explanation for the lack of an effect might be the comparatively low dose of n-3 LC-PUFAs (600 mg/day). Thus, the question of whether the consumption of nutritionally relevant amounts of n-3 LC-PUFAs might deter the onset of cognitive decline in older adults remains equivocal.


Worth Noting


### Visual Function

#### Long-Chain Omega-3s and Some Antioxidants May Lower Genetic Risks for AMD

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries and afflicts approximately 2.5 million older adults in Europe and 1.8 million in the U.S. The prognosis is more favorable if the disease is detected early, but outcomes for late AMD, especially the geographic atrophy form, are less hopeful. The ability to inhibit the progress of neovascular AMD, reduce lesion thickness and improve visual acuity with vascular endothelial growth factor inhibitor has been demonstrated in recent clinical trials and offers fresh hope to those with some forms of advanced AMD.

While treatments for acute disease are encouraging, prevention is the key to halting the increasing incidence of AMD. Prevention strategies emphasize nutritional supplements, including long-chain omega-3 PUFAs (n-3 LC-PUFAs) and antioxidant nutrients, lifestyle modifications that eliminate smoking, and filtering sunlight with sunglasses and special lenses.

Genetic and environmental factors contribute to the risk of developing AMD. Protective environmental factors include the Age-Related Eye Disease Study (AREDS) nutrients (zinc, vitamin C, β-carotene and vitamin E) and n-3 LC-PUFAs, along with lutein and zeaxanthin (carotenoïds) and B vitamins. Smoking cessation and reduced subclinical inflammation are also associated with a lower risk of AMD.

Among the most common gene variants associated with increased risk of AMD are those involving complement factor H (CFH gene), PLEKHA1/ARMS2/HTRA1 (pleckstrin homology domain-containing family A member 1, age-related maculopathy susceptibility 2, high-temperature requirement factor A1, respectively) and the LOC387715 gene. How the complement system affects AMD has been reviewed recently. It has been suggested that variants in the first two of these genes are most strongly associated with AMD, yet are insufficient to predict the development of the disease accurately. Thus, the search for new AMD-related genes presses on.

A recent report from the Rotterdam Study, a prospective, population-based study of chronic diseases in people 55 years of age or older, examined the relationship between diet, genetic risk and early AMD in participants selected on the basis of their AMD status at baseline. Participants included those who developed early AMD during the study and those who had no AMD during the entire study period. There were 2,167 participants who were re-examined 3 times after enrolment and followed for a median of 8.6 years.

The investigators examined the CFHY402H and LOC387715 A695 gene variants because each has been associated
with a significant elevation in AMD risk. The frequency of the LOC387715 gene is lower than for CFH variants. Genotyping was determined from peripheral blood leukocytes using the TaqMan assay. Diagnosis of AMD was made from fundus photographs taken at each visit and graded according to the modified international classification system. A grade of no AMD consisted of no drusen or only small hard ones. Early AMD included soft distinct drusen with pigment irregularities or soft indistinct drusen with or without pigment irregularities. Incident early AMD was defined as no sign of AMD in both eyes at baseline and the appearance of signs of early AMD in at least one eye at follow-up.

Dietary assessment occurred in 2 stages at baseline and included a home checklist by the participant and followed by a food frequency questionnaire administered by in-person interview. Data on iron, zinc, vitamins A, C and E, β-carotene; lutein/zeaxanthin and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were used in the analysis. Information about smoking status, blood pressure, carotid intima thickness, atherosclerotic plaques and a subclinical atherosclerosis score were obtained to assess confounding variables.

The investigators calculated a synergy index to assess the biological interaction with each gene and the various nutrients. The index assessed the combined effect of 2 factors relative to the sum of each factor separately. A synergy index less than 1 suggests that the protective effect of both factors together is greater than the sum of each assessed separately. All synergy calculations were adjusted for age, sex, smoking and atherosclerosis.

During the follow-up, 517 participants (23.8%) developed early AMD. Those with the disease were slightly older, less likely to have diabetes and more likely to carry the two AMD-risk genes. Participants with higher intakes of zinc, β-carotene and vitamins C and E were significantly less likely to develop early AMD, as previously reported from this study.

The sample was stratified according to the presence of each gene and nutrient intakes were evaluated on whether the individual was a non-carrier, heterozygous or homozygous for it. Significant associations between nutrient intake and risk of early AMD were observed in carriers of the CFH gene for zinc, β-carotene, EPA and DHA, and lutein and zeaxanthin. Significant associations were also observed for zinc and EPA plus DHA in carriers of the LOC387715 gene. For each genotype, homozygous carriers in the highest consumption tertile of each nutrient had the greatest reduction in the risk of early AMD compared with carriers in the lowest tertile of consumption. For example, among homozygous carriers of the CFH gene, those in the lowest tertile of zinc intake had a risk of AMD 2.25 times higher than those without the gene in the same zinc tertile. Homozygotes with the highest zinc consumption had a risk only 27% greater than non-carriers in the same tertile.

The association of EPA+DHA intake with the relative risk of early AMD among carriers and non-carriers of the CFH gene is shown in the Figure. Homozygote carriers of the CFH gene with the highest intakes of EPA+DHA were at significantly lower risk of early AMD (Hazard ratio = 1.30) compared with those in the lowest tertile of consumption (Hazard ratio = 1.97). A similar reduction in risk was observed among carriers of the LOC387715 gene who had the highest consumption of EPA+DHA. Their risk of early AMD did not differ from non-carriers of the gene.

This study observed strong associations between higher intakes of zinc, β-carotene, EPA and DHA, lutein and zeaxanthin and lower risks for early AMD in healthy older adults at increased genetic risk of the disease. The authors noted that intakes sufficient to achieve significantly lower risk of AMD were within current recommended amounts and did not require high doses. Two other studies have reported nutrient-gene interactions in the development or progression of AMD. In the AREDS study, high intakes
of zinc or zinc with antioxidants, but not antioxidants alone, were associated with a lower progression from intermediate to advanced disease in carriers of the CFH gene, but not in those with the LOC387715 gene. In the Blue Mountains Eye Study, homozgyous carriers of the CFH gene who ate fish weekly had a greater reduction in the risk of late AMD than non-carriers.

This study is one of few to report that the consumption of specific nutrients is associated with significantly lower risk of early AMD among those with a higher genetic risk. Dietary or nutrient strategies to reduce the onset or progression of AMD are among the top strategies to mitigate this disease. The antioxidants zinc and n-3 LC-PUFAs identified in these studies are easily obtained from foods selected with an eye to their nutritional profile. It is encouraging that among healthy older adults, strategic food choices to provide these nutrients might prevent AMD. Avoiding potential blindness is a powerful incentive to eat fish and veggies.

Worth noting


**CLINICAL CONDITIONS**

**Chronic kidney disease**

**Higher Fish and Long-Chain Omega-3 Intakes Linked to Lower Risk of Chronic Kidney Disease**

Chronic kidney disease is one of several major health conditions of increasing frequency in older adults. The condition is defined as a glomerular filtration rate of less than 60 ml/min per 1.73 m2 or urinary albumin-to-creatinine ratio greater than 30 mg/g. The disease affects approximately 13% of the adult population 20 years of age or older in the U.S. or about 26 million people. It is associated with diabetes, obesity, cardiovascular disease and hypertension. It is estimated that about 40% of individuals with diabetes and 42% of those with undiagnosed diabetes have the condition. The high prevalence of health conditions that increase the risk of developing chronic kidney disease and its progressive morbid nature add to the urgency of identifying factors that might reduce the likelihood of developing the condition.

The anti-inflammatory properties of some omega-6 (n-6) PUFAs and especially of the long-chain omega-3 PUFAs (n-3 LC-PUFAs) suggest that they may reduce renal inflammation and improve organ function in chronic kidney disease. A 3-year prospective study of adults aged 65 years or older reported that higher plasma levels of total, n-6 and n-3 PUFAs were associated with a slower decline in creatinine clearance and a lower risk of renal insufficiency compared with participants having low PUFA levels. In a controlled trial of fish oil supplementation in patients with severe IgA nephropathy, patients treated with low- or high-dose n-3 LC-PUFAs had significantly lower rates of renal function loss compared with the placebo-treated patients. The addition of marine n-3 LC-PUFAs to the diets of a small number of hemodialysis patients was associated with reduced C-reactive protein, a marker of systemic inflammation.

Taking the anti-inflammatory model further, animal studies with resolvin D1 and protectin D1, derivatives of n-3 LC-PUFAs, reported that these mediators of inflammation resolution were produced in animals with kidney ischemia/reperfusion injury. Administration of either of these substances prior to ischemia reduced the functional and morphological injury associated with the injury. In a study comparing n-3 and n-6 PUFAs in ischemic renal injury, animals fed the n-6 PUFA (corn oil) diet did not survive extended ischemia, while all those fed the n-3 LC-PUFA diet (menhaden oil) survived. Protection against ischemic injury correlated with decreased polymorphonuclear leukocyte recruitment and increased levels of protectin D1.
A meta-analysis of 17 trials of n-3 LC-PUFA supplementation in chronic kidney disease patients reported a reduction in urinary protein excretion, but no effect on the decline in glomerular filtration rate. Inconsistency among methods and data reporting, as well as small numbers of participants in many trials, speak to the need for larger, adequately powered, randomized trials to determine the efficacy of n-3 PUFAs in kidney disease.

The study described here, while not a large randomized controlled trial, is an observational study in a large community-based cohort of adults 50 years of age or older. It was designed to determine whether dietary PUFAs are associated with chronic kidney disease and if a diet high in fish affects the likelihood of developing the disease.

Study participants were part of the Blue Mountains Eye Study living west of Sydney, Australia. Data were available from 2,600 participants who provided information about their diet and fish intake via food frequency questionnaire. Kidney disease was assessed from serum creatinine concentrations measured in fasting venous blood. Glomerular filtration was estimated indirectly from the creatinine values, accounting for age and sex. Other health and demographic information was collected from in-person interviews at entry to the study.

There were 504 (19%) participants with chronic kidney disease of stage 3 or higher. These individuals were more likely to be older, inactive, and have hypertension, diabetes or stroke as well as higher hemoglobin and hematocrit, total cholesterol and triglycerides than participants with mild or no chronic kidney disease. Those with the disease were less likely to be male, smokers or heavy drinkers.

As shown in the Table, intake of energy-adjusted n-3 LC-PUFAs was associated with a significant 13% lower risk of chronic kidney disease, but intakes of total n-3 PUFAs or total n-6 PUFAs were unrelated to disease risk. Interestingly, increased consumption of alpha-linolenic acid was associated with a significant 18% greater risk of chronic kidney disease. Fish consumption was not related to risk.

When the data were analyzed by quartiles of n-3 PUFA consumption, those in the highest quartile of n-3 LC-PUFA consumption were 31% less likely to develop chronic kidney disease compared with those in the lowest quartile (P = 0.05) after adjusting for age, sex, body mass index, smoking, alcohol consumption, physical activity, serum homocysteine, serum total cholesterol and triglycerides, hypertension and history of diagnosed diabetes. Similarly, those in the highest quartile of fish consumption were 32% less likely to develop chronic kidney disease compared with those in the lowest quartile of fish intake (P = 0.02). In contrast, the odds of chronic kidney disease were 73% greater for those in the highest quartile of alpha-linolenic acid intake (P = 0.004).

This study reported a significant association between higher intakes of n-3 LC-PUFAs or fish and a lower risk of developing chronic kidney disease in a general population of adults 50 years of age or more. It also observed a significantly higher risk of the disease with greater intakes of the plant-based n-3 PUFA, alpha-linolenic acid. There was no association with the consumption of total n-6 PUFAs. The study provided no data on the potential involvement of immune function, reduced inflammation

<table>
<thead>
<tr>
<th>Table. Multivariate odds ratios for the relationship between fatty acid or fish intake and the risk of chronic kidney disease in adults aged 50 yr or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy-adjusted FA Intake, g/day</td>
</tr>
<tr>
<td>Total n-3 PUFA</td>
</tr>
<tr>
<td>n-3 LC-PUFA</td>
</tr>
<tr>
<td>ALA</td>
</tr>
<tr>
<td>Total n-6 PUFA</td>
</tr>
<tr>
<td>Fish</td>
</tr>
</tbody>
</table>

*Odds ratios per standard deviation calculated on data for the estimated glomerular filtration rate in ml/min per 1.73 m² using the 4-variable Modification of Diet in Renal Disease Study formula.
or changes in blood pressure or protein excretion in contributing to these associations. It is left to intervention studies to clarify the mechanisms underlying these encouraging observations.


Type 2 diabetes
Contrasting Associations Between Fish or Omega-3 Intakes and Risk of Type 2 Diabetes
Observational studies on the relationships between fish consumption or high intakes of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) and the risk of type 2 diabetes have reported mixed results. In middle-aged US adults, the consumption of n-3 PUFAs was unrelated to diabetes risk. In a large study of US adults without chronic disease at baseline, increased consumption of fish or n-3 LC-PUFAs was associated with a slightly increased risk of type 2 diabetes. High serum levels of linoleic acid, an n-6 PUFA, were associated with a lower risk of developing impaired fasting glyemia and diabetes in middle-aged men. Among older Dutch adults, higher consumption of fish was associated with a greater risk of type 2 diabetes, but the consumption of fatty fish or n-3 LC-PUFAs was not. In the US Women’s Health Study, higher intakes of n-3 LC-PUFAs were associated with higher incidence of type 2 diabetes. However, in the European Prospective Investigation of Cancer study, high total fish intake was associated with a significantly lower risk of diabetes. One cannot draw conclusions from such disparate studies.

Two studies in Chinese populations in Shanghai and Singapore suggest that the associations between fish or n-3 LC-PUFA consumption and risk of type 2 diabetes may not be clarified any time soon. In the Shanghai study, where fish consumption is high, Raquel Villegas and colleagues conducted 2 separate, prospective, population-based studies in 74,942 women aged 40 to 70 years and 61,500 men aged 40 to 74 years. Follow-up time for each study was 8.9 and 4.1 years, respectively. Baseline dietary information was collected by in-person food frequency questionnaire in each study, with additional dietary assessments every 2 years. Fish consumption was grouped into 4 categories: combined fish and shellfish, shellfish, saltwater fish and freshwater fish.

Incident type 2 diabetes was identified by participant report with confirmed cases, including at least one of the following criteria: fasting glucose concentration ≥ 7 mmol/L on 2 or more occasions, oral glucose tolerance test values of ≥ 11.1 mmol/L or use of hypoglycemic medication. There were 2,262 confirmed cases among females and 833 among males. The median intake of fish and shellfish was 39.3 g/day for females and 40.3 g/day for males.

Figure 1. Multivariate relative risks (+95% CI) of type 2 diabetes by quintile of fish and shellfish or EPA+DHA intakes in 64,193 Chinese women in Shanghai over 8.9 years. Significant trends for lower risks of type 2 diabetes with increasing fish and shellfish or EPA+DHA intakes, P=0.004 and 0.005, respectively.

Total intakes of fish and shellfish and of n-3 LC-PUFAs were associated with significantly lower risks of type 2 diabetes among women, in multivariate analysis (Figure 1). Although the trends were significant, the associations appeared nonlinear, with the lowest risks observed in the middle quintiles for fish, shellfish, combined fish and shellfish and n-3 LC-PUFA consumption. In men, the risk of type 2 diabetes was inversely associated only with shellfish consumption.

The Singapore Chinese Health Study looked at the relationships between the risk of type 2 diabetes and total n-3 PUFA consumption, marine and plant n-3 PUFAs, n-6 PUFAs and the ratio of dietary n-6:n-3 PUFAs in more than 63,000 Chinese men and women living in Singapore. Participants were between the ages of 45 and 74 years and data about demographics, medical history,
Lifestyle habits and dietary intakes were collected at baseline from in-person interviews and a food frequency questionnaire. Follow-up interviews were conducted by telephone 5 years later. Marine foods accounted for approximately 36% of the population intake of n-3 PUFAs. Participants with self-reported, physician-diagnosed diabetes at baseline were excluded from the analysis. Those who reported the development of diabetes during the follow-up interview had their diagnosis validated as previously published and a random sample of those with diabetes provided a blood sample for the determination of glycated hemoglobin. After additional exclusions for death, questionable energy intakes and migration, 43,176 participants remained. The average follow-up time was 5.7 years.

Consumption of n-6 PUFAs or the n-6:n-3 PUFA ratio were not associated with the risk of type 2 diabetes in multivariate analysis. After adjusting for dietary confounders, there was an inverse association with total n-3 PUFA intakes from the third to the fifth quintile of consumption. There was no significant association with the consumption of n-3 LC-PUFAs (Figure 2). Higher consumption of alpha-linolenic acid (ALA) in the fully adjusted multivariate analysis was significantly associated with a lower risk of type 2 diabetes. The investigators did not report the risks stratified by sex.

These two large, prospective cohort studies in Chinese adults reported contrasting associations between the consumption of n-3 LC-PUFAs and risk of type 2 diabetes. In the Shanghai study, higher intakes of fish, shellfish and n-3 LC-PUFAs were associated with significantly lower risks of diabetes in women and higher shellfish consumption was associated with lower diabetes risk in men. In contrast, n-3 LC-PUFA consumption was not associated with the risk of type 2 diabetes in the Singapore Health Study. Moreover, the Singapore study observed a significantly lower risk of diabetes with higher intakes of ALA. Inverse associations with ALA intake and disturbed glucose metabolism have been reported in Japanese Brazilians, but the associations were even stronger for total n-3 PUFAs and eicosapentaenoic acid. In middle-aged Japanese individuals, higher ALA consumption was associated with lower insulin resistance in non-obese participants, but n-3 LC-PUFAs were unrelated to insulin resistance.

What might account for the contradictory observations with respect to the consumption of n-3 LC-PUFAs and risk of type 2 diabetes in these studies? Estimated intakes of n-3 LC-PUFAs differed substantially between the two studies. The highest quintile of consumption in the Shanghai participants whose fish consumption was described as high was a median of 200 mg/day, whereas in the Singapore study, the highest quintile of EPA plus DHA intake was a mean of 600 mg/day. Each study used different databases for calculating the n-3 PUFA content of foods; this, along with differences in the type of fish consumed and other dietary variables, could account for the large differences in estimated n-3 LC-PUFA intakes. Mean body mass index values were below 25 kg/m2 in all quintiles in both studies. Consumption of n-3 LC-PUFAs remains a small portion of the total fatty acid intake and it may be that they have little involvement in the complex etiology of diabetes in spite of their strong effects in some tissues and metabolic pathways.

Note added in press: Two additional epidemiological studies on the relationship between fish or n-3 LC-PUFA intakes or biomarkers of n-3 LC-PUFA status and incident type 2 diabetes in middle-aged women and older adults appeared after this article was written. These studies by Djoussé and colleagues are noted below. In middle-aged women, higher consumption of fish or n-3 LC-PUFAs was significantly associated with a lower risk of type 2 diabetes in middle-aged women. However, no significant association was observed in men. In addition, a higher intake of ALA was associated with a lower risk of type 2 diabetes in middle-aged women, but not in men. These studies suggest that the effects of n-3 LC-PUFAs on type 2 diabetes risk may vary by sex and that ALA may have a protective effect in middle-aged women.
LC-PUFAs was associated with an increased risk of type 2 diabetes after 12 years of follow-up. The investigators observed that the increase in risk was consistent with a threshold effect of fish consumption greater than twice per week.

The second report in older adults used plasma phospholipid measurements of n-3 LC-PUFAs to assess the participants’ fatty acid status at baseline and estimated the risk of type 2 diabetes after a median follow-up of 10.6 years. In multivariate analysis, individuals with the highest concentration of EPA+DHA had a lower risk of type 2 diabetes, but overall, EPA+DHA was not associated with a higher risk of the disease. Higher intakes of ALA were also associated with a lower risk of diabetes. In this study, dietary intakes of EPA+DHA and fatty fish were not associated with diabetes.


Worth noting


