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The Use of Fish Oil Supplements in Clinical Practice: A Review

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ABSTRACT

Increasing dietary consumption of fish high in omega-3 (n-3) fatty acids is well established as a way to improve numerous health outcomes. The prevention of both primary and secondary cardiovascular events, as well as intervention for such unrelated outcomes as depression and rheumatoid arthritis are now linked with n-3 fatty acid intake. Increasing fish consumption is neither an exact science, nor without risk of consuming toxins of various kinds. The advent of highly purified fish oil supplements, now widely available, has allowed very high levels of n-3 fatty acid consumption for both preventative and therapeutic clinical use. This review will focus on the data concerning fish consumption, fish oil supplements and their fatty acids as it pertains to clinical outcomes, with an emphasis on cardiovascular health.

BACKGROUND

In the early 1970s, it was observed that high levels of fat intake in the form of long-chain omega-3 fatty acids in Greenland Eskimo populations resulted in fewer cardiovascular events than Western populations who ingested less total dietary fat.¹ In fact, these studies and others prompted

the scrutiny of fatty acids based upon whether they were omega-3 (n-3), omega-6 (n-6) or omega-9 (n-9). Fatty acids in the n-3 and n-6 families are considered essential to humans because our metabolism is unable to de-saturate (make a double-bond) between carbons-3 and 4 (n-3) or between carbons 6 and 7 (n-6); counting from the omega or last carbon (See Figure 1 for basic fatty acid information). Typical Western diets provide much in the way of polyunsaturated fatty acids from vegetable sources, which supply high levels of n-6 fatty acids. Data from numerous epidemiological studies have suggested that lowering one's ratio of n-6/n-3 in the range of 3:1 to 6:1 (typical American diet may be as high as 20:1) will have great health benefits.² The creation of trans-fatty acids through food processing and cooking further complicates the issues both metabolically and epidemiologically.

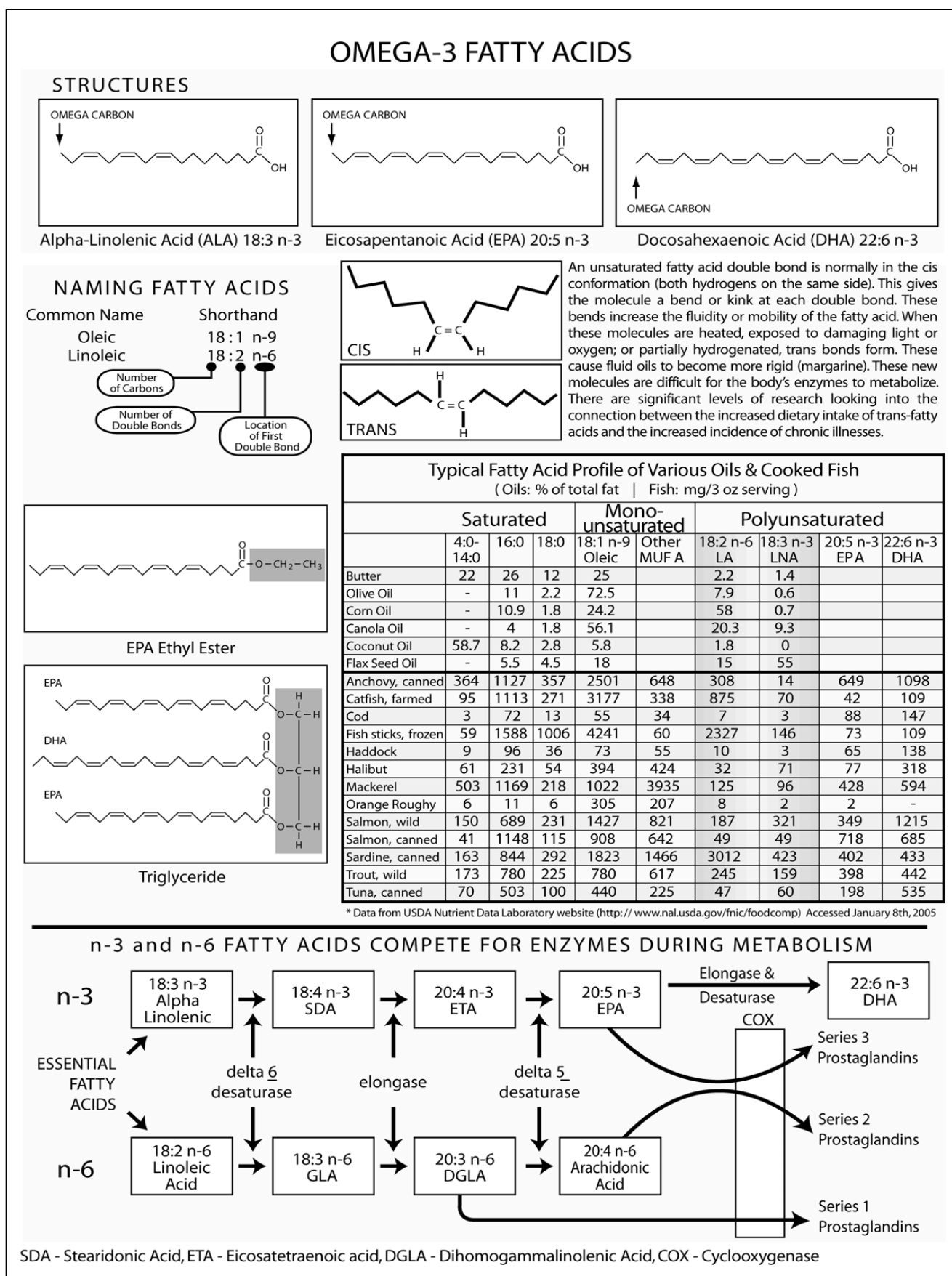
N-3 FATTY ACIDS

Alpha-linolenic acid (ALA) is an n-3 essential fatty acid found primarily in certain seeds and green leafy vegetables. Flaxseeds are one of the richest sources of ALA. Converting this 18 carbon fatty acid to the 20 and 22 carbon fatty acids found primarily in fish oils requires several steps of elongation and de-saturation (see Fig. 1), reported to be a very inefficient process in adults, suggesting that direct consumption is more reliable.^{3,4} And while some data suggests that ALA may help prevent secondary cardiovascular events,⁵ most of the focus on n-3 fatty acid research is with consumption of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) from fish and fish oil supplements. In humans, the retroconversion between ingested DHA to plasma EPA seems to be higher than the conversion of EPA to DHA.^{107,110}

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Figure 1:



CARDIOVASCULAR USES

Primary Cardiovascular Event Prevention

Numerous reviews have summarized the cardiovascular benefits of fish and fish oil consumption.^{6,7,8,9,10} The data concerning primary prevention, however, is less straightforward than the data relating to secondary prevention. In several large cohort studies, the relative risk for CHD and sudden death is reduced with increased fish consumption in men and women,^{11,12,13,22,27} while others showed no statistical differences based on fish consumption.^{14,15} Plasma EPA and DHA levels measured upon initiation of the Physicians' Health Study did not relate inversely with incidence of myocardial infarction,¹⁶ however in this same group both fish consumption, based on dietary questionnaire, and blood n-3 levels were statistically related to reduced risk of sudden cardiac death.^{17,18} In this cohort of 20,551 men, the multivariate relative risk for sudden cardiac death in those consuming 1 fish meal per week was 0.48, compared with men who consumed fish less than once per month.¹⁷ The adjusted relative risk in the 4th quartile of red cell n-3 levels was 0.19.¹⁸

The Honolulu Heart Program, following Japanese-Americans living in Hawaii, found that the relative risk for CHD mortality was cut in half for heavy smokers (>30 cig/day) if they consumed greater than 2 fish meals per week.¹⁹ Siscovick²⁰ reported that in a population-based case-control study in King County, WA that both dietary intake of seafood containing n-3 fatty acids and red blood cell membrane n-3 fatty acid concentrations were inversely related to primary cardiac arrest. Both of these associations were dose-related. Among the Nurses' Health Study cohort, fatty fish intake was associated with a reduced risk of thrombotic stroke, while there was no increased risk for hemorrhagic strokes in women.¹⁸³ A similar large cohort in the Physicians' Health Follow-up study found the same lowered risk of stroke with fish consumption in men.¹⁸⁴ The American Heart Association recommends that patients without documented coronary heart disease (CHD) eat a variety of (preferably fatty) fish at least twice a week, including oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseed and walnuts).^{9,21}

Secondary Cardiovascular Event Prevention

One of the first studies to assess the secondary prevention potential of n-3 fatty acids from fish was the diet and reinfarction trial (DART).²³ The men randomized to receive advice to increase fatty fish consumption (others were advised to increase fiber or reduce fat intake) after recovery from MI, had a 29% reduction in 2-year all cause mortality. Unfortunately, like many lifestyle changes, this advice was difficult to maintain over many decades and both compliance and benefits seem to have been diminished after a decade.²⁴

The largest secondary prevention trial to date is the GISSI-prevention trial.²⁵ In this study, over 11,000 patients (surviving a recent MI) were randomized to receive 1 g/day

n-3 fatty acids (capsules containing a minimum of 850 mg EPA and DHA as ethyl esters), 300 mg of vitamin E (acetyl *d,l*-alpha tocopherol), both or placebo. Most of these patients were concomitantly on cardiovascular pharmaceuticals of various kinds, as well as advised about diet and lifestyle changes. Total (RR=0.59) and cardiovascular mortality (RR=0.66) were significantly reduced in the fish oil group as early as 3 and 4 months into the study, respectively. The most dramatic reduction was in sudden deaths, for which relative risks of 0.37 (after 9 months) and 0.55 (42 months) were reported.²⁶ Among the lipids measured, only triglyceride levels showed significant improvements. In all, there are over 20 randomized, placebo-controlled trials of dietary n-3 fatty acid from fish in CHD patients. A meta-analysis²⁸ of these trials shows a 3-year average reduction of all cause mortality of 16% and death from MI of 24%. The American Heart Association recommends that patients with documented CHD consume about 1 g of EPA+DHA per day, preferably from fatty fish; EPA+DHA supplements could be considered in consultation with a physician.^{9,21}

Anti-arrhythmic Effects of Fish Oils

Both primary and secondary prevention studies showed that n-3 fatty acid intake was profoundly better at preventing sudden deaths than reducing the incidence of non-fatal MI. Over 50% of the deaths attributed to CHD are sudden deaths (within 1 hour) caused by sustained ventricular arrhythmias. These data suggested that n-3 fatty acids may have anti-arrhythmic effects which initially do not lower the incidence of MI, but prevent many of these events from becoming fatal.¹⁰ This anti-arrhythmic effect has been reported in several animal and cell culture models.²⁹⁻³³ It is fairly well established that the incorporation of EPA and especially DHA within the plasma membrane of electrically excitable cardiac tissue changes membrane fluidity and modulates the actions of ion channels to prevent the destabilization that permits arrhythmias and ventricular tachycardia.³⁴⁻³⁷

One small pilot study was conducted with 10 patients who had implanted cardioverter defibrillators and repeated episodes of documented, sustained ventricular tachycardia.³⁸ Compared with baseline, after these patients were infused with n-3 fatty acids, sustained ventricular tachycardia was non-inducible in 5 of the 7 (3 of the 10 patients who ate significantly more dietary fish were non-inducible at baseline). More research, including controlled trials, needs to be done using oral doses of fish oil preparations and clinical outcomes. Leaf et al.¹⁰ recommend that those with a family or personal history of CHD should supplement their diets with 600 mg of EPA plus DHA, and higher, 1 to 2 grams, if there is also a family history of sudden cardiac death.

Reducing Triglycerides

Elevated triglycerides (TG), both fasting and postprandial, are directly related to the progression of atherosclerosis and are considered independent risk factors for CHD,

especially in women.^{39,40} Long-chain n-3 fatty acids from fish like EPA and DHA have shown consistent TG lowering effects in both animals and humans.⁴² A meta-analysis of 65 published reports showed TG reduction averaging 25% was typical with fish oil consumption (mean dose 4 g/day EPA + DHA) in both normolipidemic and hypertriglyceridemic subjects.⁴¹ These data also show a dose-response relationship between fish oil intake and triglyceride lowering as well as a slight rise in LDL cholesterol (5-10%) and a smaller elevation in HDL cholesterol (1-3%).

Post-prandial (after a fatty meal) plasma TG levels may even be more correlated to atherosclerotic progression than fasting TG levels.⁴³ Chronic intake of n-3 fatty acids from fish has been shown to reduce post-prandial plasma TG levels.⁴⁴ A recent study showed that exercise when combined with fish oils was additive in post-prandial TG lowering.⁴⁵ Ten healthy recreationally-active subjects in a cross-over design were tested for changes in fasting and post-prandial (after 1,000 calorie shake- 99% fat after 12-hour fast) TG levels after 5 weeks of fish oil supplementation (4 g/day in 8 capsules of 300 mg EPA and 200 mg DHA each) or exercise (60% VO_2max on treadmill for 1 hour), both or neither (control). When exercise was added to fish oil supplementation, the peak plasma TG levels went from 38% reduction (fish oil vs. control) to 50% reduction (fish oil + exercise vs. control). Total area under the TG curve was reduced from 27% to 42% respectively. While both EPA and DHA seem to have triglyceride lowering benefits, DHA may have a more favorable effect. The American Heart Association recommends that under a physician's care, patients who need to lower triglycerides should consume 2 to 4 grams of EPA+DHA per day provided as capsules.^{9,21}

Other Cardiovascular Risk Factors

In general, fish oil supplements have a favorable, but small effect on HDL cholesterol levels (1-5%). Combined with the more widely observed TG lowering, this (this what?) improves the important TG:HDL ratio. A small study (n=14) was conducted in patients with familial combined hyperlipidemia, noted for their increased cardiovascular risk due to elevated atherogenic lipoproteins and decreased protective lipoproteins.⁵⁷ In a cross-over design, patients were given either 4 g/day of a concentrated fish oil preparation in capsules (Omacor- 44%EPA, 36% DHA as ethyl esters) or placebo (corn oil) for eight weeks. As expected, TG levels were lowered significantly (378 to 210), while HDL cholesterol rose a non-statistical 8%. The relative increase in HDL₂, a more cardioprotective lipid subfraction, was statistically significant. LDL, but not total cholesterol, was significantly increased in the fish oil group. In one group of hyperlipidemic patients, DHA (4 g/day) had a more significant (29%) increase in HDL₂ levels than equivalent levels of EPA.¹⁰⁶ Other clinical trials have also reported that DHA has a slightly more favorable effect on lipid

profiles (TG lowering, TG:HDL ratio and lipoprotein fractionation),¹⁰⁷ and post-prandial lipid margination.¹⁰⁸

It is not uncommon to see elevations in plasma LDL cholesterol after fish oil intake, especially in individuals with elevated triglyceride levels. Since total cholesterol usually remains unchanged in these subjects and it is known that most of the increase is due to an increased shift from VLDL to LDL, the clinical significance of this elevation in plasma LDL cholesterol is not yet known, but LDL subfraction analysis suggests that it is the larger, less-dense (and less atherogenic) LDL fraction which is raised and not the smaller (more atherogenic) LDL particles.^{46,186,187} One report suggested a potential down-regulation of LDL receptors to account for part of this phenomenon.⁴⁷

In a group of patients (n=64) with chronic renal failure, assigned to either 2.4 g/day fish oil (4 capsules- 3:2 EPA:DHA) or olive oil for 8 weeks; those receiving fish oil had statistically lower TG (21%), higher HDL cholesterol (8%) and no change in total or LDL cholesterol. A small, non-statistical, drop in Lp(a) was seen in these patients but Lp(a) is very rarely measured in other studies and similar drops were not reported in those studies where it was measured. Also, little effect is reported in lowering high sensitivity C-reactive protein (hsCRP), a marker of inflammation and an independent risk factor for cardiovascular disease.^{48,49}

Metabolic Syndrome and Diabetes

Metabolic syndrome is a disorder characterized by insulin resistance, high triglycerides, high LDL and low HDL cholesterol, hypertension and central adiposity. An increasingly prevalent condition considered "pre-diabetic," individuals with metabolic syndrome are also at an increased risk of cardiovascular disease even before a diabetes diagnosis.^{51,52} In both sucrose and fructose-induced animal models of metabolic syndrome, EPA and DHA from fish oils were able to prevent the onset or diminish several parameters (hypertension, adiposity, dyslipidemias) associated with the syndrome.^{53,54} One animal study concluded that insulin-sensitive GLUT4 activity is enhanced in adipocytes (not myocytes) to account for the fish oil's improvement of insulin sensitivity in these animals.⁵⁵ While many of the subjects in the TG lowering trials mentioned previously would likely be categorized as having metabolic syndrome, a trial looking at either the prevention or treatment of individuals by this diagnosis as an end-point has apparently not been performed. In one study of overweight treated hypertensive patients (n=69), likely to be deemed as having metabolic syndrome if lipids were reported, combining fatty fish consumption (dietary) with weight-loss had an additive effect on ambulatory blood pressure and decreased heart rate.⁵⁶

Like those with metabolic syndrome, type 2 diabetic patients are characterized with various lipid disorders, insulin resistance and increased risk for CHD. A cohort

within the Nurses' Health study (n=5103) who were free of CHD but with diagnosed type 2 diabetes were evaluated for CHD risk, relative to n-3 intake from fish.⁵⁸ After adjusting for age and other cardiovascular risk factors, the RRs for CHD were 0.70 (1 to 3 fish meals per month), 0.65 (2 to 4 times per week) and 0.38 (>5 times per week). Fish consumption in this cohort was more protective against CHD by quintile than it was when looking at all the women in the Nurses' Health Study,²⁷ implying that n-3 fatty acid supplementation in diabetic patients may prove even more beneficial than in the general population. Consumption of fish is associated with a significantly reduced progression of coronary artery atherosclerosis in women (a higher correlation in diabetic women) with coronary artery disease. Generally, fish and fish oil supplements reduce triglyceride levels and improve HDL levels but seem to have no clinically significant affect on fasting glucose, fasting insulin, HbA_{1c}, or glucose tolerance tests in diabetic subjects.⁵⁹⁻⁶¹

In one study, fish *protein* consumption was associated with a significantly lower risk of microalbuminuria in a nested case-control study of 1150 type 1 diabetic patients,⁶² although this lowered risk was also reported in a small group (n=16) of type 1 and 2 diabetic patients consuming only concentrated EPA (1.8 g/day).⁶³ Several animal models have suggested a role for fish oil in general, and DHA specifically, for increasing nerve conduction velocity in diabetic neuropathy. Collectively, these data suggest that diabetic patients should consume 1 to 2 grams per day of n-3 fatty acid from fish, balanced between EPA and DHA.

Hypertension

There is a dose-dependent inverse relationship between n-3 fatty acid intake and blood pressure in hypertensive patients, but little effect is noted in normotensive or borderline hypertensives. A meta-analysis of 31 placebo-controlled trials found an average -0.66/-0.35 mm Hg drop in systolic/diastolic blood pressure per gram of n-3 fatty acid consumed in hypertensive patients.⁶⁷ Many of these trials used doses in excess of 5 grams per day and were associated with gastrointestinal complaints. Another meta-analysis reported an average reduction of 5.5/3.5 mm Hg in hypertensive patients given at least 3 g/day of n-3 fatty acids. Fish oil consumption (~3.6 g/day from diet) had an additive effect when combined with weight loss in overweight hypertensives (-6.0/-3.0 fish alone, -5.5/-2.2 weight loss alone, -13.0/-9.3 mm Hg combined).⁵⁶ The authors conclude that given the magnitude of the BP reduction with the fish/weight loss combination, withdrawal of antihypertensive therapy may have been possible.

DHA and EPA have been tested separately for their hypertensive activities. Mori et al. has reported that 4 g/day of DHA, but not EPA, reduces ambulatory blood pressure and has favorable effects on arterial compliance.^{104,105}

Additional Cardiovascular Mechanisms⁷⁷

Discussing the various potential biological mechanisms in detail is beyond the scope of this review. For the sake of those interested in pursuing this avenue, however, a list of reported potential mechanisms attributed to n-3 fatty acids and several references are included below.

- Anti-inflammatory⁶⁸⁻⁷³
- Arterial compliance^{74,75,76}
- NO- induced endothelial relaxation^{78,79}
- Reduced asymmetric dimethyl arginine (ADMA)^{80,81}
- Reducing atherogenic adhesion molecules^{82,83,84}
- Anti-thrombogenic^{85,86,87}
- Stabilizing atherosclerotic plaques⁸⁸
- Peroxisome proliferator-activated receptors (PPAR) regulation^{89,90}

NON-CARDIOVASCULAR USES

Anti-inflammatory- Rheumatic Diseases^{115,116}

The well-known pathways which convert the 20 carbon n-6 fatty acid arachidonic acid into pro-inflammatory cytokines is often termed the arachidonic acid cascade. Key enzymes in the formation of pro-inflammatory prostaglandins and leukotrienes are the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Inhibition of these enzymes is one of the most popular anti-inflammatory mechanisms in the pharmaceutical trade. Since the substrate for each of these enzymes is a 20 carbon fatty acid, eicosapentanoic acid (EPA) is capable of both competing for the use of the enzyme as well as forming eicosanoids which function to counteract the activity of eicosanoids derived from arachidonic acid.¹²⁷ These mechanisms have led to the proposal that increasing n-3 (especially EPA from fish) and lowering n-6 fatty acid intake would have a favorable benefit on the overall inflammatory burden, particularly in individuals with chronic conditions such as rheumatoid arthritis.^{117,118}

Omega-3 fatty acids from fish oil have been studied extensively in patients with rheumatoid arthritis.¹¹⁹ Meta-analysis data suggest a modest improvement in tender joints and morning stiffness with the addition of fish oil supplementation.¹²⁰ Dosing and fish oil content vary widely in different clinical trials. The most significant benefits seem to require at least 3 grams/day, although benefits were seen in some trials with 2.6 grams/day,¹²¹ 30 mg/kg/day¹²² and 40 mg/kg/day.¹²³ Significantly more benefit is seen when patients who use fish oil supplements are also consuming a low arachidonic acid, anti-inflammatory diet.¹²²

The role of fish oils has also been explored in patients with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Reviews of the various clinical trials have shown that doses as high as 4.5 and 5.4 grams per day have limited benefit on preventing relapses, but often

reduce the dependence on steroid therapy and dramatically reduce inflammatory markers.¹²⁴ A specially prepared enteric-coated, free fatty acid preparation (1.8 g/day EPA, 0.9 g/day DHA) was able to significantly reduce the level of relapse compared to placebo in a group of Crohn's disease patients (n=78).¹²⁵ Another group recently reported that stimulated T-cells and monocytes taken from Crohn's disease patients supplemented with fish oil (1.6 g/day EPA, 1.08 g/day DHA- non-enteric coated) and an antioxidant blend (Vit. A, C, E, selenium, manganese) produced lower interferon-gamma and PGE₂, compared to placebo.¹²⁶ In general, these data suggest that individuals with inflammatory bowel conditions may be benefited by increasing fish oil intake equivalent to 2.5-5 grams per day.

Depression and Other Mood Disorders

Long chain n-3 fatty acids are important components of membranes within neurological organs and tissues. They affect membrane fluidity and excitability, influence synaptic function, and perhaps serotonin and dopamine metabolism.^{128,145} In several epidemiological studies, fish consumption is related to decreased risk of depression, especially in women.^{129,130,131} Although not all cohort studies proved statistically significant,^{132,133} a recent case-controlled study (China) reported that low red blood cell EPA levels are associated with increased risk for attempting suicide.¹³⁹ Previous reports suggest there is a link between violent suicides and seasonal intake of EPA.¹⁴⁰

Several clinical trials have used n-3 fatty acids to treat depression and related disorders.¹⁴¹ Most of the studies to date have used a preparation of pure EPA (EE form). Peet et al.¹⁴² reported that 1 gram (but not 2 grams) of EPA improved depression scores in patients (n=17 each group) with ongoing medicated depression. However, Nemets et al.¹⁴³ reported that similar patients (n=20) receiving 2 grams per day of a comparable preparation had highly significant reduction in Hamilton depression scale scores (mean 12.4 point reduction vs. 1.6 for placebo). This same group attempted to use this preparation at the same dose to treat medicated patients with obsessive compulsive disorder (OCD) without success.¹⁴⁴ Pure DHA (2 g/day) had only a small, non-statistical benefit in patients with major depression. Bipolar patients given high doses of fish oil (6.2 g EPA/3.2 g DHA) had a significantly longer period before relapse than similar patients taking olive oil.¹⁴⁷ Physicians treating patients with depression or related disorders should consider measuring patient serum fatty acid levels and including fish oil supplements (particularly EPA) at 1-2 grams per day.

Maternal and Infant Care

Maternal fatty acid levels, especially DHA levels steadily drop in late pregnancy,¹³⁵ increasing risk for post-partum depression.^{136,137} A meta-analysis of 41 studies showed that lower fish consumption and breast milk DHA content were associated with increased risk for post-partum

depression.¹³⁴ Low doses of DHA (200 mg/day -algae-derived) given post-delivery, however, were unable to significantly lower symptoms of post-partum depression.¹³⁸

The role of n-3 fatty acids in maternal gestation and parturition, as well as offspring development has been reviewed elsewhere.¹⁴⁸ Generally, women with higher n-6 to n-3 intake have a higher likelihood to deliver prematurely. This phenomenon is thought to be related to changes in eicosanoid production (prostaglandins, leukotrienes) which take place prior to parturition. Epidemiological studies suggest that gestation is generally longer in women with higher intake of n-3 fatty acids from fish in some cohorts,^{149,150} but not in others.^{151,152,153} High n-6 to n-3 fatty ratios also correlate to an increased risk for preeclampsia.^{154,155} Intervention trials, during high risk pregnancies have shown some improvement in prolonging gestation (2.7 g/day n-3),^{156,157} but not in pregnancy related hypertension.¹⁵⁷⁻¹⁶⁰

Rapid growth in the brain occurs during the last trimester of pregnancy and the first several postnatal months. The need for maternal DHA is critical during these months since fetal and newborn fatty acid metabolism is inadequate to provide proper levels of DHA for brain development. Several reports suggest that maternal supplementation of fish oils or DHA alone during the third trimester and while breast-feeding can improve cognitive development in newborns,¹⁶¹ improve sleep patterns (a measure of brain development),¹⁶² and even increase IQ scores at age 4.¹⁶³ Maternal fish oil supplementation (3.7 g/day n-3, 56% DHA) in atopic women (offspring considered at high risk for allergic diseases) significantly increased breast milk levels of the protective Immunoglobulin A (IgA) and CD14.¹⁶⁴ Children born from these mothers have reduced levels of allergic related cytokines and allergen-specific immune responses.^{165,166,167,168} Children at high risk for atopic diseases had reduced allergy-related cough at age 3 if they were supplemented with fish oil (500 mg of tuna oil/d- 185 mg n-3) from 6 months to 3 years.¹⁶⁹ Eating high levels of n-3 fatty acids directly from fish is contraindicated in young children and pregnant women due to the potential for ingesting mercury and other toxins. Fish oil supplements, virtually free of these toxins,^{170,171} are safer and allow for specific dosing regimens. Many liquid as well as capsule preparations can be used which provide varying levels of DHA, some of which are specially prepared and flavored for children.

Ocular and Cognitive Health

As a specialized portion of the nervous system, the retina has one of the highest levels of long-chain fatty acids in the human body; especially concentrated is the level of DHA.^{172,173} Infant visual acuity is diminished in n-3 deficiency. Children supplemented with DHA (115 mg/day) from 6 months to 1 year of age had significantly better improved visual acuity than similar control children.¹⁷⁴ The long-term visual benefits for infant supplementation is not

yet known. In adults, fish and DHA intake (determined by food questionnaire) reduces the risk for age-related macular degeneration.^{175,176} Preventative or intervention trials in patients with or at risk for macular degeneration have not been published.

The relationship between DHA and retinitis pigmentosa (RP) is currently being investigated. RP patients have lower levels of DHA,¹⁷⁷ partly due to reduced activity of the enzyme delta-5-desaturase.¹⁷⁸ Despite this relationship, trials attempting to slow the progression of RP with supplementation of DHA have been unsuccessful,^{179,180} although chronic vitamin A users who added 1200 mg/d of DHA had some slowing in progression after 2 years.¹⁸¹

Increased dietary intake of fish and DHA (but not EPA) is correlated (cohort of 815) with a decreased risk of Alzheimer's disease.¹⁸² Whether this correlation will prove to be of preventative or therapeutic benefit is yet to be determined. Studies also suggest that DHA is protective against dendritic cell damage in a mouse model of Alzheimer's disease.¹⁸⁵

Fish Oil- The Product

Recommendations to increase fish consumption are not always straightforward. Some fish have high levels of EPA and DHA; others do not (see chart figure 1). How the fish is prepared also has a significant affect on whether these long-chain fatty acids will be beneficial. In a population-based cohort study, dietary fish consumption was correlated with increased plasma n-3 levels and reduced risk of cardiovascular death in individuals consuming tuna or other similar fish (broiled or baked), but neither was associated with fried fish or fish sandwiches (fish burgers).⁹¹ The same group reported similar differences for reducing the risk of atrial fibrillations in these different populations based on type of fish consumed.⁹² The susceptibility to loss or modification of EPA and DHA has been reported in various cooking processes, especially deep-frying.⁹³ The additional potential hazard of consuming environmental toxins such as methyl mercury and other heavy metals or pesticides like DDT, DDE or PCBs is a concern for many. The Environmental Protection Agency warns those most at risk (pregnant women, nursing mothers and their infants and young children) to limit fish intake to avoid potentially dangerous mercury levels.⁹⁴ Several advantages of fish oil supplements directly address these concerns. Levels of EPA and DHA are consistently dosed in capsule or liquid products. Levels of heavy metals and pesticides can be dramatically reduced, often below detectable limits, when using fish oil supplements in lieu of consuming more fish.^{170,171} Fish oil is inherently more susceptible to oxidation, requiring that most products contain additional fat-soluble antioxidants such as natural vitamin E, fat soluble ascorbates or other natural antioxidants to protect them from becoming rancid under normal storage conditions.

Commercial fish oil is a by-product of the fish meal industry. It is typically a blend of many different fish species including mackerel, anchovies, sardines, tuna, salmon and others. The raw oil from these fish is then purified and concentrated by removing (hydrolyzing) the individual fatty acids from the fish triglycerides so the various fatty acids can be separated and concentrated. This process allows for the separation of contaminant toxins, proteins (which may increase allergenicity and burping), and other non n-3 fatty acids. These concentrated fatty acids remain as free fatty acids (FFA) before they are stabilized by esterification to ethanol (ethyl esters, EE) or further esterified back to a glycerol backbone to create a re-esterified triglyceride (rTG). Both EE and rTG forms of varying concentration (30-70% EPA+DHA) are used in the dietary supplement industry throughout the United States.

Few studies have looked at differences between fish oil supplements provided as EE or rTG. One study reported that plasma EPA and DHA levels were higher when equivalent levels of these fatty acids were consumed directly from salmon than from fish oil supplements provided as ethyl esters.⁹⁵ Whether the ethyl ester form diminished or some fish component enhanced bioavailability is not known. Several studies have shown that plasma bioavailability of the EE form is less than 50% of that from the rTG form.^{96,97,98} Other studies, however, show no difference in bioavailability between these two forms.^{99,100} All of these studies were uncontrolled and involved very few subjects. Dyerberg et al.¹¹⁴ completed a study involving 72 subjects, comparing the bioavailability of EPA and DHA from natural fish triglycerides, EE, rTG, cod liver oil and FFA. They found that compared to natural fish TG (100% standard), the bioavailability of EPA and DHA combined was highest from the re-esterified TG (124%) and lowest from EE (73%). The EPA and DHA incorporated into phospholipids was 62% and 290% greater when consumed as rTG rather than EE. At this time there are no trials comparing the potential differences in the EE and rTG forms as it pertains to clinical outcomes (triacylglyceride lowering, hypertension, etc.); many reports don't specify the forms used. Since data suggests that individuals are likely to absorb the rTG form better, and lipase and biological incorporation of the EE is diminished,^{99,101} clinical trials should be done to assess whether the rTG form may have better clinical outcomes, or require lower doses for equivalent results. Consistent results at a lower dose would help increase compliance and reduce both side-effects and cost.

As with any dietary supplement, choosing a high-quality fish oil product is important. The Council for Responsible Nutrition (CRN), along with many of the leading fish oil manufacturers in the world, published a monograph in 2002 outlining various quality aspects which the industry should use to regulate fish oil products.¹⁰² This monograph stipulates upper limits for mercury and other

heavy metals, pesticide levels and oxidation levels such as peroxide and anisidine values. These guidelines have been adopted by the United States Pharmacopoeia (USP) for their current n-3 fatty acid from fish oil monograph.¹⁰³ Additionally, some companies monitor the production from catch to finished product in order to provide kosher products to the market.

Side-effects and Contraindications

High-dose fish oil supplementation is extremely well tolerated in nearly all individuals. The most common side-effect is a fishy aftertaste or "burping" associated with high doses. When products are consumed with meals and carbonated beverages are avoided, this unpleasant feature is dramatically reduced. The complete purification of the fatty acids from fish proteins virtually eliminates the potential for allergic components in the fish oil supplements. Because fish oil is prone to oxidation, consuming high doses without additional antioxidant protection (from diet or supplemental sources) may increase vulnerability to lipid peroxidation, especially in warm and sunny climates. While the in vivo consequences of this vulnerability are still being debated, antioxidant supplementation should be recommended for every individual consuming high amounts (3 grams or more) of fish oil daily. These high doses can be consumed directly from bottles for those wanting to avoid gelatin capsules due to concerns about consuming non-fish animals in general or bovine-derived products specifically.

The most frequent contraindication concern is the combination of high dose fish oil with pharmaceutical drugs that affect blood clotting (coumadin, aspirin, etc.), used by many cardiovascular patients. A group of 250 patients who had undergone coronary artery bypass surgery were given 4 g/day of fish oil concentrate and either aspirin (300 mg/d) or warfarin therapy.¹¹¹ Compared to patients not receiving fish oil, these patients had no increase in bleeding time. Another report showed no change in INR when 6 g/day of fish oil was given to patients on chronic warfarin therapy.¹¹² However, one case report has been published of a woman (67 years old on coumadin, 1.5 years at 1.5 mg/day) who had an increased INR (2.8 to 4.3) in the month she doubled her fish oil supplement from 1 to 2 g/day.¹¹³ These data suggest that the concern for bleeding times is generally not an issue, but INR should be checked in patients on both warfarin and fish oil therapies.

CONCLUSION

Epidemiological evidence is quite clear in demonstrating numerous health benefits in consuming long-chain polyunsaturated n-3 fatty acid from fish, especially as a ratio to n-6 fatty acids derived from vegetable oils. Even an "Omega-3 Index" of RBC EPA and DHA levels is being proposed as a routine laboratory test for measuring cardiovascular risk.¹⁰⁹ In the past decade, the clinical use of fish

oil supplements has greatly increased, as has the data supporting their use. While dietary and lifestyle changes are ideal ways to modify a number of cardiovascular risk factors, many individuals with personal or family history of cardiovascular disease cannot safely consume high levels of n-3 fatty acids from fish alone, or do not maintain the dietary habit.²⁴ Since fish oil supplements have been shown to have beneficial effects on nearly every risk factor for cardiovascular disease, and so many individuals are currently at risk, the recommendation to use these supplements in clinical practice is encouraged. There are few patients who would not realize some benefit by increasing their fatty fish consumption or adding fish oil supplements to their daily routine. Patients with previous CHD, hypertriglyceridemia, hypertension, type II diabetes or metabolic syndrome should be taking at least 2 g/day of n-3 fatty acids from fish oil daily via supplements. Pregnant women should be encouraged to consume fish oil supplements to increase n-3 fatty acids, particularly DHA throughout the second half of pregnancy and while breast-feeding.

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REFERENCES

1. Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr.* 1975;28(9):958-66.
2. Wijendran V, Hayes KC. Dietary n-6 and n-3 fatty acid balance and cardiovascular health. *Annu Rev Nutr.* 2004;24:597-615.
3. Burdge GC, Wootton SA. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *Br J Nutr.* 2002;88(4):411-20.
4. Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. *Curr Opin Clin Nutr Metab Care.* 2004;7(2):137-44.
5. de Lorgeril M, Renaud S, Mamelle N et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet.* 1994; 343(8911):1454-9.
6. Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease—fishing for a natural treatment. *BMJ.* 2004; 328(7430):30-5.
7. Holub DJ, Holub BJ. Omega-3 fatty acids from fish oils and cardiovascular disease. *Mol Cell Biochem.* 2004; 263(1-2):217-25.
8. Covington MB. Omega-3 fatty acids. *Am Fam Physician.* 2004; 70(1):133-40.
9. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002; 106(21):2747-57.

10. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation*. 2003; 107(21):2646-52.
11. Daviglus ML, Stamler J et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med*. 1997; 336(15):1046-53.
12. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985; 312(19):1205-9.
13. Dolecek TA, Granditis G. Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev Nutr Diet*. 1991;66:205-16.
14. Lapidus L, Andersson H, Bengtsson C, Bosaeus I. Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Am J Clin Nutr*. 1986; 44(4):444-8.
15. Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med*. 1995; 332(15):977-82.
16. Guallar E, Hennekens CH, Sacks FM, Willett WC, Stampfer MJ. A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. *J Am Coll Cardiol*. 1995; 25(2):387-94.
17. Albert CM, Hennekens CH et al. Fish consumption and risk of sudden cardiac death. *JAMA*. 1998; 279(1):23-8.
18. Albert CM, Campos H et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002; 346(15):1113-8.
19. Rodriguez BL, Sharp DS et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. *Circulation*. 1996; 94(5):952-6.
20. Siscovick DS, Raghunathan T et al. Dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr*. 2000; 71(1 Suppl):208S-12S.
21. American Heart Association Website <http://www.american-heart.org> Accessed Dec 17, 2004
22. Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol*. 2001; 154(9):809-16.
23. Burr ML, Fehily AM et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*. 1989; 2(8666):757-61.
24. Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). *Eur J Clin Nutr*. 2002; 56(6):512-8.
25. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999; 354(9177):447-55.
26. Marchioli R, Barzi F et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002; 105(16):1897-903.
27. Hu FB, Bronner L, Willett WC et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA*. 2002; 287(14):1815-21.
28. Yzebe D, Lievre M. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. *Fundam Clin Pharmacol*. 2004; 18(5):581-92.
29. Pepe S, McLennan PL. Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. *J Nutr*. 1996; 126(1):34-42.
30. McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *Am Heart J*. 1988; 116(3):709-17.
31. McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Dietary lipid modulation of ventricular fibrillation threshold in the marmoset monkey. *Am Heart J*. 1992; 123(6):1555-61.
32. McLennan PL. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr*. 1993; 57(2):207-12.
33. Leifert WR, Jahangiri A, Saint DA, McMurchie EJ. Effects of dietary n-3 fatty acids on contractility, Na(+) and K(+) currents in a rat cardiomyocyte model of arrhythmia. *J Nutr Biochem*. 2000; 11(7-8):382-92.
34. Leaf A, Xiao YF, Kang JX. Interactions of n-3 fatty acids with ion channels in excitable tissues. *Prostaglandins Leukot Essent Fatty Acids*. 2002; 67(2-3):113-20.
35. Xiao YF, Ke Q, Chen Y, Morgan JP, Leaf A. Inhibitory effect of n-3 fish oil fatty acids on cardiac Na⁺/Ca²⁺ exchange currents in HEK293t cells. *Biochem Biophys Res Commun*. 2004; 321(1):116-23.
36. McLennan PL. Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. *Lipids*. 2001; 36 Suppl:S111-4.
37. Leaf A, Kang JX, Xiao YF, Billman GE, Voskuyl RA. The antiarrhythmic and anticonvulsant effects of dietary N-3 fatty acids. *J Membr Biol*. 1999; 172(1):1-11.
38. Schrepf R, Limmert T, Claus Weber P, Theisen K, Sellmayer A. Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia. *Lancet*. 2004; 363(9419):1441-2.
39. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998; 81(4A):7B-12B.

40. Cullen P. Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol.* 2000; 86(9):943-9.
41. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr.* 1997; 65(5 Suppl):1645S-1654S.
42. Roche HM, Gibney MJ. Effect of long-chain n-3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism. *Am J Clin Nutr.* 2000; 71(1 Suppl):232S-7S.
43. Patsch JR, Miesenbock G et al. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. *Arterioscler Thromb.* 1992; 12(11):1336-45.
44. Harris WS, Connor WE, Alam N, Illingworth DR. Reduction of postprandial triglyceridemia in humans by dietary n-3 fatty acids. *J Lipid Res.* 1988; 29(11):1451-60.
45. Smith BK, Sun GY, Donahue OM, Thomas TR. Exercise plus n-3 fatty acids: additive effect on postprandial lipemia. *Metabolism.* 2004; 53(10):1365-71.
46. Lu G, Windsor SL, Harris WS. Omega-3 fatty acids alter lipoprotein subfraction distributions and the in vitro conversion of very low density lipoproteins to low density lipoproteins. *J Nutr Biochem.* 1999; 10(3):151-158.
47. Theobald HE, Chowienzyk PJ et al. LDL cholesterol-raising effect of low-dose docosahexaenoic acid in middle-aged men and women. *Am J Clin Nutr.* 2004; 79:558-63.
48. Geelen A, Brouwer IA, Schouten EG, Kluft C, Katan MB, Zock PL. Intake of n-3 fatty acids from fish does not lower serum concentrations of C-reactive protein in healthy subjects. *Eur J Clin Nutr.* 2004; 58(10):1440-2.
49. Mori TA, Woodman RJ et al. Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and inflammatory markers in treated-hypertensive type 2 diabetic subjects. *Free Radic Biol Med.* 2003; 35(7):772-81.
50. Szapary PO, Rader DJ. The triglyceride-high-density lipoprotein axis: an important target of therapy? *Am Heart J.* 2004; 148(2):211-21.
51. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002; 287(3):356-9.
52. Isomaa B. A major health hazard: the metabolic syndrome. *Life Sci.* 2003; 73(19):2395-411.
53. Huang YJ, Fang VS et al. Amelioration of insulin resistance and hypertension in a fructose-fed rat model with fish oil supplementation. *Metabolism.* 1997; 46(11):1252-8.
54. Aguilera AA, Diaz GH, Barcelata ML, Guerrero OA, Ros RM. Effects of fish oil on hypertension, plasma lipids, and tumor necrosis factor-alpha in rats with sucrose-induced metabolic syndrome. *J Nutr Biochem.* 2004; 15(6):350-7.
55. Peyron-Caso E, Fluteau-Nadler S et al. Regulation of glucose transport and transporter 4 (GLUT-4) in muscle and adipocytes of sucrose-fed rats: effects of N-3 poly- and monounsaturated fatty acids. *Horm Metab Res.* 2002; 34(7):360-6.
56. Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension.* 1998; 32(4):710-7.
57. Calabresi L, Villa B et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. *Metabolism.* 2004; 53(2):153-8.
58. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation.* 2003; 107(14):1852-7.
59. Sirtori CR, Paoletti R et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study. *Am J Clin Nutr.* 1997; 65(6):1874-81.
60. Goh YK, Jumpsen JA, Ryan EA, Clandinin MT. Effect of omega 3 fatty acid on plasma lipids, cholesterol and lipoprotein fatty acid content in NIDDM patients. *Diabetologia.* 1997; 40(1):45-52.
61. Rivellese AA, Maffettone A et al. Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes Care.* 1996; 19(11):1207-13.
62. Mollsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001; 24(5):805-10.
63. Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S. Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. *Lipids.* 1990; 25(9):541-5.
64. Gerbi A, Maixent JM et al. Fish oil supplementation prevents diabetes-induced nerve conduction velocity and neuroanatomical changes in rats. *J Nutr.* 1999; 129(1):207-13.
65. Coste TC, Gerbi A, Vague P, Pieroni G, Raccach D. Neuroprotective effect of docosahexaenoic acid-enriched phospholipids in experimental diabetic neuropathy. *Diabetes.* 2003; 52(10):2578-85.
66. Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004; 80(3):626-32.
67. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation.* 1993; 88(2):523-33.
68. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep.* 2004; 6(6):461-7.
69. Roland I, De Leval X et al. Modulation of the arachidonic cascade with omega3 fatty acids or analogues: potential therapeutic benefits. *Mini Rev Med Chem.* 2004; 4(6):659-68.

70. Yaqoob P, Calder PC. N-3 polyunsaturated fatty acids and inflammation in the arterial wall. *Eur J Med Res.* 2003; 8(8):337-54.
71. Lopez-Garcia E, Schulze MB et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr.* 2004; 134(7):1806-11.
72. Pischon T, Hankinson SE et al. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation.* 2003; 108(2):155-60.
73. Zhao G, Etherton TD et al. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr.* 2004; 134(11):2991-7.
74. Nestel P, Shige H et al. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans. *Am J Clin Nutr.* 2002; 76(2):326-30.
75. Nestel PJ, Pomeroy SE et al. Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability. *Arterioscler Thromb Vasc Biol.* 1997; 17(6):1163-70.
76. McVeigh GE, Brennan GM et al. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb.* 1994; 14(9):1425-9.
77. Calder PC. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin Sci (Lond).* 2004; 107(1):1-11.
78. Lopez D, Orta X et al. Upregulation of endothelial nitric oxide synthase in rat aorta after ingestion of fish oil-rich diet. *Am J Physiol Heart Circ Physiol.* 2004; 287(2):H567-72.
79. Das UN. Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-beta to prevent human essential hypertension. *Eur J Clin Nutr.* 2004; 58(2):195-203.
80. Boger RH. Association of asymmetric dimethylarginine and endothelial dysfunction. *Clin Chem Lab Med.* 2003; 41(11):1467-72.
81. Raimondi L, Lodovici M et al. n-3 polyunsaturated fatty acids supplementation decreases asymmetric dimethyl arginine and arachidonate accumulation in aging spontaneously hypertensive rats. *Eur J Nutr.* 2004 Sep 14-Online.
82. Nomura S, Kanazawa S, Fukuhara S. Effects of eicosapentaenoic acid on platelet activation markers and cell adhesion molecules in hyperlipidemic patients with Type 2 diabetes mellitus. *J Diabetes Complications.* 2003; 17(3):153-9.
83. Thies F, Miles EA et al. Influence of dietary supplementation with long-chain n-3 or n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. *Lipids.* 2001; 36(11):1183-93.
84. De Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. *Am J Clin Nutr.* 2000; 71(1 Suppl):213S-23S.
85. Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. *Arterioscler Thromb Vasc Biol.* 1997; 17(2):279-86.
86. Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids.* 2001;36 Suppl:S79-82.
87. Vanschoonbeek K, Feijge MA et al. Variable hypocoagulant effect of fish oil intake in humans: modulation of fibrinogen level and thrombin generation. *Arterioscler Thromb Vasc Biol.* 2004; 24(9):1734-40.
88. Thies F, Garry JM, Yaqoob P et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet.* 2003; 361(9356):477-85.
89. Chambrier C, Bastard JP et al. Eicosapentaenoic acid induces mRNA expression of peroxisome proliferator-activated receptor gamma. *Obes Res.* 2002; 10(6):518-25.
90. Diep QN, Touyz RM, Schiffrin EL. Docosahexaenoic acid, a peroxisome proliferator-activated receptor-alpha ligand, induces apoptosis in vascular smooth muscle cells by stimulation of p38 mitogen-activated protein kinase. *Hypertension.* 2000; 36(5):851-5.
91. Mozaffarian D, Lemaitre RN et al. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation.* 2003; 107(10):1372-7.
92. Mozaffarian D, Psaty BM et al. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004; 110(4):368-73.
93. M. Candela, I. Astiasarán, Bello J. Deep-Fat Frying Modifies High-Fat Fish Lipid Fraction *J. Agric. Food Chem.* 1998; 46(7): 2793 -2796
94. <http://www.epa.gov/waterscience/fish/>- accessed Dec 23, 2004
95. Visioli F, Rise P, Barassi MC, Marangoni F, Galli C. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids.* 2003; 38(4):415-8.
96. Lawson LD, Hughes BG. Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. *Biochem Biophys Res Commun.* 1988; 152(1):328-35.
97. Beckermann B, Beneke M, Seitz I. Comparative bioavailability of eicosapentaenoic acid and docosahexaenoic acid from triglycerides, free fatty acids and ethyl esters in volunteers. *Arzneimittelforschung.* 1990; 40(6):700-4. Article in German- Abstract only
98. Lawson LD, Hughes BG. Absorption of eicosapentaenoic acid and docosahexaenoic acid from fish oil triacylglycerols or fish oil ethyl esters co-ingested with a high-fat meal. *Biochem Biophys Res Commun.* 1988; 156(2):960-3.
99. Krokan HE, Bjerve KS, Mork E. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. *Biochim Biophys Acta.* 1993; 1168(1):59-67.

100. Nordoy A, Barstad L, Connor WE, Hatcher L. Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans. *Am J Clin Nutr.* 1991; 53(5):1185-90.
101. Hong DD, Takahashi Y, Kushiro M, Ide T. Divergent effects of eicosapentaenoic and docosahexaenoic acid ethyl esters, and fish oil on hepatic fatty acid oxidation in the rat. *Biochim Biophys Acta.* 2003; 1635(1):29-36.
102. CRN website <http://www.crnusa.org/shellnr100802B.html> Accessed Dec 23, 2004
103. USP Website <http://www.uspverified.org/standards/monographs.html>
104. Mori TA, Bao DQ, et al. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension.* 1999; 34(2):253-60.
105. Mori TA, Watts GF et al. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. *Circulation.* 2000; 102(11):1264-9.
106. Mori TA, Burke V et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *Am J Clin Nutr.* 2000; 71(5):1085-94.
107. Buckley R, Shewring B et al. Circulating triacylglycerol and apoE levels in response to EPA and docosahexaenoic acid supplementation in adult human subjects. *Br J Nutr.* 2004; 92(3):477-83.
108. Park Y, Jones PG, Harris WS. Triacylglycerol-rich lipoprotein margination: a potential surrogate for whole-body lipoprotein lipase activity and effects of eicosapentaenoic and docosahexaenoic acids. *Am J Clin Nutr.* 2004; 80(1):45-50.
109. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev Med.* 2004; 39(1):212-20.
110. Grimsgaard S, Bonna KH, Hansen JB, Nordoy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr.* 1997; 66(3):649-59.
111. Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis.* 1995; 6(1):17-22.
112. Bender NK, Kraynak MA et al. Effects of Marine Fish Oils on the Anticoagulation Status of Patients Receiving Chronic Warfarin Therapy. *J Thromb Thrombolysis.* 1998; 5(3):257-261.
113. Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. *Ann Pharmacother.* 2004; 38(1):50-2.
114. Dyerberg J, Madsen P et al. Bioavailability on n-3 fatty acid formulations. *N-3 Fatty Acids: Prevention and Treatment in Vascular Disease.* 1995; Bi & Gi Publisheshers, Verona-Springer Verlag, London.
115. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep.* 2004; 6(6):461-7.
116. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr.* 2002; 21(6):495-505.
117. Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. *Proc Natl Acad Sci U S A.* 2003; 100(4):1751-6.
118. Calder PC. N-3 polyunsaturated fatty acids and inflammation: from molecular biology to the clinic. *Lipids.* 2003; 38(4):343-52.
119. Cleland LG, James MJ, Proudman SM. The role of fish oils in the treatment of rheumatoid arthritis. *Drugs.* 2003;63(9):845-53.
120. Fortin PR, Lew RA et al. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *J Clin Epidemiol.* 1995; 48(11):1379-90.
121. Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. A 12-month, double-blind, controlled study. *Arthritis Rheum.* 1994; 37(6):824-9.
122. Adam O, Beringer C et al. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatol Int.* 2003; 23(1):27-36.
123. Volker D, Fitzgerald P, Major G, Garg M. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *J Rheumatol.* 2000; 27(10):2343-6.
124. Belluzzi A. N-3 fatty acids for the treatment of inflammatory bowel diseases. *Proc Nutr Soc.* 2002; 61(3):391-5.
125. Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med.* 1996; 334(24):1557-60.
126. Trebble TM, Arden NK et al. Fish oil and antioxidants alter the composition and function of circulating mononuclear cells in Crohn disease. *Am J Clin Nutr.* 2004; 80(5):1137-44.
127. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr.* 2000; 71(1 Suppl):343S-8S.
128. Hibbeln JR, Linnoila M et al. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol Psychiatry.* 1998; 44(4):235-42.
129. Timonen M, Horrobin D et al. Fish consumption and depression: the Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004; 82(3):447-52.

130. Tanskanen A, Hibbeln JR et al. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001; 52(4):529-31.
131. Hibbeln JR. Fish consumption and major depression. *Lancet.* 1998; 351(9110):1213.
132. Hakkarainen R, Partonen T et al. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry.* 2004; 161(3):567-9.
133. Jacka EN, Pasco JA et al. Dietary omega-3 fatty acids and depression in a community sample. *Nutr Neurosci.* 2004; 7(2):101-6.
134. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord.* 2002; 69(1-3):15-29.
135. Al MD, van Houwelingen AC et al. Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. *Br J Nutr.* 1995; 74(1):55-68.
136. Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Docosahexaenoic acid and post-partum depression - is there a link? *Asia Pac J Clin Nutr.* 2003;12 Suppl:S37.
137. Otto SJ, de Groot RH, Hornstra G. Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. *Prostaglandins Leukot Essent Fatty Acids.* 2003; 69(4):237-43.
138. Llorente AM, Jensen CL et al. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol.* 2003; 188(5):1348-53.
139. Huan M, Hamazaki K et al. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. *Biol Psychiatry.* 2004; 56(7):490-6.
140. De Vriese SR, Christophe AB, Maes M. In humans, the seasonal variation in poly-unsaturated fatty acids is related to the seasonal variation in violent suicide and serotonergic markers of violent suicide. *Prostaglandins Leukot Essent Fatty Acids.* 2004; 71(1):13-8.
141. Logan AC. Omega-3 fatty acids and major depression: A primer for the mental health professional. *Lipids Health Dis.* 2004; 3(1):25.
142. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry.* 2002; 59(10):913-9.
143. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry.* 2002; 159(3):477-9.
144. Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. *J Psychiatr Res.* 2004; 38(3):323-5.
145. Hirashima F, Parow AM et al. Omega-3 fatty acid treatment and T(2) whole brain relaxation times in bipolar disorder. *Am J Psychiatry.* 2004; 161(10):1922-4.
146. Marangell LB, Martinez JM et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry.* 2003; 160(5):996-8.
147. Stoll AL, Severus WE et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry.* 1999; 56(5):407-12.
148. Allen KG, Harris MA. The role of n-3 fatty acids in gestation and parturition. *Exp Biol Med.* 2001; 226(6):498-506.
149. Olsen SF, Secher NJ. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *BMJ.* 2002; 324(7335):447.
150. Olsen SF, Hansen HS et al. Gestational age in relation to marine n-3 fatty acids in maternal erythrocytes: a study of women in the Faroe Islands and Denmark. *Am J Obstet Gynecol.* 1991; 164(5 Pt 1):1203-9.
151. Rogers I, Emmett P, Ness A, Golding J. Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. *J Epidemiol Community Health.* 2004; 58(6):486-92.
152. Olsen SF, Hansen HS et al. Gestation length and birth weight in relation to intake of marine n-3 fatty acids. *Br J Nutr.* 1995; 73(3):397-404.
153. Oken E, Kleinman KP, Olsen SF et al. Associations of seafood and elongated n-3 fatty acid intake with fetal growth and length of gestation: results from a US pregnancy cohort. *Am J Epidemiol.* 2004; 160(8):774-83.
154. Williams MA, Zingheim RW, King IB, Zebelman AM. Omega-3 fatty acids in maternal erythrocytes and risk of preeclampsia. *Epidemiology.* 1995; 6(3):232-7.
155. Velzing-Aarts FV, van der Klis FR, van der Dijs FP, Muskiet FA. Umbilical vessels of preeclamptic women have low contents of both n-3 and n-6 long-chain polyunsaturated fatty acids. *Am J Clin Nutr.* 1999; 69(2):293-8.
156. Olsen SF, Sorensen JD et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet.* 1992; 339(8800):1003-7.
157. Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. *BJOG.* 107(3):382-95.
158. Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *Br J Obstet Gynaecol.* 1995; 102(2):95-100.
159. Salvig JD, Olsen SF, Secher NJ. Effects of fish oil supplementation in late pregnancy on blood pressure: a randomised controlled trial. *Br J Obstet Gynaecol.* 1996; 103(6):529-33.

160. Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. *Br J Obstet Gynaecol.* 1995; 102(2):123-6.
161. Colombo J, Kannass KN et al. Maternal DHA and the development of attention in infancy and toddlerhood. *Child Dev.* 2004; 75(4):1254-67.
162. Cheruku SR, Montgomery-Downs HE et al. Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. *Am J Clin Nutr.* 2002; 76(3):608-13.
163. Helland IB, Smith L et al. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics.* 2003; 111(1):e39-44.
164. Dunstan JA, Roper J et al. The effect of supplementation with fish oil during pregnancy on breast milk immunoglobulin A, soluble CD14, cytokine levels and fatty acid composition. *Clin Exp Allergy.* 2004; 34(8):1237-42.
165. Barden AE, Mori TA et al. Fish oil supplementation in pregnancy lowers F2-isoprostanes in neonates at high risk of atopy. *Free Radic Res.* 2004; 38(3):233-9.
166. Dunstan JA, Mori TA et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol.* 2003; 112(6):1178-84.
167. Dunstan JA, Mori TA et al. Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. *Clin Exp Allergy.* 2003; 33(4):442-8.
168. Denburg JA, Hatfield HM et al. Fish Oil Supplementation in Pregnancy Modifies Neonatal Progenitors at Birth in Infants at Risk of Atopy. *Pediatr Res.* 2004; 57(2):pp not available (epub)
169. Peat JK, Mihrshahi S et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol.* 2004; 114(4):807-13.
170. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med.* 2003; 127(12):1603-5.
171. Melanson SF, Lewandrowski EL, Flood JG, Lewandrowski KB. Measurement of organochlorines in commercial over-the-counter fish oil preparations: implications for dietary and therapeutic recommendations for omega-3 fatty acids and a review of the literature. *Arch Pathol Lab Med.* 2005; 129(1):74-7.
172. Jeffrey BG, Weisinger HS, Neuringer M, Mitchell DC. The role of docosahexaenoic acid in retinal function. *Lipids.* 2001; 36(9):859-71.
173. Uauy R, Hoffman DR, Peirano P, Birch DG, Birch EE. Essential fatty acids in visual and brain development. *Lipids.* 2001; 36(9):885-95.
174. Hoffman DR, Theuer RC et al. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. *J Nutr.* 2004; 134(9):2307-13.
175. Cho E, Hung S et al. Prospective study of dietary fat and the risk of age-related macular degeneration. *Am J Clin Nutr.* 2001; 73(2):209-18.
176. Smith W, Mitchell P, Leeder SR. Dietary fat and fish intake and age-related maculopathy. *Arch Ophthalmol.* 2000; 118(3):401-4.
177. Hoffman DR, Birch DG. Docosahexaenoic acid in red blood cells of patients with X-linked retinitis pigmentosa. *Invest Ophthalmol Vis Sci.* 1995; 36(6):1009-18.
178. Hoffman DR, DeMar JC et al. Impaired synthesis of DHA in patients with X-linked retinitis pigmentosa. *J Lipid Res.* 2001; 42(9):1395-401.
179. Hoffman DR, Locke KG et al. A randomized, placebo-controlled clinical trial of docosahexaenoic acid supplementation for X-linked retinitis pigmentosa. *Am J Ophthalmol.* 2004; 137(4):704-18.
180. Berson EL, Rosner B et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. *Arch Ophthalmol.* 2004; 122(9):1297-305.
181. Berson EL, Rosner B et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: subgroup analyses. *Arch Ophthalmol.* 2004; 122(9):1306-14.
182. Morris MC, Evans DA et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol.* 2003; 60(7):940-6.
183. Iso H, Rexrode KM et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA.* 2001; 285(3):304-12.
184. He K, Rimm EB et al. Fish consumption and risk of stroke in men. *JAMA.* 2002; 288(24):3130-6.
185. Calon F, Lim GP et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron.* 2004; 43(5):633-45.
186. Thomas TR, Smith BK et al. Effects of omega-3 fatty acid supplementation and exercise on low-density lipoprotein and high-density lipoprotein subfractions. *Metabolism.* 2004 Jun;53(6):749-54.
187. Griffin BA. The effect of n-3 fatty acids on low density lipoprotein subfractions. *Lipids.* 2001;36 Suppl:S91-7.

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