Fish and cardiovascular health

By Ingrid Undeland[1], Lars Ellegård[2] and Ann-Sofie Sandberg[1]

[1]Department of Chemistry and Bioscience–Food Science, Chalmers University of Technology, Göteborg, Sweden;
[2]Department of Clinical Nutrition, Göteborg University, Sahlgrenska University Hospital, Göteborg, Sweden

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.

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
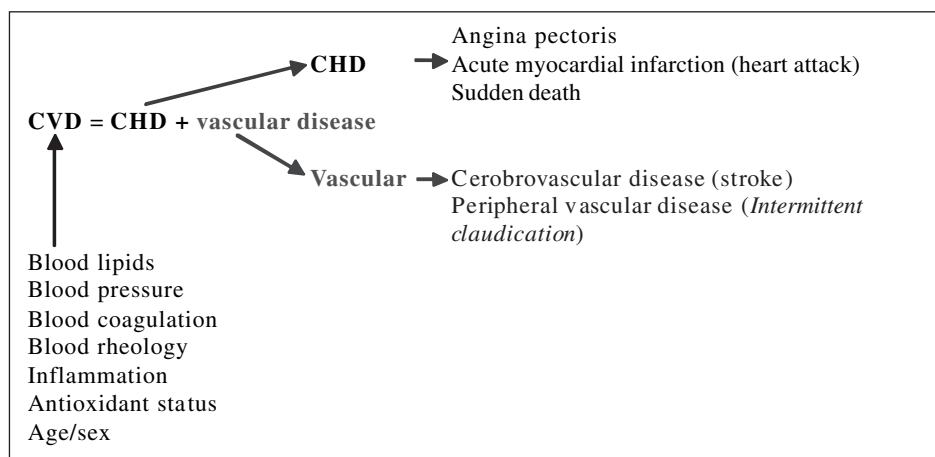
Fig. 1. Schematic description of the term cardiovascular disease (CVD). CHD: coronary heart disease.

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 Marckmann, there are insufficient data to conclude whether the consumption of fish per se influences CVD mortality and morbidity in the general population.

Reduced coronary mortality has been found in studies with low to moderate fish intakes, irrespective of the n-3 PUFA content (16), which indicates a possible role of other constituents in fish. The fish muscle matrix in which the n-3 PUFA are distributed is highly complex, and also contains, for example, monounsaturated fatty acids, proteins, proteoglucans, steroids and low molecular weight compounds such as amino acids, organic acids, trace elements and peptides with specific amino acid sequences (17, 18). These compounds have been ascribed antioxidative, hormonal, anti-inflammatory and blood pressure lowering effects *in vivo*, among other effects (14). 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 A_2 (TXA_2) 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 I_3 (PGI_3) and TXA_3 in association with reduced synthesis of TXA_2.

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. Reinfarction/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	84 688 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	18 244 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	21 185 M	4	<1 to ≥5 × week^{-1}	MI, stroke and CVD death unaffected
26	20 551 M	11	<1 to >5 × week^{-1}	Total MI, non-sudden cardiac death, total CHD mortality unaffected
44	44 895 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	100 000 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,

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 $>1 \times week^{-1}$	↓ Stroke
54	43 671 M	12	<1 vs $1–3 \times month^{-1}$	↓ Ischaemic stroke. Haemorrhagic stroke unaffected
55	79 839 F	14	$\leq 1 \times month^{-1}$ to $\geq 5 \times week^{-1}$	↓ 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	$<1 \times month^{-1}$ to $>5 \times week^{-1}$	↓ Non-fatal MI
56	462 M, 283 F	2	≤ 1 to $\geq 2.6 \times week^{-1}$	↓ Q-wave MI
26	20551 M	11	<1 to $>5 \times week^{-1}$	Total MI unaffected
46	21 185 M	4	<1 to $\geq 5 \times week^{-1}$	MI and stroke unaffected
40	3010 M & F	9.3	$<1 \times month^{-1}$ to $>3 \times week^{-1}$	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 $\geq 1 \times week^{-1}$	↓ MI risk
61	287 F (+649 controls)	5	<1 to $>1 \times week^{-1}$	↓ MI risk
59	632 (+1214 controls)		<2 to $>4 \times week^{-1}$	Non-significant ↓ in MI
Ecological studies				
20	6500 M & F		0–0.9 to 19.9–119 g day^{-1}	↓ CVD

M: males; F: females; ↑: increased; ↓: decrease(d); MI: myocardial infarction; CVD: cardiovascular disease.

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).

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 Grönbäck (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, Savige (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), dieldrin, 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.

References

1. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial. Lancet 1999; 354: 447–55.
2. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetman PM, et al. Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 30: 757–61.
3. Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper HH, ed. Advances in nutrition research. New York: Plenum Press; 1980. p. 1–22.
4. Kris-Etherton PM, Harris WS, Appel LJ, AHA Nutrition Committee American Heart Association. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arteroscler Thromb Vasc Biol 2003; 23: 151–2.
5. Kris-Etherton PM, Harris WS, Appel LJ, AHA Nutrition Committee American Heart Association. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Arteroscler Thromb Vasc Biol 2003; 23: 20–30.
6. Nestel P. Effects of fish oils and fish on cardiovascular disease. Curr Atheroscler Rep 2001; 3: 68–73.
7. Connor WE. n-3 fatty acids from fish and fish oil: panacea or nostrum? Am J Clin Nutr 2001; 74: 415–6.
8. Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids 1996; 31: 243–52.
9. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997; 65(Suppl): 1645–54S.
10. de Deckere EA, Korver O, Verschuren PM, Katan MB. Health aspects of fish and n-3 polyunsaturated fatty acids from plant and marine origin. Eur Clin Nutr 1998; 52: 749–53.
11. Katan MB. Fish and heart disease. N Engl J Med 1995; 332: 1024–5.
12. Stone NJ. Fish consumption, fish oil, lipids and coronary heart disease. Circulation 1996; 94: 2337–40.
13. Marckmann P, Grönbäck M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. Eur J Clin Nutr 1999; 53: 585–90.
14. Skerrett PJ, Hennekens CH. Consumption of fish and fish oils and decreased risk for stroke. Prev Cardiol 2003; 6: 38–41.
15. Marckman P. Fishing for heart protection. Am J Clin Nutr 2003; 78: 1–2.
16. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985; 312: 1205–9.
17. Savige GS. Candidate foods in the Asia-Pacific region for cardiovascular protection: fish, fruit and vegetables. Asia Pacific J Clin Nutr 2001; 10: 134–7.
18. Elvevoll EO, Österud B. Impact of processing on nutritional quality of marine food items. In: Elmadfa IAE, Konig JS, eds. Modern aspects of marine food items – present knowledge and future perspectives. Basel: Karger; 2003. p. 337–41.
19. Fisher S, Weber PC. Thromboxane A3 (TXA3) is formed in human platelets after dietary eicosapentaenoic acid (C20:5ω3). Biochem Biophys Res Commun 1983; 116: 1091–9.
20. Wang Y, Crawford MA, Chen J, Li J, Ghebremeskel K, Campell TC, et al. Fish consumption, blood docosahexaenoic acid and chronic diseases in Chinese rural populations. Comp Biochem Physiol Part A 2003; 136: 127–40.

21. Leaf A, Kang JX, Xiao YF, Billman GE, Voskuyl RA. The antiarrhythmic and anticonvulsant effects of n-3 fatty acids. J Membr Biol 1999; 172: 1–11.

22. Hjartåker A. Fish consumption and risk of breast, colorectal and prostate cancer: a critical evaluation of epidemiological studies. Scand J Nutr 2003; 47: 111–22.

23. Burr ML, Ashfield-Watt PAL, Dunstan FDJ, Fehily AM, Breay P, Ashton T. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr 2003; 57: 193–200.

24. Bulliyya G. Fish intake and blood lipids in fish eating vs non-fish eating communities of coastal south India. Clin Nutr 2000; 19: 165–70.

25. Marcovina SM, Kennedy H, Bon GB, Cazzolato G, Galli C, Caiglia E, et al. Fish intake, independent of Apo(a) size, accounts for lower plasma lipoprotein(a) levels in bantu fishermen in Tanzania. Atheroscler Thromb Vasc Biol 1999; 19: 1250–6.

26. Albert CM, Hennekens CH, O'Donell CJ, Ajani UA, Willett WC, Ruskin JN, et al. Fish consumption and risk for sudden cardiac death. JAMA 1998; 279(1): 23–8.

27. Hu FB, Bronner L, Willet WC, Stampfler MJ, Rexrode KM, Albert CM, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002; 287: 1815–21.

28. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and the risk for coronary heart disease and total mortality in diabetic women. Circulation 2003; 107: 1852–7.

29. van Houwelingen AC, Hornstra G, Kromhout D, de Lezenne Coulander C. Habitual fish consumption, fatty acids of serum phospholipids and platelet function. Atherosclerosis 1989; 75: 157–65.

30. Svensson B-G, Åkesson B, Nilsson A, Skerfving S. Fatty fish composition of serum phsophatidylcholine in healthy subjects consuming varying amounts of fish. Eur J Clin Nutr 1993; 47: 132–40.

31. Yang YJ, Lee SH, Hong SJ, Chung BC. Comparison of fatty acid profiles in the serum of patients with prostate cancer and benign prostatic hyperplasia. Clin Biochem 1999; 32: 405–9.

32. Torres IC, Mira L, Ornelas CP, Melim A. Study of the effects of dietary fish intake on serum lipids and lipoproteins in two populations with different dietary habits. Br J Nutr 2000; 83: 371–9.

33. Mann N, Sinclair A, Pille M, Johnsson L, Warrick G, Reder E, et al. The effect of short-term diets rich in fish, red meat, or white meat on thromboxane and prostacyclin synthesis. Lipids 1997; 32: 635–44.

34. Bönå KH, Bjerve KS, Nordöy A. Habitual fish consumption, plasma phospholipid fatty acids, and serum lipids: the Tromsö study. Am J Clin Nutr 1992; 55: 1126–34.

35. Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, et al. Fish consumption and the 30 year-risk of fatal myocardial infarction. N Engl J Med 1997; 336: 1046–53.

36. Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. Int J Epidemiol 1995; 24: 340–5.

37. Rodriguez BL, Sharp DS, Abbott RD, Burchfiel CM, Masaki K, Chyou PH, et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. Circulation 1996; 94: 952–6.

38. Shekelle RB, Paul O, Shryock AM, Stamler J. Fish consumption and mortality from coronary heart disease. N Engl J Med 1985; 313: 820.

39. Yuan J-M, Ross RK, Gao Y-T, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. Am J Epidemiol 2001; 154: 809–16.

40. Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovivk DS. Cardiac benefits of fish consumption may depend on the type of fish consumed. The cardiac health study. Circulation 2003; 107: 1372–7.

41. Ness AR, Hughes J, Elwood PC, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Trial (DART). Eur J Clin Nutr 2002; 56: 512–8.

42. Oomen CM, Feskens JM, Räsänen L, Fidanza F, Nissinen AM, Menotti A, et al. Fish consumption and coronary heart disease mortality in Finland, Italy and the Netherlands. Am J Epidemiol 2000; 151: 999–1006.

43. Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin Nutr 2003; 78: 65–71.

44. Aschierio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willet WC. Dietary intake of marine n-3 fatty acids, fish intake and the risk of coronary disease among men. N Engl J Med 1995; 332: 977–82.

45. Gillum RF, Mussolino M, Madans JH. The relation between fish consumption, death from all causes and incidence of coronary heart disease. J Clin Epidemiol 2000; 53: 237–44.

46. Morris MC, Manson JE, Rosner B, Buring JE, Willet WC, Hennekens CH. Fish consumption and cardiovascular disease in the Physicians' Health Study. Am J Epidemiol 1995; 142: 166–75.

47. Simonsen T, Nordöy A. Ischaemic heart disease, serum lipids and platelets in Norwegian populations with traditionally low or high fish consumption. J Intern Med 1989; 225(Suppl 1): 83–9.

48. Salonen JT, Seppänen K, Nyyssönen K, Korpela H, Kauhanen J, Kantola M, et al. Intake of mercury from fish, lipid peroxidation and the risk of myocardial infarction and coronary, cardiovascular, and any death in Eastern Finnish men. Circulation 1995; 91: 645–55.

49. Albert CM, Campos H, Stampfer ML, Ridker PM, Manson JE, Willet WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk for sudden death. N Engl J Med 2002; 346: 1113–8.

50. Siscovick DS, Raghunthan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995; 274: 1363–73.

51. Zhang J, Sasaki S, Amano K, Kesteloot H. Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study. Prev Med 1999; 28: 520–9.

52. Crombie IK, McLoone P, Smith WC, Thomsson M, Pedoe HT. International differences in coronary heart disease mortality and consumption of fish and other foodstuffs. Eur Heart J 1987; 8: 560–3.

53. Gillum RF, Mussolino ME, Madans JH. The relationship between fish consumption and stroke incidence. Arch Intern Med 1996; 156: 537–42.

54. He K, Rimm EB, Merchant A, Rosner BA, Stamfer MJ, Willet WC, Ascherio A. Fish consumption and risk for stroke in men. JAMA 2002; 288: 3130–6.

55. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. Intake of fish and omega-3 fatty acids and risk for stroke in women. JAMA 2001; 285: 304–12.

56. Landmark K, Abdelnoor M, Kilhovd B, Dorum HP. Eating fish may reduce infarct size and the occurrence of Q wave infarcts. Eur J Clin Nutr 1998; 52: 40–4.

57. Keli SO, Feskens EJ, Kromhout D. Fish consumption and risk of stroke. The Zuthpen study. Stroke 1994; 25: 328–32.

58. Orencia AJ, Daviglus ML, Dyer AR, Shekelle RB, Stamler J. Fish consumption and stroke in men. Stroke 1996; 27: 204–9.

59. Sasazuki S, Fukuokoka Heart Study Group. Case–control study of nonfatal myocardial infarction in relation to selected foods in Japanese men and women. Jpn Circ J 2001;65:200–6.

60. Hallgren CG, Hallmans G, Jansson J-H, Marklund SL, Huhtasaari F, Schutz A, et al. Markers for high fish intake are associated with decreased risk of first myocardial infarction. Br J Nutr 2001; 86: 397–404.

61. Gramenzi A, Gentile A, Fasoli M, Negri E, Parazzini F, Vecchia CL. Association between certain foods and the risk for acute myocardial infarction in women. Br Med J 1990; 300: 771–3.

62. Pauletto P, Puato M, Caroli MG, Casilia E, Munhambo AE, Cazzolato G, et al. Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villages in Tanzania: the Lugalawa study. Lancet 1996; 348: 784–8.

63. Kromhout D, Katan MB, Havekes L, Groener A, Hornstra G, de Lezenne Coulander C. The effect of 26 years of habitual fish consumption on serum lipid and lipoprotein levels (the Zutphen study). Nutr Metab Cardiovasc Dis 1996; 6: 65–71.

64. Dallongeville J, Yarnell J, Ducimetiere P, Arveiler D, Ferrieres J, Montaye M, et al. Fish consumption is associated with lower heart rates. Circulation 2003; 108: 820–5.

65. Lindgren FT, Adamson GL, Shore VG, Nelson GJ, Schmidt PC. Effect of a salmon diet on the distribution of plasma lipoproteins and apolipoproteins in normolipidemic adult men. Lipids 1991; 26: 97–101.

66. Fehily AM, Burr ML, Phillips KM, Deadman NM. The effect of fatty fish on plasma lipid and lipoprotein concentrations. Am J Clin Nutr 1983; 38: 349–51.

67. Brown AJ, Roberts DC, Pritchard JE, Truswell AS. A mixed Australian fish diet and fish-oil supplementation: impact on the plasma lipid profile of healthy men. Am J Clin Nutr 1990; 52: 825–33.

68. Wolmarans P, Benade AJ, Kotze TJ, Daubitzer AK, Marais MP, Laubscher R. Plasma lipoprotein response to substituting fish for red meat in a diet. Am J Clin Nutr 1991; 53: 1171–6.

69. Hänninen OO, Ågren JJ, Laitinen MV, Jääskeläinen IO, Penttilä IM. Dose–response relationship in blood lipids during moderate freshwater fish diet. Ann Med 1989; 21: 203–7.

70. Hänninen OO, Ågren JJ. Effects of moderate fresh water fish diet on lipid metabolism of Finnish students. J Intern Med 1989; 225(Suppl 1): 77–81.

71. Ågren JJ, Hanninen O, Julkunen A, Fogelholm L, Vidgren H, Schwab U, et al. Fish diet, fish oil and docosahexaenoic acid rich oil lower fasting postprandial plasma lipid levels. Eur J Clin Nutr 1996; 50: 765–71.

72. Mori TA, Dunstan DW, Burkee V, Croft KD, Rivera JH, Beilin LJ, et al. Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin dependent diabetic patients. Metabolism 1999; 48: 1402–8.

73. Mori TA, Vandongen R, Beilin LJ, Burke V, Morris J, Ritchie J. Effects of varying dietary fat, fish, and fish oils on blood lipids in a randomized controlled trial in men at risk of heart disease. Am J Clin Nutr 1994; 59: 1060–8.

74. Nenseter MS, Österud B, Larsen T, Ström E, Bergei C, Hewitt S, et al. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. Nutr Metab Cardiovasc Dis 2000; 10: 323–30.

75. Brown AJ, Roberts DCK. Fish and fish oil intake: effect on haematological variables related to cardiovascular disease. Thromb Res 1991; 64: 169–78.

76. Tidwell DK, McNaughton JP, Pellum LK, McLaurin BP, Chen S-C. Comparison of the effects of adding fish high or low in n-3 fatty acids to a diet conforming to the dietary guidelines for Americans. J Am Diet Assoc 1993; 93: 1124–8.

77. Jacques H, Noreau L, Moorjani S. Effects on plasma lipoproteins and exogenous sex hormones of substituting lean white fish for other animal-protein sources in diets of postmenopausal women. Am J Clin Nutr 1992; 55: 896–901.

78. Cobiac L, Clifton PM, Abbey M, Belling GB, Nestel PJ. Lipid, lipoprotein, and hemostatic effects of fish vs fish-oil n-3 fatty acids in mildly hyperlipidemic males. Am J Clin Nutr 1991; 53: 1210–6.

79. Gerhard GT, Patton BD, Lindquist SA, Wander RC. Comparison of three species of dietary fish: effects on serum concentrations of low-density-lipoprotein cho-

lesterol and apolipoprotein in normotriglyceridemic subjects. Am J Clin Nutr 1991; 54: 334–9.

80. Gillum RF, Mussolino ME, Madhans JH. Fish consumption and hypertension incidence in African Americans and whites: the NHANES I Epidemiological follow up study. J Natl Med Assoc 2001; 93: 124–8.

81. Vandongen R, Mori TA, Burke V, Beilin LJ, Moris J, Ritchie J. Effects on blood pressure of ω-3 fats in subjects at increased risk of cardiovascular disease. Hypertension 1993; 22: 371–9.

82. Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. Hypertension 1998; 32: 710–7.

83. van Houwelingen AC, Nordöy A, van der Beek E, Houtsmuller U, de Metz M, Hornstra G. Effect of a moderate fish intake on blood pressure, bleeding time, hematology, and clinical chemistry in healthy males. Am J Clin Nutr 1987; 46: 424–36.

84. Ness AR, Whitley E, Burr ML, Elwood PC, Smith GD, Ebrahim S. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the diet and reinfarction trial. J Hum Hypertens 1999; 13: 729–33.

85. Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. Atheroscler Thromb Vasc Biol 1997; 17: 279–86.

86. Ågren JJ, Vaisanen S, Hanninen O, Muller AD, Honstra G. Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosahexaenoic acid supplementation. Prostaglandins Leukot Essent Fatty Acids 1989; 57: 419–21.

87. Emeis JJ, van Houwelingen AC, van den Hoogen CM, Hornstra G. A moderate fish intake increases plasminogen activator type-1 in human volunteers. Blood 1989; 74: 233–7.

88. Marckman P, Bladbjerg EM, Jespersen J. Dietary fish oil (4 g daily) and cardiovascular risk markers in healthy men. Thromb Vasc Biol 1997; 17: 3384–91.

89. Livsmedelsverk Statens. Livsmedelstabeller. Stockholm: Svenskt Tryck; 1988. (In Swedish.)

90. Weber C, Bysted A, Holmer G. The coenzyme Q10 content of the average Danish diet. Int Vitam Nutr Res 1994; 67: 123–9.

91. Kondo K, Iwamoto T, Hosoda K, Kamiyama M, Hirano R, Kidou T, et al. Inhibition of low-density lipoprotein oxidation by fish protein and antioxidants. In: XIIth International Symposium on Atherosclerosis, 25–29 June 2001, Stockholm; 2001. p. 113 (P18:W12).

92. Matsufuji H, Matsui T, Seki E, Osajima K, Nakashima M, Osajima Y, et al. Angiotensin I-converting enzyme inhibitory peptides in an alkaline protease hydrolysate derived from sardine muscle. Biosci Biotechnol Biochem 1994; 58: 1144–5.

93. Yoshikawa M, Fujita H, Matoba N, Takenaka Y, Yamamoto T, Yamauchi R, et al. Bioactive peptides derived from food proteins preventing lifestyle-related diseases. Biofactors 2000; 12: 143–6.

94. Cao MJ, Osatomi K, Hara K, Ishihara T. Purification of a novel myofibril-bound serine protease inhibitor (MBSPI) from the skeletal muscle of lizard fish. Comp Biochem Physiol B Biochem Mol Biol 2001; 128: 19–25.

95. Sidhu KS. Health benefits and potential risks related to consumption of fish or fish oils. Regul Toxicol Pharmacol 2003; 38: 336–44.

96. Guallar E, Sanz-Gllardo I, van't Veer P, Aro A, Gomez-Aracena J, Kark JD, et al. Heavy metals and myocardial infarction study group. Mercury, fish oils and the risk of myocardial infarction. N Engl J Med 2002; 347: 1747–54.

97. Yoshikawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, et al. Mercury and the risk of coronary heart disease in men. N Engl J Med 2002; 347: 1755–60.

98. Chan HM, Egeland GM. Fish consumption, mercury exposure, and heart diseases. Nutr Rev 2004; 62(2): 68–72.

99. Wicklund Glynn A, Darnerud PO, Andersson Ö, Atuma S, Johnsson H, Linder C-E, et al. Revised fish consumption advisory regarding PCBs and dioxins. Uppsala: Livsmedelsverket, National Food Administration (NFA); 1996. Report No. 4.

100. Allard JP, Kurian R, Aghdassi E, Muggli R, Royall D. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. Lipids 1997; 32: 535–41.

101. Meydani M, Natiello F, Goldin B, Free N, Woods M, Schaefer E, et al. Effects of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. J Nutr 1991; 121: 484–91.

102. Korpela R, Seppo L, Laakso J, Lilja J, Karjala K, Lähteenmäki T, et al. Dietary habits affect the susceptibility of low-density lipoprotein to oxidation. Eur J Clin Nutr 1999; 52: 802–7.

103. Susukawa M, Abbey M, Howe PRC, Nestel PJ. Effects of fish oil fatty acids on low density lipoprotein size, oxidizability and uptake by macrophages. J Lipid Res 1995; 36: 473–84.

104. Wolmarans P, Labadarios D, Benade AJ, Kotze TJ, Luow ME. The influence of consuming fatty fish instead of red meat on plasma levels of vitamins A, C and E. Eur J Clin Nutr 1993; 47: 97–103.

105. Nelson GJ, Morris VC, Schmidt PC, Levander O. The urinary excretion of thiobarbituric acid reactive substances and malondialdehyde by normal adult males after consuming a diet containing salmon. Lipids 1993; 28: 757–61.

Ingrid Undeland
Department of Chemistry and Bioscience–Food Science
Chalmers University of Technology
SE-402 29 Göteborg
Sweden
E-mail: iu@fsc.chalmers.se