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Omega-3 Fatty Acids: Novel Insight into Cardiovascular Events, Cardiovascular Disease (CVD), and Cardiac Arrhythmias

Muralidharan Velappan and Deecaraman Munusamy

Abstract

It is a common knowledge that fish is a significant source of docosahexaenoic acid and eicosapentaenoic acid, two long-chain omega-3 fatty acids that have been linked to improve cardiovascular health in general. The cardiac function of humans is benefited by omega-3 fatty acids found in fish eating. Previous studies have shown that eating fish in moderation lowers the risk of coronary heart disease. Recent epidemiological research on the relationship between fish consuming and coronary disease have produced mixed results. Omega-3 fatty acids may not, according to a recent study, lower the incidence of cardiovascular events, strokes, cardiac arrhythmias, or fatalities from coronary heart disease; consequently, it continues to be a contentious issue.

Keywords: fish consumption, omega-3 fatty acids, epidemiology, cardiovascular disease, deaths

1. Introduction

Most of the types of fats that the human body requires can be produced by it from other fats or raw materials. The case with omega-3 fatty acids is different; these are necessary fats that the body cannot produce on its own and must obtain from food. Fish, vegetable oils, almonds, walnuts, flaxseeds, flaxseed oil, and green vegetables are among the foods high in omega-3 fatty acids. Additionally, they have a significant role in human physiology [1]. According to a number of study reports, eating seafood at least once a week lowers your risk of heart disease compared to eating it occasionally or never [2]. In 2017, globally, cardiovascular disease (CVD) was the top disease that leads to premature death and contributes to 8.9 million deaths from coronary heart disease (CHD), which is a major cause of death in the UK and worldwide. CHD is sometimes called ischaemic heart disease or coronary heart disease.

According to past studies, the cardioprotective benefits of eating fish have long attracted scientific attention. In recent years, numerous studies have focused on long-chain omega-3 polyunsaturated fatty acids (PUFAs) found in finfish, such as

eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), 22:5 n-3, and docosahexaenoic acid (DHA), 22:6 n-3 [3]. On the other hand, this meta-analysis suggests that consuming fish twice or three times per week may protect against fatal CHD and sudden cardiac death. Review findings from Refs. [4, 5] claim that the dose response analysis on CHD incidence and mortality were reduced by 4% with a 20 g/day increase in fish consumption.

The tentative contribution from polyunsaturated fatty acids (PUFA) or omega-3 PUFA are the healthy lipid molecules that have two or more carbon-carbon double bonds and it is derived from fish oil. Omega 3 fatty acids are of 3 types: alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. In recent days, these findings have received much scientific attention, with the word “omega-3” fetching a synonym for fish mostly from salmon and other cold-water fish [6]. According to the author [7] reported, there is conflicting information regarding the impact of fish oil on LDL cholesterol (LDL-C), but he also emphasizes the overwhelming majority of studies that have discovered decreased LDL-C levels. Consequently, regular intake of fish oil shows LDL-C levels either do not change or may increase. N-3 PUFA may also lower CVD through acting as antithrombotic, anti-inflammatory, and antiarrhythmic drugs, as well as by improving endothelial function. According to the research carried out by Kris-Etherton et al. [8] and her co-workers, N-3 PUFA actions and the relation to CVD are schematically presented in **Figure 1**.

Furthermore, the study reports from Refs. [6, 9] evaluated that 116,764 people had a diet of fish or fish oil and CHD mortality. Their review indicated that fish consumption and CHD mortality had an inverse dose-dependent relationship, with an optimal dose of about 40/60 g of fish per day-1, but only in those at high risk for CHD. Several findings indicated that low-risk people who eat fish and maintain healthy lives would not experience any additional protection against CHD. According to past editorial reports [10], regular fish or fish oil diet reduces CVD and overall mortality in patients recovering from myocardial infarction (MI). In addition, Popoff et al. [11] also mentioned that the adult patients with acute myocardial infarction (AMI) are unlikely to notice any notable benefits from omega 3 fatty acid treatment after myocardial infarction. In addition, other meta-analyses demonstrate that CHD death

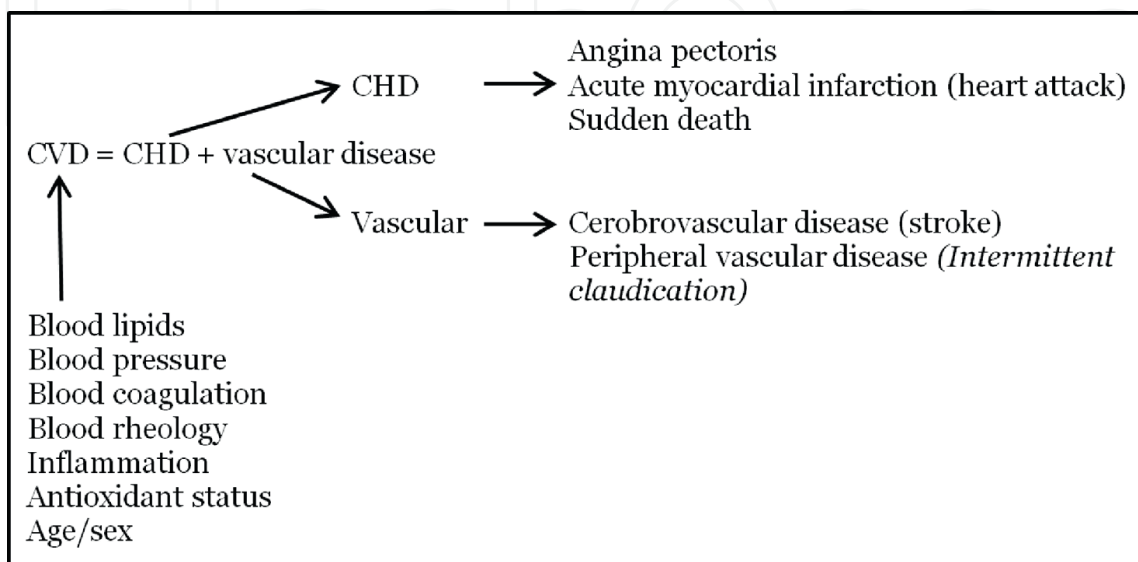


Figure 1.
Source: *Fish and cardiovascular health* by Undeland et al. [6].

or incidence is not correlated with one another [12–15]. In people who are at high risk for or who already have heart disease, taking omega-3 supplements increases the risk of atrial fibrillation (A-fib), a condition characterised by an irregular and frequently very rapid heartbeat (arrhythmia) that can lead to blood clots in the heart, and there is no correlation between the intake of omega-6 fatty acids and the level of linoleic acid (LA) in circulating lipids and triglycerides. These findings are based on the novel study cited in Ref. [16].

Benefits of n-3 PUFA for coronary heart disease mortality and sudden cardiac death appear to be most consistent in prospective observational studies and adequately powered randomised clinical trials. Less is known about potential impacts on other cardiovascular events, such as non-fatal myocardial infarction, ischemic stroke, atrial fibrillation, recurrent ventricular arrhythmias, and heart failure, which have inconsistent evidence from observational studies and/or randomised trials. The relative significance of various physiological and molecular mechanisms, the precise dose-responses of physiological and clinical effects, the question of whether fish oil provides all the health benefits of fish consumption, and the clinical effects of plant-derived n-3 PUFA are all areas of research that need to be addressed [17]. This review's major goals are to assess (a) fish oil supplements and coronary artery disease, (b) the dosage of omega-3 fatty acids for cardiovascular events, (c) the contribution of fish n-3 fatty acids to CVD and potential risks associated with increased fish consumption, and (d) the proportion of people who take fish oil and experience atrial fibrillation or erratic heartbeats.

2. Omega-3 fatty acid dosage for cardiovascular protection

Since the initial American Heart Association (AHA) Science Advisory was published in 1996, significant new findings regarding the benefits of omega-3 fatty acids on (CVD) have been reported. Fatty fish such as mackerel, halibut, salmon, bluefish, mullet, sablefish, menhaden, anchovy, herring, lake trout, coho, and sardines, which give 1 g or more of omega fatty acids per 100 g (3.5 oz) of fish, are the marine sources with the greatest level of omega-3 fatty acids. Additionally, marine-based sources include tuna, seal, and shellfish [18–22]. The Mayo Clinic Proceedings study and recently released Harvard University study on omega-3 intake and cardiovascular benefits and both agree that an optimal target for daily omega-3 intake is upward of 1000 mg. However, given that the typical daily consumption of EPA and DHA in United States is around 100 mg, additionally, the researchers discovered that the cardiovascular advantages seem to grow with dosage. An additional 1000 mg of (EPA) and (DHA) per day decreased the risk of heart attack by 9.0% and cardiovascular disease by 5.8%, respectively. The trial used daily doses ranging from 400 mg to 5500 mg [23]. According to Dr. Carl J. Lavie, a cardiologist at John Ochsner Heart and Vascular Institute in New Orleans and his colleagues reported, people should consider using omega-3 supplements to help them reach total daily intake of 1000–2000 mg as a relatively low-cost, high-impact way to improve heart health with few associated risks [24]. The AHA also advises consuming at least two servings of fatty fish per week. On the other hand, clinical studies recommend consuming a minimum of 2 g of omega-3 fatty acids per day when triglycerides are raised and a maximum of 4 g per day when coronary heart disease is present. Typically, fish oil supplements have 1000 mg of fish oil, which is equivalent to 300–400 mg of EPA and DHA.

3. A debate on pure N-3 polyunsaturated fatty acids for cardiovascular disease

For more than 50 years, experts have disagreed over whether or not long-chain n-3 polyunsaturated fatty acids (n-3 PUFA) are the effective treatments for cardiovascular disease (CVD). Considering that 8% of Americans consume these chemicals on a daily basis and that the worldwide omega-3 market is worth USD 31.4 billion (KWD 9,460,820,000.00), further data may be useful for public health policy-makers as they discuss the efficacy of the practise. Every nation experiences unacceptably high rates of morbidity and mortality from this condition, especially coronary heart disease (CHD), and despite the adoption of cutting-edge treatments, fatal instances continue. In fact, “fish oil” has consistently rated among the most talked-about topics in the lay press over the past few decades. Due to these variables, it is appropriate to update the research on the potential benefits of these substances for both those with and without cardiac illness [25–27].

4. Biomarkers for omega-3 polyunsaturated fatty acids and coronary heart disease

Omega-3 polyunsaturated fatty acids (PUFAs) have been shown to have a preventative effect on clinical risk factors and coronary heart disease (CHD) risk pathways, according to a review of experimental research and randomised clinical trials [26]. Significant conflicts do, however, still exist. First, randomised clinical trials using fish oil supplements for (CHD) cases have produced inconsistent findings [27, 28]. While taking multiple cardiovascular drugs, the bulk of trials only offered supplements for a brief period to people who already had (CHD) or were at high risk for getting it. In these trials, baseline food consumption was not generally examined, and thus, many participants may have received adequate nourishment from other sources. We do not yet know how generalizable they are or how relevant they are for dietary N-3 PUFA effects on primary (CHD) prevention. In addition, in a study by Kasim et al. [29], a number of earlier observational studies found inverse correlations between N-3 PUFAs from seafood and (CHD) death; however, the effects on non-fatal myocardial infarction (MI) or total (CHD) are less clear. According to this review by Friday et al. [30], the majority of research also used self-reported dietary questionnaires, which can lead to bias or inaccuracies in recollection.

Several studies have assessed the objective levels of circulating or tissue N-3 PUFAs, according to a prior review, although these results may be constrained by publication bias. Prior studies of specific biomarkers were also typically insufficient to investigate any potential changes in effects related to participant-level factors, medication usage, or genetic variation. As a result, questions still surround the impact of N-3 PUFAs on CHD. The majority of investigations have examined combined intakes or biomarker levels of long-chain –3 PUFAs [31, 32]. Individual omega-3 PUFAs, such as eicosapentaenoic acid EPA; 20:5-3 and docosapentaenoic acid DPA; 22:5-3 and docosahexaenoic acid DHA; 22:6-3, may, however, have complementary and shared benefits [33]. Similar to this, the majority of prior studies [34] have concentrated on long-chain omega-3 PUFAs produced from seafood, and the potential CHD effects of plant-derived alpha-linolenic acid ALA; 18:3-3 are significantly less well known.

5. Consumption of fish and dietary omega-3 fatty acids and the risk of type-2 diabetes

An increased risk of death is linked to type 2 diabetes (T2D), which also has expensive medical implications. To create successful preventative methods, it is crucial to identify pertinent risk factors and safeguards. However, information on how omega-3 fatty acids affect insulin sensitivity and glucose metabolism has been scarce and inconsistent [35]. According to Refs. [36, 37] observation revealed the deleterious effects of high doses of fish oils on glycaemic control in individuals with T2D. A greater omega-3 fish oil intervention (6 g omega-3/d) was linked in a randomised control experiment to elevate blood glucose levels and impaired insulin sensitivity in T2D patients. However, in a 6-week trial of (T2D) patients, Bowman et al. [38] found no impact of 4 g pure eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on insulin sensitivity or fasting insulin concentrations. It is yet unknown whether EPA and DHA, especially when consuming very small amounts, have long-term impacts on given the brief periods and greater dosages of omega-3 employed in these experiments. Omega-3 fatty acids may increase the risk of (T2D) in the general population, however this is unknown. Although it is unknown whether findings were the same in men and women, data from the Atherosclerosis Risk in Communities (ARIC) research [39] found no correlation between marine omega-3 fatty acids and T2D risk. Researchers made similar findings from the Kouopio Ischemic Heart Disease Risk factor study [40], although these study only included men and 34 cases of incident diabetes. In contrast, the Iowa Women's Health Study [41] showed a threshold effect, where a little increase in the incidence of (T2D) was only seen in the fifth quintile of marine omega-3 fatty acids. Recent research from three prospective cohorts (the Nurses' Health Study I and II and the Health Professionals Follow-Up Study) suggested that women, but not men, might have a slightly higher risk of (T2D) with higher consumption of long-chain omega-3 and seafood [42]. Wu et al. [43] stated that it is unknown if long-chain omega-3 plays a part in the connection between fish and diabetes. Determining whether consuming small-to-moderate amounts of total and particular omega-3 has a detrimental effect on (T2D) risk is still vital. We therefore sought to prospectively examine in the Women's Health Study the association between dietary omega-3 fatty acids, specifically α -linolenic acid (ALA), fish consumption, and incident diabetes [24]. In addition, Zoler [44] also mentioned that the people who were randomised to consume more long-chain omega-3 fats in the form of fish oils had the same risk of diabetes diagnosis as the control group who did not take more fish oil, despite the fact that over 58,000 participants were enrolled in long-term trials and 4% of those participants developed diabetes. People who take and do not take supplemental fish oils had similar levels of blood glucose, insulin, and glycated haemoglobin, markers of how well our bodies handle carbohydrates (glucose metabolism) and significant indicators of diabetes risk.

Fish oils (long-chain omega-3 fatty acids) had no discernible impact on any of these diabetes risk variables. However, there was some limited evidence that suggested persons may experience worsening glucose metabolism when taking high dosages of fish oils. An example of a fat is omega-3.

The food we eat contains trace levels that are necessary for health. Alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid are the three main forms of omega 3 fatty acids (DHA). ALA is typically found in plant-based lipids like those found in nuts and seeds (walnuts and rapeseed are rich sources).

EPA and DHA are referred to as long-chain omega-3 fats and are naturally found in fatty fish, such as salmon and fish oils including cod liver oil [45]. Results from 83 randomised controlled trials involving 121,070 people with and without diabetes and all lasting at least 6 months are combined in the systematic review. In studies, published between the 1960s and 2018, participants included men and women from North America, South America, Europe, Australia, and Asia, some of whom were in good health and others who already had diabetes. The study examined the impact on diabetes and glucose metabolism of increasing long-chain omega-3 fats, ALA, omega-6, and polyunsaturated fatty acids (PUFAs) [46].

6. Atrial fibrillation and the percentage of those consuming fish oil

The most prevalent form of abnormal heart rhythm, atrial fibrillation causes the heart to beat erratically and occasionally too rapid. Brown et al. [47] reported that omega-3 supplements are linked to an increased risk of developing atrial fibrillation in persons with high blood lipid level. That is the conclusion of the study, which was recently published in the European Society of Cardiology's journal, *European Heart Journal—Cardiovascular Pharmacotherapy (ESC)*. The most prevalent heart rhythm issue, atrial fibrillation, has been linked in certain clinical studies to omega-3 fatty acids and an increased risk of the condition. According to Hindricks et al. [48], people with the disease have a five-fold higher chance of suffering a stroke. In the investigation, five randomised controlled trials that looked at the impact of omega-3 fatty acid supplementation on cardiovascular outcomes were included. Participants had excessive triglyceride levels and either had cardiovascular disease in the early stages or were at high risk for it. There were 50,277 patients in all received fish oils or a placebo and were monitored for 2–7 years.

Fish oil dosages ranged from 0.84 g to 4 g daily with an incidence rate ratio of 1.37 (95% confidence interval 1.22–1.54; $p < 0.001$), and the researchers discovered that taking supplements of omega-3 fatty acids was substantially more likely to cause atrial fibrillation than taking a placebo. According to the National Health Interview Survey, 2012, the results are notable, and nearly 19 million adult Americans, or 7.8%, are thought to take fish oil supplements. Recent research suggests neither vitamin D nor the omega fatty acids contained in fish oil prevent the development of atrial fibrillation, according to Christine M. Albert, professor of cardiology and chief of the department of cardiology at the Smidt Heart Institute. Confusion among medical professionals and the public resulted from other clinical trials carried out outside of Cedars-Sinai that suggested patients receiving omega-fatty acid treatment had a higher risk of developing atrial fibrillation.

7. Potential flaws in fish-based research

When reading the present review on the connection between fish and sickness, it should be remembered that it frequently has methodological flaws. Hjartaker [49] examined these flaws, for instance, lean fish and fatty fish are frequently considered to be the same type of meal despite having quite different amounts of energy, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids. Additionally, fatty fish have slightly lower quantities of water-soluble substances like calcium but higher levels of fat-soluble vitamins (A, D, and α -tocopherol). Fish from

freshwater and saltwater habitats are frequently mixed together. Variations related to time of the year that fish are caught, how they are stored and cooked, how much fish is eaten, and the things that go with fishmeal are frequently ignored or not mentioned. Studies involving vegetarians suggest that effects may be brought on by the consumption of an animal protein source rather than fish [50, 51]. Different definitions of sudden death, residual confounding from reference groups with a less healthy lifestyle, variable endpoints evaluated, various study populations, and potential confounding effects from an increase in haemorrhagic stroke are further causes of epidemiological inconsistency. The majority of the fish studies that are now accessible are conducted on men, and Hu et al. [52] concluded women's studies have not been published in studies for a while.

8. Conclusion

The prevalence of CVD is increasing globally, especially in elderly people. The relationship between fish consumption and the incidence of CVD is uncertain, despite the fact that n-3 fatty acids have effects that may favourably influence CVD risk. Consuming tuna or other baked or broiled fish, but not fried fish, is linked to a decreased prevalence of CVD in older persons. Observational data show a modest, inverse relationship between eating fish and long-chain omega 3 fatty acids and the risk of cerebrovascular accidents. The protective impact of fish consumption on cerebrovascular risk may be mediated by a complicated interplay between varieties of nutrients that are frequently found in fish. However, there was no proof that long chain omega 3 fatty acids evaluated as circulating biomarkers in observational studies or supplements in primary and secondary prevention trials had a similar inverse relationship with cerebrovascular illness. Furthermore, study investigation shows associations between fish intake and risk of CVD, poised to become the leading cardiovascular health burden in coming decades. According to the review and the validation of these results in additional studies, further research into potential mechanisms of benefit and risk, with special emphasis on various fishmeal, is warranted.

Acknowledgements

The author is extremely grateful to my mentor, Prof. Dr. M. Deecaraman, for his ongoing support, encouragement, and helpful criticism. The author also thanks Prof. Dr. Ingrid Undeland of Chalmers University of Technology in Goteborg, Sweden, for granting me permission to copy the figures so I could finish this review article.

Conflict of interest

We declare that we have no conflict of interests.

Abbreviations

CHD	coronary heart disease
CVD	cardiovascular disease

PUFAs	polyunsaturated fatty acids
EPA	eicosapentaenoic acid
DPA	docosapentaenoic acid
LDL-C	low-density lipoprotein-cholesterol
N-3 PUFA	N-3 polyunsaturated fatty acids
MI	myocardial infarction
A-fib	atrial fibrillation
LA	linoleic acid
ALA	alpha-linolenic acid
T2D	type-2 diabetes
ARIC	atherosclerosis risk in communities
AHA	American Heart Foundation
ESC	European Society Cardiology
HDL	high-density lipoprotein

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