Fish and cardiovascular health

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Abstract

The antiatherogenic and antithrombotic effects of fish-oil-derived n-3 (omega-3) polyunsaturated fatty acids have given these compounds a dominating role in explaining the tentatively beneficial effects of fish, e.g. in the prevention of cardiovascular disease (CVD). As a result, the words “omega-3” and “fish” are often lumped together in both experimental studies and reviews. There are, however, strong reasons for separating fish lipids from whole fish muscle. The fish muscle matrix is highly complex, and many other compounds therein have been suggested as bioactive. This review summarizes data from epidemiological and intervention studies addressing effects of fish consumption per se on CVD. Potential roles of fish in CVD protection, and some risks connected to excessive fish eating, i.e. biocides and oxidation, are also discussed. Twelve out of 18 prospective cohort studies, two out of two case-control studies and two out of three ecological studies indicated reduced coronary mortality among subpopulations eating more fish, often at low fish intakes. Two cohort studies indicated increased risk for cardiovascular mortality. Out of 16 epidemiological studies in total, six prospective cohort studies, two case-control studies and one ecological study indicated a reduced risk of coronary morbidity with higher fish consumption, and one cohort study indicated an elevated risk of coronary morbidity. Two intervention studies on men with coronary heart disease produced different results, one indicating decreased total mortality, with lower coronary morbidity, but the other indicating an elevated risk for coronary mortality without affecting total morbidity. Thus, ample epidemiological data favour fish intake for reducing mortality and morbidity in cardiovascular disease, although evidence from intervention studies is inconsistent. Among risk factors for CVD that have been proven to be affected by a fish-containing diet are high-density lipoprotein cholesterol, serum triglycerides and blood clotting, the former increasing and the latter two decreasing.

Keywords: cardiovascular; coronary health; diet; fish; n-3 PUFA

Introduction

Background

A large number of epidemiological studies has indicated an inverse association between intake of fish and the risk for cardiovascular disease (CVD) and coronary mortality. The tentative contribution from the n-3 polyunsaturated fatty acids (n-3 PUFA or omega-3 PUFA) derived from fish oil in these findings has received much scientific attention, with the word “omega-3” almost becoming a synonym for fish. n-3 PUFA from fish oil have been shown either to reduce total mortality after myocardial infarction, or to reduce postinfarction morbidity (1). The same has been shown from intervention studies with dietary advice on fatty fish and fish oil intake (2).

The studies initiating the “n-3 boom” were those of Bang and Dyerberg in Greenland Inuits (3), which pointed to the n-3 PUFA as potential antiatherogenic agents. As recently summarized by Kris-Etherton et al. (4, 5), n-3 PUFA may also prevent CVD by acting as antithrombotic agents, anti-inflammatory agents and antiarrhythmic agents, as well by improving endothelial function. The links among these actions and their relation to CVD are described schematically in Fig. 1.

The effects of fish and fish oils on coronary heart disease (CHD), serum lipids, blood pressure and inflammatory diseases have been summarized in several reviews (4–14). In most cases, however, fish and fish oil have been lumped together, making it difficult to isolate the effects from fish per se. Kris-Etherton et al. and the American Heart Association (AHA) (4, 5) recently published recommendations for the American population regarding suitable intake of n-3 PUFA from fish and fish oil. For patients without documented CHD, a variety of
fish, preferably oily, should be eaten at least twice a week. For patients with documented CHD, 1 g eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) day\(^{-1}\) from oily fish or capsules should be consumed.

In 1999, Marckmann and Grønbæck (13) reviewed 11 prospective cohort studies (a total of 116,764 individuals) to examine the relationship between intake of fish and/or fish oil and CHD mortality. The review concluded that an inverse dose-dependent relation could be found between fish intake and CHD mortality; an optimum was seen at approximately 40–60 g fish day\(^{-1}\), but only in people with high risk for CHD. According to the authors, low-risk people with a healthy lifestyle do not gain additional protection against CHD from eating fish. In a recent editorial (15), Marckmann wrote that fish and fish oil lower CVD and total mortality in post-myocardial infarction (MI) patients, but only as long as the consumption of fish or fish oil is continued. The strongest explanations put forth are the antiarrhythmic affects of the n-3 PUFA. According to Marckman (15), cardioprotective nutrients such as fish proteins, selenium and other antioxidants make fish more beneficial than fish oil.

The aim of this review is to summarize data from epidemiological and intervention studies addressing the effects from fish consumption per se on CVD and coronary mortality. The review is introduced by a brief background on the known role of n-3 PUFA in CVD, and ends with a discussion about the intervention trials and epidemiological studies that have been carried out to explain mechanisms for fish-induced CVD protection. The role of fish-derived compounds other than n-3 fatty acids in CVD, and potential negative side-effects from elevated fish consumption, i.e. biocides and oxidative stress, are also discussed.

**Role of pure n-3 polyunsaturated fatty acids in cardiovascular disease**

Atherosclerosis and thrombosis are two major mechanisms behind CVD. The antiatherogenic role of n-3 PUFA consists of their ability to alter blood lipids, slightly reduce blood pressure and inhibit the growth of atherosclerotic plaques (4). Documented alterations in blood lipids involve reduced serum concentration of triglycerides (TG), apolipoprotein B [Apo(B)] and very low-density lipoprotein (VLDL) cholesterol, small increases in
plasma concentrations of high-density lipoprotein (HDL) cholesterol (7) and occasional increases in low-density lipoprotein (LDL).

The antithrombotic mechanism of n-3 PUFA is partially mediated by the ability of the n-3 PUFA to reduce the production of the vasoconstrictive and prothrombotic thromboxane A2 (TXA2) from arachidonic acid in the platelets. n-3 PUFA also increases the production of prostacyclins, which are vasodilators and antithrombotic factors. Fisher and Weber (19) formulated the hypothesis that reduced platelet aggregability and increased bleeding times after EPA ingestion may be due to the formation of prostaglandin I3 (PGI3) and TXA3 in association with reduced synthesis of TXA2.

The suggested antiarrhythmic effect of n-3 PUFA might explain the beneficial effect on sudden death (20). n-3 PUFA, particularly DHA, can reduce the risk of ventricular tachycardia and fibrillation (21). The anti-inflammatory effect that has been documented for the fish-derived n-3 PUFA is mediated through eicosanoids, thromboxanes, prostaglandins and leukotrienes produced from these fatty acids, which are less inflammatory than those produced from n-6 fatty acids, such as arachidonic acid.

The concept of n-3 PUFA and CVD has recently been reviewed by Kris-Etherton et al. (5), and the reader is referred to this article.

**Methodology**

**Search criteria**

For this review, a search was done for epidemiological studies, intervention studies and reviews in the databases PubMed and FSTA (Food Science and Technology Abstracts), in reference lists of retrieved articles and using informal sources. With the aim of tracing as many as possible of the available publications addressing the effect from a fish-containing diet on human health, a large number of indexing terms was used and combined. Some examples are “cardiovascular disease”, “coronary disease”, “health”, “disease”, “cardiac”, “fish”, “seafood”, “herring”, “mackerel”, “fatty fish”, “lean fish” and “dark muscle fish”. Studies comprising diets with fish oil, DHA-EPA concentrates and fish were included if results regarding effects from fish intake alone could be isolated and interpreted.

**Rejection criteria**

Studies were rejected if they were presented only as letters or abstracts, or in languages other than English or any Scandinavian language. Studies were also rejected if they focused only on purified n-3 PUFA without a fish intervention. Studies where the dietary intervention was not controlled, or could not be fully interpreted from the reports, or where statistical analysis had not or could not be performed, were also rejected.

**Sorting and weighing of studies**

Epidemiological and intervention studies were each further subdivided into three and two groups, respectively, as their value differed largely depending on the design used. The epidemiological studies were sorted into ecological (cross-sectional studies), case–control studies and cohort studies. The lowest value was given to the ecological studies which compare various countries or regions. Although the range of fish consumption may be wide, these studies often lack appropriate control of potential confounding factors. Furthermore, it is not certain that a relationship seen at a population level will hold at an individual level (ecological fallacy) (22). The case–control studies have somewhat higher value than ecological studies. Those found were mostly retrospective, which implies a certain bias in the collection of information. Most emphasis should be put on cohort studies, which were mostly prospective.

Intervention studies, which can test a preset hypothesis, can be sorted into cross-over or parallel studies. The former are most powerful when applicable (i.e. when the endpoint is something other than mortality) as subjects act as their own controls, thus removing individual differences. The only two interventions included in the result section (2, 23) were both parallel and with a factorial design.

**Potential weaknesses in fish-based studies**

It should be kept in mind when reading the current review that epidemiological studies on the relation between fish and disease often suffer from methodological weaknesses. Such weaknesses were recently reviewed by Hjartåker (22). For example, fatty fish and lean fish are commonly regarded as one homogeneous food item, although they differ widely in content of energy, saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids (22). Further, fatty fish contain higher
levels of fat-soluble vitamins (A, D, α-tocopherol), but slightly lower levels of water-soluble compounds such as calcium. Freshwater and saltwater fish are also usually not separated. Variations originating in catching season, storage method, cooking method, amounts of fish consumed and items accompanying the fish dish are also often neglected or not reported. Other differences between studies are their adjustment for potential confounding factors as well as details and quality of dietary assessment methods. It should also be kept in mind that any favourable effect of fish may be due to replacement of unfavourable foods such as red meat (22). In studies involving vegetarians (24, 25), effects may be the result of the intake of an animal protein source rather than fish.

Epidemiological inconsistencies can also be due to different definitions of sudden death, residual confounding of reference groups with a less healthy lifestyle, variable endpoint studied, different study populations, and possible confounding effects from increase in haemorrhagic stroke (5, 26). It should finally be noted, that the majority of the fish studies available are performed on men. Studies addressing women have not been published until recently (27, 28).

Markers for fish consumption: compliance
Dietary intake of fish is strongly related with the concentration of DHA and EPA in plasma, erythrocyte membranes and platelets/platelet membranes (29–34). These characteristics are therefore often used as markers of fish intake. It has been claimed that EPA and DHA in erythrocyte membranes are the best markers to use.

Summary of results
Tables 1 and 2 summarize results from epidemiological and intervention studies addressing the relation between fish consumption and cardiovascular mortality, as well as fish consumption and cardiovascular morbidity.

Fish and cardiovascular mortality
There are only two intervention studies, by Burr et al. (2, 23), addressing the role of fish in cardiovascular mortality (Table 1). In the earlier study, from 1989, the role of changes in fat, fish and fibre intake was evaluated among 2033 men who had recovered from MI. In 257 of these subjects, increased fish intake was the single variable studied. With advice to eat 300 g week$^{-1}$ of fatty fish, all-cause mortality was reduced by 29% over 2 years, with no changes in reinfarction rate but lower fatality rate from MI. It must be stressed that 14–22% of the subjects in this study chose to take fish oil capsules instead of fish. In a recent intervention study by the same first author, published in 2003, dietary advice on four diets (“n-3 PUFA”, “fruit, vegetables, oats”, “both”, “no advice”) was given to 3114 men with angina. In the n-3 PUFA group, fish intake was lumped together with fish oil intake, and the adjusted hazard ratio for cardiac death was surprisingly higher, at 1.26, particularly after intake of capsules. However, the 95% confidence intervals (1.00–1.58) included a possibility of no effect.

Twenty-three epidemiological studies that addressed the role of a fish-containing diet on coronary mortality fulfilled the inclusion criteria (Table 1). Eighteen of these were prospective cohort studies (16, 26–28, 35–48), two were case-control studies (49, 50) and three were ecological studies (32, 51, 52) (Table 1). Sixteen studies (12 prospective cohorts, two case-control studies and two ecological studies) (16, 27, 28, 32, 35–41, 43, 45, 49–51), including those with the highest numbers of subjects and longest follow-up time, reported reduced coronary mortality in subpopulations eating more fish. In the study by Kromhout et al. (16), such a reduction was already significant at 1–14 g lean white fish day$^{-1}$. Mozaffarian et al. (40) only found risk reductions with canned, baked or broiled fish, but not with fried fish or fish burgers. Among the 16 studies above, all-cause mortality was reduced in five (28, 39, 43, 45, 51) and unaffected in one (36). In the 10 year follow-up of the DART study by Burr et al. (2, 41), all-cause mortality was even raised between years 2 and 5 (41). Thus, after a mean follow-up of 15 years, all-cause mortality in the two study groups was almost identical. In four studies, three prospective cohorts (42, 44, 46) and one ecological study (52), no effect of fish consumption on coronary mortality could be seen. Among these, Oomen et al. (42), however, found that fatty fish reduced coronary mortality compared with lean fish. In two prospective cohort studies (47, 48), there was an increase in coronary mortality in the population having the highest fish intake. In one of these (47), the very high intake of saturated fat in both populations may have masked a positive effect from fish n-3 PUFA.
Table 1. Summary of studies addressing the role of fish in cardiovascular mortality

| Ref. no. | Subjects | Length (years) | Fish diet | Effects of higher vs lower fish intake |
|----------|----------|----------------|-----------|---------------------------------------|
| Intervention studies | 23 | 3114 M | 3–9 | 0 vs 2 × week⁻¹ | ↑ Non-sudden/sudden cardiac death. All-cause mortality unaffected |
| 2 | 2033 M | 2 | 0 vs 300 g week⁻¹ | ↓ 2-year all-cause mortality. Reinforcement/death in IHD unaffected |
| Prospective cohort studies | 35 | 1822 M | 30 | 0 to >35 g day⁻¹ | ↓ CHD death, total MI death, non-sudden MI death |
| 43 | 285 M, 30 F | 5 | 0 to >57 g day⁻¹ | ↓ Death and CAD death |
| 45 | 8825 M & F | 19–22 | 0 to >1 × week⁻¹ | ↓ Total death. Non-significant ↓ in CVD death |
| 27 | 8468 F | 16 | <1 × month⁻¹ to >5 × week⁻¹ | ↓ CHD risk, CHD deaths, non-fatal MI |
| 28 | 5103 F | 16 | <1 × month⁻¹ to >5 × week⁻¹ | ↓ CHD mortality and total mortality |
| 16 | 852 M | 20 | 0 to ≥45 g day⁻¹ | ↓ CHD mortality |
| 36 | 272 M & F | 17 | 0 vs 24 g day⁻¹ | ↓ CHD mortality. Total mortality unaffected |
| 40 | 3010 M & F | 9.3 | <1 × month⁻¹ to >3 × week⁻¹ | ↓ Total IHD death and arrhythmic IHD death. Non-fatal MI unaffected |
| 38 | 1930 M | 25 | 0 to >35 g day⁻¹ | ↓ CHD mortality and total mortality |
| 37 | 8006 M | 23 | <2 vs ≥2 × week⁻¹ | ↓ CHD mortality |
| 39 | 18244 M | 12 | <50 to >200 g week⁻¹ | ↓ Fatal acute MI, total mortality and MI mortality. Death in stroke or IHD other than MI unaffected |
| 42 | 2738 M | 20 | 18 to 38 g day⁻¹ | CHD mortality unaffected by total and lean fish |
| 46 | 21185 M | 4 | <1 to ≥5 × week⁻¹ | MI, stroke and CVD death unaffected |
| 26 | 20551 M | 11 | <1 to >5 × week⁻¹ | Total MI, non-sudden cardiac death, total CHD mortality unaffected |
| 44 | 44895 M | 6 | <1 to >6 × week⁻¹ | CHD death unaffected |
| 41 | 879 M | 2–13 | 44 vs 37 g day⁻¹ | ↑ All-cause mortality, ↓ coronary mortality. Stroke unaffected |
| 48 | 1833 M | 5 | 0 to ≥30 g day⁻¹ | ↑ MI risk and CVD death |
| 47 | 20 M | 10 | 55 vs 132 g day⁻¹ | ↑ CHD mortality |
| Case control studies | 49 | 178 M | 17 | <1 × month⁻¹ to >5 × week⁻¹ | ↓ Sudden death |
| 50 | 334 (493 controls) | 6 | 0.96–13.7 g n-3 PUFA from seafood month⁻¹ | ↑ Primary cardiac arrest |
| Ecological studies | 51 | 100000 M & F | 2–30 | 0.23–10.4 energy% | ↓ All-cause mortality, IHD death and death in stroke |
| 52 | People from 21 countries | 2 | <10 to >100 g day⁻¹ | CHD mortality unaffected |
| 32 | 87 M | 26 vs 218 g day⁻¹ | ↓ IHD mortality |

M: males; F: females; PUFA: polyunsaturated fatty acids; ↑: increased; ↓: decrease(d); IHD: ischaemic heart disease; CHD: coronary heart disease; MI: myocardial infarction; CAD: coronary artery disease; CVD: cardiovascular disease.

**Fish and cardiovascular morbidity**

Sixteen epidemiological studies were found, of which 12 were prospective cohort studies (26, 27, 40, 41, 46, 48, 53–58), three were case–control studies (59–61) and one was an ecological study (20) addressing the association between fish intake and cardiovascular morbidity, including stroke (Table 2). Of these, six prospective cohort studies (27, 53–57), including by far the largest number of subjects, as well as two case–control studies (60, 61) and the ecological study (20), reported lower morbidity risk among fish eaters. In seven of the studies, there was a lack of a significant association found (26, 40, 41, 46, 55, 58, 59), and one reported higher morbidity among freshwater fish eaters (48). Based on eight prospective cohort studies, the risk for stroke was either reduced (53–55, 57) or unaffected (41, 46, 55, 58) by increased fish intake. In the Nurses’ Health Study (55), positive effects were seen only on total stroke incidence and thrombotic stroke, but not on haemorrhagic stroke. He et al. (54) found positive effects on ischaemic stroke, but not on haemorrhagic stroke. Two prospective cohorts (27, 56) and the three case–control studies (59–61) found reduced risk for MI. MI was unaffected in three prospective cohort studies (26, 40, 46) and increased in one (48).

Thus, substantial epidemiological evidence favours fish as a beneficial dietary factor against cardiovascular disease and mortality. However,
interventional proof is, so far, dependent on one single study.

**Discussion**

This review reports several epidemiological studies showing favourable effects on cardiovascular morbidity and mortality, but also studies with no or even negative effects. Among the 12 prospective cohort studies, two case-control studies and two ecological studies that pointed at reduced coronary mortality among subpopulations eating more fish, several showed significant effects already at low intakes of fish (<60 g day$^{-1}$). Six prospective cohort studies, two case-control studies and one ecological study indicated that fish also reduced coronary morbidity; including stroke and MI. One cohort study indicated elevated risk of coronary morbidity. One intervention study showed a fish diet to reduce all-cause mortality by 29% in men after MI, without affecting reinfarction rate, but lowering postinfarction fatality. However, the most recent intervention study, by the same author, failed to find any positive effects on dietary fish advice in men with angina, and the results even indicated a higher hazard ratio for cardiac death, especially in men taking fish oil capsules. This effect is so far unexplained, but may be triggered by changes in risk-taking behaviour (23).

**Fish and risk factors for cardiovascular disease**

Reasons behind the many positive results from a fish-containing diet on CVD could involve effects on blood lipids, blood pressure and haemostatic parameters. Findings on fish-derived effects on these variables are summarized and discussed below.

**Fish and blood lipids**

In general, studies comprising either fish or fish oil have given the same results on blood lipids (9), indicating the central role of n-3 PUFA in such effects. The latter is also strengthened by the numerous findings that DHA and EPA from fish are efficiently incorporated into the membranes of erythrocytes, granulocytes and platelets, for example, as well as into plasma lipids (29–34). Accordingly, the AHA recently recommended 2–4 g of EPA+DHA day$^{-1}$ as capsules for patients with elevated TG (4).

**Table 2. Summary of studies addressing the role of fish in cardiovascular morbidity**

| Ref. no. | Subjects | Length (years) | Fish diet | Effects of higher vs lower fish intake |
|----------|----------|----------------|-----------|---------------------------------------|
| Prospective cohort studies |
| 53 | 6299 M & F | 12–16 | 0 to >1 x week$^{-1}$ | Stroke |
| 54 | 43 671 M | 12 | <1 vs 1–3 x month$^{-1}$ | Ischaemic stroke. Haemorrhagic stroke unaffected |
| 55 | 79 839 F | 14 | ≤1 x month$^{-1}$ to ≥5 x week$^{-1}$ | Stroke and thrombotic infarct. Haemorrhagic stroke unaffected |
| 57 | 552 M | 15 | <20 vs >20 g day$^{-1}$ | Stroke |
| 58 | 1847 M | 30 | 0 to >35 g day$^{-1}$ | Stroke unaffected |
| 41 | 879 M | 2–13 | 44 vs 37 g day$^{-1}$ | Stroke unaffected |
| 27 | 84 688 F | 16 | <1 x month$^{-1}$ to >5 x week$^{-1}$ | Non-fatal MI |
| 56 | 462 M, 283 F | 2 | ≤1 to ≥2.6 x week$^{-1}$ | Q-wave MI |
| 26 | 20551 M | 11 | <1 to >5 x week$^{-1}$ | Total MI unaffected |
| 46 | 21 185 M | 4 | <1 to ≥5 x week$^{-1}$ | MI and stroke unaffected |
| 40 | 3010 M & F | 9.3 | <1 x month$^{-1}$ to >3 x week$^{-1}$ | Non-fatal MI unaffected |
| 48 | 1833 M | 5 | 0 to >30 g day$^{-1}$ | MI risk |
| Case control studies |
| 60 | 78 (+156 controls) | <1 vs >1 x week$^{-1}$ | MI risk |
| 61 | 287 F (+649 controls) | <1 vs >1 x week$^{-1}$ | MI risk |
| 59 | 632 (+1214 controls) | <2 vs >4 x week$^{-1}$ | Non-significant in MI |
| Ecological studies |
| 20 | 6500 M & F | 0.9 to 19.9–119 g day$^{-1}$ | CVD |

M: males; F: females; ↑: increased; ↓: decrease(d); MI: myocardial infarction; CVD: cardiovascular disease.
Six ecological studies (20, 24, 30, 32, 34, 62) and one prospective cohort study (63) have shown fish intake to be correlated with reduced TG levels. There are also indications from ecological studies on correlations between fish and reduced total serum cholesterol levels (24, 32, 62), as well as reduced lipoprotein (a) levels (25, 62). HDL was increased in two ecological studies (34, 64) and Apo(A) in one (34).

Supporting the epidemiological data, nine intervention studies have shown fish intake to reduce serum TG levels: four with cross-over designs (65–68) and five with parallel designs (69–73). The amounts of fish used in these studies have mostly varied between 130 and 200 g day\(^{-1}\), and the TG-lowering potential has varied between 7 and 30%. In two cross-over and two parallel studies (74–77) fish intake did not affect blood TG levels. Two of them used lean fish (75, 77), and one of these (75) showed 16% reductions in TG levels after extra addition of 5 g fish oil day\(^{-1}\). Intervention studies have also revealed that fish intake raises HDL-cholesterol (65, 72, 73, 77, 78) and reduces Apo(A) (65, 70). Reductions in LDL-cholesterol (68, 73, 76) and in Apo(B) (69, 70) have been reported after fish intake, but the opposite has also been reported (79). Many studies have also failed to find any significant effect of fish intake on total cholesterol (66, 71, 74, 76, 78), LDL-cholesterol (66, 74, 78), HDL-cholesterol (66, 74) and Apo(B) (74, 78). Among the latter, the study by Nenseter et al. (74) is special, as it is the only double-blind study considering fish and health.

Thus, fish intake seems to reduce TG and probably raise HDL, while the effects on total cholesterol and LDL are usually negligible.

**Fish and blood pressure**

Two epidemiological studies were found addressing the relation between fish and blood pressure (62, 80). Blood pressure was lower among people in a fish-eating than vegetarian village in Tanzania (62). In the prospective NHANES I follow-up study (80) there was no consistent relation between fish consumption and hypertension.

In parallel intervention trials, a modest reduction in blood pressure was achievable by fish consumption in patients with hypertension (81, 82). In normotensive subjects, no reduction in blood pressure during fish intake was recorded (78, 83, 84).

All in all, the hypotensive potential of fish seems to be of minor importance for clinical benefit, and thus for explaining how fish could reduce CVD.

**Fish and haemostasis**

One epidemiological study was found addressing fish and haemostasis (29). In their prospective cohort study, van Houwelingen et al. (29) reported no differences in bleeding time, platelet number, platelet aggregation and adenosine triphosphate release in citrated blood among 40 healthy elderly men from the Zutphen study population on a low or a high fish diet (2 vs 32 g day\(^{-1}\)). The intervention trials of Mori et al. (85), van Houwelingen et al. (83) and Ågren et al. (86) indicated that fish supplementation slightly reduced collagen-induced platelet aggregation in platelet-rich plasma. Cobiac et al. (78) reported increased bleeding time along with reduced fibrinogen and thromboxane levels after a diet containing very large amounts of fish. Platelet thromboxane levels were also reduced in the studies by Hänninen and Ågren (70) and Mann et al. (33). Emeis et al. (87) found that 135 g mackerel day\(^{-1}\) increased total plasma plasminogen activator inhibitor (PAI) activity by 45% owing to a 71% increase in PAI type 1.

To summarize, most studies on fish and haemostasis have shown increased bleeding time, most often assigned to decreased platelet aggregability, possibly caused by changes in the ratio of thromboxanes and other eicosanoids.

**Role of fish-derived compounds other than n-3 polyunsaturated fatty acids in cardiovascular disease**

**Epidemiological indications**

Both Marckmann and Grønbæk (13) and Kromhout et al. (16) stressed that it is unlikely that the n-3 PUFA alone explain the cardioprotective effect seen after low to moderate fish consumption. A daily intake of 0.9 g n-3 PUFA, which corresponds to 40–60 g mixed fish day\(^{-1}\), had no significant impact on CHD risk factors such as LDL-cholesterol, fibrinogen or most other risk factors for atherosclerosis (13). The postprandial TG profile was regarded as an exception, since it was markedly reduced with only 0.9 g n-3 PUFA per day (88).

**Potential candidate compounds**

Elvevoll and Österud (18) suggested several fish-derived components such as monounsaturated fatty acids, minerals, trace elements [potassium, calcium...
(Ca), magnesium, zinc, selenium (Se) and iodine] as being of potential interest as bioactive substances. In addition, Savage (17) highlighted the role of calcium, selenium, coenzyme Q and vitamin D in CVD. Calcium favourably influences blood pressure, but as fish muscle contains 10–70 mg Ca 100 g⁻¹ (89), fish intake is not normally an important source of dietary calcium. However, the intake increases when small bones are consumed along with the muscle, such as in sardines and herring. Selenium is important for the activity of glutathione peroxidase and other antioxidative enzymes. Thus, selenium could prevent atherosclerosis via reducing in vivo lipid oxidation (17). In addition, selenium deficiency favours thromboxane production over prostacyclin production, which may result in vasoconstriction and platelet aggregation. Fish contain about 20–30 µg Se 100 g⁻¹ muscle (89), which make fish and shellfish intake important contributors to total selenium intake. This is accentuated in Scandinavia where soils are low in selenium, and thus cereals, dairy products, meat and vegetables are relatively low in selenium. In vitro, coenzyme Q protects LDL from oxidation, and may also protect against atherosclerosis (90). The levels of coenzyme Q in fish range from 4 to 64 µg g⁻¹ (90). Fatty fish is an important source of vitamin D, with a concentration of approximately 10 µg 100 g⁻¹ (89), which may dampen atherogenesis via its important role in cell differentiation (17).

Kondo et al. (91) showed that fish proteins and fish-derived astaxanthin inhibited oxidation of human LDL ex vivo. Potent peptides with high antihypertensive activities (angiotensin-converting enzyme inhibitors) have been isolated from fish hydrolysates (92, 93). Fish also contain protease inhibitors of the serpin family (serine protease inhibitors) (94). This is a family of glucoproteins among which some control, for example, blood coagulation, fibrinolysis, complement activation and inflammation processes (18).

Elvevoll and Österud (18) compared the effects from virgin cold pressed marine oils and refined marine oils on healthy volunteers. The cold pressed oils had additional positive effects on parameters related to CHD development despite a lower n-3 PUFA level. This indicates that additional compounds in the fish lipid fraction other than n-3 PUFA may have bioactive effects. It also indicates that there may be a significant difference between fish fat ingested as fish (unrefined) and fish fat ingested as, for example, capsules (refined).

To summarize, there are some indications but there is no solid evidence that factors other than n-3 PUFA may also be responsible for the effects of fish on CVD. The suggested compounds include minerals, trace elements, amino acids, peptides, proteins and lipid-soluble vitamins.

Potential negative effects from fish intake

Biocides and heavy metals

Contradicting the positive effects from the n-3 PUFA of fish fat, some carcinogenic contaminants [e.g. dichlorodiphenyltrichloroethane (DDT), dielodrin, heptachlor, polychlorinated biphenyls (PCBs) and dioxins] and non-carcinogenic contaminants (e.g. methyl mercury) can accumulate in the adipose tissue of fatty fish (5, 95). Levels are higher in older, larger, predatory fish and marine mammals. Two recent epidemiological studies on men reported conflicting data on the correlation between methyl mercury and CVD, one showing a positive correlation (96) and one no significant correlation (97). The relationship between fish consumption, mercury exposure and heart disease has very recently been reviewed, suggesting that high mercury content may diminish the cardioprotective effect of fish intake (98). Official recommendations on the safe intake of free-living fatty fish have been issued by several official agencies. The Swedish recommendations state a maximum of one meal of potentially contaminated fish per month for pregnant women, and one meal per week for others (99). The US recommendations (4) stress that for middle-aged and older men and women after the menopause, the benefits of eating fish far outweigh the risks when consumed according to the guidelines of, for instance, the US Food and Drug Administration (4).

Oxidative stress

Methods to estimate in vivo oxidation status have been a matter of debate, and care has to be taken when extrapolating, for example, Cu/Fe-catalysed LDL-oxidation data from in vitro to in vivo situations. In addition, analyses of oxidation products such as thiobarbituric acid reactive substances (TBARS) may take into account TBARS that are directly adsorbed from food.

It has been reported that ingestion of purified n-3 PUFA or fish oil has been linked to reduced serum...
antioxidant status (100, 101) and increased in vivo oxidation of LDL (102, 103). However, few studies have addressed how fish intake influences antioxidative defence and production of oxidation products, e.g. from LDL (20, 72, 91, 104, 105). Wolmarans et al. (104) noted a decrease in plasma vitamin E with large daily intakes of fish, while glutathione peroxidase activity was found to be positively correlated (20) or uncorrelated with higher fish intake (60).

Thus, there is no clear consensus as to whether fish consumption can affect the antioxidant levels or activities and the production of oxidation products. Both reductions and increases have been seen when different methods for estimating in vivo oxidation have been used.

Conclusions
Epidemiological data favour fish intake for reducing mortality and morbidity in CVD, although evidence from intervention studies is inconsistent.

Fish seems to reduce serum triglycerides and increase HDL-cholesterol, effects that appear to be attributable to the n-3 PUFA. Fish also affects haemostasis. The small levels of lean fish that seem to reduce CHD mortality suggest that the n-3 PUFA may not be solely responsible for all underlying mechanisms. Proteins, peptides, amino acids, trace elements and minerals have been suggested to contribute, although there is insufficient experimental evidence confirming which components may be involved.

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