**www.stannsannquest.com**

**ANNQUEST MAY 2022**

 **ISSN: 2321-3043**

# **FISH, FISH OILS& SUPPLEMENTS IN PREVENTION OF CVD:A REVIEW**

*Dr. Meena Kumari Patangay, Mrs. Hannah Jessie Francis.T, Mrs. Y.V. Phani Kumari, Syeda Uzma Rabia, Sheema Aqhtar, Sara Raheen, Tahoora Fatima, Vepuri Grace Angel, G.P Jessy Anjula*

**ABSTRACT**

The role of fish oil and omega-3 fatty acids in prevention of cardiovascular diseases. In this review we will focus on the uses of omega-3 fatty acids and their effects in CVD events.

Omega-3 Fatty Acids are Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), Docosapentaenoic acid (DPA), and Alpha-linolenic acid (ALA), these are essential long-chain and very-long-chain polyunsaturated fatty acids. EPA, DHA, and DPA are found in fish as well as other seafood as dietary marine oils, and also supplements prepared from these foods as marine oil supplements. ALA is present in oils such as canola, soy, flaxseed, walnuts and leafy green vegetables.

**KEYWORDS:**

Omega 3 fatty acids, Fish oils, Cardiovascular disease (CVD), Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA), Alpha-linolenic acid (ALA).

**ABBREVIATIONS:**

Cardiovascular disease (CVD), Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA), Alpha-linolenic acid (ALA), Ischemic Cardiac Disease (ICD) , PAD (Peripheral Arterial Disease)

**INTRODUCTION**

**Cardiovascular disease (CVD)** is a general term used for conditions affecting the heart or blood vessels. It is the leading cause of death worldwide. It is frequently linked to fatty deposits in the arteries (atherosclerosis) and an elevation in the risk of blood clots. The dietary factors play an important role in determining CVD risk as well as pathogenesis of CVD. The dietary variables are modified to reduce the risk of CVD. [1]One specific type of fatty acid that has received great attention for its effects in the cardiovascular system is the omega-3 fatty acids (also called n-3 or ω-3 fatty acids).[1]. Humans are unable to synthesize the long chain polyunsaturated fatty acids. Due to which, the ω-3 fatty acids synthesized in plants and in marine microalgae are essential components of the human diet.[2]

The human body can make most of the types of fats it needs from other fats or raw materials, but isn’t the case for omega-3 fatty acids (also called omega-3 fats and n-3 fats). These are the essential fats—the body can’t make them from scratch but must get them from food. Sources of Omega-3 fatty acids include fish, vegetable oils, nuts (especially walnuts), flax seeds, flaxseed oil, and leafy vegetables.In the body, omega-3 fatty acids are primarily available as EPA and DHA but less abundantly available as docosapentaenoic acids (DPA) [3]

The evidence of benefits of the ω-3 PUFA are obtained for Eicosapentaenoic acid (EPA) as well as docosahexaenoic acid (DHA),which are the long-chain fatty acids in this family as well as there is,evidence for benefits from alpha-linolenic acid (ALA), the plant-based precursor of EPA. [4]

Omega 3 fatty acids are found in many foods, such as fish and flaxseed, and in dietary supplements, such as fish oil.

Fish oil is obtained in the human diet through the consumption of oily fish such as herring, mackerel, salmon, albacore tuna, and sardines, as well as through the use of fish oil supplements or cod liver oil. However, fish do not produce these oils naturally, but rather obtain them from the marine microorganisms that are the original source of the omega-3 polyunsaturated fatty acids (-3 PUFA) found in fish oils via the ocean food chain.

Consuming a lot of fish has been linked to better cardiovascular health. As a result, a fish diet should be encouraged, particularly in subjects with cardiovascular problems.

PUFA has been obtained for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the long-chain fatty acids in this family.However, there is some epidemiological support for benefit from alpha-linolenic acid (ALA),the plant-based precursor of EPA. The American HeartAssociation (AHA) has currently endorsed the use of omega -3 .PUFA at a dose of approximately 1 g/day of combinedDHA and EPA, either in the form of fatty fish or fish oilsupplements (in capsules or liquid form) in patients with documented CHD .

[5]

 In patients coronary heart disease, omega-3 fatty acids have been proven to reduce the risk of sudden death due to cardiac arrhythmias and all-cause mortality. Omega-3 fatty acids also treats hyperlipidemia and hypertension. The health benefits of these long-chain fatty acids are numerous and remain an active area of research[6]

Fish and fish oils dietary supplementation are the rich sources of ω-3 fatty acids showed the beneficial effects to patients with dyslipidemia, atherosclerosis, hypertension, obesity and inflammatory diseases. [7]

A healthy lifestyle is promoted for CVD prevention. The lifestyle changes include smoking cessation, increased physical activity level, and adopting a healthier diet. Dietary guidelines emphasize the importance of n-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). [8]

Moderate fish oil consumption lowers the risk of major CV events such as myocardial infarction (MI), sudden cardiac death (SCD), coronary heart disease (CHD), atrial fibrillation (AF), and, most recently, death in heart failure patients (HF). A healthy lifestyle is promoted for CVD prevention.Fish consumption is the major source of EPA–DHA in the diet. [9]

Dietary guidelines emphasize the importance of n-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).Studies and trials showed that 250 mg/day of EPA–DHA reduced fatal CHD by 36% compared with no EPA–DHA.6 Fish consumption, the major source of EPA–DHA in the diet, was inversely related to incident stroke in a meta-analysis of cohort studies. [10]

# **REVIEW**

**STUDIES OF OMEGA-3 FATTY ACIDS IN CVD IN HUMANS:**

**CVD** is the cause of 38% of mostly all the deaths of which many of which are preventable. Therefore, different studies were carried out on the effects of omega-3 fatty acids in CVD.(14,15) The studies were conducted on effect of EPA (Eicosapentanoic) acid and DHA (Docosahexaenoic acid).

 A meta-analysis of both prospective cohort studies and trials showed that 250 mg/day of EPA–DHA reduced fatal CHD by 36% compared with no EPA–DHA. [11]. Less evidence exists for a protective effect of α-linolenic acid (ALA), the plant-derived n-3 fatty acid, against CVD. [12 ,13]

Chronic inflammation is thought to be as the cause of many chronic diseases which also includes cardiovascular disease. EPA (Eicosapentanoic) acid and DHA (Docosahexaenoic acid) have anti-inflammatory effects and a have a role in oxidative stress As well as improve cellular function through changes in the gene expression. A study was conducted on the EPA+DHA intake in humans. A study was conducted on 89 patients by treating them with EPA+DHA (16,17,18,19).

In other studies, Omega-3 fatty acids were found to play a role in atherosclerosis and peripheral arterial disease (PAD). Another study was carried out on the consumption of omega-3 fatty acid sources (20,21,22).

A study was carried also out which compared patients with impaired glucose metabolism with normoglycemic patients by supplementing the patient with Eicosapentanoic acid supplementation.

Several studies about EPA and DHA and their use with respect to major coronary events and their use after myocardial infarction).

 A study was also conducted using EPA (Eicosapentanoic) supplementation in combination with a statin, compared with statin therapy alone. Another study was conducted with EPA+DHA supplementation group and a control group in those patients treated after myocardial infarction.

In other studies, Omega-3 fatty acids increased platelet responsiveness to subtherapeutic anticoagulation therapies, including aspirin. In patients with stable coronary artery disease taking low-dose aspirin, EPA+DHA supplementation is proven to be as effective as aspirin dose escalation to 325 mg/d for anticoagulation benefits (23).

In a study, patients receiving standard dual antiplatelet therapy (aspirin 75 mg/d and clopidogrel 600-mg loading dose followed by 75 mg/d) were assigned either EPA+DHA supplementation or placebo. After 1 month of treatment, the P2Y12 receptor reactivity index (an indicator of clopidogrel resistance) was significantly lower, by 22%, for patients taking EPA+DHA compared with patients taking placebo (P = 0.020) (24).

In the recent study of Cardiovascular Events in Diabetes (ASCEND) Trial, a mixture of DHA and EPA, used as a primary preventive measure in patients with diabetes without prevalent cardiovascular disease, & did not reduce the incidence of serious vascular events (25)

Intake of ω-3 polyunsaturated fatty acids (PUFA) reduces overall mortality, mortality due to myocardial infarction and sudden death in patients with CHD. The meta-analysis of randomized control trial (RCT) included 7951 patients in the intervention and 7855 patients in the control group, observed that risk ratio of non-fatal myocardial infarction (MI) in patients who were on Omega-3 PUFA rich diet compared with the control was 0.8 and the risk of fatal myocardial infarction was 0.7, sudden death was associated with a risk ratio of 0.7 and overall mortality was 0.8. [32]

EPA+DHA supplementation have shown to improve endothelial function in patients with PAD by decreasing the plasma levels of soluble thrombomodulin and improve brachial artery flow–mediated dilation .

**FISH:**

Depending on the population studied, the dose of fish oil supplementation, the type of omega-3 PUFA preparation, the study period, and the endpoints to estimate clinical effects for primary or secondary CVD prevention differ. In a study, a meta-analysis of large-scale prospective cohort studies and randomized studies reported that fish and fish oil consumption reduced coronary heart disease (CHD)-related mortality and sudden cardiac death. (26).

Another subsequent meta-analysis of 13 randomized controlled trials found a significant reduction in cardiac death after fish oil supplementation (27). In the Japanese general population, omega-3 PUFA intake was inversely and independently associated with the long-term risk of total Cardiovascular disease mortality (28).

 It was observed that the dietary and circulating EPA and DHA, but not ALA or omega-6 PUFA, are inversely associated with CVD incidence. These findings indicate that fish oil may reduce fatal Myocardial infraction or sudden cardiac death.Although the secondary prevention analysis of trail did show a benefit for omega-3 PUFA (29).

In other studies, participants were treated with aspirin, beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, and statins during the studies. Another large-scale Risk and Prevention Study showed that omega-3 PUFA did not clearly reduce CHD-related mortality in patients having multiple CVD risk factors. A possible reason for the failure of these secondary prevention studies to demonstrate significant benefits of fish oil as omega-3 fatty acid supplementation is that the patients or participants of the study had received aggressive pharmacotherapy, which may reduce the effectiveness of omega-3 PUFA against cardiac death.

In primary prevention of CVD, the intake of tuna and dark fish, ALA, and marine omega-3 PUFA is not associated with the risk of major CVD in a cohort of women without a history of Cardiovascular diseases.

**FISH OIL:**

Under a study, a meta-analysis of randomized studies has reported that fish oil supplementation lowers blood pressure caused by reduced systemic vascular resistance, but does not lower cardiac output.Another meta-analysis reveals that the intake of omega-3 PUFA improves flow-mediated vasodilation, among other parameters of endothelial function. Omega-3 PUFA improves endothelial function with a parallel anti-inflammatory effect in adults with metabolic syndrome. It was seen that omega-3 PUFA consumption improves the small peripheral artery function in patients with intermediate to high CVD risk, as evaluated by small artery reactive hyperemia index. It was studied that omega-3 PUFA supplementation improves the arterial elasticity measured by pulse contour analysis of the radial artery in patients on statin therapy for familial hypercholesterolemia.

**CARDIOVASCULAR EFFECTS OF OMEGA-3 FATTY ACIDS:**

Under a study, 25 trials were carried out that evaluated the risk of CHD events as a function of in vivo levels of ω-3 PUFA and it showed that there is a reduction in major CV events which are related inversely with the tissue levels of EPA, and with DHA.

EPA and DHA obtained by consuming different types of fish were more beneficial in CHD as well as SCD. [30]

In other studies, the intake of ω-3 polyunsaturated fatty acids (PUFA) reduces overall mortality, mortality due to myocardial infarction and sudden death in patients with CHD.The meta-analysis of randomized control trial (RCT) included 7951 patients in the intervention and 7855 patients in the control group. [32]. It was seen that higher doses of ω-3 fatty acids lowered the elevated serum triglycerides level. [33]

ω-3 Supplements whether from dietary source or fish oil,

A study on elderly adults also showed that consumption of tuna or other broiled or baked fish sources of omega-3 fatty acids are associated with lower incidence of atrial fibrillation (AF) and also the intake influences the risk of common cardiac arrhythmias. [40]

Fish oil supplementation was recommended in the patients with risk factors for SCD such as prior cardiac infarction or high-grade ventricular dysrhythmias, left ventricular dysfunction, left ventricular hypertrophy. [31]

The dangerous consequences after MI and ischemic arrhythmia in ischemic cardiac disease (ICD) patients were reduced by the ω-3 fatty acid therapy. ω-3 fatty acids derived from fish and fish oil showed great role in secondary prevention of CVD through their anti-arrhythmic action and ability to promote plaque stabilization. [34]

The majority of effect of ω-3 fatty acids are seen in anti-arrhythmic than anti-thrombotic and little effect observed on blood coagulability and fibrinolysis. [35] .The study reported that fish oil supplements were associated with a significant reduction in death from cardiac causes but did not show any effect on arrhythmia**.**[36]A study compared the QTc interval of resting electrocardiogram in non-fish consumers and those consuming fish, showed that those consumed fish >300g/week had 13.6% lower QTc interval and long-term consumption of fish provides anti-arrhythmic protection at the population level. [37]

Dietary fish oil prevents arrhythmia by modulating its pacemaker activity and reduces the cellular CA overload which is responsible for the arrhythmia.

[38].In high-risk individuals of fatal arrhythmias, regular daily intake of fish oil fatty acids significantly reduced potentially reduced it. [39].

A systematic review showed that fish oil reduces the triglyceride levels particularly in people with elevated triglycerides and also improves HDL cholesterol, increases LDL cholesterol and no effect on total cholesterol. ω-3 Fatty acid in the diet increases the proteins present in the HDL and modifies the protein part of HDL particles.

**RESULT:**

In a study, EPA+DHA intake in humans changed the expression of 1040 genes which resulted in a decreased expression of genes which were involved in inflammatory and atherogenesis-related pathways.Circulating markers of inflammation, such as C-reactive protein (CRP), TNF etc., correlate with an increased probability of experiencing a cardiovascular event. Inflammatory markers alsosuch as IL-6 trigger CRP, and elevated levels of CRP are associated with an increased risk of the development of cardiovascular diseases.

**Patients having PAD (peripheral arterial disease) and were supplemented with EPA experienced a significantly lower major coronary event HR than those who did not consume EPA (HR: 0.44; 95% CI: 0.19–0.97; P = 0.041) (9,10,11).**

EPA+DHA and cardiovascular events after myocardial infarction, of 4837 patients, a major cardiovascular event occurred in 671 patients (13.9%). A post analysis of the data from these patients showed that rates of fatal coronary heart disease and arrhythmia-related events were lower among patients in the EPA+DHA group than among the placebo group [11,12]

The study of 89 patients resulted that those treated with EPA+DHA had a reduction in high-sensitivity CRP which is a marker of inflammation associated with increased risk of CVD. (66.7%, P < 0.01) . The study also showed a significant reduction in heat shock protein 27 antibody titers (57.69%, P < 0.05), which are overexpressed in heart muscle cells after a return of blood flow after a period of ischemia and may  have a cardioprotective effect.[14,15,16,17]

The study in which patients receiving standard dual antiplatelet therapy were assigned either EPA+DHA supplementation or placebo resulted that After 1 month of treatment, the P2Y12 receptor reactivity index (an indicator of clopidogrel resistance) was significantly lower, by 22%, for patients taking EPA+DHA compared with patients taking placebo (P = 0.020)



Another study resulted that EPA+DHA is associated with a reduced risk of recurrent coronary artery events and sudden cardiac death after an acute myocardial infarction (RR, 0.47; 95% CI: 0.219–0.995) and a reduction in heart failure events (adjusted HR: 0.92; 99% CI: 0.849–0.999) [22,23,24]

In a study, patients receiving standard dual antiplatelet therapy (aspirin 75 mg/d and clopidogrel 600-mg loading dose followed by 75 mg/d) were assigned either EPA+DHA supplementation or placebo. After 1 month of treatment, the P2Y12 receptor reactivity index (an indicator of clopidogrel resistance) was significantly lower, by 22%, for patients taking EPA+DHA compared with patients taking placebo (P = 0.020) [25]. Another recent experimental study from laboratory showed that the treatment of hyperlipidemic mice induced a beneficial lipid profile and reduced atherosclerosis , these results hence pointed possible activation of proresolving pathways as a result of pure EPA (eicosapentanoic acid) supplementation. [25,34].

Another study was conducted which found that there was no significant difference in sudden cardiac death or total mortality between an EPA+DHA supplementation group and a control group in those patients treated after myocardial infarction. These studies appear to be negative in their results. (29).

The EPA reduces the pro-atherogenic factor, remnant lipoprotein (RLP) which is produced from triacylglycerol-rich chylomicrons and VLDL in hyperlipidemic patients. [41,42,43]. In middle aged people high consumption of fish was associated with decreased risk of CHD more specifically myocardial infarction and nonfatal CHD compared to moderate intake. [44]

Another study resulted that EPA and DHA, decrease endothelial activation, improve plaque stability and improve vascular permeability, thereby decrease the chance of experiencing a cardiovascular event events including myocardial infarction, sudden cardiac death, etc. It was seen that EPA supplementation is associated with significantly higher amounts of EPA, which may lead to decreased plaque inflammation and increased stability and decreased incidence of CVD.

In another study, biochemical markers of inflammation were affected by increased intake of n-3 Fatty acids. Plasma levels of the cytokines IL-6 and TNFα, were decreased with increased n-3 intake in both healthy people and in patients with CVD.

**The study which compared patients with impaired glucose metabolism with normoglycemic patients resulted that impaired glucose metabolism patients had a significantly higher rate of coronary artery disease HR (1.71 in the non-EPA group and 1.63 in  EPA group).**

 The primary endpoint of the study was any major coronary event including myocardial infarction, sudden cardiac death, and other nonfatal events. The treatment of impaired glucose metabolism patients with EPA showed a significantly lower major coronary event HR of 0.78 compared with the non–EPA-treated impaired glucose metabolism patients (95% CI: 0.60–0.998; P = 0.048), which results that EPA significantly suppresses major coronary events including myocardial infarction, sudden cardiac death, etc.

The evidences from the studies indicated that dietary intake of marine oils (including from fish) may be associated with lower risk of CVD death and total stroke (mainly ischemic stroke) .

Based on the articles reviewed:

* DHA: Evidence was sufficient to permit conclusions about the effects of or associations between DHA and any clinical outcome for CVD.
* EPA or DPA: Evidence was low or insufficient to permit conclusions about the benefit of EPA or DPA, individually, on any clinical or intermediate outcome for CVD.
* ALA: Evidence was low or insufficient to permit conclusions about the effects of or associations between ALA and any clinical outcome of CVD.

**CONCLUSION:**

The convincing evidences from extensive research over the past year points out the potential beneficial effects of ω-3 PUFA in primary prevention of CHD and post-MI, SCD, HF, atherosclerosis, and AF.

On the whole,, a number of studies offer evidence to support the hypothesis that fish, fish oil, or ALA supplement consumption reduces all‐cause mortality and various CVD outcomes, although there is strongest evidence for fish or fish oil**.**

**ACKNOWLEDGEMENT :**

We would like to express our special thanks of gratitude to our lecturers , Mrs. Hannah Jessie Francis.T, andMrs. Y.V. Phani Kumari as well as our department head Dr. Meena Kumari Patangay who gave us the golden opportunity to do this wonderful review article on the topic "Role of Omega-3 Fatty Acids in CVD". It also helped us in doing a lot of research & helped us in gaining experience and knowledge and will really be helpful for our future projects. We would also like to show our gratitude to all the authors whose articles we have chosen for our review article. We are really thankful to all of them.

**BIBLIOGRAPHY:**

1. Alissal EM, Ferns GA. Functional Foods and Nutraceuticals in the Primary Prevention of Cardiovascular Diseases. J.Nutr and Metab. 2012; (2012): 1-16 doi10.1155/2012/569486.

2. Weitz D, Weintraub H, Fisher E, Schwartzbard AZ. Fish oil for the treatment of Cardiovascular Disease. Cardiol Rev. 2010; 18(5): 258-263.

**3.**[Carl J. Lavie](https://www.jacc.org/doi/10.1016/j.jacc.2009.02.084), [Richard V. Milani](https://www.jacc.org/doi/10.1016/j.jacc.2009.02.084), [Mandeep R. Mehra](https://www.jacc.org/doi/10.1016/j.jacc.2009.02.084), and [Hector O. Ventura](https://www.jacc.org/doi/10.1016/j.jacc.2009.02.084), [J Am Coll Cardiol](https://www.jacc.org/journal/jacc). Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Disease 2009 Aug, 54 (7) 585–59

**4**.[Lisa M. Freeman](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorRaw=Freeman%2C+Lisa+M), Beneficial effects of omega-3 fatty acids in cardiovascular disease, 29 July 2010

5.Kris-Etherton PM, Harris WS, Appel LJ, for the American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in Circulation 2003;107:512]. Circulation 2002;106:2747–57.

6. Masson S, Latini R, Tacconi M, Bernasconi R: Incorporation and washout of n-3 polyunsaturated fatty acids after diet supplementation in clinical studies. *J Cardiovasc Med*, 2007; 8 Suppl 1: S4-10 [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/17876198)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=J+Cardiovasc+Med&title=Incorporation+and+washout+of+n-3+polyunsaturated+fatty+acids+after+diet+supplementation+in+clinical+studies&author=S+Masson&author=R+Latini&author=M+Tacconi&author=R+Bernasconi&volume=8&issue=Suppl+1&publication_year=2007&pages=S4-10&)]

7. Aarsetoey H, Greendt H, Nyqaard O, Nilsen DW. The role of long chained marine N-3 Manjula et al. European Journal of Biomedical and Pharmaceutical Sciences www.ejbps.com 175 polyunsaturated fatty acids in cardiovascular disease. Caridol Res Pract. 2012; (2012): 30345 doi 10.1155/2012/303456

8. The U.S. Departments of Agriculture and Health and Human ServicesReport of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans http://www.cnpp.usda.gov/dietaryguidelines.htm (6 July 2011)

9. He K, Song Y, Daviglus M, Liu K, Van Horn L, Dyer A, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies, Circulation, 2004, vol. 109 (pg. 2705-2711) Google ScholarCrossref PubMed 10.Simone R.B.M. Eussen, Johanna M. Geleijnse, Erik J. Giltay, Cathy J.M. Rompelberg, Olaf H. Klungel, Daan KromhoutEffects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction .European Heart Journal, Volume 33, Issue 13, July 2012, Pages 1582–1588

11. Mozaffarian D, Rimm E. Fish intake, contaminants, and human health: evaluating the risks and the benefits, J Am Med Assoc, 2006, vol. 296 (pg. 1885-1899)Google ScholarCrossref

12.Wendland E, Farmer A, Glasziou P, Neil A. Effect of alpha linolenic acid on cardiovascular risk markers: a systematic review, Heart, 2006, vol. 92 (pg. 166-169)Google ScholarCrossrefPubMed

13. Brouwer I, Katan M, Zock P. Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis, J Nutr, 2004, vol. 134 (pg. 919-922)

14. Kelley DS, Siegel D, Fedor DM, Adkins Y, Mackey BE. DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men. J Nutr. 2009;139:495–501.

15. Schubert R, Kitz R, Beermann C, Rose MA, Baer PC, Zielen S, Boehles

H. Influence of low-dose polyunsaturated fatty acids supplementation

on the inflammatory response of healthy adults. Nutrition. 2007;23: 724–30.

**16**. Bloomer RJ, Larson DE, Fisher-Wellman KH, Galpin AJ, Schilling BK.

Effect of eicosapentaenoic and docosahexaenoic acid on resting and

exercise-induced inflammatory and oxidative stress biomarkers: a randomized, placebo controlled, cross-over study. Lipids Health Dis. 2009;

8:36.

**17.** Bouwens M, van de Rest O, Dellschaft N, Bromhaar MG, de Groot LC,

Geleijnse JM, Muller M, Afman LA. Fish-oil supplementation induces

antiinflammatory gene expression profiles in human blood mononuclear cells. Am J Clin Nutr. 2009;90:415–24.

**18.** Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects

of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic

individuals. Atherosclerosis. 2009;204:476–82.

**19.** Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ,

Gudmundsen O, Vige R, Payne SP, Ye S, et al. Eicosapentaenoic acid

(EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is

associated with decreased plaque inflammation and increased stability.

Atherosclerosis. 2010;212:252–9.

**20.** Schiano V, Laurenzano E, Brevetti G, De Maio JI, Lanero S, Scopacasa

F, Chiariello M. Omega-3 polyunsaturated fatty acid in peripheral arterial disease: effect on lipid pattern, disease severity, inflammation profile, and endothelial function. Clin Nutr. 2008;27:241–7.

**21.** Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S,

Sasaki J, Hishida H, Itakura H, Kita T, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral

artery disease. Circ J. 2010;74:1451–7.

**22.** Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito

Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with

impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009;206:535–9.

**23.** Lev EI, Solodky A, Harel N, Mager A, Brosh D, Assali A, Roller M,

Battler A, Kleiman NS, Kornowski R. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. J Am Coll

24. Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated

omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI

(OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) study. J Am Coll Cardiol. 2010;55:1671–8.

**25**. Magnus Bäck,Göran K. Hansson, Omega-3 fatty acids, cardiovascular risk, and the resolution of inflammation First published: 17 January 2019

**26**.  Mozaffarian D, Rimm EB: Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*, 2006; 296: 1885-1899 [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/17047219)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=JAMA&title=Fish+intake,+contaminants,+and+human+health:+evaluating+the+risks+and+the+benefits&author=D+Mozaffarian&author=EB+Rimm&volume=296&publication_year=2006&pages=1885-1899&pmid=17047219&)]

**27.**  Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS: Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*, 2012; 308: 1024-1033 [[PubMed](https://www.ncbi.nlm.nih.gov/pubmed/22968891)] [[Google Scholar](https://scholar.google.com/scholar_lookup?journal=JAMA&title=Association+between+omega-3+fatty+acid+supplementation+and+risk+of+major+cardiovascular+disease+events:+a+systematic+review+and+meta-analysis&author=EC+Rizos&author=EE+Ntzani&author=E+Bika&author=MS+Kostapanos&author=MS+Elisaf&volume=308&publication_year=2012&pages=1024-1033&pmid=22968891&)]

**28**. Miyagawa N, Miura K, Okuda N, Kadowaki T, Takashima N, Nagasawa Sy, Nakamura Y, Matsumura Y, Hozawa A, Fujiyoshi A, Hisamatsu T, Yoshita K, Sekikawa A, Ohkubo T, Abbott RD, Okamura T, Okayama A, Ueshima H: Long-chain n-3 polyunsaturated fatty acids intake and cardiovascular disease mortality risk in Japanese: A 24-year follow-up of NIPPON DATA80. *Atherosclerosis*, 2014; 232: 384-389

**29.** Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik

M, Steinbeck G, Del Castillo U, Sack R, et al. OMEGA, a randomized,

placebo-controlled trial to test the effect of highly purified omega-3

fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010;122:2152

30. Artham SM, Lavie CJ, Milani RV, Anand RG, OKeefe JH, Ventura HO. Fish oil in Primary and Secondary Cardiovascular Prevention. Ochs. J. 2008; 8(2): 49-60.

**31**. Bucher HC, Hengstler P, Schindler C, et al. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2002; 112(4): 298–304.

32. OKeefe JH, Harris WS. From Inuit to implementation: Omega-3 fatty acids come of age. Mayo clinic Proc. 2000; 75(6): 607–614

**33.** Jinnie J. Rhee, MSc, ScD,1,2,3,4,5 Eunjung Kim, MSc,3 Julie E. Buring, ScD,1,3 and Tobias Kurth, MD, ScD1,3, Fish Consumption, Omega-3 Fatty Acids, and Risk of Cardiovascular Disease

34. Jacobson TA. Secondary prevention of coronary artery disease with omega-3 fatty acids. Am J Cardiol. 2006; 98(4A): 61i–70i.

35. Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. Lipids. 2001; 36: S79 – S82

36. Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. Brit. Med. J. 2008; 337: a2931.doi: 10.1136/bmj.a2931.

37. Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region--the ATTICA study. Am J Clin Nutr. 2007; 85(5): 1385-1391.

38. McLennan PL. Cardiac physiology and clinical efficacy of dietary fish oil clarified through cellular mechanisms of omega-3 polyunsaturated fatty acids. Eur. J. Appl. Physiol, 2014; 114(7): 1333-1356.

39. Leaf A, Albert CM, Josephson M, et al., Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circ. 2005; 112(18): 2762–2768

40. Mozaffarian D, Psaty B, Rimm EB, et al., Fish intake and risk of incident atrial fibrillation. Circu. 2004; 110: 368–373.

41. Sampath H, Ntambi JM. Polyunsaturated fatty acid regulation of genes of lipid metabolism. Annu Rev Nutr, 2005; 25: 317–340.

42. Oi K, Shimokawa H, Hiroki J, Uwatoku T, Abe K, Matsumoto Y, Nakajima Y, Nakajima K, Takeichi S, Takeshita A. Remnant lipoproteins from patients with sudden cardiac death enhance coronary vasospastic activity through upregulation of Rhokinase. Arterioscler Thromb Vasc Biol, 2004; 24: 918–922.

 43. Oi K, Shimokawa H, Hirakawa Y, Tashiro H, Nakaike R, Kozai T, Ohzono K, Yamamoto K, Koyanagi S, Okamatsu S, Tajimi T, Kikuchi Y, Takeshita A. Postprandial increase in plasma concentrations of remnant-like particles: an independent risk factor for restenosis after percutaneous coronary intervention. J Cardiovasc Pharmacol, 2004; 44: 66–73.

44. Montori VM, Farmer A, Wollan PC, et al., Fish oil supplementation in type 2 diabetes: a quantitative systematic review. Diab. Care. 2000; 23(9): 1407–1415.

45. Balk E, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar;(93):1-6. PMID: 15133887.

46. Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar;(94):1-8. PMID: 15133888.