



PUFA NEWSLETTER

Volume 18 • Issue 1

April 2013 Contents

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Does Eating Fish Bring a Breath of Fresh Air?

This newsletter revisits the discussion of omega-6 (n-6) PUFAs in the prevention of heart disease. Recommendations to increase the consumption of PUFAs in place of saturated and *trans* fatty acids are widely endorsed, but how much of PUFAs and the proportion of n-6 and n-3 PUFAs are disputed. It has been argued that high intakes of n-6 PUFAs increase the risk of heart disease and reduce tissue uptake of n-3 PUFAs, which are already under-consumed in most Western diets. Christopher Ramsden and colleagues obtained the original data from the Sydney Diet Heart Study and reanalyzed them, concluding that replacing saturated fatty acids with high levels of the n-6 linoleic acid increased the risk of mortality from coronary heart disease and cardiovascular diseases. Two other studies on cardiovascular health reported that higher dietary EPA and higher blood levels of EPA and DHA were associated with a lower risk of heart failure mortality.

Three observational studies examined the connections between fish consumption in pregnancy, infancy or early adulthood and the risk of asthma or wheeze. Data on the association between fish or long-chain (LC) n-3 PUFA consumption in pregnancy are inconsistent in spite of several positive reports. Results from the Danish National Cohort indicated that eating fish five times per week or more during pregnancy was associated with significantly less asthma in children at 18 months and 7 years of age. A second study reported that children in the Netherlands who first ate fish between the ages of 6 and 12 months of age were less likely to experience wheeze at 48 months of age compared with children who did not eat fish in the first year of life. A third study examined the incidence of asthma in adults 18 to 30 years of age and reported that those who consumed the highest levels of n-3 LC-PUFAs

or DHA were at a significantly lower risk of developing asthma compared with those with the lowest intakes.

Increasingly, n-3 LC-PUFAs consumed after brain or spinal cord injury are associated with less nerve damage, neuronal protection and improved functional recovery. A new report describes faster nerve recovery and better sensory and motor function in animals pretreated with a fish oil-rich diet for 8 weeks before spinal cord injury. Improvements were sustained after injury, even though the post-operative diet was not enriched with fish oil.

In other research, the children of mothers with higher levels of n-6 PUFAs and linoleic acid in late pregnancy were more likely to have greater fat mass and a lower percent of lean body mass at 4 and 6 years of age. Fat mass and lean body mass were not related to maternal n-3 LC-PUFA concentrations. In a study on the effects of n-3 LC-PUFAs and sunburn sensitivity, women whose skin sunburned easily consumed a high-dose of EPA-rich oil or a placebo for 12 weeks prior to UV radiation exposure. Women taking the EPA-rich oil had less immunosuppression at low UV-radiation levels compared with women who consumed the placebo. At higher UV exposures, there was no difference in immunosuppression between the groups.

Catching another breath, we wish you enjoyable reading.



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■ CARDIOVASCULAR HEALTH

Doubts About Linoleic Acid for Secondary Prevention of Heart Disease

Current dietary advice advocates replacing dietary saturated fatty acids with PUFAs from both the omega-3 and omega-6 families. A new analysis of old data questions the effect of high levels of omega-6 PUFAs.

A tenet of the received wisdom about dietary practices to reduce the risk of cardiovascular disease and the chance of dying from it is the [substitution](#) of foods rich in saturated and *trans* fatty acids with those rich in monounsaturated fatty acids and [PUFAs](#). A pooled analysis of 11 cohort

studies concluded that replacing saturated fatty acids with PUFAs rather than monounsaturated fatty acid or carbohydrates prevents coronary heart disease over a wide range of intakes. [Persuasive data](#) from Finland, where following this recommendation was associated with an 80% decrease in cardiovascular mortality, added further support for this advice.

The case might have been considered closed at this point were it not for lingering concerns about the possible undesirable effects of diets relatively high in n-6 PUFAs in conjunction with a low intake of n-3 PUFAs. It was thought that such diets might increase the production of pro-inflammatory eicosanoids, thus contributing to an underlying cause of cardiovascular disease. For this reason, some experts recommended [reducing](#) the consumption of n-6 PUFAs, while increasing the consumption of n-3 PUFAs. However, we now know that dietary linoleic acid has [no effect](#) on a variety of markers of inflammation in healthy individuals. In addition, the derivatives of arachidonic acid, a long-chain product of linoleic acid metabolism, have both [pro- and anti-inflammatory properties](#).

Others reported that diets high in linoleic acid, the predominant n-6 PUFA in the diet, [reduced the concentration of EPA](#) in plasma phospholipids, while low linoleic acid diets increased EPA in healthy men. High linoleic acid diets have also been negatively [implicated](#) in nonalcoholic fatty liver disease, endothelial dysfunction, cardiovascular disease and atherosclerosis, several chronic inflammatory conditions, Alzheimer's disease and [obesity](#). Recently, patients who consumed a [reduced their dietary linoleic acid](#) from 6.7% to 2.4% for 4 weeks exhibited significantly lower levels of circulating oxidized metabolites of linoleic acid that

have previously been associated with atherosclerosis, Alzheimer's disease, nonalcoholic fatty liver disease and chronic pain.

Some consider the evidence supporting recommended intakes of linoleic acid flimsy. Yet diets in which saturated fatty acids were largely replaced by PUFAs from both families have been associated with an 80% reduction in cardiovascular mortality. How much linoleic acid should we consume?

Dietary recommendations for n-6 PUFA consumption have come under renewed scrutiny. [Stephen Cunnane](#) suggested that the evidence for linoleic acid intakes was flimsy and that key information about linoleic acid metabolism is missing. Others reported that meta-analyses of randomized controlled trials yielded equivocal

[results](#) depending on whether trials increased the intakes of n-6 and n-3 PUFAs or just n-6 PUFAs. Those employing higher n-6 PUFAs without increased intake of n-3 PUFAs resulted in a significant 13% higher risk of nonfatal myocardial infarction and coronary heart disease death. These findings suggested that flawed data in previous analyses were obscuring the different effects of n-6 and n-3 PUFAs on the risk of heart disease mortality. The [American Heart Association](#) robustly defended its recommendation to consume at least 5 to 10% of energy from n-6 PUFAs to reduce the risk for cardiovascular disease, further commenting that reducing current n-6 PUFA intakes from their current levels would be more likely to increase than decrease the risk of coronary heart disease.

There is now a more extensive analysis of the original data from the [Sydney Diet Heart Study](#), a controlled intervention trial conducted from 1966 to 1973, in which 458 middle-aged men who had experienced a myocardial infarction, acute coronary insufficiency or angina were randomized to consume safflower oil and safflower margarine or received no specific dietary guidance beginning 8 weeks or more after their coronary event. The objective of the intervention was to replace dietary saturated fats and cholesterol with safflower oil, up to the level of 15% total energy. Safflower oil contains 75% linoleic acid and no other PUFAs. This protocol resulted in the increased consumption of linoleic acid without additional n-3 PUFAs. The study was single-blinded, as the dietitians involved administered the safflower oil to the intervention group and no placebo was used. Median follow-up time was 39 months.

At the final follow-up, participants in the safflower oil group experienced a significantly higher risk of cardiovascular or coronary heart disease mortality, 70% and 74%, respectively compared with the control patients (Figure). The risk of dying from any cause (62%) was also higher in the intervention participants ($P = 0.051$). This was likely due to the relatively small number of participants and deaths. The investigators reported that the intervention group achieved a PUFA

A more detailed analysis of the original data from the Sydney Diet Heart Study reported that patients who consumed high safflower oil diets rich in linoleic acid were significantly more likely to die from cardiovascular and coronary heart disease.

consumption of 15.4% of energy. The control group also increased its PUFA consumption from 6.2% at baseline to 8.4% energy at follow-up. Saturated fat intake fell in both groups. The changes in PUFA and saturated fat intakes in the control group were not significantly associated with the risk of death. Alcohol consumption and smoking modified the risk of death in the whole sample, but not in the intervention group alone.

The Sydney Diet Heart Study is important, not only for its findings and the new rigorous analysis, but because it is one of only three randomized controlled trials that have looked at the effect on heart disease mortality of selectively increasing the consumption of linoleic acid without increasing the intake of n-3 PUFAs. The increased risks of cardiovascular and coronary heart disease mortality with a high intake of linoleic acid are consistent with the two previous trials. With the original data, these investigators were able to separate cardiovascular and coronary heart disease deaths from total mortality, making the results more specific.

The re-analysis of the Sydney Diet Heart Study has its own problems. The [original study](#) authors noted that the results could not be interpreted because the intervention turned out to be multifactorial. Many participants in both groups adopted more healthy lifestyles, such as smoking less—the percentage of nonsmokers increased from 30% at infarction to 62% at entry into the study. Participants in both groups consumed more polyunsaturated-rich margarines and less saturated fat and cholesterol at follow-up compared with entry to the study. This change reduced the differences in dietary fat intakes between the groups. Other changes included weight loss (4.7 kg in both groups since infarction) and greater physical activity. In the original multivariate analysis, the investigators found that the most important contributor to a patient's prognosis was the extent of coronary and myocardial disease at entry to the study. Recreational physical activity had a significant protective effect.

The margarine provided to the safflower participants [may have contained](#) higher levels of *trans* fatty acids than originally thought and, if appreciable, would be expected to increase the risk of heart disease mortality. As data on the change in *trans* fatty acid consumption are lacking, it is possible that the revised findings may not be solely attributable to the effect of increased linoleic acid intake. Caution is also warranted because there were only 63 deaths from coronary or cerebrovascular disease in the whole study.

For comparison, the [corn oil study](#) enrolled 80 patients with heart disease and randomized them to high-fat diets containing 80 g/day of olive oil or corn oil compared with a control group, which was not advised about dietary fat. Study groups were advised to avoid fried and fatty foods, fatty meats, ice cream and cheese and were restricted in milk, eggs and butter. Dietary assessments during the second year of the study suggested that the control group consumed approximately 70 g/day of fat and the olive oil and corn oil groups approximately 45 and 50 g/day,

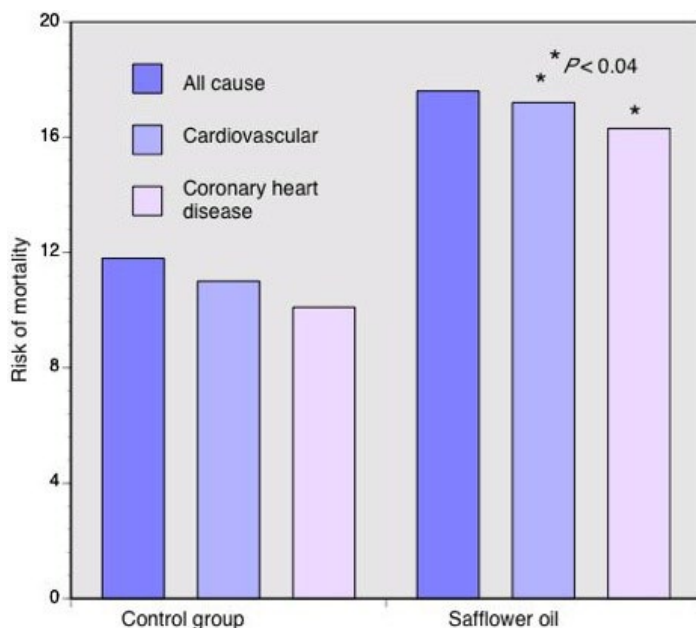


Figure. Risk of mortality from all causes, cardiovascular disease or coronary heart disease in middle-aged men with myocardial infarction of acute coronary insufficiency who consumed 15% of energy from safflower oil or their regular diet (control) for a median of 39 months. Risk of death from cardiovascular disease or coronary disease was significantly higher in the safflower group compared with the controls, $P < 0.04$.

respectively. At completion, 75% of the control patients were free of major cardiac events compared with 52% of the corn oil group and 57% of the olive oil group. The difference among groups approached statistical significance, but the number of participants was very small.

In the [Minnesota Coronary Survey](#), over 9,000 institutionalized mental patients were served the usual hospital diet containing 42% energy from fat and 4.3% energy from PUFAs or a high PUFA diet containing about 20% energy from PUFAs and 45% energy from fat. The treatment diet was based on a combination of the National Diet-Heart Study diets B and C rich in vegetable oils. Over 4.5 years of study, there were no significant differences between the groups in those who survived without cardiac events. Deaths among men and women did not differ between the groups. For participants who remained in the study more than one year, deaths among the treated patients were greater than those on the control diet (31.0 vs. 26.1 deaths per 1000 person-years).

However, deaths from arteriosclerotic heart disease were greater among treated men than controls (18 vs. 13), but did not differ for women. The total number of deaths was small, so that statistical analysis was not reported. This study does not provide strong evidence one way or the other.

Reanalysis of data from the Sydney Diet Heart Study suggests that higher intakes of linoleic acid may be associated with a greater risk of mortality compared with a usual diet. However, questions about the dietary fatty acids consumed and changes in participants' lifestyles suggest that these findings may be inconclusive.

A positive note in this report is that intervention studies in which the consumption of [both n-6 and n-3 PUFA increased](#) have been associated with significantly lower cardiovascular mortality and [regression](#) of coronary artery disease. This new analysis is unlikely to alter dietary recommendations to replace

saturated (and *trans*) fatty acids with PUFAs from both PUFA families as supported in more [recent studies](#). As Philip Calder observed in his editorial, "there is reason to be cautious about high intakes of omega-6 PUFAs." Their effect in reducing tissue concentrations of n-3 PUFAs and associations with a host of chronic diseases suggest that we will hear more about this question.

*Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, Ringel A, Davis JM, Hibbeln JR. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ* 2013;346:e8707. [[PubMed](#)] [Open Access](#)*

*Calder PC. Old study sheds new light on the fatty acids and cardiovascular health debate. [Editorial] *BMJ* 2013;346:f493. [[PubMed](#)] [Open Access](#)*

Dietary n-3 PUFAs Linked to Reduced Carotid Intima-Media Thickness in Adults with Impaired Fetal Growth

It is now clear that events in fetal life, such as impaired growth and low birthweight are associated with a higher risk of cardiovascular disease in adulthood. Risk factors for heart disease are present in children. Is that the time to intervene?

The presence in children of atherosclerosis and elevated risk factors for cardiovascular disease (CVD) has been well documented, with [accelerated infant growth](#) and childhood overweight and [obesity](#) among the contributing factors. Events in fetal life, such as

impaired growth, as well as [low birthweight](#) have been associated with a higher risk of CVD in adulthood and with childhood [endothelial dysfunction](#) and structural vascular changes. One clinical feature of early atherosclerosis in children is [increased carotid intima-media thickness](#) (cIMT). In a recent study, investigators reported that [impaired fetal growth](#) or low birthweight was inversely associated with cIMT, whereas infants supplemented with n-3 LC-PUFAs from 6 months of age until 5 years exhibited no association between cIMT and birth weight. cIMT is an established [biomarker](#) for predicting future cardiovascular events in some age groups.

In a variation on studies designed to examine impaired fetal growth or low birthweight and subsequent CVD risk factors, Michael Skilton from the University of Sydney and colleagues at several Finnish universities examined the change in cIMT over 6 years and the consumption and serum concentrations of total n-3 PUFAs and DHA in young adults who had experienced impaired fetal growth. Participants were selected from the Cardiovascular Risk in Young Finns Study, a population-based study of atherosclerosis risk factors from childhood to adulthood for whom birth weight and preterm delivery data were available. Dietary data were obtained

27 years after enrolment when the participants were 31 years of age. Measurements of cIMT and serum fatty acids were performed 21 and 27 years after enrolment providing a 6-year interval to observe changes in cIMT. Data were available for 1,573 participants.

Impaired fetal growth was defined as those born at term with a birthweight below the 10th percentile for sex or born preterm with birthweight below the 25th percentile for gestational age and sex. There were 193 participants with impaired fetal growth. This group had significantly higher LDL cholesterol levels, triglycerides, high-sensitivity C-reactive protein and cIMT at the 21-year assessment.

In the analysis adjusted for the greatest number of confounding variables (dietary, CVD risk factors and medications), dietary consumption of total n-3 PUFAs was significantly and inversely associated with the 6-year progression in the mean and maximum cIMT in participants with impaired fetal growth ($P = 0.01$). Similarly, serum n-3 PUFAs and DHA were inversely associated with the 6-year change in the maximum cIMT. The study showed clearly that higher consumption of n-3 PUFAs, which leads to higher serum n-3 PUFA concentrations, was associated with a reduction in cIMT measurements in young adults. However, the association with serum n-3 PUFAs was not statistically significant when adjusted for CVD risk factors.

Participants with normal fetal growth showed no association between the 6-year change in maximum cIMT and dietary intakes or serum concentrations of n-3 PUFAs. On the other hand, serum DHA concentration was inversely associated with the 6-year increase in cIMT in those with normal fetal growth.

Impaired fetal growth and low birthweight may be viewed as markers for [increased CVD risk factors](#) in childhood and greater risk of CVD later in life. Evidence for these risks is based on the associations between impaired fetal growth and [early thickening](#) of the

Young adults with impaired fetal growth had increased carotid intima-media thickness (cIMT), a risk factor for heart disease. Those with higher intakes of n-3 PUFAs over 6 years experienced a significant decrease in their average and maximum cIMT values compared with those with normal fetal growth.

arterial wall at the age of 8 years, elevated blood lipids, impaired flow-mediated dilatation and increased cIMT. Some of these risk factors can be mitigated by the increased consumption of n-3 PUFAs, as demonstrated in this study and [another](#) on early arterial wall thickening.

There was no effect of total n-3 PUFA consumption in participants with normal fetal growth, but DHA intake was associated with lower cIMT. It is noted that in at least 2 studies in children or young adults, increased consumption of n-3 PUFAs was associated with a regression of carotid intima-media thickness, but in adults, only [one study](#) has reported a decrease in cIMT with the consumption of EPA and several have reported no effect of n-3 PUFA consumption. One might ask whether the increased cIMT in young adults is more plastic than in older adults, and thus more amenable to dietary intervention. It will take more data to answer this question. These reports suggest that childhood is not too soon to increase the consumption of these fatty acids to reduce the risk of CVD in adulthood. These observations also increase the imperative of preventing low birthweight deliveries.

Skilton MR, Mikkilä V, Würtz P, Ala-Korpela M, Sim KA, Soininen P, Kangas AJ, Viikari JS, Juonala M, Laitinen T, Lehtimäki T, Taittonen L, Kähönen M, Celermajer DS, Raitakari OT. Fetal growth, omega-3 (n-3) fatty acids, and progression of subclinical atherosclerosis: preventing fetal origins of disease? The Cardiovascular Risk in Young Finns Study. Am J Clin Nutr 2013;97:58-65. [PubMed]

Table. Relationship between dietary n-3 PUFA consumption and 6-year change in cIMT in 31-year-old adults who experienced impaired or normal fetal growth

Change in cIMT*	Impaired fetal growth	P	Normal fetal growth	P
Dietary n-3 PUFAs				
6-yr change in mean cIMT	-68 (-124 to -13)	0.02	4 (-14 to 22)	0.65
6-yr change in max cIMT	-75 (-134 to -16)	0.01	5 (-14 to 24)	0.58

*Dietary n-3 PUFA data log-transformed; results are changes in cIMT associated with a 100% increase in dietary n-3 PUFAs under isocaloric conditions

Heart failure

Higher EPA Linked to Lower Cardiovascular Mortality in Chronic Heart Failure

Chronic heart failure greatly increases the risk of death. Emerging evidence suggests that higher blood levels of EPA, but not DHA, may reduce the risk of mortality in these patients.

In chronic [heart failure](#), a person's heart is unable to pump sufficient blood to meet the body's needs. As a result, the individual experiences shortness of breath, fatigue and swollen ankles, feet and legs. In 2008,

about [5.7 million U.S. patients](#) experienced heart failure, a leading cause of hospitalization. Approximately half those diagnosed with heart failure will die within 5 years. Yet, the heart failure [hospitalization rate fell](#) 29% between 1998 and 2008, mainly because fewer patients were hospitalized with the condition. One-year mortality rates also fell. In spite of some improvements, heart failure is a major burden on personal health and medical costs.

[Risk](#) of heart failure is greater among those with previous heart disease, diabetes, high blood pressure, hypercholesterolemia, overweight and obesity, smoking and arrhythmias. Preventing or controlling these factors could substantially reduce the occurrence of heart failure. However, dietary strategies involving higher intakes of long-chain omega-3 PUFAs (n-3 LC-PUFAs) may improve the prognosis of patients with chronic heart failure. Older individuals without heart disease who have higher levels of circulating n-3 LC-PUFAs or EPA (but not DHA) were [less likely](#) to develop congestive heart failure, but others reported [no relationship](#) between fish consumption or the consumption of n-3 LC-PUFAs and the risk of heart failure. In contrast, n-3 LC-PUFA consumption was associated with a significantly [lower risk](#) of heart failure in Swedish men with no history of heart failure, myocardial infarction or diabetes. In a secondary prevention trial, treatment of patients with chronic heart failure with approximately 1 g/day of n-3 LC-PUFAs for a median of 3.9 years resulted in a small, but statistically [significant reduction](#) in mortality and cardiovascular hospital admissions.

In this report, the GISSI-HF investigators enrolled 1,203 patients with chronic, stable heart failure in a multicenter study to evaluate the effects of usual and supplementary n-3 LC-PUFA consumption on biomarkers of inflammation, metabolism and cardiac stress in a 3-month trial. The supplement consisted of 850 to

882 mg of EPA + DHA, ratio 1.2:1. Control patients were given a placebo capsule. All patients received pharmacologic therapies for their medical condition. The investigators measured plasma n-3 LC-PUFA concentrations, adiponectin, C-reactive protein, pentraxin-3 (an acute phase response protein found in [atherosclerotic lesions](#) involving macrophages, neutrophils, dendritic cells or smooth muscle cells), n-terminal probrain natriuretic peptide (a biomarker for systolic/diastolic dysfunction and the risk of mortality) and high-sensitivity cardiac troponin T. Pentraxin-3 has been suggested as a [biomarker](#) for inflammatory cardiovascular disease.

As expected, plasma phospholipid levels of n-3 LC-PUFAs were associated with the frequency of eating fish. Baseline EPA and DHA levels were more than twice as high in patients in the highest tertile of fish consumption (3 or more times per week) compared with those in the lowest third. Baseline EPA and DHA concentrations ranged from 0.55 mol% to 1.31 mol% and 2.22 mol% to 4.63 mol%, respectively, across the three tertiles of n-3 LC-PUFA consumption. After 3 months' n-3 LC-PUFA supplementation all plasma n-3 LC-PUFA concentrations increased significantly, while n-6 PUFAs decreased by 5%. Supplementation also increased the concentration

Heart failure patients who ate fish 3 or more times per week or consumed long-chain omega-3 supplements had higher circulating levels of these fatty acids. Those with the highest EPA levels had a significantly lower risk of dying from any cause or from cardiovascular disease compared with those having the lowest EPA levels.

of EPA, DHA and total n-3 LC-PUFAs in plasma phospholipids, regardless of the amount of fish consumed. However, DHA increased in plasma phospholipids most in those who almost never ate fish and least in those who ate fish 3 or more times per week ($P = 0.03$).

Baseline levels of circulating EPA, but not DHA, were inversely associated with all the biomarkers assessed.

Supplementation with EPA and DHA for 3 months led to a further significant decrease in the concentration of pentraxin-3, which was associated with higher levels of EPA, but not with DHA. Supplementation was not associated with changes in any other biomarker.

Circulating levels of EPA, but not DHA or total n-3 LC-PUFAs, were associated with a significantly lower risk of all-cause and cardiovascular mortality

(Figure). These associations remained significant after adjustment for anthropometric, clinical, laboratory values and medications, but not after additional adjustment for circulating biomarkers.

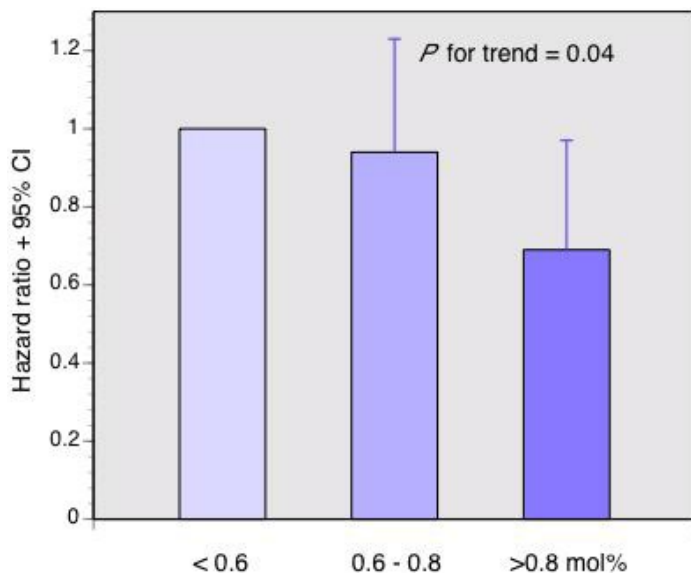


Figure. Risk of cardiovascular mortality (hazard ratios) by tertiles of circulating plasma EPA in patients with stable chronic heart failure. Analysis was adjusted for age, sex and laboratory values.

The key finding in this study is the association between higher circulating levels of EPA with a significantly lower risk of all-cause and cardiovascular mortality in patients with chronic heart failure. Mortality was not associated with circulating DHA concentrations. Regardless of fish consumption, even at levels of 3 times per week, circulating and phospholipid concentrations of n-3 LC-PUFAs were increased by supplementation with about 1 g per day of EPA + DHA in heart failure patients. In addition, higher levels of plasma EPA were associated with significantly lower concentrations of [pentraxin-3](#), an inflammatory biomarker involved in the pathogenesis of atherosclerosis and ischemic heart disease. Although this marker is associated with the development of vascular inflammation and atherosclerosis, it has been suggested that its increase in atherosclerosis may be a [protective response](#). Thus, decreases in pentraxin-3 levels with higher levels of EPA may be complicated to interpret. This study increases the evidence that EPA and DHA may affect cardiovascular disease through different mechanisms.

Masson S, Marchioli R, Mozaffarian D, Bernasconi R, Milani V, Dragani L, Tacconi M, Marfisi RM, Borgese L, Cirrincione V, Febo O, Nicolis E, Maggioni AP, Tognoni G, Tavazzi L, Latini R. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: Relation with fish intake, circulating biomarkers, and mortality. Am Heart J 2013;165:208-215. [PubMed] Open Access

Higher EPA and DHA Linked to Lower Risk of Heart Failure and Mortality After Myocardial Infarction

As evidence accumulates that n-3 LC-PUFAs may reduce the risk of developing heart failure, investigators in Japan were curious whether n-3 LC-PUFA levels might be related to the occurrence of heart failure after an

Long-chain omega-3 PUFAs may reduce the risk of developing heart failure in healthy adults. Whether they are related to the risk of heart failure after an acute myocardial infarction has not been explored until now.

acute myocardial infarction. Existing cardiovascular disease is associated with a higher risk of developing heart failure. The researchers recruited 712 participants from those enrolled in the Osaka Acute Coronary Insufficiency Study, a multicenter prospective study on patients with an

acute myocardial infarction. The study was designed to determine whether serum n-3 LC-PUFA levels were associated with how long patients remained free from heart failure after their infarction.

Participants in the study were mostly male (78%), 65 years of age on average, likely to have hypertension (67%) and smoke (63%). Approximately 10% of participants had a previous myocardial infarction. Blood samples were taken within 10 days of the onset of myocardial infarction to avoid the effects of acute phase responses and 3, 6 and 12 months thereafter. The investigators monitored the participants for 5 years. The primary outcome was duration of survival without heart failure, with hospitalization for heart failure and all-cause mortality as secondary outcomes. Patients were grouped according to baseline tertiles of serum EPA and DHA concentrations. The DHA tertiles were: low, $\leq 61.4 \mu\text{g/mL}$; intermediate, 61.5 to 83.5 $\mu\text{g/mL}$; high, $> 83.5 \mu\text{g/mL}$. Corresponding tertiles for EPA were: low, $\leq 24.6 \mu\text{g/mL}$; intermediate, 24.7 to 38.8 $\mu\text{g/mL}$; high, $> 38.8 \mu\text{g/mL}$.

As shown in the Figure, survival rates free from heart failure were significantly greater for patients in the highest 2 tertiles of either EPA or DHA compared with those in the lowest tertile. Risk of hospitalization for heart failure was also greatest in patients in the lowest EPA tertile, but all-cause mortality was highest for those in the lowest DHA tertile. These findings for heart failure support those of one other study that reported a significantly [lower risk](#) of incident heart failure in adults without heart disease who had the

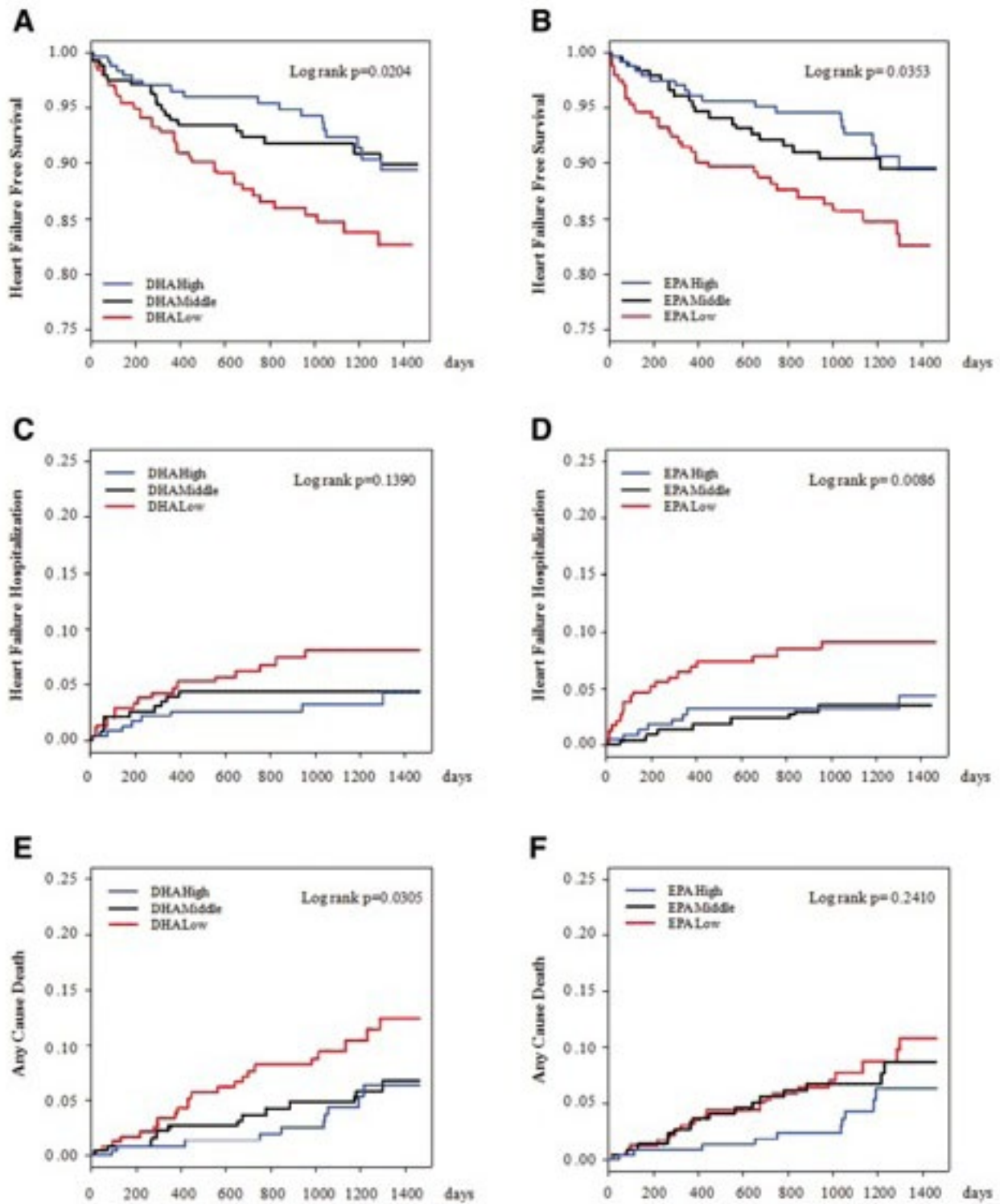


Figure. Kaplan-Meier survival and event rates for (A, B) survival free of heart failure, (C, D) hospitalization for heart failure and (E, F) all-cause mortality by tertiles of serum DHA (left panels) and EPA (right panels) in 712 survivors of acute myocardial infarction. Image ©2013 by the Japanese Circulation Society. Reproduced with permission from Hara M *et al*, *Circ J* 2013;77:153-162.

highest levels of plasma phospholipid EPA. In that study, low DHA levels were not associated with the risk of heart failure.

Taken together, these studies demonstrate a benefit of n-3 LC-PUFAs on the outcomes of heart failure following

myocardial infarction. In addition, another study reported improvements in [ejection fraction](#) in heart failure patients with higher levels of n-3 LC-PUFAs. As shown in the current study, EPA in particular may benefit those at risk of heart failure for any reason or because of a myocardial infarction. A reduced risk of heart failure was observed in

Following a myocardial infarction, patients with the highest levels of EPA and DHA in their blood survived significantly longer without developing heart failure compared with patients in the lowest third of EPA and DHA. They were also less likely to die from any cause.

myocardial infarction survivors with plasma EPA levels of at least 24.7 µg/mL. Low DHA levels were associated with a higher risk of all-cause death. Thus, higher rather than lower levels of EPA and DHA may be beneficial in reducing the risk of heart failure, hospitalization for

Maternal diets in pregnancy have been linked to health effects and obesity in the offspring in childhood and beyond. A new study examined the association between maternal fatty acids and body composition in the offspring.

have been associated with greater [adiposity](#) in the child. [Catchup growth](#) after intrauterine growth restriction has been associated with alterations in the expression of insulin-signaling proteins, which may foreshadow insulin resistance. Western-style [diets high in linoleic acid](#) have been associated with greater fat mass

heart failure and death from any cause in patients who have incurred an acute myocardial infarction.

*Hara M, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Hamasaki T, Doi Y, Nishino M, Sato H, Kitamura T, Nanto S, Hori M, Komuro I; Osaka Acute Coronary Insufficiency Study (OACIS) Investigators. Low levels of serum n-3 polyunsaturated fatty acids are associated with worse heart failure-free survival in patients after acute myocardial infarction. *Circ J* 2013;77:153-162. [[PubMed](#)] [Open Access](#)*

Worth Noting

*Gustafson KM, Carlson SE, Colombo J, Yeh H-W, Shaddy DJ, Li S, Kerling EH. Effects of docosahexaenoic acid supplementation during pregnancy on fetal heart rate and variability: A randomized clinical trial. *Prostaglandins Leukot Essent Fatty Acids* 2013; doi:10.1016/j.plefa.2013.01.009 [[PubMed](#)]*

*Kelsall CJ, Hoile SP, Irvine NA, Masoodi M, Torrens C, Lillycrop KA, Calder PC, Clough GF, Hanson MA, Burdge GC. Vascular dysfunction induced in offspring by maternal dietary fat involves altered arterial polyunsaturated fatty acid biosynthesis. *PLoS One* 7:e34492. doi:10.1371/journal.pone.0034492. [[PubMed](#)] [Open Access](#)*

*Skilton MR, Raitakari OT, Celermajer DS. High intake of dietary long-chain ω-3 fatty acids is associated with lower blood pressure in children born with low birth weight: NHANES 2003-2008. *Hypertension* 2013;61:972-976. [[PubMed](#)]*

■ MATERNAL AND INFANT HEALTH

Plasma Levels of n-6 PUFAs in Pregnancy Associated with Greater Fat in Offspring

The effects of maternal diet and nutrition during pregnancy may reach into adulthood in the offspring. For example, maternal under- or over-nutrition and diabetes

in successive generations of experimental animals and [may be implicated](#) in human obesity. The effects on body composition of maternal and infant consumption of long-chain omega-3 PUFAs (n-3 LC-PUFAs) are [inconsistent](#). Supplementation of pregnant women with n-3 LC-PUFAs during pregnancy and lactation has generally shown no association with body mass index or skinfold thickness in the offspring through 19 years of age.

Investigators at the University of Southampton, U.K., conducted a [study of healthy nonpregnant women](#) aged 20 to 34 years to characterize preconceptional maternal factors with the potential to affect fetal growth and development and monitored the development of the offspring of all pregnancies. This report focused on the relationship between maternal PUFAs in late pregnancy and the body composition of the children. From a total of 1,987 singleton live births, 293 mother-child pairs completed the assessment of maternal plasma phosphatidylcholine (PC) fatty acids at 34 weeks' gestation and anthropometric measurements in the children at ages 4 and 6. The researchers measured the children's body composition using dual-energy x-ray absorptiometry from which lean and fat mass were calculated.

Boys and girls were similar in height and weight at 4 and 6 years of age, but girls had significantly greater fat mass and less lean mass than boys at both ages. Some maternal PUFAs were significantly related to the children's height and weight at 4 and 6 years of age, but these associations were not statistically significant when the analysis was adjusted for maternal age, parity, social class and 8 other variables. Maternal total and individual n-3 PUFAs were not associated with the children's height, weight, fat or lean mass at either age in multivariate analysis. The investigators observed a trend toward a positive association between maternal n-3 PUFAs and EPA and the child's height at age 4, but these associations were not observed in multivariate analysis. The observation with total n-3 PUFAs and height was significant at age 6, however (Table).

Table. Associations (β -coefficients \pm 95% CI†) between maternal plasma PC n-6 and n-3 PUFAs at 34 weeks' gestation and offspring body composition at 6 years

Maternal fatty acid	Height	Weight	Fat mass	Lean mass
<i>n-6 PUFAs</i>				
Total	0.09 (-0.03 – 0.22)	0.07 (-0.01 – 0.15)	0.11 (0.01 – 0.22)*	0.01 (-0.06 – 0.08)
LA	0.08 (-0.04 – 0.20)	0.07 (-0.01 – 0.15)	0.13 (0.02 – 0.23)*	0.01 (-0.07 – 0.08)
ARA	0.09 (-0.03 – 0.21)	0.06 (-0.02 – 0.14)	0.07 (-0.03 – 0.18)	0.03 (-0.05 – 0.10)
<i>n-3 PUFAs</i>				
Total	0.12 (0.00 – 0.24)*	0.07 (-0.01 – 0.15)	0.07 (-0.04 – 0.18)	0.04 (-0.04 – 0.11)
EPA	0.12 (-0.01 – 0.24)	0.04 (-0.04 – 0.12)	0.00 (-0.11 – 0.11)	0.05 (-0.03 – 0.12)
DHA	0.11 (-0.01 – 0.24)	0.07 (-0.01 – 0.15)	0.07 (-0.04 – 0.18)	0.04 (-0.03 – 0.11)

† β -coefficients \pm 95% CI, relative change in SD of outcome for each SD change in predictor.

*Statistically significant in multivariate analysis, $P < 0.05$.

In contrast, maternal plasma PC total n-6 PUFAs and linoleic acid were significantly associated with greater fat mass and percent fat mass in the multivariate analysis of children at both 4 and 6 years of age (Table).

Maternal plasma total n-6 PUFAs and linoleic acid were significantly associated with greater fat mass and percent fat mass in the offspring at 4 and 6 years of age.

Only total n-6 PUFAs did not reach statistical significance in the adjusted analysis of the percent fat mass in 6-year-old children. Arachidonic acid was not associated with any body composition measurement in the adjusted analysis of children at both ages.

Lean body mass was not associated with any maternal PUFA in multivariate analysis, but percent lean mass was significantly lower with higher maternal linoleic acid in the adjusted analysis at both ages.

The observation that maternal plasma PC n-6 PUFAs and linoleic acid were associated with greater adiposity in the offspring at age 4, which persisted to age 6, suggests that prenatal exposure to n-6 PUFAs in the presence of low concentrations of n-3 LC-PUFAs might increase the risk of childhood obesity. Such a relationship has been demonstrated in [animals](#), but was [not observed](#) in a U.S. pregnancy cohort. However, high intakes of linoleic acid have been postulated as an [early determinant](#) of childhood obesity. It will be worth watching to see whether the risk of obesity is greater in the offspring of mothers with higher concentrations of n-6 PUFAs when they are older. It would be noteworthy, too, if these observations were confirmed in other studies, especially those using dual x-ray absorptiometry to assess body fat. Whether these associations

would be observed in the presence of higher maternal concentrations of n-3 LC-PUFAs is also unknown.

Moon RJ, Harvey NC, Robinson SM, Ntani G, Davies JH, Inskip HM, Godfrey KM, Dennison EM, Calder PC, Cooper C; the SWS Study Group. Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood. J Clin Endocrinol Metab 2013;98:299-307. [PubMed]

Obesity Associated with Lower n-3 PUFAs, EPA and DHA in Breast Milk

Factors associated with childhood obesity may relate to conditions *in utero*. For instance, [maternal obesity](#) in pregnancy and [excess gestational weight gain](#) have been associated with greater fat mass and percent body fat in the neonate. As suggested in the preceding article, a child's greater fat mass may also be related to

Little is known about the fatty acid and long-chain PUFA composition of breast milk in normal-weight and obese mothers. This study compared the fatty acids in obese and normal-weight mothers through 2 months postpartum.

the mother's plasma n-6 PUFA and linoleic acid concentrations in late pregnancy. [Low birthweight](#) has also been associated with a higher risk of central obesity in adulthood. On the other hand, [breastfeeding](#) has been associated with a lower risk of childhood overweight and obesity. The [lower](#)

[protein](#) content of breast milk compared with infant formula may be one reason why breastfeeding is less conducive to childhood overweight.

More recently, a greater exposure to n-6 PUFAs in the presence of relatively low amounts of n-3 PUFAs has been associated with increased adiposity and fat mass in animals and humans (see preceding article). Maternal dietary fatty acid patterns are reflected in the fatty acid composition of breast milk, which generally reflect the abundant consumption of n-6 PUFAs and low intakes of long-chain (LC) n-3 PUFAs. The abundance of n-6 PUFAs might not be a worry were it not for their [links to obesity](#) and their ability to [reduce](#) the incorporation of n-3 LC-PUFAs into tissues.

In this report, investigators at the Karolinska Institute, Sweden, compared the fatty acid composition of the breast milk from normal-weight and obese nondiabetic mothers along with the plasma phospholipids of their infants. A subgroup of obese mothers participated in a weight control program during pregnancy. Mother-infant pairs were excluded for preterm delivery, multiple births and major infant malformations. Forty-one obese and 41 normal-weight mothers enrolled in the study, with another 29 obese women taking part in the weight control program. Participants were intended to reflect the general population of a medium-high socioeconomic area of Stockholm.

The weight control intervention for women with a BMI >30kg/m² included dietary advice and increased physical activity beginning at the first prenatal visit at 8 to 10 weeks' gestation. The program continued until 6 to 8 weeks postpartum. In Sweden, all pregnant women are advised to eat fish 2 to 3 times a week.

Infant blood samples were collected on the third day after birth. Breast milk samples were obtained after

nursing at days 3 and 10, then 1 and 2 months after birth. Obese mothers were more likely to smoke, deliver by Cesarean section and eat less fish than control mothers.

Infant birth characteristics and neonatal outcomes did not differ among the 3 groups. At 12 months of age, there were no differences in body weight, length and BMI among the infants. At 3 days postpartum, the phospholipid fatty acids in the infants' plasma were higher in linoleic acid in the intervention group compared with the infants of the control or obese mothers. Total n-3 PUFAs and EPA were significantly lower in the infants of obese mothers compared with those of control or intervention mothers.

For breast milk PUFAs, the total n-6 PUFA content was highest in the control group at 3 days postpartum and increased significantly over the 2-month period only in the intervention mothers. Likewise, linoleic concentrations were significantly higher in the control than the obese mothers and increased significantly by 2 months only in the intervention mothers (Table). Arachidonic acid concentrations decreased over the study period in all groups. Total n-3 PUFA concentrations were highest in the control mothers' breast milk and significantly lower in the obese mothers, remaining so over the 2-month period. DHA and EPA concentrations were highest in the control group, lowest in the obese mothers, and decreased in all groups over the study period.

Breast milk fatty acid composition reflects the mother's diet, especially her [fish consumption](#), but can be affected by [genetic factors](#), [smoking](#), [diabetes](#) and [preterm delivery](#). In this study, obesity was accompanied

Table. Breast milk linoleic and docosahexaenoic acids (mol%) from normal-weight, obese and obese mothers on a weight control program at different times postpartum. Data are means ± SEM*

Days	Control	Obese	Weight control
LA			
3	9.99 ± 0.11	8.93 ± 0.08	9.31 ± 0.08
10	11.4 ± 0.09	10.3 ± 0.11	10.4 ± 0.05
30	10.7 ± 0.06	11.1 ± 0.17	10.3 ± 0.09
60	11.0 ± 0.07	9.11 ± 0.08	10.9 ± 0.08
DHA			
3	0.56 ± 0.01	0.30 ± 0.0	0.50 ± 0.02
10	0.46 ± 0.0	0.38 ± 0.0	0.36 ± 0.01
30	0.37 ± 0.01	0.24 ± 0.01	0.59 ± 0.01
60	0.41 ± 0.01	0.22 ± 0.01	0.30 ± 0.01

*Values for LA and DHA differ significantly between control and obese mothers at each time point except 30 days

by a reduction in total n-6 and n-3 PUFAs, and lower linoleic acid and DHA concentrations in breast milk samples obtained at 3 days and 2 months postpartum. The study also reported that weight control intervention among obese women during pregnancy partially restored the PUFA patterns of breast milk toward those observed in normal-weight mothers.

Compared with normal-weight mothers, obese women had significantly lower linoleic acid, EPA and DHA concentrations in their breast milk for the first 2 months after delivery.

The only [other study](#) that compared the fatty acid composition of breast milk between normal, overweight and obese mothers reported a significant increase in total n-6 PUFAs and linoleic acid with increasing BMI. Patterns of n-3 PUFAs, including DHA, did not differ significantly among the three groups. However,

the number of participants in each group was small, with only 9 observations for obese mothers.

The study flags the association of obesity in pregnancy with a significantly lower concentration of n-3 PUFAs, especially EPA and DHA in the mothers' breast milk. When intakes of n-3 LC-PUFAs are already low among women with Western dietary habits, the further apparent reduction in breast milk n-3 LC-PUFAs suggests that pregnant obese women might benefit from counseling to increase their fish and n-3 LC-PUFA consumption and for weight control.

Storck Lindholm ES, Strandvik B, Altman D, Möller A, Kilander CP. Different fatty acid pattern in breast milk of obese compared to normal-weight mothers. Prostaglandins Leukot Essent Fatty Acids 2013;88:211-217. [PubMed]

Worth Noting

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■ IMMUNE FUNCTION

Fish Consumption in Pregnancy: Linked to Less Childhood Asthma

The incidence of asthma has been increasing worldwide and now affects about [193 million](#) individuals globally. In Denmark, the prevalence of asthma [doubled](#) from 5.3% to 11.7% over the period from 1986 to 2001. Recognized

Fish consumption in pregnancy has been associated with a lower risk of childhood asthma, but not in all studies. A large Danish study reported that children whose mothers did not eat fish during pregnancy were significantly more likely to develop asthma at 18 months and 7 years of age than children whose mothers ate fish frequently.

as a heterogeneous condition, asthma often follows persistent childhood wheeze. Among the factors related to the development of asthma, are maternal history of asthma, maternal smoking and [air pollution](#), presence of hay [fever](#), [eczema](#), [female sex](#), [exercise](#) and more recently, [low birthweight](#). Links to maternal diet in pregnancy, especially dietary

fat, have been explored at least since the late 1990s with mixed findings. It has been popular to suggest that dietary changes away from the consumption of n-3 PUFAs toward [higher intakes of n-6 PUFAs](#), specifically linoleic acid, which are frequently pro-inflammatory, have contributed to the rise in asthma. Yet intervention studies to evaluate the effects of maternal PUFA consumption in pregnancy have been inconsistent. Several studies have reported [protective effects](#) of higher maternal fish consumption in pregnancy and childhood wheeze or asthma, while others have found [no effect](#). The potential for higher maternal intakes of fish to reduce the risk of childhood asthma is sufficiently compelling to warrant detailed studies with strong design.

This report analyzes data from the Danish National Birth Cohort, a very large observational study on early life factors and the risk of disease in later life. Of the 101,045 participants originally enrolled, the investigators limited their analysis to the first enrolled pregnancy of women with a singleton birth who did not take fish oil during pregnancy and for whom fish intake data were available. The total number of participants was 28,936. Fish consumption was determined from 2 interviews during pregnancy and the frequency divided into 5 categories: never, monthly or less, weekly, weekly with low frequency and weekly with high frequency, i.e., hot meals or sandwiches more than 5 times per week.

The occurrence of asthma at 18 months of age, as reported by the parent, was defined as a doctor diagnosis, with wheeze considered as wheezing or whistling in the chest. Asthma at age 7 was based on standardized questions, with current asthma being

a positive response to ever having a doctor-diagnosis of asthma and wheezing symptoms in the past 12 months. The investigators also collected all hospital admissions for asthma, emergency room treatments and outpatient contacts from the Danish National Patient Registry. They used the Register of Medical Product Statistics to determine the number of asthma prescription drugs that had been filled.



The investigators noted significant differences in fish consumption with age, with younger mothers less likely to eat fish. Thus, analyses were adjusted for maternal age. Only 5% of women reported eating no fish. The odds ratios for asthma were adjusted only for socioeconomic variables. Interestingly, breastfeeding accounted for the largest reduction in risk of asthma. Because of missing outcome data, 7,643 participants were excluded from the analysis at 18 months of age.

Asthma occurred in 17 percent of children at 18 months of age and wheeze in 27%. Multivariate analysis of asthma and wheeze at 18 months of age showed that never eating fish during pregnancy was associated with a 30 percent greater risk of childhood asthma compared with eating fish several times per week (OR = 1.30, 95% CI, 1.05 – 1.63, $P = 0.02$). Wheeze was not associated with maternal fish consumption.

Eating fish 5 times per week or more in pregnancy was associated with a significantly lower risk of doctor-diagnosed asthma in children at 18 months and 7 years of age. Fish consumption was not associated with wheeze.

At the age of 7, asthma was present in 6 percent of children as defined above and 31 percent according to hospital admission and prescription data. About 4 percent of children were considered to have current

asthma. As at the earlier age, children whose mothers never ate fish during pregnancy were more likely to have an asthma diagnosis by hospital admission (OR = 1.46, 95% CI, 0.99 – 2.13, $P = 0.05$). The relationship for current asthma was in the same direction but did not reach statistical significance.

This study documented a significant relationship between higher consumption of fish during pregnancy and a lower risk of doctor-diagnosed asthma at 18 months and 7 years of age, about the time that [asthma peaks](#). Maternal fish consumption was not associated with childhood wheeze or allergic rhinitis. The associations between asthma and maternal fish consumption were significant when doctor-diagnosis, hospital admission or prescription asthma medicine were assessed, but not for self-reported asthma. Another interesting finding was the protective effect of longer breastfeeding, i.e., for 7 to 9 months or longer. Women who breastfed longer were more likely to consume fish frequently, but the two factors were only modestly correlated. The investigators found no association between childhood asthma and dietary n-3 PUFA intakes based on food frequency questionnaire data, nor with early childhood fish consumption. This study supports other reports in which higher fish consumption in pregnancy was associated with a lower risk of childhood asthma.

Maslova E, Ström M, Oken E, Campos H, Lange C, Gold D, Olsen SF. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. Br J Nutr 2013; Mar 8:1-13. [PubMed]

Fish Consumption in Infancy: Associated with Less Childhood Wheeze

Evidence for a relationship between a mother's consumption of fish, especially fatty fish, during pregnancy

Maternal fish consumption in pregnancy may reduce the risk of childhood wheeze and asthma, but the evidence is inconsistent. Two reports from a large observational study in The Netherlands examined maternal and infant fish consumption related to childhood wheeze.

and the risk of her child developing asthma in childhood is inconsistent. Consumption of [fish oil](#) during pregnancy was associated with a significantly lower rate of allergic asthma at age 16 years. Some studies reported a [lower occurrence](#) of

wheeze or asthma in early childhood or decreased severity of the condition among infants and children at high-risk of developing asthma, but others observed [no effect](#). A few studies reported a lower risk of asthma or [other atopic diseases](#) in early childhood with fish consumption in the first year of life. Thus, there are questions about the effectiveness of fish or long-chain n-3

PUFA (n-3 LC-PUFA) consumption on the risk of asthma or wheeze, the best timing for exposure to fish or n-3 LC-PUFAs, and the dose or frequency of eating fish. Two new observational studies examined the relationship between fish consumption either in pregnancy or the first year of life and asthmatic symptoms or wheezing in childhood. Both reports are based on the Generation R birth cohort in Rotterdam, The Netherlands.

In the first, the investigators looked at maternal fish consumption in pregnancy and the risks of wheezing or eczema in childhood in the first 4 years of life. They focused on the types of fish and frequency of seafood consumption. Participants included 2,796 mothers whose fish consumption was assessed during the first trimester of pregnancy. Fish categories included total, fatty, lean and shellfish. On average, mothers ate 83 g (3 oz) of fish per week, with nearly 19% of women not eating any fish. Thirty-eight percent of mothers had a history of asthma or atopy.

This study provides no evidence that maternal fish consumption of any type in pregnancy is associated with a lower risk of childhood wheezing or eczema. It raises the question of whether eating small amounts of shellfish increases the risk of childhood eczema.

There was no association between the consumption of all fish or fatty fish during pregnancy with childhood wheezing from ages 1 to 4 years in multivariate-adjusted analysis. However, at age 3, a higher intake of lean fish was associated with a lower risk of

wheezing, with a significant trend for less wheezing as fish consumption increased. In contrast, eating 1 to 13 g (< ½ oz) per week of shellfish, but not larger amounts, was linked to a significantly higher risk of wheezing in the first 4 years of life. The investigators also observed a higher risk of eczema in infants whose mothers ate 35 to 69 g of fatty fish per week (~1 to 2.5 oz per week), but risk was not greater with higher intakes. Eating small amounts of shellfish (1 to 13 g/week) was also associated with a higher risk of eczema, but the association was not observed with intakes above 14 g per week (½ oz). Stratification by maternal history of asthma or atopy abolished the statistical significance of the associations with eczema, but not for asthma.

This study provides little evidence that maternal fish consumption of any type in pregnancy is associated with a lower risk of childhood wheezing or eczema. Instead, it raises the question of whether consuming fatty fish

or a small amount of shellfish in the first trimester increases the risk of eczema. These observations have not been previously reported and need confirmation in other studies before they can be considered reliable.

In the second report, the investigators looked at the relationship between the timing of the introduction of fish into a child's diet and asthma-like symptoms at 36 or 48 months of age. There is some evidence that introducing fish into the child's diet before the age of 1 year is associated with a lower risk of [recurrent wheeze](#). Others reported a [lower occurrence](#) of allergic disease in children who consume fish before their first birthday. However, parents may hesitate to introduce fish into the child's diet too early because of the risk of fish allergy.

Children who first ate fish between the ages of 6 and 12 months were significantly less likely to experience wheeze at 48 months of age compared with those who did not eat any fish.

These findings are based on nutritional and medical data for 7,210 children obtained using a food frequency questionnaire when the child was 14 months of age. Parents were twice asked how old the child was when first given fish. Fish

was defined as fatty fish, other fish, including fish fingers, and white fish and consumption categories were none, less than half a serving per week or at least half a serving per week. The categories of introducing fish into the diet in the first year of life were never, 0 to 6 and 6 to 12 months. The presence of wheeze and shortness of breath was determined by questionnaire when the children were 36 and 48 months of age. Agreement with physician diagnosis was 75%.

In this population, only 0.1% of the children did not eat any fish at 14 months of age. Those who ate fish in the first year of life ate more fish at 14 months of age than those who were introduced to fish after 1 year of age. Children who first ate fish between 6 and 12 months of age were significantly less likely to experience wheezing at 48 months of age compared with children who did not eat fish in their first year (Table). Wheezing at 36 months of age was also lower in this group, but the difference was not statistically significant.

In contrast to these observations, the prevalence of wheeze at 48 months of age was greater in children whose fish introduction was between 0 and 6 months of age and in those who did not eat fish when compared with children given fish between 6 and 12 months of age. The amount and type of fish consumed

Table. Association between the timing of introducing fish into an infant's diet and the occurrence of wheeze at 36 or 48 months of age

When fish was added to an infant's diet	Multivariate Odds Ratio*	P
Wheezing at 36 mo		
Never in first year	Reference	
0 to 6 mo	1.31 (0.53 – 3.29)	0.48
6 to 12 mo	0.72 (0.51 – 1.03)	0.07
Wheezing at 48 mo		
Never in first year	Reference	
0 to 6 mo	0.98 (0.6 – 1.59)	0.92
6 to 12 mo	0.64 (0.43 – 0.94)	0.03

*Adjusted for maternal age, BMI, alcohol and smoking during pregnancy and 13 other variables

was unrelated to the risk of wheeze. Although these findings do not provide conclusive answers to questions about the early consumption of fish and the risk of asthma-like symptoms, they confirm previous reports of a lower risk of wheeze in children who eat fish in the first year of life. In addition, they suggest that fish is best introduced between 6 and 12 months of age and that consumption before 6 months of age confers no advantage and might increase the risk of wheeze.

Taken together, these studies suggest that a lower risk of childhood wheeze is associated with fish consumption between 6 and 12 months of age and that maternal fish consumption during pregnancy is not associated with the risk of wheeze in childhood.

Leermakers ET, Sonnenschein-van der Voort AM, Heppe DH, de Jongste JC, Moll HA, Franco OH, Hofman A, Jaddoe VW, Duijts L. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: The Generation R Study. Eur J Clin Nutr 2013;67:353-359. [PubMed]

Kiefte-de Jong JC, deVries JH, Franco OH, Jaddoe VW, Hofman A, Raat H, de Jongste JC, Moll HA. Fish consumption in infancy and asthma-like symptoms at preschool age. Pediatrics 2012;130:1060-1068. [PubMed] Open Access

n-3 LC-PUFA But Not Fish Intakes in Young Adults: Linked to Lower Risk of Asthma

The [prevalence of asthma](#) in the U.S. increased from 7.3 to 8.2% during 2001 to 2009, and now afflicts about 25 million persons, or 1 in 12. On a [global basis](#), some 193 million adults suffer from asthma. The prevalence is

highest in the Americas and among poor U.S. children at 13.5%. Only about one-third of U.S. individuals with asthma use long-term medications to control their condition, indicating substantial need for improved health care. A combination of environmental factors and genetics contributes to the condition. In susceptible individuals, allergens such as pollen, strenuous exercise, respiratory infections, cold air, air pollutants and other factors can be involved. Although various medications offer effective treatment, there are few ways to reduce the occurrence of asthma.

Prenatal and childhood exposures to long-chain n-3 PUFAs may reduce the risk of asthma in childhood and beyond. Data on prenatal exposures are inconsistent, but some data among adults suggest beneficial links. This observational study examined dietary n-3 PUFA consumption and the 20-year risk of asthma in young U.S. adults.

Prenatal influences and [epigenetics](#)—heritable changes in gene expression caused by chemical modifications in a chromosome—have emerged as important contributors to the development of asthma and allergic diseases, especially in high-risk infants. The [mother's allergic](#) and asthma status also has a strong influence on the

development of allergic disease in the infant. Exposures during [fetal and early infant life](#) have become the center of studies on the development of asthma and other allergic diseases. The involvement of n-3 LC-PUFAs in the development of asthma receives considerable attention because of the anti-inflammatory effects of these PUFAs, their relatively low intakes during pregnancy and their ability to modify immune development during fetal life. [Observational data](#) suggest that children whose mothers ate more fruits, vegetables and oily fish weekly during pregnancy were significantly less likely to develop asthma at the age of 3 years.

Studies in which pregnant women have consumed n-3 LC-PUFA supplements or DHA have produced inconsistent results. Some have reported a [significant reduction](#) in the occurrence of asthma, while others observed [no effects](#). A recent systematic [review](#) reported that n-3 LC-PUFA supplementation in pregnancy was associated with a significant reduction in childhood asthma in 2 trials. A primary health care [intervention](#) in Norway to reduce childhood allergies reported that increased oily fish and n-3 LC-PUFA consumption along with a reduction in smoking during pregnancy and early childhood

was associated with a significant reduction in asthma in the offspring at the age of 2. The reduction in asthma was particularly dramatic in girls.

Weekly fish intake associated with fewer asthmatic symptoms in Norwegian adults, and higher n-3 PUFA intakes were linked to improved asthma control in a Portuguese study. In Japan, fish consumption was associated with a higher risk of asthma.

In adults, studies on fatty acids and asthma have been inconsistent. A prospective study among adult women reported [no association](#) with intakes of linoleic or n-3 PUFAs. Similarly, plasma n-3 PUFAs were [not associated](#) with the risk of asthma in young adults. An [observational study](#) of dietary patterns in

3 European countries reported that neither the intake of fish, fruits and vegetables, nor meats and potatoes, was associated with the risk of asthma in adults. In Japan, the consumption of fish 1 to 2 times per week was associated with a higher risk of asthma in children 6 to 15 years of age. In contrast, middle-aged adults with higher intakes of n-3 PUFAs and alpha-linolenic acid had [improved asthma control](#), while a high ratio of n-6:n-3 PUFA was linked to a greater risk of uncontrolled asthma. In Norway, weekly fish intake among adults was associated with [fewer asthmatic symptoms](#) and those who never ate fish in childhood experienced a greater risk for asthma. Fish oil supplementation in exercise-induced bronchoconstriction in asthmatic athletes was associated with [improved pulmonary function](#) and less use of bronchodilator therapy.

Investigators at the University of North Carolina, U.S., and other American institutions, examined data from the Coronary Artery Risk Development in Young Adults study to assess the relationship between the consumption of fish and n-3 LC-PUFAs and the 20-year incidence of asthma. Participants were African American and white men and women aged 18 to 30 recruited from 4 U.S. cities in 1985 to 1986. They were monitored until 2005 and provided dietary, medical and demographic information and blood samples. Participants were excluded if data were missing on n-3 LC-PUFA consumption, asthma, key factors such as smoking and alcohol consumption and if energy intakes were implausible or participants were pregnant. A total of 4,162 individuals were assessed.

Asthma was identified by physician diagnosis or the use of asthma-control medicine at any follow-up exam.

Long-term n-3 LC-PUFA consumption was determined using cumulative average intakes from 3 follow-up assessments over the course of the study. For analysis, participants were divided into quintiles by n-3 LC-PUFA intake, with consumption ranging from ≤ 0.050 g/day in the lowest group to ≥ 0.24 g/day in the highest quintile. Three hazard regression models were developed, each adjusting for additional confounding variables. Controlling for the most confounding variables, the investigators reported that the 20-year risk of incident asthma was significantly lower with increasing consumption of total n-3 LC-PUFAs, EPA and DHA, with the strongest effect (HR = 0.30, 95% CI, 0.22 to 0.41) observed for the highest quintile of DHA intake (Figure). Non-fried fish consumption was not associated with risk of asthma.

In a sub-analysis, the investigators explored the effect of n-6 PUFA intakes on the risk of asthma. Consumption of n-6 PUFAs weakened the lower risk associated observed with n-3 LC-PUFA intakes, but the trend for reduced asthma risk remained significant for n-6 PUFA intakes below the median. With n-6 PUFA intakes above the median, the trend for reduced risk observed with n-3 PUFAs did not reach statistical significance ($P = 0.06$). This finding suggests that higher intakes of n-6 PUFAs interfere with or counteract the protective effects of higher n-3 LC-PUFA consumption on the risk of asthma.

Asthma appears responsive to higher intakes of n-3 LC-PUFAs, which have anti-inflammatory properties. The observation that higher levels of DHA were associated with lower risks compared with EPA is consistent with

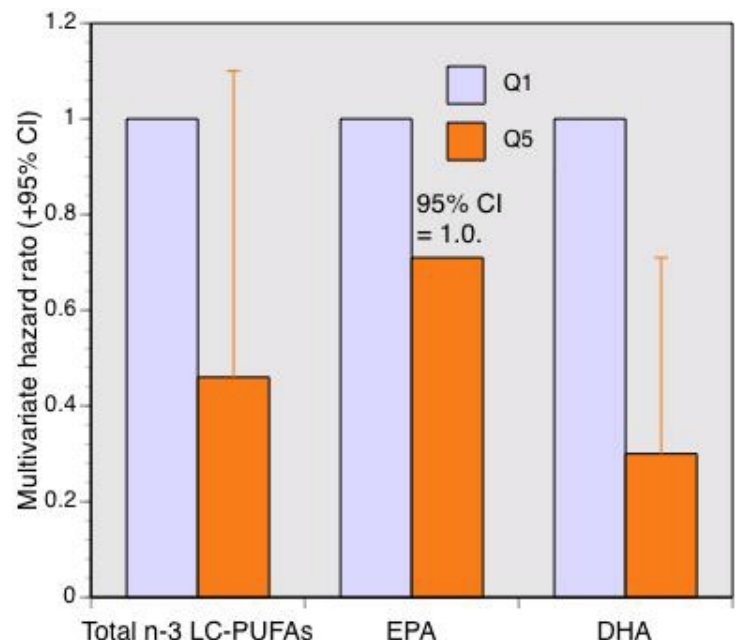


Figure. Risk of asthma by cumulative intakes (quintiles) of total n-3 LC-PUFAs, EPA and DHA in young U.S. adults.

other studies reporting the [greater potency of DHA](#) in weakening inflammatory responses. As this study observed, intakes as little as 240 mg per day, the amount some recommend for reducing the risk of cardiovascular disease, might also reduce the risk of asthma in adults.

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MENTAL HEALTH & COGNITION

High-Dose DHA-Rich Fish Oil May Improve Memory in Early Cognitive Impairment

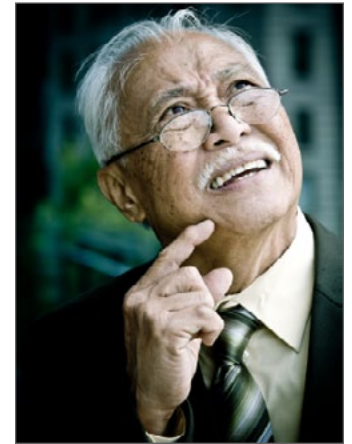
Many characteristics of Alzheimer's disease are agreed, but the origins, cause, physiological processes and

Mild cognitive impairment is one of the first clinical symptoms of dementia, but not everyone with this condition progresses to advanced disease. Scientists are searching for effective interventions that deter or retard cognitive decline in aging. DHA may have potential benefit.

progression of this debilitating condition are not. For example, it has been suggested that mild cognitive impairment (MCI) is a [transitional phase](#) between normal cognitive changes in aging and the development of dementia. Some estimate that [more than half](#) the individuals with MCI advance to Alzheimer's disease

studies appeared, so that [current models](#) suggest that abnormal amyloid biomarkers, such as cerebrospinal fluid amyloid beta42 appear first, followed by biomarkers of neurodegeneration, such as increased concentrations of the abnormal protein *tau* in cerebrospinal fluid, structural changes in brain as observed by magnetic resonance imaging and then clinical symptoms. Abnormal amyloid biomarkers may appear [5 to 10 years](#) before a clinical diagnosis of dementia.

Considerable effort has been expended to find effective interventions that deter or retard the progression of MCI to more advanced disease. In this regard, long-chain omega-3 PUFAs (n-3 LC-PUFAs) have been investigated because they [may be low](#) in individuals with MCI, have been associated with a [lower risk](#) of developing MCI and supplementation with them has been associated with improved cognitive function in [animals](#), though less frequently in [human studies](#). DHA [reduces the production](#) of abnormal amyloid beta protein, which may delay or prevent the onset of Alzheimer's disease and has many other neuroprotective functions. Considering that the consumption of n-3 LC-PUFAs is very low in



Western countries and in some other parts of the world it is important to establish what, if any, contribution increased consumption of these fatty acids can make to the maintenance of cognitive function, especially in individuals with MCI.

Recognizing that [MCI in Asia](#) is a growing challenge, Lai Kuan Lee and colleagues at the Universiti Kebangsaan, Malaysia, conducted a randomized clinical study in 36 individuals aged 60 years or more who were of low to middle socioeconomic status and without physical or mental illness. Participants were eligible if they met preset criteria as determined by professional neuropsychological assessments and were living in their own home, but not alone. Those taking vitamin, omega-3 PUFAs or ginkgo biloba supplements were ineligible. Participants were randomized to consume either fish oil or corn oil capsules for 12 months. The fish oil capsules provided 1.3 g of DHA and 450 mg of EPA per day.

Outcome measures included neuropsychological tests, depressive symptoms and global cognitive function evaluation along with plasma fatty acids assessed at

baseline, 6 and 12 months. The neuropsychological tests included Visual Reproduction tests I and II from the revised Wechsler Memory Scale, Rey Auditory Verbal Learning Test (RAVLT), Digit span backward and forward from the revised Wechsler Adult Intelligent Scale, executive function and attention by the Clock Drawing Test, psychomotor speed and visuospatial skills, also from the Wechsler Adult Intelligent Scale. Depressive symptoms were assessed using the Geriatric Depression Scale and global cognition from the Mini-Mental State Examination. A total of 35 participants completed the study.

After 1 year, participants who consumed 1.4 g/day of DHA-rich fish oil had significantly improved memory scores compared with the placebo group. There were no differences in other evaluations between the two groups.

At baseline, those in the fish oil group were older (66 vs. 64 yr) and had higher blood pressure (systolic and diastolic) than the control participants. The mean Mini-Mental State Examination score was 26.4, suggestive of MCI.

At the end of 1 year, those who consumed the fish oil supplements had significantly improved cognitive scores for the digit span, visual reproduction and auditory verbal learning assessments compared with the control group. In other assessments, the fish oil participants showed significant improvements in memory and executive function/attention compared with baseline values, but only the improvements in memory showed a statistically significant difference between treatments, favoring the fish oil treatment ($P = 0.001$). The overall memory score was determined by averaging the 5 individual test scores related to memory function from the neuropsychological tests. Scores on the MMSE and depression rating scale did not differ between the two groups or with the duration of the study.

The study demonstrated a beneficial effect of 12 months' consumption of a DHA-rich fish oil supplement on overall memory in 65-year old adults with MCI. There were no significant group differences in executive function, psychomotor speed or visuospatial skills. These findings support the results of an earlier [trial with algal DHA](#) on immediate and delayed verbal recognition memory in healthy older adults with MCI. The authors suggest that the beneficial effects on memory observed here might be attributable to the very early stage of cognitive impairment in their participants, in contrast to the lack of effect in several other studies. As has been recently suggested,

MCI may be an early clinical sign of future dementia, but for Alzheimer's disease, biochemical markers of the disease may be present as early as 10 years before clinical symptoms appear. Thus, for many potential candidates, protection of cognitive function may have to begin years before the risk of dementia becomes clinically apparent. It would be most useful to have this study repeated in a larger study with more participants.

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■ BRAIN AND NERVE

Pretreatment with High-Dose n-3 LC-PUFAs Mitigates Damage and Improves Recovery from Spinal Cord Injury

The importance of DHA in the recovery from spinal cord or traumatic brain injuries has been demonstrated in DHA-treated animals that exhibit dramatic improvements in [motor function](#), greatly reduced neuronal loss, [improved learning](#), [less oxidative stress](#), and [more rapid recovery](#). This work suggests that supplementation with DHA immediately after injury would improve cellular and functional recovery in humans as well. A recent [case report](#) describing the use of high-dose EPA and DHA (19.2 g n-3 LC-PUFAs/day) for more than a year in a patient with severe traumatic brain injury has done

just that. The report described dramatic cognitive and physical improvements in the patient over the first 4 months post-injury, continuing for at least 2 years. This demonstration of the effectiveness of n-3 LC-PUFAs in the recovery from brain and spinal cord injury heralds a new and additional approach for treating such patients.

Animals with spinal cord and brain injuries treated with DHA shortly after injury show improved motor, cognitive and sensory function and speedier recovery. What if n-3 LC-PUFAs were given before the injury?

One unanswered question is whether pretreatment with DHA or n-3 LC-PUFAs prior to [spinal cord injury](#) would improve the outcomes observed afterward. Johnny Figueroa and colleagues at Loma Linda University, U.S., addressed this issue in a study of laboratory rats that were fed either soybean or menhaden oil-rich diets for 8 weeks prior to surgical contusion (bruising) spinal cord injury. This is the most common type of spinal cord injury in humans and results in disability, inflammation and bleeding from nearby blood vessels. The severity of the injury determines the extent of functional damage and recovery. These investigators had [previously reported](#) that animals pretreated with DHA prior to spinal cord injury exhibited sparing of white matter, improved axonal preservation, less cell death and significantly better locomotor behavior.

The underlying hypothesis for the current study is that pretreatment with DHA would enhance the balance between restorative and destructive signals in damaged neuronal tissue. As [suggested recently](#), these signals could include lipids and neurofilaments, uncontrolled oxidative stress and apoptotic cell death. For example, increased neuronal membrane content of DHA might counteract the proinflammatory effects of the release of arachidonic acid at the site of injury, leading to reduced inflammation and oxidative stress.

Animals were fed a control or menhaden oil-rich diet for 8 weeks prior to spinal cord injury and for 8 weeks thereafter. Restoration of autonomic and motor function was significantly faster and more extensive in the fish oil-fed group.

The investigators fed animals diets containing either soybean or menhaden oil (6% of dry weight) for 8 weeks and then divided each group

into injured or sham-operated, continuing the same diets after surgery for another 8 weeks. The menhaden oil diet provided 12.8 and 6.9 g of DHA and EPA, respectively, per 100 g of diet. Food intake data indicated that the animals consumed approximately 500 mg of DHA and 250 mg of EPA per kg of body weight. The spinal cord injury was performed at thoracic level 10. Animals were evaluated post-operatively for restoration of bladder control and motor function using open-field locomotion ([BBB assessment](#)), joint movement, paw placement and other assessments. The researchers performed sensory testing by measuring the withdrawal response of the hindpaws following a mechanical stimulus.

At the end of the experimental period, animals in both groups lost 8% to 10% body weight, but compared with baseline weight, significant weight loss occurred only in the control animals. Baseline weight was re-established after 3 weeks. Full recovery of bladder control was achieved significantly earlier in the n-3 LC-PUFA-fed animals compared with controls, 6.1 vs 9.5 days ($P < 0.0001$) post injury (Figure 1).

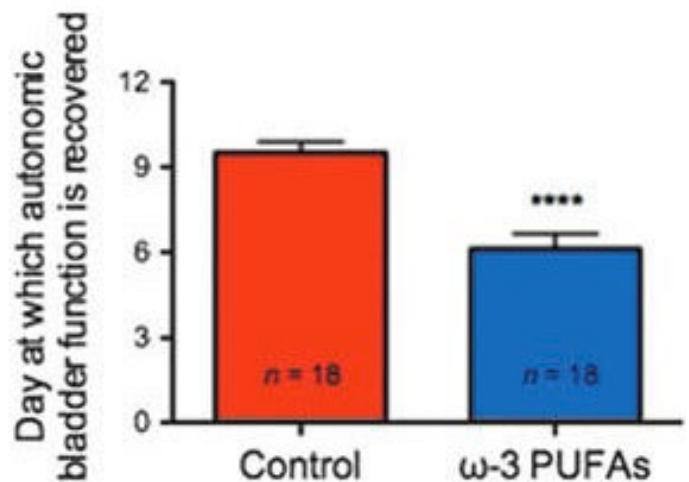


Figure 1. Days after spinal cord injury to attain full bladder function in animals pretreated with control or menhaden oil-rich diets prior to injury. Figure from Figueroa *et al.*, *J Neurotrauma* 2013; Feb 6. Reproduced with permission from the publisher.

Locomotor recovery was significantly faster in the n-3 LC-PUFA-fed animals compared with the controls as observed in the BBB locomotor scale ratings, extensive joint movements and occasional weight-supported steps at 1 week post-injury. Compared with control animals, the fish oil-fed animals exhibited weight-supported plantar steps, consistent coordination and paw rotation during locomotion at 8 weeks after injury. Recovery in control animals reached a plateau at 4 weeks after injury, whereas in the fish oil-treated animals continued to improve through 8 weeks after surgery.

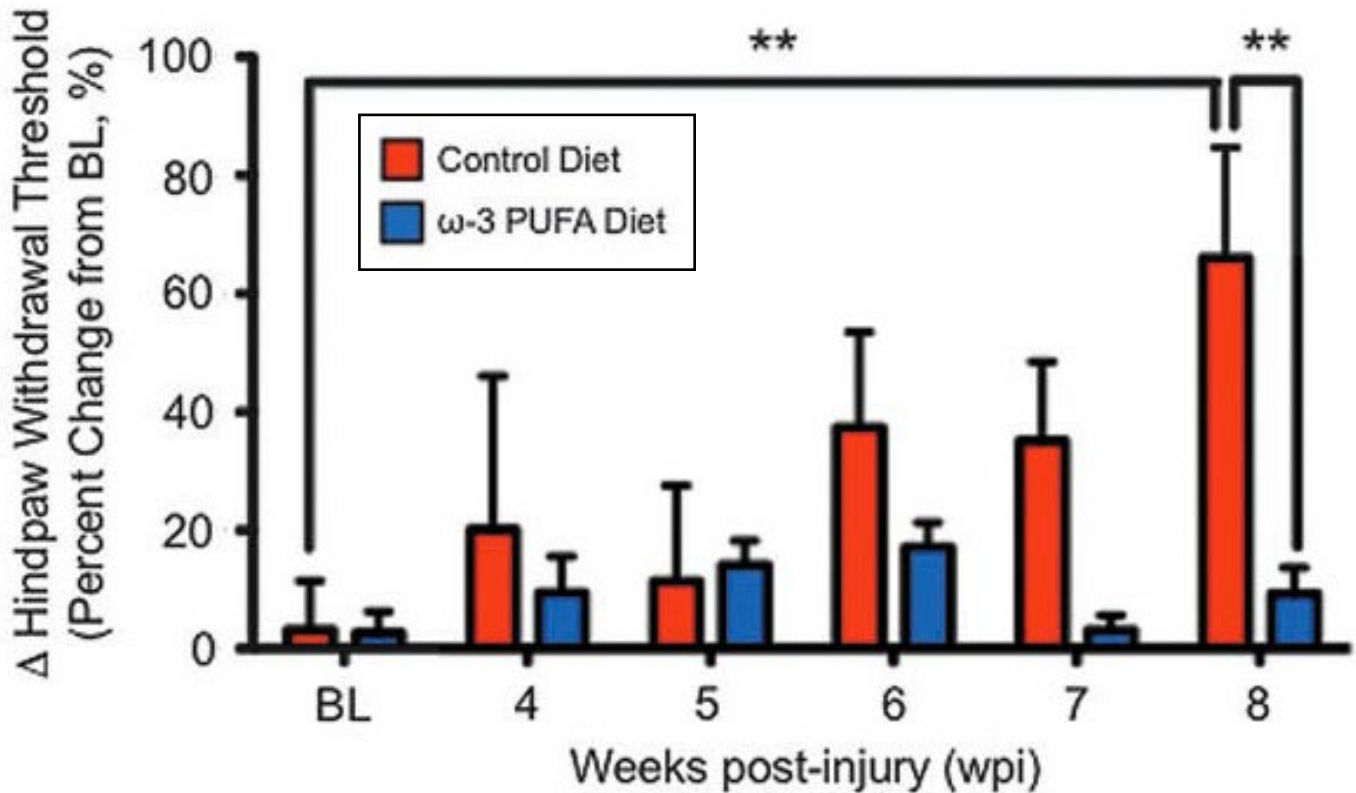


Figure 2. Increased sensory threshold in animals with spinal cord injury 8 weeks after injury. Pretreatment with dietary menhaden oil abolished the sensory loss in injured animals. Figure from Figueroa *et al.*, *J Neurotrauma* 2013; Feb 6. Reproduced with permission from the publisher.

Typically in spinal cord injuries of this type, animals experience sensory loss, which can be assessed by hindpaw withdrawal from a blunt mechanical probe applied with measured force. However, in the n-3 LC-PUFA-fed animals, only 23% showed sensory dysfunction, whereas 75% of the controls had sensory deficits. At 8 weeks after injury, control animals developed sensory thresholds approximately 66% greater than baseline (Figure 2), but the fish oil-fed animals had only a nonsignificant 9% change from baseline values, suggesting that fish oil pretreatment abolished sensory deficits.

The investigators also performed fatty acid analysis on spinal cord tissue 8 weeks after injury and found that injured animals had significantly higher concentrations of n-6 docosapentaenoic acid (DPA) and significantly lower levels of DHA. The ratio of these 2 fatty acids, a [marker of DHA deficiency](#), was significantly higher in injured compared with sham-operated controls in both the control and fish oil-fed animals (Figure 3). Although the ratio of n-6 DPA:DHA was similar in the sham-operated animals in both groups, it was significantly lower in the injured animals fed the fish oil diet compared with the controls, indicating that pretreatment with n-3 LC-PUFAs reduced the loss of DHA.

Differences in the DPA:DHA ratio were also associated with the recovery of autonomic bladder function and the locomotor scores. Increases in the DPA:DHA ratio were positively associated with the number of days to full bladder recovery in control animals, but negatively associated with locomotor scores. In addition, the DPA:DHA ratio was associated with the hindpaw sensitivity scores, increasing with a higher threshold of sensitivity. Animals fed the n-3 LC-PUFA diet were 54% less likely to develop major sensory dysfunction compared with controls ($P = 0.02$). These observations suggest that DHA loss in the injured spinal cord is associated with greater functional damage and delayed recovery. Others have shown that [DHA is reduced](#) in spinal cord injury and that increased DHA is associated with improved functional recovery.

The investigators also examined the Akt and cyclic-AMP response element-binding protein (CREB) signaling pathways to determine whether they were responsive to the dietary treatments. Messenger RNA for CREB was significantly increased in the n-3 LC-PUFA-fed animals at 8 weeks post injury and protein expression for both molecules was also significantly increased. These molecules are thought to be involved in neural plasticity, neuroprotection and repair and may contribute to the improved neurological responses in the fish oil-fed group.

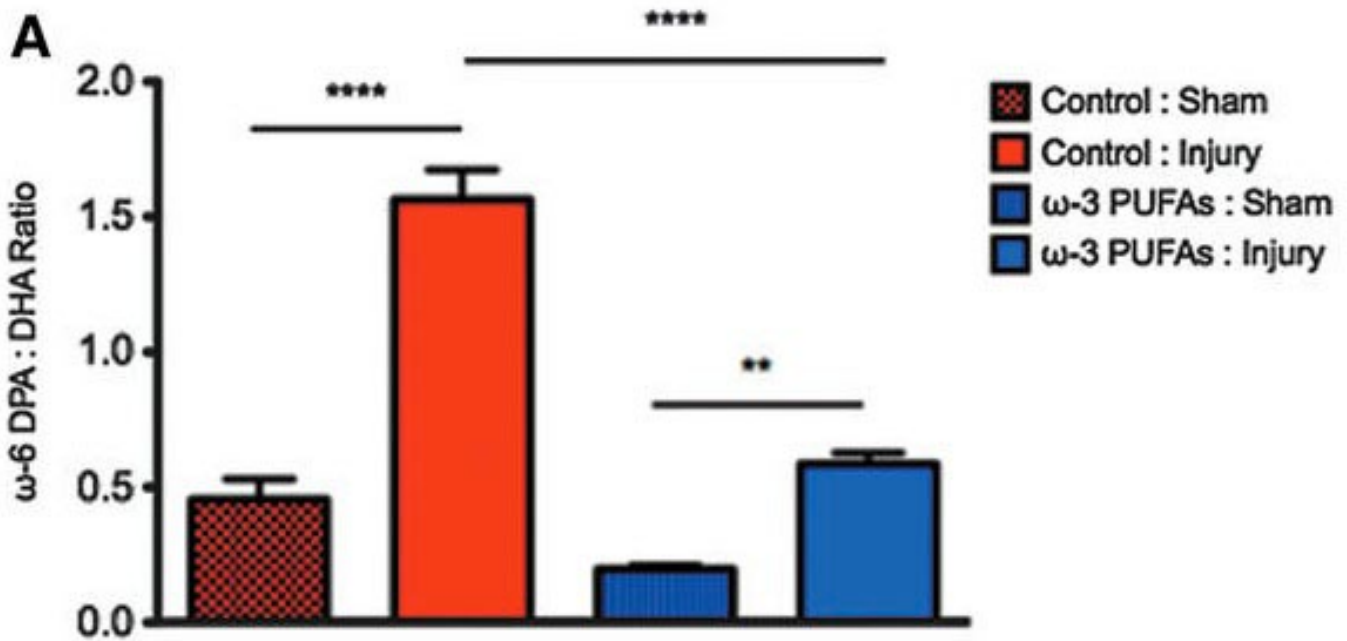


Figure 3. Increase in the ratio of n-6 DPA:DHA, an indicator of DHA deficiency, with spinal cord injury (red bars). DHA deficiency was significantly reduced in the injured animals fed a menhaden oil-rich diet prior to injury compared with the animals on the control diet (blue bars). Figure from Figueroa *et al.*, *J Neurotrauma* 2013; Feb 6. Reproduced with permission from the publisher.

This study contributes several important observations about the involvement of n-3 LC-PUFAs in contusion spinal cord injury and recovery from it. The study furnishes additional evidence that DHA-rich diets hasten and improve the autonomic, motor and sensory recovery from spinal cord injury. It shows that pretreatment with dietary n-3 LC-PUFAs reduces the damage from spinal cord injury and improves and hastens functional recovery, as shown in the full and rapid recovery of bladder function in

This study showed that contusion spinal cord injury is accompanied by DHA loss, which was overcome by feeding the animals a menhaden oil-rich diet prior to injury. The fish oil diet was associated with more rapid and improved recovery of autonomic, sensory and motor function after spinal cord injury.

the n-3 LC-PUFA-fed animals. The study is the first to show that pretreatment with high levels of n-3 LC-PUFAs followed by the same diet for another 8 weeks after spinal cord injury was sufficient to lead to marked improvement in autonomic and motor function.

and demonstrate that pretreatment with dietary n-3 LC-PUFAs mitigates this loss. As the authors suggest, the effectiveness of high-dose n-3 LC-PUFA pretreatment implies the importance of endogenous n-3 LC-PUFAs in easing the damage from neurotrauma. The study also provides additional evidence that the Akt and CREB signaling pathways are enhanced by dietary n-3 LC-PUFAs in such injuries and are likely involved in the recovery from the damage such injuries incur.

This study and the rapidly expanding literature on this topic suggest that n-3 LC-PUFAs are intimately involved in the damage, mitigation of and recovery from the effects of traumatic brain and spinal cord injury. A [recent report](#) that n-3 PUFA deficiency since gestation increases the vulnerability of animals to traumatic brain injury further suggest that improving n-3 LC-PUFA status may improve one's resistance to the damage from brain and spinal cord injury.

Figueroa JD, Cordero K, Illan MS, De Leon M. Dietary omega-3 polyunsaturated fatty acids improve the neurolipidome and restore the DHA status while promoting functional recovery after experimental spinal cord injury. J Neurotrauma 2013; Feb 6. [PubMed]

Lewis M, Ghassemi P, Hibbeln J. Therapeutic use of omega-3 fatty acids in severe head trauma. Am J Emerg Med 2013;31:273.e5j-e8. [PubMed] Open Access

These findings support the observation that spinal cord injury is accompanied by a loss of tissue DHA

■ CLINICAL CONDITIONS

High-Dose EPA Associated with Less Immunosuppression from UV Radiation

Exposure to the sun's ultraviolet (UV) radiation is the primary cause of [nonmelanoma skin cancers](#), the most

Nonmelanoma skin cancer is the most common cancer among white-skinned individuals. Exposure to UV radiation from the sun increases the risk of skin cancer in these people. Animal studies have reported radiation-protecting effects with omega-3 PUFAs. Could they help protect humans?

common cancer among white-skinned individuals. Although the condition carries a very low mortality rate, morbidity and treatment costs can be high. The incidence of these cancers is [increasing worldwide](#), with the highest rates found in Australia. In North America, the incidence increases with decreasing

[latitude](#), while skin type and sunbathing also affect the incidence significantly. In the U.S., the incidence of nonmelanoma skin cancer among Medicare patients—those age 65 or more—increased [nearly 77%](#) over the 15 years from 1992 to 2006. There was an estimated 3.5 million of these cancers in the U.S. in 2006.

Nutritional status, especially for vitamin D, has been associated with the risk of nonmelanoma skin cancer, but there is a trade-off. Exposure to sunlight increases the skin's production of protective vitamin D3, but also increases the risk of nonmelanoma skin cancer. [Deficiency in vitamin D3](#) has been associated with a higher risk of skin cancers and several other diseases. To ensure adequate production of vitamin D3, some experts recommend 5 to 10 minutes of [sun exposure](#) of the arms and legs or hands, arms and face, 2 or 3 times per week. Increased consumption of vitamin D, mainly from supplements and fortified foods, can ensure adequate levels of this vitamin. Otherwise, using broad-spectrum sunscreen with an SPF of 15 or higher and [sun-blocking habits](#), such as UV-blocking sunglasses, long sleeved clothing and wide-brimmed hats, also protect against excessive UV exposure.

Chronic low-dose exposure to UV radiation [suppresses immunity](#) in the skin and internal organs. However, UV exposure is also associated with a reduced expression of [allergic airway disease](#) and some [other types of cancer](#). Long-chain omega-3 PUFAs (n-3 LC-PUFAs)

Individuals who consumed high doses of EPA were less sensitive to sunburn and rates of nonmelanoma skin cancer were significantly lower in individuals with high intakes of n-3 PUFAs or fish.

have been associated with protective immune responses in animals exposed to UV radiation for over 20 years. Animals fed an n-3 PUFA-enriched diet and exposed to UV radiation exhibited a marked [reduction in inflammatory response](#) and

delayed hypersensitivity to dinitrochlorobenzene. It was later reported that [EPA](#), but not DHA, protected against UVB-radiation-induced immunosuppression in mice, suggesting that EPA might have protective effects against UV radiation-induced skin cancer. Consistent with this hypothesis was a report that healthy individuals who consumed 4 g of purified EPA per day for 3 months experienced significantly reduced [sensitivity to sunburn](#) and a range of early genotoxic markers compared with individuals who consumed oleic acid. In 2000, an [observational study](#) reported that the risk of squamous cell carcinoma of the skin, one of the 2 main subtypes of nonmelanoma skin cancer, tended to be lower among those with higher intakes of n-3 PUFAs. A case-control study in Australia also observed a significant inverse relationship between the risk of skin cancer and high [intakes of fish](#). Overall, studies in humans are few.

In a new report, investigators at the University of Manchester and other universities in the U.K. examined the effects of n-3 LC-PUFA supplementation on UV radiation-induced immune responses in human volunteers. In a randomized controlled study, they evaluated whether supplementation with n-3 LC-PUFAs would reduce the immunosuppression induced by UV radiation. Participants included 79 healthy women between the ages of 18 to 60 years (median age, 44 years) whose skin sunburned easily with little or no tan and who were also allergic to nickel. Skin sensitivity to nickel can be used to assess cell-mediated immune responses because nickel acts as a recall antigen prompting an allergic response. Nickel sensitivity is relatively common, affecting about 15% of women. Participants were recruited from the dermatology unit at the Salford Hospital in Manchester and from general advertisements.

Eligible participants were assigned randomly to consume 5 capsules per day providing a total of 3.5 g of EPA and 500 mg of DHA or 5 g per day of short-chain saturated fatty acids for 12 weeks. Nickel allergy



Figure. High intensity solar radiation simulator. Image courtesy of Newport Corp.

was confirmed prior to enrolment by patch tests that elicited an eczematous response after 24 hours. Participants were exposed to UV radiation from a solar simulator with a 1,000 watt xenon arc lamp from which UVC was filtered out (Figure). Radiation was applied to the mid-back at 3 separate 2.5-cm² (1 sq inch) sites, each receiving 1.9, 3.8 or 7.6 J/cm² simulated solar radiation for 3 consecutive days. The highest dose was equivalent to ~70% of the average threshold UV dose that elicited an erythematous response, i.e., a low dose. The nickel patch containing the predetermined dose needed to elicit a response for each participant was applied to each exposed site plus 3 additional unexposed sites adjacent to the irradiated sites on the mid-back. After 48 hours, investigators removed the nickel patch and 24 hours later measured the erythematous response using a reflectance instrument. The percentage of immunosuppression was calculated by subtracting the mean response of the exposed sites from the mean of the unexposed sites.

At the end of the study, 73 participants remained, of which 3 in the n-3 LC-PUFA group were excluded from the analysis because of poor compliance. Immunosuppression in response to the nickel patch increased in both groups as the dose of UV radiation increased. In the controls, the response increased from 15% suppression at a dose of 1.9 J/cm² to 43% suppression with 7.6 J/cm² (Table). Participants who consumed the EPA-rich n-3 LC-PUFAs experienced less immunosuppression compared with controls at each UV dose. Suppression by n-3 LC-PUFAs was approximately 50% of control values at the two lowest radiation exposures. There was no significant interaction between the UV dose and the treatment. Adjustment of the responses for hormone replacement therapy did not affect the results.

Table. Reduced UV-induced immunosuppression (%) in nickel-allergic women who consumed 4 g/day of EPA-rich n-3 LC-PUFAs for 12 weeks

UV Radiation dose J/cm ²	Control % (95% CI)	n-3 LC-PUFA % (95% CI)
1.9	15 (3.7 – 25.2)	8 (-0.5 – 16.7)
3.8	21 (13.9 – 28.1)	10 (2.3 – 17.9)*
7.6	43 (34.9 – 50.8)	40 (29.7 – 49.3)

*Significantly different from control, *P* = 0.04.

The 2 lowest UV exposures where n-3 LC-PUFAs attenuated the immunosuppression were equivalent to about 8 and 15 minutes of midday summer sun exposure. However, at the equivalent of 30 minutes of midday sun, n-3 LC-PUFAs did not reduce the immunosuppression response to UV radiation. Especially in sun-sensitive individuals, n-3 LC-PUFAs might contribute to protection from the skin-damaging effects of short exposures to UV radiation.

The consumption of high-dose, EPA-rich n-3 LC-PUFAs for 3 months by sun-sensitive women reduced UV-induced immunosuppression at low exposures to UV radiation, the equivalent of 15 min of midday summer sun.

The key finding in this study supports results in animal studies and observational reports in humans that consumption of n-3 LC-PUFAs, especially EPA, reduces the immunosuppressive effects of low exposures to UV radiation. The

study used large amounts of n-3 LC-PUFAs (~ 4 g per day) for 3 months in women who sunburn easily. Whether regular consumption of smaller amounts of n-3 LC-PUFAs or DHA alone would yield similar results is not known. The investigators used EPA-rich n-3 LC-PUFAs based on a report that EPA was more effective than DHA in reducing immunosuppression in mice. The possible effectiveness of DHA or EPA + DHA in humans merits further investigation. Finally, whether n-3 LC-PUFAs or purified EPA reduce UV radiation-induced immunosuppression in the general population of white-skinned people remains to be explored.

Pilkington SM, Massey KA, Bennett SP, Al-Aasswad NMI, Roshdy K, Gibbs NK, Friedmann PS, Nicolaou A, Rhodes LE. Randomized controlled trial of oral omega-3 PUFA in solar-simulated radiation-induced suppression of human cutaneous immune responses. Am J Clin Nutr 2013;97:646-652. [PubMed] Open Access

