

## Appendix 2: Omega-3 Research Abstracts

### Brain/neurological

- Depression
- Parkinson's
- Bipolar
- Alzheimer's disease
- Anxiety Schizophrenia
- Migraine headaches

Altern Med Rev. 2007 Sep;12(3):207-27.



[Links](#)

#### **Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids.**

##### **Kidd PM.**

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The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are orthomolecular, conditionally essential nutrients that enhance quality of life and lower the risk of premature death. They function exclusively via cell membranes, in which they are anchored by phospholipid molecules. DHA is proven essential to pre- and postnatal brain development, whereas EPA seems more influential on behavior and mood. Both DHA and EPA generate neuroprotective metabolites. In double-blind, randomized, controlled trials, DHA and EPA combinations have been shown to benefit attention deficit/hyperactivity disorder (AD/HD), autism, dyspraxia, dyslexia, and aggression. For the affective disorders, meta-analyses confirm benefits in major depressive disorder (MDD) and bipolar disorder, with promising results in schizophrenia and initial benefit for borderline personality disorder. Accelerated cognitive decline and mild cognitive impairment (MCI) correlate with lowered tissue levels of DHA/EPA, and supplementation has improved cognitive function. Huntington disease has responded to EPA. Omega-3 phospholipid supplements that combine DHA/EPA and phospholipids into the same molecule have shown marked promise in early clinical trials. Phosphatidylserine with DHA/EPA attached (Omega-3 PS) has been shown to alleviate AD/HD symptoms. Krill omega-3 phospholipids, containing mostly phosphatidylcholine (PC) with DHA/EPA attached, markedly outperformed conventional fish oil DHA/EPA triglycerides in double-blind trials for premenstrual syndrome/dysmenorrhea and for normalizing blood lipid profiles. Krill omega-3 phospholipids demonstrated anti-inflammatory activity, lowering C-reactive protein (CRP) levels in a double-blind trial. Utilizing DHA and EPA together with phospholipids and membrane antioxidants to achieve a triple cell membrane synergy may further diversify their currently wide range of clinical applications.

PMID: 18072818 [PubMed - indexed for MEDLINE]

#### **Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: evidence from animal studies.**

**Calon F, Cole G.**

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Studies in animals clearly show that oral intake of docosahexaenoic acid (DHA) can alter brain DHA concentrations and thereby modify brain functions. This provides us with an opportunity to use DHA as a nutraceutical or pharmaceutical tool in brain disorders such as Alzheimer disease (AD) and Parkinson disease (PD). Most of the published epidemiological studies are consistent with a positive association between high reported DHA consumption or high DHA blood levels and a lower risk of developing AD later in life. Such observations have prompted the investigation of DHA in three different transgenic models of AD. These analyses show that animal models of AD are more vulnerable to DHA depletion than controls and that DHA exerts a beneficial effect against pathological signs of AD, including A beta accumulation, cognitive impairment, synaptic marker loss, and hyperphosphorylation of tau. Multiple mechanisms of action can be associated with the neuroprotective effects of DHA and include antioxidant properties and activation of distinct cell signaling pathways. Although the first randomized clinical assays have yet failed to demonstrate convincing beneficial effects of DHA for AD patients, the knowledge gathered in recent years holds out a hope for prevention and suggests that the elderly and people bearing a genetic risk for AD should at least avoid DHA deficiency.



1: *J Affect Disord.* 2008 Dec;111(2-3):351-9. Epub 2008 May 15.

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FULL-TEXT ARTICLE [Links](#)

## **Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation.**

**da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss A, Andreatini R, Ferraz AC.**

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**BACKGROUND:** Effect of fish oil supplementation in parkinsonian patients with depression measured by Montgomery-Asberg Rating Scale (MADRS), the Clinical Global Impressions Scale (CGI) and Beck Depression Inventory (BECK). **METHOD:** Double-blind, placebo-controlled study analyzed depression in 31 patients with Parkinson's Disease and Major Depression (DSM-IV). The patients were double-blind separated in 2 groups that received fish oil (containing omega-3 fatty acids) or mineral oil capsules for 3 months; each group was separated in 2 new groups: one taking antidepressant medication and another one not taking it. **RESULTS:** 29 patients completed the 12-week trial, 58% were female and the mean age was 64.4 years old. Patients supplemented with fish oil showed a significant decrease in MADRS and CGI-Depression scores, and there was no difference among groups in BDI. 14 patients (42%) met criteria for > or = 50% reduction in MADRS score, 7 patients (22%) met criteria for remission (final MADRS total score < or = 12), and 2 patients (6%) discontinued supplementation of fish oil. HPLC analysis of fatty-acid profile showed increase of omega-3 fatty acid in the erythrocyte membrane of patients taking fish oil.

**CONCLUSION:** These results reveal that PD [Parkinson's disease] patients taking fish oil, with or without antidepressants, presented improvement in depressive symptoms and indicate that the intake of omega-3 can be used with an antidepressant effect or as adjuvant therapy with some other medication. This is a first pilot study with parkinsonian patients and omega-3 supplementation and requires replication in a larger sample.



## Postmortem brain fatty acid profile of levodopa-treated Parkinson disease patients and parkinsonian monkeys.

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Fatty acids play a critical role in brain function but their specific role in the pathophysiology of Parkinson disease (PD) and levodopa-induced motor complications is still unknown. From a therapeutic standpoint, it is important to determine the relation between brain fatty acids and PD because the brain fatty acid content depends on nutritional intake, a readily manipulable environmental factor. Here, we report a postmortem analysis of fatty acid profile by gas chromatography in the brain cortex of human patients (12 PD patients and nine Controls) as well as in the brain cortex of monkeys (four controls, five drug-naïve MPTP monkeys and seven levodopa-treated MPTP monkeys). Brain fatty acid profile of cerebral cortex tissue was similar between PD patients and Controls and was not correlated with age of death, delay to autopsy or brain pH. Levodopa administration in MPTP monkeys increased arachidonic acid content (+7%;  $P < 0.05$ ) but decreased docosahexaenoic acid concentration (-15%;  $P < 0.05$ ) and total n-3:n-6 polyunsaturated fatty acids ratio (-27%;  $P < 0.01$ ) compared to drug-naïve MPTP animals. Interestingly, PD patients who experienced motor complications to levodopa had higher arachidonic acid concentrations in the cortex compared to Controls (+13.6%;  $P < 0.05$ ) and to levodopa-treated PD patients devoid of motor complications (+14.4%;  $P < 0.05$ ). Furthermore, PD patients who took an above-median cumulative dose of levodopa had a higher relative amount of saturated fatty acids but lower monounsaturated fatty acids in their brain cortex ( $P < 0.01$ ). These results suggest that changes in brain fatty acid relative concentrations are associated with levodopa treatment in PD patients and in a non-human primate model of parkinsonism.

### [Lipids, depression and suicide]

[Article in French]

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Polyunsaturated fatty acids are made out of a hydrocarbonated chain of variable length with several double bonds. The position of the first double bond (omega) differentiates polyunsaturated omega 3 fatty acids (for example: alpha-linolenic acid or alpha-LNA) and polyunsaturated omega 6 fatty acids (for example: linoleic acid or LA). These two classes of fatty acids are said to be essential because they cannot be synthesised by the organism and have to be taken from alimentation. The omega 3 are present in linseed oil, nuts, soya beans, wheat and cold water fish whereas omega 6 are present in maize, sunflower and sesame oil. Fatty acids are part of phospholipids and, consequently, of all biological membranes. The membrane fluidity, of crucial importance for its functioning, depends on its lipidic components. Phospholipids composed of chains of polyunsaturated fatty acids increase the membrane fluidity because, by bending some chains, double bonds prevent them from compacting themselves perfectly. Membrane fluidity is also determined by the

phospholipids/free cholesterol ratio, as cholesterol increases membrane viscosity. A diet based on a high proportion of essential polyunsaturated fatty acids (fluid) would allow a higher incorporation of cholesterol (rigid) in the membranes to balance their fluidity, which would contribute to lower blood cholesterol levels. Brain membranes have a very high content in essential polyunsaturated fatty acids for which they depend on alimentation. Any dietary lack of essential polyunsaturated fatty acids has consequences on cerebral development, modifying the activity of enzymes of the cerebral membranes and decreasing efficiency in learning tasks.

**EPIDEMIOLOGICAL DATA:** The prevalence of depression seems to increase continuously since the beginning of the century. Though different factors most probably contribute to this evolution, it has been suggested that it could be related to an evolution of alimentary patterns in the Western world, in which polyunsaturated omega 3 fatty acids contained in fish, game and vegetables have been largely replaced by polyunsaturated omega 6 fatty acids of cereal oils. Some epidemiological data support the hypothesis of a relation between lower depression and/or suicide rates and a higher consumption of fish. These data do not however prove a relation of causality.

**CHOLESTEROL AND DEPRESSION:** Several cohort studies (on nondepressed subjects) have assessed the relationship between plasma cholesterol and depressive symptoms with contradictory results. Though some results found a significant relationship between a decrease of total cholesterol and high scores of depression, some other did not. Studies among patients suffering from major depression signalled more constantly an association between low cholesterol and major depression. Besides, some trials showed that clinical recovery may be associated with a significant increase of total cholesterol.

**CHOLESTEROL AND SUICIDAL BEHAVIOR:** The hypothesis that a low cholesterol level may represent a suicidal risk factor was discovered accidentally following a series of epidemiological studies which revealed an increase of the suicidal risk among subjects with a low cholesterol level. Though some contradictory studies do exist, this relationship has been confirmed by several subsequent cohort studies. These findings have challenged the vast public health programs aimed at promoting the decrease of cholesterol, and even suggested to suspend the administration of lipid lowering drugs. Recent clinical studies on populations treated with lipid lowering drugs showed nevertheless a lack of significant increase of mortality, either by suicide or accident. In addition, several controlled studies among psychiatric patients revealed a decrease of the concentrations of plasma cholesterol among patients who had attempted suicide in comparison with other patients.

**POLYUNSATURATED FATTY ACID AND DEPRESSION:** In major depression, all studies revealed a significant decrease of the polyunsaturated omega 3 fatty acids and/or an increase of the omega 6/omega 3 ratio in plasma and/or in the membranes of the red cells. In addition, two studies found a higher severity of depression when the level of polyunsaturated omega 3 fatty acids or the ratio omega 3/omega 6 was low. Parallel to these modifications, other biochemical perturbations have been reported in major depression, particularly an activation of the inflammatory response system, resulting in an increase of the pro-inflammatory cytokines (interleukins: IL-1b, IL-6 and interferon g) and eicosanoids (among others, prostaglandin E2) in the blood and the CSF of depressed patients. These substances cause a peroxidation and, consequently a catabolism of membrane phospholipids, among others those containing polyunsaturated fatty acids. The cytokines and eicosanoids derive from polyunsaturated fatty acids and have opposite physiological functions according to their omega 3 or omega 6 precursor. Arachidonic acid (omega 6) is, among others, precursor of pro-inflammatory prostaglandin E2 (PGE2), whereas polyunsaturated omega 3 fatty acids inhibit the formation of PGE2. It has been shown that a dietary increase of polyunsaturated omega 3 fatty acids reduced strongly the production of IL-1 beta, IL-2, IL-6 and TNF-alpha (tumor necrosis factor-alpha). In contrast, diets with a higher supply of linoleic acid (omega 6) increased significantly the production of pro-inflammatory cytokines, like TNF-alpha. Therefore, polyunsaturated omega 3 fatty acids could be associated at different levels in the pathophysiology of major depression, on the one hand through their role in the membrane fluidity which influences diverse steps of neurotransmission and, on the other hand, through their function as precursor of pro-inflammatory cytokines and eicosanoids disturbing neurotransmission. In addition, antidepressants could exhibit an immunoregulating effect by reducing the release of pro-inflammatory cytokines, by increasing the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 and, finally, by acting like inhibitors of

cyclo-oxygenase. THERAPEUTIC USE OF FATTY ACIDS: Data available concerning the administration of supplements of DHA (docosahexanoic acid) or other polyunsaturated fatty acids omega 3 are limited. In a double blind placebo-controlled study on 30 patients with bipolar disorder, the addition of polyunsaturated omega 3 fatty acids was associated with a longer period of remission. Moreover, nearly all the other prognosis measures were better in the omega 3 group. Very recently, a controlled trial showed the benefits of adding an omega 3 fatty acid, eicosopentanoic acid, among depressed patients. After 4 weeks, six of the 10 patients receiving the fatty acid were considered as responders in comparison with only one of the ten patients receiving placebo. CONCLUSIONS: Some epidemiological, experimental and clinical data favour the hypothesis that polyunsaturated fatty acids could play a role in the pathogenesis and/or the treatment of depression. More studies however are needed in order to better precise the actual implication of those biochemical factors among the various aspects of depressive illness.

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## Skin

Collagen

### **Polyenoic Fatty Acid Ratios Alter Fibroblast Collagen Production *Via* PGE<sub>2</sub> and PGE Receptor Subtype Response**

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## Abstract

Previous experiments have shown that dietary *n*-6 and *n*-3 polyenoic fatty acids (PFA) have different effects on collagen production, a process that may be related to the formation of prostaglandins (PG). This study tested the hypothesis that fibroblast collagen production could be regulated by different *n*-6:*n*-3 PFA ratios and that the effects were mediated by PGE<sub>2</sub> and altered signaling via the different PGE receptor subtypes. Compared to a bovine serum albumin control, eicosapentaenoic acid (EPA; 20:5 *n*-3) treated cells significantly ( $P < 0.05$ ) increased both collagen production and collagen as a percentage of total cellular protein (C-PTP), but arachidonic acid (AA; 20:4 *n*-6) reduced collagen production and C-PTP. As the amount of AA decreased and that of EPA increased, collagen production and C-PTP increased, especially when ratio of *n*-6:*n*-3 PFA was less than 1:1. C-PTP was significantly correlated with the amount of PGE<sub>2</sub> in the medium. AA- or EPA-treated cells produced similar C-PTP when incubated with 10<sup>-6</sup> M indomethacin, a cyclooxygenase inhibitor. Addition of exogenous PGE<sub>2</sub> to cell cultures treated with 10<sup>-6</sup> M indomethacin for 48 hrs decreased C-PTP in both AA and EPA groups. Decreased C-PTP was observed in AA-treated cells exposed to EP1, EP2, and EP4 PGE receptor agonists and in EPA-treated cells exposed to EP2 and EP4 agonists. AA-treated cell responded to activators of cyclic adenosine monophosphate and protein kinase C by decreasing C-PTP, but EPA-treated cells were unresponsive. In conclusion, collagen production in 3T3-Swiss fibroblasts induced by different *n*-6:*n*-3 PFA ratios was correlated with PGE<sub>2</sub> production and altered responsiveness and signaling *via* the different PGE receptor subtypes.

# Lungs

- Asthma
- Cystic fibrosis (a hereditary gland disease)
- Chronic obstructive pulmonary disease (COPD)

## The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases

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Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.

# Female

- Breast-feeding importance for babies development and IQ
- Dysmenorrhea (painful menstruation)
- Endometriosis
- Estrogen and bone
- PMS and dysmenorrhea

## **Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids.**

### **Kidd PM.**

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The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are orthomolecular, conditionally essential nutrients that enhance quality of life and lower the risk of premature death. They function exclusively via cell membranes, in which they are anchored by phospholipid molecules. DHA is proven essential to pre- and postnatal brain development, whereas EPA seems more influential on behavior and mood. Both DHA and EPA generate neuroprotective metabolites. In double-blind, randomized, controlled trials, DHA and EPA combinations have been shown to benefit attention deficit/hyperactivity disorder (AD/HD), autism, dyspraxia, dyslexia, and aggression. For the affective disorders, meta-analyses confirm benefits in major depressive disorder (MDD) and bipolar disorder, with promising results in schizophrenia and initial benefit for borderline personality disorder. Accelerated cognitive decline and mild cognitive impairment (MCI) correlate with lowered tissue levels of DHA/EPA, and supplementation has improved cognitive function. Huntington disease has responded to EPA. Omega-3 phospholipid supplements that combine DHA/EPA and phospholipids into the same molecule have shown marked promise in early clinical trials. Phosphatidylserine with DHA/EPA attached (Omega-3 PS) has been shown to alleviate AD/HD symptoms. Krill omega-3 phospholipids, containing mostly phosphatidylcholine (PC) with DHA/EPA attached, markedly outperformed conventional fish oil DHA/EPA triglycerides in double-blind trials for premenstrual syndrome/dysmenorrhea and for normalizing blood lipid profiles. Krill omega-3 phospholipids demonstrated anti-inflammatory activity, lowering C-reactive protein (CRP) levels in a double-blind trial. Utilizing DHA and EPA together with phospholipids and membrane antioxidants to achieve a triple cell membrane synergy may further diversify their currently wide range of clinical applications.

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## **The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases**

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Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6

polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. **The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk.** A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. **A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.**

## **Omega-3 Polyunsaturated Fatty Acids and Skeletal Health**

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### **Abstract**

This minireview on skeletal biology describes the actions of prostaglandins and cytokines involved in the local regulation of bone metabolism, it documents the role of lipids in bone biology, and it presents relationships between fatty acids and other factors that impact skeletal metabolism. **The data presented herein show consistent and reproducible beneficial effects of omega-3 (n-3) fatty acids on bone metabolism and bone/joint diseases.** Polyunsaturated fatty acids modulate eicosanoid biosynthesis in numerous tissues and cell types, alter signal transduction, and influence gene expression. These effects have not been explored in the skeletal system. Future research on n-3 fatty acids in bone biology should focus on the following two aspects. First, the further elucidation of how n-3 fatty acids alter biochemical and molecular processes involved in bone modeling and bone cell differentiation, and second, the evaluation of the potential pharmaceutical applications of these nutraceutical fatty acids in maintaining bone mineral status and controlling inflammatory bone/joint diseases.

The best deterrent for osteoporosis is **for women to build strong bones** early in life by consuming a well-balanced diet (vitamin D, calcium, n-6 and n-3 fatty acids, and phytochemicals) and to follow a routine exercise program pre- and postmenopause. Thus far, direct evidence of any beneficial effect of dietary n-3 fatty acids on human osteoporosis is still lacking. However, experiments using animal and cell culture models, and epidemiological data suggest promising applications of n-3 PUFA on this widespread public health problem.

The primary pathogenesis involved in postmenopausal osteoporosis is an uncoupling of bone formation and resorption, which means that the bone resorption rate exceeds that for bone formation. The effect of n-3 fatty acids on bone formation and/or bone resorption was examined in both normal and ovariectomized rats. Iwami-Morimoto *et al.* (122)

studied alveolar bone resorption in 4-week-old rats given diets supplemented with 10% of either fish oil or corn oil for 6 weeks. Dietary fish oil reduced osteoclastic activity (OC number was only 60% of control) and subsequent alveolar bone resorption (80% of control).

Consequently, n-3 fatty acids worked synergistically with estrogen to exert a stimulatory effect on bone mineral deposition and an inhibitory effect on bone resorption.

These studies suggest that using n-3 fatty acid supplements, which are antagonistic to AA in the sense of eicosanoid action, could help maintain bone mineral content after menopause in women. Considering the results from these ovariectomized rat studies (inhibitory to bone resorption) and our findings on n-3 fatty acids in bone modeling (promoting bone formation), it is plausible that consuming diets rich in n-3 fatty acids will help to build and maintain a healthy skeleton in the human

## Other

- Better surgical outcomes on numerous conditions
- Phenylketonuria (specific enzyme deficiency)
- Sickle cell anemia
- Anti-inflammatory
- Immune function
- Autoimmune disease
- Chronic fatigue syndrome
- Type 1 diabetes
- Type 2 diabetes

## Differential Effects of Fatty Acids and Exercise on Body Weight Regulation and Metabolism in Female Wistar Rats

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### Abstract

High-fat diets made with different fats may have distinct effects on body weight regulation and metabolism. In the present study, the metabolic effects of high-fat (HF) diets made with fish oil, palm oil, and soybean oil were compared with a low-fat diet in female Wistar rats that were either exercised (EX, swimming) or that remained sedentary as controls. Each adult rat was exposed to the same diet that their dams consumed during pregnancy and lactation. When they were 9 weeks old, rats began an EX regimen that lasted for 6 weeks. Twenty-four hours after the last EX bout, rats were sacrificed in a fasted state. It was observed that HF feeding of soybean oil induced more body weight and fat gain, as well as insulin resistance, as indicated by insulin/glucose ratios, than other oils. Female rats fed a HF diet made with fish oil had body weight and insulin sensitivity not different from that observed in low fat fed control rats. For rats fed HF diets made with soybean oil or palm oil, EX also exerted beneficial effects by reducing body fat %, blood insulin, triglyceride and leptin levels, as well as improving insulin sensitivity.

## Introduction

It is well established that diets high in fat content induce rapid weight gain, obesity, and insulin resistance in rats (1, 2), mice (3, 4), and humans (5, 6). It has also been reported that different types of fatty acids have different effects on body weight gain and insulin resistance. Saturated fatty acids (SFAs) produce more weight gain and insulin resistance than polyunsaturated fatty acids (PUFAs) in some studies (7–12). However, Hill *et al.* reported more weight gain in rats fed PUFAs than those fed SFAs (13). Of all the PUFAs, long-chain PUFAs (LCPUFAs), such as arachidonic acid (20:4, n-6), eicosapentanoic acid (EPA, 20:5, n-3), and docosahexenoic acid (DHA, 22:6, n-3), exert a more favorable influence on both body weight and metabolic profile compared with other n-6 PUFAs (14, 15). Mice fed soybean oil (mainly n-6 PUFAs) or palm oil (mainly SFAs) gained more weight than mice fed a fish oil diet (mainly n-3 PUFAs; Ref. 4). High intake of linoleic acid also increased fasting blood glucose levels (4). Borkman *et al.* (16) have reported that blood insulin concentration (an indicator of insulin resistance) was negatively correlated with LCPUFA content in muscle. Dietary linoleic acid (18:2, n-6) content, however, is positively associated with blood insulin levels, and it may impair insulin action in animals and humans (4, 17). Partial replacement of the linoleic acid with fish oil (n-3 PUFAs) prevents the onset of insulin resistance (14). Countries with high linoleic acid intake, such as Israel, suffer the highest rate of insulin resistance, Type II diabetes, and cardiovascular diseases (18). SFAs are also known to induce insulin resistance, especially in obese humans (19, 20). Thus, not all fatty acids produce the same effects on body weight regulation and metabolism. High intakes of linoleic acid or SFAs may not be beneficial.

Exercise is commonly recommended to obese patients to reduce body weight gain and insulin resistance (21–23). Exercise also reduces the adverse effects of dietary fat on insulin levels in women (17) and improves insulin sensitivity in high fat fed animals (23).

The interaction of dietary fatty acid composition and exercise on body weight regulation and insulin resistance has not been thoroughly investigated. Bell *et al.* (24) reported that voluntary exercise reduced body fat in mice fed a low fat diet or high fat diets made with beef fat or canola oil without any change in lean body mass. However, beef fat induced more body fat gain in both exercised and nonexercised mice compared with low-fat and canola oil-fed mice. Thus, the quantity of the fat in the diets as well as the type of fats used will affect the body weight regulation. Considering the fact that soybean oil consumption has increased from less than 2 billion pounds in 1950 to 12 billion pounds in 1995–1996 (25), the effects of soybean oil consumption on body weight regulation and metabolism need to be examined. The present study was designed to test the hypothesis that different fatty acids would interact differently with exercise on body weight regulation in female Wistar rats.

## The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases

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and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.

## Differential immunomodulation with long-chain n-3 PUFA in health and chronic disease.

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The balance of intake of n-6 and n-3 PUFA, and consequently their relative incorporation into immune cells, is important in determining the development and severity of immune and inflammatory responses. Some disorders characterised by exaggerated inflammation and excessive formation of inflammatory markers have become among the most important causes of death and disability in man in modern societies. The recognition that long-chain n-3 PUFA have the potential to inhibit (excessive) inflammatory responses has led to a large number of clinical investigations with these fatty acids in inflammatory conditions as well as in healthy subjects.

## Intestinal/Stomach

- Ulcerative colitis (an inflammatory disease of the digestive system)
- Colon cancer
- Pancreatitis

## Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases.

Calder PC.

Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, UK. [pcc@soton.ac.uk](mailto:pcc@soton.ac.uk)

With regard to inflammatory processes, the main fatty acids of interest are the n-6 PUFA arachidonic acid (AA), which is the precursor of inflammatory eicosanoids like prostaglandin E(2) and leukotriene B(4), and the n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are found in oily fish and fish oils. EPA and DHA inhibit AA metabolism to inflammatory eicosanoids. They also give rise to mediators that are less inflammatory than those produced from AA or that are anti-inflammatory. In addition to modifying the lipid mediator profile, n-3 PUFAs **exert effects on other aspects of inflammation** like leukocyte chemotaxis and inflammatory cytokine

production. Some of these effects are likely due to changes in gene expression, as a result of altered transcription factor activity. Fish oil has been shown to decrease colonic damage and inflammation, weight loss and mortality in animal models of colitis. Fish oil supplementation in patients with inflammatory bowel diseases results in n-3 PUFA incorporation into gut mucosal tissue and modification of inflammatory mediator profiles. Clinical outcomes have been variably affected by fish oil, although some trials report improved gut histology, decreased disease activity, use of corticosteroids and relapse.

PMID: 18504706 [PubMed - indexed for MEDLINE]

## **The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases**

**Artemis P. Simopoulos<sup>1</sup>**

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Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.

## **Skeletal**

- Osteoarthritis
- Rheumatoid arthritis
- Osteoporosis

## **[Active rheumatoid arthritis: effect of dietary supplementation with omega-3 oils. A controlled double-blind trial]**

[Article in Spanish]

**Astorga G, Cubillos A, Masson L, Silva JJ.**

Departamento de Medicina (Sección Reumatología), Facultad de Medicina, Universidad de Chile, Santiago.

We evaluated the effect of dietary supplementation with eicosapentaenoic acid in 8 patients with active rheumatoid arthritis. An appropriate placebo was given in a randomized double blind fashion to 8 control subjects. After 12 weeks of therapy a significant improvement in prehensile function was detected in patients receiving active treatment, other clinical parameters remaining unchanged. No significant side effects were detected. A larger trial may help define a possible therapeutic role for omega-3 fatty acids in patients with rheumatoid arthritis.

PMID: 1842119 [PubMed - indexed for MEDLINE]

## **Session 3: Joint Nutrition Society and Irish Nutrition and Dietetic Institute Symposium on 'Nutrition and autoimmune disease' PUFA, inflammatory processes and rheumatoid arthritis.**

**Calder PC.**

Institute of Human Nutrition, School of Medicine, University of Southampton, IDS Building, MP887, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. [pcc@soton.ac.uk](mailto:pcc@soton.ac.uk)

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease manifested by swollen and painful joints, bone erosion and functional impairment. The joint lesions are characterised by infiltration of T lymphocytes, macrophages and B lymphocytes into the synovium and by synovial inflammation involving eicosanoids, cytokines and matrix metalloproteinases. In relation to inflammatory processes, the main fatty acids of interest are the n-6 PUFA arachidonic acid, which is the precursor of inflammatory eicosanoids such as PGE2 and leukotriene B4, and the n-3 PUFA EPA and DHA, which are found in oily fish and fish oils. Eicosanoids derived from the n-6 PUFA arachidonic acid play a role in RA, and the efficacy of non-steroidal anti-inflammatory drugs in RA indicates the importance of pro-inflammatory cyclooxygenase pathway products of arachidonic acid in the pathophysiology of the disease. EPA and DHA inhibit arachidonic acid metabolism to inflammatory eicosanoids. EPA also gives rise to eicosanoid mediators that are less inflammatory than those produced from arachidonic acid and both EPA and DHA give rise to resolvins that are anti-inflammatory and inflammation resolving. In addition to modifying the lipid mediator profile, n-3 PUFA exert effects on other aspects of immunity relevant to RA such as antigen presentation, T-cell reactivity and inflammatory cytokine production. Fish oil has been shown to slow the development of arthritis in an animal model and to reduce disease severity. Randomised clinical trials have demonstrated a range of clinical benefits in patients with RA that include reducing pain, duration of morning stiffness and use of non-steroidal anti-inflammatory drugs.

PMID: 18847518 [PubMed - indexed for MEDLINE]

## The role of fish oils in the treatment of rheumatoid arthritis.

Cleland LG, James MJ, Proudman SM.

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Fish oils are a rich source of omega-3 long chain polyunsaturated fatty acids (n-3 LC PUFA). The specific fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are homologues of the n-6 fatty acid, arachidonic acid (AA). This chemistry provides for antagonism by n-3 LC PUFA of AA metabolism to pro-inflammatory and pro-thrombotic n-6 eicosanoids, as well as production of less active n-3 eicosanoids. In addition, n-3 LC PUFA can suppress production of pro-inflammatory cytokines and cartilage degradative enzymes. In accordance with the biochemical effects, beneficial anti-inflammatory effects of dietary fish oils have been demonstrated in randomised, double-blind, placebo-controlled trials in rheumatoid arthritis (RA). Also, fish oils have protective clinical effects in occlusive cardiovascular disease, for which patients with RA are at increased risk. Implementation of the clinical use of anti-inflammatory fish oil doses has been poor. Since fish oils do not provide industry with the opportunities for substantial profit associated with patented prescription items, they have not received the marketing inputs that underpin the adoption of usual pharmacotherapies. Accordingly, many prescribers remain ignorant of their biochemistry, therapeutic effects, formulations, principles of application and complementary dietary modifications. Evidence is presented that increased uptake of this approach can be achieved using bulk fish oils. This approach has been used with good compliance in RA patients. In addition, an index of n-3 nutrition can be used to provide helpful feedback messages to patients and to monitor the attainment of target levels. Collectively, these issues highlight the challenges in advancing the use of fish oil amid the complexities of modern management of RA, with its emphasis on combination chemotherapy applied early.

PMID: 12678571 [PubMed - indexed for MEDLINE]

## Dietary n-3 fatty acids and therapy for rheumatoid arthritis.

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**OBJECTIVE:** To examine the potential for dietary n-3 fats to be component of therapy for rheumatoid arthritis (RA). **METHODS:** Studies of encapsulated fish oil use in RA were reviewed and critiqued, and possible biochemical mechanisms for fish oil effects were examined. The potential for use of n-3 fats was evaluated within a dietary framework rather than a quasi-pharmaceutical framework. **RESULTS:** There is consistent evidence from double-blind, placebo-controlled clinical trials that dietary n-3 fats, supplied as fish oil, can have beneficial effects in RA. The beneficial effects appear modest, but their size and extent may have been moderated by common trial design factors such as high n-6 polyunsaturated fat diets and concurrent antiinflammatory drug use. Mechanisms for the clinical effects of n-3 fats in RA may involve their ability to suppress production of inflammatory mediators, including n-6 eicosanoids and proinflammatory cytokines. Suppression of n-6 eicosanoid and cytokine production will be possible using foodstuffs that are rich in n-3 fats and poor in n-6 fats. **CONCLUSIONS:** There are many overlapping biochemical effects of n-3 fatty acids and antiinflammatory pharmaceuticals that could explain the clinical actions of n-3 fats in RA. They suggest that there is the potential for complementarity between drug therapy and dietary choices that increase intake of n-3 fats and decrease intake of n-6 fats. In particular, there is the potential for drug-sparing effects. Future studies with n-3 fats in

RA need to address the fat composition of the background diet and the issue of concurrent drug use.

PMID: 9355207 [PubMed - indexed for MEDLINE]

## **The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases**

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Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.

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## **Omega-3 Polyunsaturated Fatty Acids and Skeletal Health**

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### **Abstract**

This minireview on skeletal biology describes the actions of prostaglandins and cytokines involved in the local regulation of bone metabolism, it documents the role of lipids in bone biology, and it presents

relationships between fatty acids and other factors that impact skeletal metabolism. The data presented herein show consistent and reproducible beneficial effects of omega-3 (n-3) fatty acids on bone metabolism and bone/joint diseases. Polyunsaturated fatty acids modulate eicosanoid biosynthesis in numerous tissues and cell types, alter signal transduction, and influence gene expression. These effects have not been explored in the skeletal system. Future research on n-3 fatty acids in bone biology should focus on the following two aspects. First, the further elucidation of how n-3 fatty acids alter biochemical and molecular processes involved in bone modeling and bone cell differentiation, and second, the evaluation of the potential pharmaceutical applications of these nutraceutical fatty acids in maintaining bone mineral status and controlling inflammatory bone/joint diseases.

The best deterrent for osteoporosis is for women to build strong bones early in life by consuming a well-balanced diet (vitamin D, calcium, n-6 and n-3 fatty acids, and phytochemicals) and to follow a routine exercise program pre- and postmenopause. Thus far, direct evidence of any beneficial effect of dietary n-3 fatty acids on human osteoporosis is still lacking. However, experiments using animal and cell culture models, and epidemiological data suggest promising applications of n-3 PUFA on this widespread public health problem.

The primary pathogenesis involved in postmenopausal osteoporosis is an uncoupling of bone formation and resorption, which means that the bone resorption rate exceeds that for bone formation. The effect of n-3 fatty acids on bone formation and/or bone resorption was examined in both normal and ovariectomized rats. Iwami-Morimoto *et al.* (122) studied alveolar bone resorption in 4-week-old rats given diets supplemented with 10% of either fish oil or corn oil for 6 weeks. Dietary fish oil reduced osteoclastic activity (OC number was only 60% of control) and subsequent alveolar bone resorption (80% of control).

Consequently, n-3 fatty acids worked synergistically with estrogen to exert a stimulatory effect on bone mineral deposition and an inhibitory effect on bone resorption.

These studies suggest that using n-3 fatty acid supplements, which are antagonistic to AA in the sense of eicosanoid action, could help maintain bone mineral content after menopause in women. Considering the results from these ovariectomized rat studies (inhibitory to bone resorption) and our findings on n-3 fatty acids in bone modeling (promoting bone formation), it is plausible that consuming diets rich in n-3 fatty acids will help to build and maintain a healthy skeleton in the human

Dietary intervention with n-3 fatty acids demonstrates consistent positive effects on inflammatory joint diseases. n-3 PUFA acts as a competitive inhibitor of eicosanoid biosynthesis in the treatment of RA. Several studies evaluating n-3 PUFA dietary supplements ranging from 3 to 6 g/day showed a modest, but rather consistent beneficial effect of these fatty acids in joint disease (132–141). At the same time, the syntheses of pro-inflammatory factors IL-1, IL-2, and TNF in cartilage tissue were suppressed by dietary supplementation with fish oil containing both EPA and DHA (142). Dietary fish oil supplementation given to rheumatoid arthritis patients resulted in a 19% to 20% reduction of neutrophil LTB<sub>4</sub> production from baseline and a decrease of 38.5% to 40.6% of macrophage IL-1 production (143). The use of flaxseed in domestic food preparation for 4 weeks also reduced the production of TNF- $\alpha$  and IL-1 $\beta$  by 30% in healthy volunteers (144). In addition, recent clinical trials indicate that some patients with RA are able to discontinue nonsteroidal anti-inflammatory drug NSAID use while receiving a source of n-3 fatty acids (145), suggesting that the mode of n-3 fatty acid action in RA patients could be related to eicosanoid biosynthesis. One explanation for this phenomenon is that the EPA metabolite PGE<sub>3</sub> is much less inflammatory compared with PGE<sub>2</sub> (146). Lowering PGE<sub>2</sub> in the diseased joint with diets rich in long-chain n-3 fatty acids could further benefit RA patients by reducing bone resorption since PGE<sub>2</sub> stimulates osteoclast activity, which results in secondary osteoporosis (145). Since PGE<sub>2</sub>

activation of the IGF-I/IGFBP axis may play an important role in cartilage biology and collagen and proteoglycan synthesis (147), dietary fatty acids may also be important for supporting joint repair. Investigations are needed to describe the effects of nutraceutical fatty acids and the ratio of n-6/n-3 fatty acids on cartilage biology, joint disease, and ligament healing since dietary sources of these fatty acids exert potent effects on prostanoid biosynthesis in controlling cell activity in these processes

## **Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain.**

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**BACKGROUND:** The use of NSAID medications is a well-established effective therapy for both acute and chronic nonspecific neck and back pain. Extreme complications, including gastric ulcers, bleeding, myocardial infarction, and even deaths, are associated with their use. An alternative treatment with fewer side effects that also reduces the inflammatory response and thereby reduces pain is believed to be omega-3 EFAs found in fish oil. We report our experience in a neurosurgical practice using fish oil supplements for pain relief. **METHODS:** From March to June 2004, 250 patients who had been seen by a neurosurgeon and were found to have nonsurgical neck or back pain were asked to take a total of 1200 mg per day of omega-3 EFAs (eicosapentaenoic acid and decosaheptaenoic acid) found in fish oil supplements. A questionnaire was sent approximately 1 month after starting the supplement. **RESULTS:** Of the 250 patients, 125 returned the questionnaire at an average of 75 days on fish oil. Seventy-eight percent were taking 1200 mg and 22% were taking 2400 mg of EFAs. Fifty-nine percent discontinued to take their prescription NSAID medications for pain. Sixty percent stated that their overall pain was improved, and 60% stated that their joint pain had improved. Eighty percent stated they were satisfied with their improvement, and 88% stated they would continue to take the fish oil. There were no significant side effects reported. **CONCLUSIONS:** Our results mirror other controlled studies that compared ibuprofen and omega-3 EFAs demonstrating equivalent effect in reducing arthritic pain. omega-3 EFA fish oil supplements appear to be a safer alternative to NSAIDs for treatment of nonsurgical neck or back pain in this selective group.

PMID: 16531187 [PubMed - indexed for MEDLINE]

## **Eyes**

- Macular degeneration
- Glaucoma

Arch Ophthalmol. 2009 May;127(5):656-65.



## **Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the**

## **Blue Mountains Eye Study.**

**Tan JS, Wang JJ, Flood V, Mitchell P.**

Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, Westmead Hospital, Westmead, NSW, Australia.

**OBJECTIVE:** To assess the relationship between baseline dietary fatty acids and 10-year incident age-related macular degeneration (AMD). **METHODS:** In an elderly Australian cohort, 3654 participants were examined at baseline and 2454 were examined 5 and/or 10 years later. We assessed AMD from retinal photographs. Participants completed a semiquantitative food frequency questionnaire. **RESULTS:** After adjusting for age, sex, and smoking, 1 serving of fish per week was associated with reduced risk of incident early AMD (relative risk, 0.69 [95% confidence interval, 0.49-0.98]), primarily among participants with less than the median linoleic acid consumption (0.57 [0.36-0.89]). Findings were similar for intake of long-chain omega-3 polyunsaturated fatty acids. One to 2 servings of nuts per week was associated with reduced risk of incident early AMD (relative risk, 0.65 [95% confidence interval, 0.47-0.91]). Protective associations between the intake of nuts and reduced risk of pigmentary abnormalities were seen among nonsmokers, participants with less than the median ratio of serum total to high-density lipoprotein cholesterol, and those with beta carotene intake greater than the median level. **CONCLUSIONS:** This study provides evidence of protection against early AMD from regularly eating fish, greater consumption of omega-3 polyunsaturated fatty acids, and low intakes of foods rich in linoleic acid. Regular consumption of nuts may also reduce AMD risk. Joint effects from multiple factors are suggested.

PMID: 19433717 [PubMed - in process]

J Fr Ophthalmol. 2005 Mar;28(3):312-6.



## **[Hypothesis on the role of nutritional factors in ocular hypertension and glaucoma]**

[Article in French]

**Desmettre T, Rouland JF.**

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Recent notions in connection with oxidative stress and the fat balance of long chain polyunsaturated fatty acids (PUFA) families have brought new insight to a probable role of nutritional factors in glaucoma and intraocular hypertony. The modifications of the extracellular matrix of the trabecula could be influenced by oxidative stress. On the one hand, collagen apoptosis and remodeling (associated with an increase in intraocular pressure) are mainly influenced by hydrosoluble antioxidants such as glutathione. On the other hand, elastin apoptosis and remodeling (correlated with the occurrence of optic atrophy) are particularly influenced by liposoluble antioxidants such as vitamin E. In addition, the dietary ratio of omega3/omega6PUFA intake could influence the balance of intraocular pressure. Omega-3 PUFA could influence cyclooxygenase competition. A diet with increased omega-3 and decreased omega-6 could thus favor an increase in intraocular pressure reducing synthesis of PG-F2, leading to a decrease in uveoscleral outflow. The true importance of these factors has not yet been solidly determined and studies are in progress to

clarify the real implication of these nutritional factors.

PMID: 15883498 [PubMed - indexed for MEDLINE]

## Heart/Vessel

- Heart attack (less death in those who have suffered a heart attack)
- High cholesterol
- High Blood Pressure
- High triglycerides
- Intermittent claudication (muscle pain often associated with severe atherosclerosis)
- Raynaud's disease (a vascular disorder that affects blood flow)



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### **Blood Levels of Long-Chain n–3 Fatty Acids and the Risk of Sudden Death**

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#### **ABSTRACT**

*Background* Experimental data suggest that long-chain n–3 polyunsaturated fatty acids found in fish have antiarrhythmic properties, and a randomized trial suggested that dietary supplements of n–3 fatty acids may reduce the risk of sudden death among survivors of myocardial infarction. Whether long-chain n–3 fatty acids are also associated with the risk of sudden death in those without a history of cardiovascular disease is unknown.

*Methods* We conducted a prospective, nested case–control analysis among apparently healthy men who were followed for up to 17 years in the Physicians' Health Study. The fatty-acid composition of previously collected blood was analyzed by gas–liquid chromatography for 94 men in whom sudden death occurred as the first manifestation of cardiovascular disease and for 184 controls matched with them for age and smoking status.

*Results* Base-line blood levels of long-chain n–3 fatty acids were inversely related to the risk of sudden death both before adjustment for potential confounders (P for trend = 0.004) and after such adjustment (P for trend = 0.007). As compared with men whose blood levels of long-chain n–3 fatty acids were in the lowest quartile, the relative risk of sudden death was significantly lower among men with levels in the third quartile (adjusted

relative risk, 0.28; 95 percent confidence interval, 0.09 to 0.87) and the fourth quartile (adjusted relative risk, 0.19; 95 percent confidence interval, 0.05 to 0.71).

*Conclusions* The n-3 fatty acids found in fish are strongly associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease.

We previously reported that fish consumption was associated with a reduced risk of sudden death from cardiac causes, but not a reduced risk of myocardial infarction, in the Physicians' Health Study.<sup>1</sup> It is hypothesized that the long-chain n-3 polyunsaturated fatty acids found in fish, primarily eicosapentaenoic acid and docosahexaenoic acid, may be responsible for this association. Experimental data from studies in animals and at the cellular level suggest that these n-3 fatty acids have antiarrhythmic properties,<sup>2,3</sup> and a recent randomized trial testing supplements of these n-3 fatty acids in survivors of myocardial infarction found a statistically significant 45 percent reduction in the risk of sudden death, with no effect on nonfatal myocardial infarction.<sup>4</sup> However, prospective data on blood levels of long-chain n-3 fatty acids and sudden death from cardiac causes are sparse, and there have been no randomized trials of the effects of long-chain n-3 fatty acids in the diet or as supplements among persons without a history of cardiovascular disease, who represent over half of all cases of sudden death from cardiac causes.<sup>5</sup>

To address the hypothesis that the long-chain n-3 fatty acids found in fish are associated with a reduced risk of sudden death from cardiac causes in those without known cardiovascular disease, we performed a prospective, nested case-control analysis of the fatty-acid composition of whole blood in men without a confirmed history of cardiovascular disease who were participants in the Physicians' Health Study.

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**Artemis P. Simopoulos<sup>1</sup>**

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