



## Review

# Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies

P Marckmann<sup>1\*</sup> and M Grønbaek<sup>2</sup>

<sup>1</sup>Research Department of Human Nutrition, Royal Veterinary and Agricultural University, Rolighedsvej 30, DK-1958 Frederiksberg, Denmark; and <sup>2</sup>Danish Epidemiology Science Centre at the Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark

**Objectives:** To review all prospective cohort studies examining the relationship between fish intake and coronary heart disease mortality, and to assess the strength and consistency of their findings.

**Design:** Systematic review of studies based on individual records of fish or n-3 polyunsaturated fatty acid consumption and coronary heart disease death. Studies were given scientific quality scores and divided into categories of high, intermediate, or insufficient quality.

**Main outcome measure:** Coronary heart disease mortality.

**Results:** Eleven studies were identified. The cohorts counted a total of 116 764 individuals. Of four studies judged to be of high quality, the two largest ( $n = 44\ 895$  and  $20\ 051$ ) were performed in populations at low risk of coronary heart disease. They found no protective effect of fish consumption. The other two high-quality studies were relatively small ( $n = 852$  and  $1822$ ) and included individuals at higher risk. They both found an inverse relationship between fish consumption and coronary heart disease death, suggesting that 40–60 g fish per day is optimal and associated with a risk reduction of 40–60%. Results of four studies of intermediate quality support that fish consumption is inversely associated with coronary heart disease mortality in high-risk populations only. Three studies were judged to be of insufficient quality to be used for drawing conclusions.

**Conclusions:** Fish consumption is not associated with reduced coronary heart disease mortality in low-risk populations. However, fish consumption at 40–60 g daily is associated with markedly reduced coronary heart disease mortality in high-risk populations. The underlying biochemical mechanism is not known and causal inference premature.

**Descriptors:** fish oil; diet; n-3 polyunsaturated fatty acids; nutrition; epidemiology

## Introduction

Cross-sectional studies among Inuits and Danes, and different Japanese populations suggested that fish consumption was protective against coronary heart disease (CHD) (Bang *et al*, 1980; Hirai *et al*, 1989). Later cross-sectional findings were less reassuring, however, and recent case-control studies reached conflicting conclusions (Simonsen *et al*, 1987; Bjerregaard, 1996; Siscovick *et al*, 1995; Guallar *et al*, 1995). Biochemical research revealed that the very long-chained n-3 polyunsaturated fatty acids (n-3 VLCPUFA), abundantly present in fish fat, are potent modulators of human metabolism. Among numerous metabolic effects, n-3 VLCPUFA lower fasting and postprandial plasma concentrations of triglyceride-rich lipoproteins and their remnants, and they modify the eicosanoid profile and cardiac excitability in a way that might lead to a reduced risk of CHD (Harris, 1989; Dyerberg, 1981; Schacky *et al*, 1985; Nordøy *et al*, 1994; McLennan *et al*, 1993; Kang &

Leaf, 1994). Potentially athero- and thrombogenic effects have also been reported. These include delayed low density lipoprotein (LDL) clearance, increased LDL oxidisability, and fibrinolytic inhibition (Schechtman *et al*, 1996; Hau *et al*, 1996; Emeis *et al*, 1989; Marckmann *et al*, 1991; Schmidt, 1997). The health implication of an increased n-3 VLCPUFA intake is therefore not unequivocal. The diverging results of trials in which animals were fed n-3 VLCPUFA further underscore this uncertainty (Weiner *et al*, 1986; Davis *et al*, 1987; Fincham *et al*, 1991; Barbeau *et al*, 1997). Accordingly, it is still a controversial issue whether fish protects against CHD. In this present study we made an overall assessment of the evidence derived from prospective cohort studies relating fish consumption to CHD mortality.

## Methods

We restricted our review to prospective cohort studies based on individual recordings of fish or n-3 VLCPUFA consumption, and CHD death. We searched for studies in MEDLINE (Medline 1966 and on; search date: January 9, 1998; indexing terms: fish, coronary heart disease, journal article; total number of hits: 324), in reference lists of retrieved articles, and using informal sources. Our search identified eleven studies. Nine were published as full-length

\*Correspondence: Dr P Marckmann, Research Department of Human Nutrition, Royal Veterinary and Agricultural University, Rolighedsvej 30, DK-1958 Frederiksberg, Denmark.

Received 27 November 1998; revised 22 February 1999; accepted 5 March 1999

original papers (Kromhout *et al*, 1985; Dolecek & Grandits, 1991; Ascherio *et al*, 1995; Salonen *et al*, 1995a; Kromhout *et al*, 1995; Rodriguez *et al*, 1996; Daviglus *et al*, 1997; Mann *et al*, 1997; Albert *et al*, 1998). One study was reported in two separate original papers after followup periods of 4 y (Morris *et al*, 1995) and 11 y (Albert *et al*, 1998). They reached similar conclusions. We selected the report of Albert *et al* for our review because of its longer followup period and higher statistical power. One study was presented in a letter (Vollset *et al*, 1985), and one as a short report (Norell *et al*, 1986).

Each study was scored for its scientific quality on a scale from 0–6 points. Studies scoring 5–6 points were considered of high quality, those scoring 3–4 points of intermediate, and those scoring 2 points or less of insufficient quality. Points were scored according to dietary assessment method (3 points for cross-check dietary history, 2 for semiquantitative food-frequency questionnaire (FFQ), 1 for non-quantitative FFQ, four-day food records, and repeated 24 h recalls, and 0 for unrepresented details), CHD death ascertainment (1 point if based on individual medical records, 0 if based on death certificates), number of CHD deaths (1 point if 100+ deaths, 0 if  $\leq 100$ ), and statistical presentation (1 point if multivariate analyses were included, 0 if lacking). All studies fulfilled our high-quality criteria for study duration (more than 5 y), and completeness of follow-up (more than 95% of all individuals followed up).

Graphs showing the relation between fish intake and CHD death based on actual figures presented in original papers judged of high quality were prepared. If fish intake was presented as a range, for example, 15–30 g fish daily, we assigned the mean of the range for that intake category. For those categories of intake in which intakes below or above a certain level were presented, for example, more than 45 g daily, mean intakes were estimated by us.

## Results

The sample size and the length of follow-up varied grossly between studies; from 272–44 895 individuals and from 5–30 y (Table 1). Only three studies included females.

### Study quality

Four studies were judged of high scientific quality (scientific score: 5–6 points), but none scored the maximum of 6 points (Table 2). Another four studies were judged of

**Table 2** Scientific quality scores (0–6 points) of eleven prospective cohort studies on fish consumption and coronary heart disease (CHD) mortality and main conclusion of each study

First author, year	Score (points)	Main conclusion Do fish protect against CHD death?
Kromhout, 1985	5	Yes
Ascherio, 1995	5	No
Daviglus, 1997	5	Yes
Albert, 1998 <sup>a</sup>	5	No
Dolecek, 1991	4	Yes
Kromhout, 1995	4	Yes
Rodriguez, 1996	4	No
Mann, 1997	3	No
Salonen, 1995	2	No
Vollset, 1985	2	No
Norell, 1985	1	Yes

<sup>a</sup>Similar conclusion was reached after the first four years of follow-up (Morris *et al*, 1995).

intermediate quality (3–4 points). Their lower scoring was caused either by their use of less valid dietary assessment methods, small numbers of CHD deaths, or less rigid ascertainment of CHD deaths. Finally, three studies were judged to have insufficient quality ( $\leq 2$  points) to be included in the overall assessment of the relation between fish consumption and CHD death. Dietary assessment methods were poor or poorly described in these studies. Also, they did not validate the CHD death reports individually, only counted small numbers of CHD deaths, or lacked important statistical analyses.

### Study outcomes

The observed association between fish intake and relative risk of CHD death after adjustment for multiple confounders in the four studies of high quality is presented in Figure 1.

Relative risks were not significantly different from 1.0 for most intake categories due to wide confidence intervals. An inverse and graded relationship between fish intake and CHD death was observed by Kromhout *et al* (1985) and Daviglus *et al* (1997), but it was absent in the other two studies of much larger cohorts (*P*-values for trend: 0.19 and 0.49) (Ascherio *et al*, 1995; Albert *et al*, 1998). However, Ascherio *et al* (1995) observed that eating any amount of fish as compared with eating no fish was associated with an insignificantly lowered risk of CHD death (RR 0.74, 95%

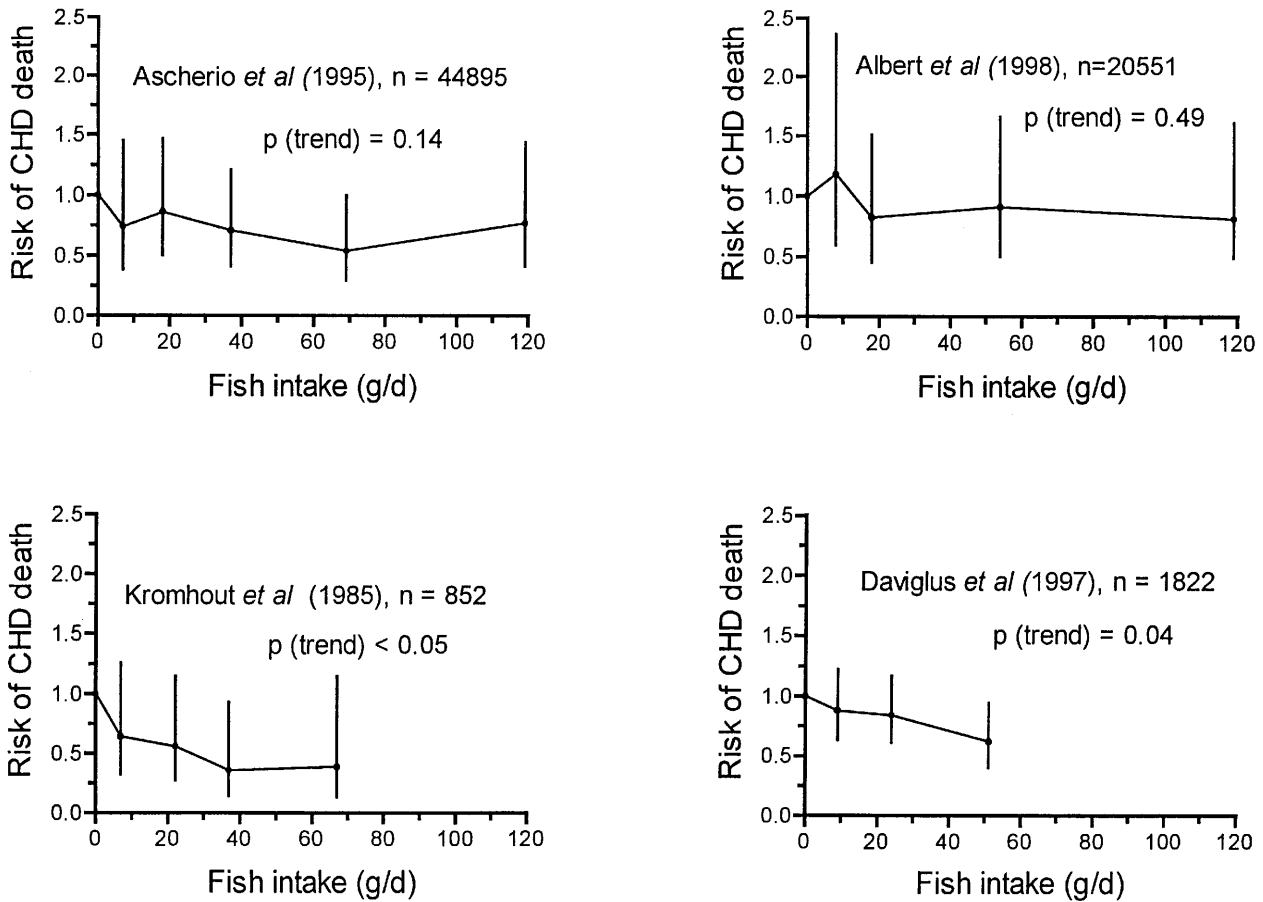
**Table 1** Key characteristics of eleven prospective cohort studies on fish consumption and coronary heart disease (CHD) mortality

First author, year	Population (n)	Follow-up (y)	CHD deaths	CHD death rate (per 1000y) <sup>a</sup>	Mean fish intake (g/d) <sup>b</sup>	Mean n-3 intake (g/d) <sup>b</sup>	Dietary assessment method
Kromhout, 1985	852 M	20	78	4.6	20	0.2	Cross-check dietary history
Dolecek, 1991	6258 M	13	175	2.2	—	0.18	24 h recalls at baseline and after 1, 2, 3 and 6 y
Ascherio, 1995	44895 M	6	264	1.0	35	0.24	Semiquantitative FFQ
Salonen, 1995	1833 M	5	18	2.0	47	—	4 d weighed records
Kromhout, 1995	272 MF	17	58	12.5	14	—	Cross-check dietary history
Rodriguez, 1996	7513 M	23	536 <sup>b</sup>	3.1 <sup>b</sup>	25	—	Nonquantitative FFQ
Daviglus, 1997	1822 M	30	430	7.9	25	—	Cross-check dietary history
Mann, 1997	10802 MF	13	64	0.5	20	—	Semiquantitative FFQ
Albert, 1998 <sup>c</sup>	20051 M	11	308	1.4	35	0.20	Semiquantitative FFQ
Vollset, 1985	1100 M	14	967	6.2	60	—	Nonquantitative FFQ
Norell, 1986	10966 MF	14	800	5.2	?	—	No details Presented

Abbreviations: M = males. F = females. FFQ = food frequency questionnaire.

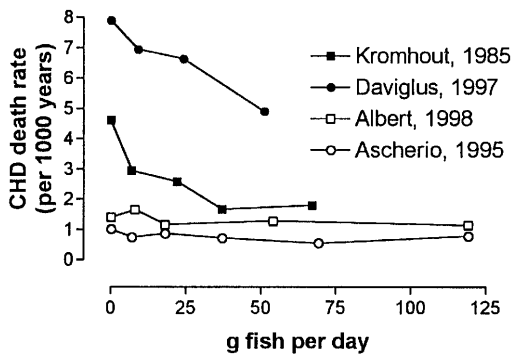
<sup>a</sup>Estimated from the equation: CHD death rate = (CHD deaths  $\times$  1000)/(population (n)  $\times$  follow-up period (y)).

<sup>b</sup>Best estimate based on the original data. <sup>c</sup>Four-year followup results were reported in a previous publication (33).



**Figure 1** Multivariate adjusted relative risk of coronary heart disease (CHD) death and 95% confidence intervals as a function of fish consumption in four high-quality studies. Two found fish consumption to be uncorrelated with CHD death (Ascherio *et al* (1995); Albert *et al* (1998)), and two found an inverse association (Kromhout *et al*, (1985); Daviglus *et al* (1997)). P-values for the presence of a trend across intake categories is also presented.

CI: 0.44–1.23). Paradoxically, the risk of any CHD event was slightly increased among individuals with the highest fish intake as compared with those eating the least fish in the same study (RR 1.14, 95% CI: 0.86–1.51). The papers by Ascherio *et al* (1995) and Albert *et al* (1998) included information about the incidence of myocardial infarction. It was unrelated to fish consumption in both studies. Estimated absolute CHD death rates in the four high-quality studies are presented in Figure 2.



**Figure 2** The association between fish consumption and absolute coronary heart disease (CHD) death rates (deaths/1000 y) in four high-quality studies. Absolute death rates were calculated as published relative risk of each intake category times average CHD death rate in the total population (cf. Table 1). This gives an incorrect, but reasonable crude estimate.

The conclusions reached in the four studies of intermediate quality also diverged (Table 2). Dolecek & Grandits (1991) reported an inverse relationship between quintiles of dietary n-3 VLCPUFA intake and CHD mortality (the amount of fish consumed was not reported). In a small Dutch cohort ( $n=272$ ), Kromhout *et al* (1995) observed that fish consumers with an average fish intake of 24 g/d had an adjusted relative risk of CHD death of 0.51 (95% CI: 0.29–0.89) as compared with those not eating fish. In contrast, Rodriguez *et al* (1996) and Mann *et al* (1997) were unable to demonstrate any association between fish consumption and CHD death in their studies in which participants were divided into two or three categories of fish consumption, respectively.

The three studies of insufficient quality concluded that fish consumption was associated with an increased, an unaltered, or a lowered risk of CHD death (Table 2).

### Discussion

Fish consumption is closely linked to a series of other dietary variables as well as non-dietary lifestyle factors that may have an impact on CHD mortality (Kromhout *et al*, 1985; Ascherio *et al*, 1995; Morris *et al*, 1995; Albert *et al*, 1998). Although most of the reviewed studies made statistical adjustments for known potential confounders, residual confounding can never be ruled out.

### *Studies showing no protective effect of fish consumption*

Four important studies (two of high and two of intermediate quality) found no significant association between fish consumption and CHD mortality (Ascherio *et al.*, 1995; Rodriguez *et al.*, 1996; Mann *et al.*, 1997; Albert *et al.*, 1998). All four studies were large, their cohorts counting from 7513–44 985 individuals. In three of the studies (Ascherio *et al.*, 1995; Rodriguez *et al.*, 1996; Albert *et al.*, 1998), the number of CHD deaths and the variability in fish intake among participants was sufficiently large to detect an inverse association between fish consumption and CHD mortality similar to that reported by Kromhout *et al.* (1985) with considerable statistical power. In line with these negative studies, a recent cross-cultural study concluded that fish consumption did not contribute significantly to the differences in CHD mortality between the sixteen cohorts of the Seven Countries Study (Kromhout *et al.*, 1996). In that study crude data analysis showed an inverse association between fish consumption and CHD death, but it disappeared when adjustments were made for the intake of saturated fat, and flavonoids and smoking. It is of note that the flavonoid intake was not adjusted for in any of the studies included in the present review.

One relatively small study from Finland ( $n=1833$ ) concluded that fish consumption may be associated with increased CHD mortality (Salonen *et al.*, 1995a). The dietary assessment method was not optimal in that study. However, corresponding results were obtained when a biomarker for fish consumption (serum concentrations of fatty acids) was used in the statistical analyses which strongly supports the finding (Salonen *et al.*, 1995b). The authors underlined that a high intake of mercury from polluted fish promoting lipid peroxidation could be the more likely explanation of their unexpected observation.

### *Studies showing a protective effect of fish or n-3 VLCPUFA*

Four studies (two of high and two of intermediate quality) showed a protective effect of fish or n-3 VLCPUFA intake on CHD death (Kromhout *et al.*, 1985; Dolecek & Grandits, 1991; Kromhout *et al.*, 1995; Daviglus *et al.*, 1997). Three of them were based on relatively small cohorts ( $n=272-1822$ ). The two smallest cohorts were Dutch and comprised randomly selected individuals born in the beginning of the century (Kromhout *et al.*, 1985, 1995). The larger study by Dolecek & Grandits (1991) was based on observations of the control group of the MRFIT study ( $n=6258$  males). Participants of this control group were all diagnosed as having an increased risk of CHD at study entry, but had been randomised to usual care. Fish consumption data were not presented, but a protective effect of n-3 VLCPUFA was found. A particular problem relating to this study was that the n-3 VLCPUFA intake was calculated as the average of five 24 h recalls obtained at baseline and after 1, 2, 3, and 6 y of follow-up. This approach entails a considerable risk of biased estimates because individuals classified as having a high average n-3 VLCPUFA intake are likely to be the ones that improved their overall life-style during follow-up. The statistical analyses did not take that problem into account.

The most recent report showing that fish may protect against CHD death was based on 30 y follow-up data on 1822 males from the Chicago area (Daviglus *et al.*, 1997; Shekelle *et al.*, 1981, 1985). The protective effect was not apparent in the crude analysis, but appeared in the multivariate analysis as a significant trend ( $P=0.04$ ). It was

primarily explained by a strong inverse association between fish intake and nonsudden cardiac death among those 47 y or older at study entrance (Daviglus *et al.*, 1997). This finding contrasts remarkably with observations reported by Albert *et al.* (1998), who found fish to protect against sudden, but not against nonsudden cardiac death. Furthermore, total CHD mortality was unrelated to fish consumption in Albert's study.

The dose-response data presented in the two high-quality studies with positive outcome indicate that the protective effect is graded until a possible optimum of around 40–60 g fish equivalent with an estimated 0.6–0.9 g n-3 VLCPUFA per day (see Figures 1 and 2). As compared with not eating fish, a relative risk of 0.4–0.6 of dying from CHD might be achieved at this optimal intake. Corresponding results were reported from a case-control study (Siscovick *et al.*, 1995). In that study, an average intake of 13.65 g n-3 VLCPUFA per month (0.45 g/d) was associated with a relative risk of primary cardiac arrest of 0.4 (95% CI: 0.2–0.7).

### *Combining the evidence*

The two large high-quality studies that were both negative included American health professionals with healthy life-styles (Ascherio *et al.*, 1995; Albert *et al.*, 1998). Among these individuals there were few current smokers (8–13%), they had low saturated fat intakes of less than 10% of total energy intake, desirable total cholesterol concentrations around 5 mmol/L (only presented in Ascherio's paper), and low CHD death rates (1.0 and 1.4 CHD deaths for every 1000 person years of follow-up (Table 1)). In contrast, the two high-quality studies showing a protective effect of fish comprised participants at a much higher absolute risk of CHD and with unhealthy lifestyles. The CHD death rate was 4.6 for every 1000 person years in the study by Kromhout *et al.* (1985), and 7.9 in the Western Electric Study (Daviglus *et al.*, 1997). Furthermore, participants had average saturated fat intakes of 16–18% of energy. In the latter study average cholesterol concentrations were close to 6 mmol/L, and almost 60% were smokers.

A similar pattern of differences between studies showing or not showing an association between fish and CHD death applies to the four intermediate-quality studies. The two negative studies investigated cohorts with relatively low rates of CHD mortality for age (Rodriguez *et al.*, 1996; Mann *et al.*, 1997). In contrast, both studies showing a protective effect of fish was conducted in high-risk cohorts (Dolecek & Grandits, 1991; Kromhout *et al.*, 1995). In the Dutch study, participants were characterised by 70% of the men and 20% of the women being smokers, by average saturated fat intakes of 17–18% of energy, average cholesterol concentrations above 6 mmol/L, and a CHD death rate of 12.5 for every 1000 person years (Kromhout *et al.*, 1995). Participants of the study by Dolecek & Grandits (1991) were high-risk individuals by definition (inclusion criteria for MRFIT).

### **Conclusions**

Our overall conclusion is that individuals at low risk of CHD and with healthy life-styles do not gain any additional protection against CHD from eating fish. On the other hand, high-risk individuals appear to benefit in a dose-dependent manner from increasing their fish consumption up to an optimum of 40–60 g. At the optimal fish intake, risk of

CHD death may be only around half the risk of individuals not eating fish at all. Results of a large intervention study of post-infarct patients support that increased fish consumption lowers CHD mortality in high-risk individuals (Burr *et al*, 1989). In this study, increasing fish intake from an estimated 10–20 g daily to 30–60 g daily (200–400 g weekly) resulted in a 30% reduction in CHD mortality. The question remains whether the apparent protection in high-risk individuals is directly caused by the fish itself. There is yet no definitive answer to that question. Dietary intervention studies demonstrated that the consumption of up to 0.9 g n-3 VLCPUFA daily—corresponding to a daily intake of 40–60 g fish of mixed type (lean, intermediate, and fatty)—has no significant impact on classical CHD risk factors such as low density lipoprotein cholesterol and fibrinogen, or most other putative mediators of atherothrombogenesis (Lervang *et al*, 1993; Schmidt *et al*, 1996; Marckmann *et al*, 1997). The postprandial triglyceride profile is one obvious exception. At a daily intake of 0.9 g n-3 VLCPUFA, a marked depression of postprandial triglyceride concentrations is seen (Marckmann *et al*, 1997). Also, n-3 VLCPUFA accumulate in tissues even at low intakes which might, theoretically, have an impact on membrane function and cardiac excitability. Taking the absent influence on stronger determinants of CHD risk into account, it nevertheless seems unlikely that n-3 VLCPUFA effects could solely explain the very marked cardioprotective effect of moderate fish consumption. The same opinion was expressed earlier by Kromhout *et al* (1985). Supporting this viewpoint, Ascherio *et al* (1995) and Albert *et al* (1998) found no protective effect of n-3 VLCPUFA in specific analyses of their large data materials. The link between fish consumption and CHD mortality in high-risk populations therefore might be due to other fish components than n-3 VLCPUFA. Alternatively, the link might be explained by undetected dietary or non-dietary confounders. That possibility is supported when the fish-CHD link is compared with the evidence linking alcohol and CHD. The association is much more consistent in the latter case (Maclure, 1993).

Additional prospective cohort studies and in particular intervention studies are obviously needed to further clarify the role of fish consumption in the prevention of CHD death. Future studies should focus on high-risk individuals and preferably include a test of the underlying biochemical hypotheses. Based on current evidence, we believe that it is justified to recommend increased fish consumption up to an optimum of 40–60 g/d for fatal CHD prevention in high-risk populations. There is not sufficient evidence to assume that corresponding amounts of n-3 VLCPUFA taken as a dietary supplement can be similarly protective.

## References

- Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN & Manson JE (1998): Fish consumption and risk of sudden cardiac death. *JAMA* **279**, 23–28.
- Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL & Willett WC (1995): Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N. Engl. J. Med.* **332**, 977–998.
- Bang HO, Dyerberg J & Sinclair HM (1980): The composition of the Eskimo food in north western Greenland. *Am. J. Clin. Nutr.* **33**, 2657–2661.
- Barbeau ML, Klemp KF, Guyton JR & Rogers KA (1997): Dietary fish oil. Influence on lesion regression in the porcine model of atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **17**, 688–694.
- Bjerregaard P (1996): Cardiovascular disease and environmental pollutants: The arctic aspect. *Arct. Med. Res.* **55**, Suppl 1, 25–31.
- Burr ML, Gilbert JF, Holliday RM, Elwood PC, Fehily AM, Rogers S, Sweetnam PM & Deadman NM (1989): Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet And Reinfarction Trial (DART). *Lancet* **ii**, 757–761.
- Daviglus ML, Stamler J, Orenca AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D & Shekelle RB (1997): Fish consumption and the 30-year risk of fatal myocardial infarction. *N. Engl. J. Med.* **336**, 1046–1053.
- Davis HR, Bridenstine RT, Vesselinovitch D & Wissler RW (1987): Fish oil inhibits development of atherosclerosis in rhesus monkeys. *Arteriosclerosis* **7**, 441–449.
- Dolecek TA & Grandits G (1991): Dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial (MRFIT). *World Rev. Nutr. Diet.* **66**, 205–216.
- Dyerberg J (1981): Platelet-vessel wall interaction: Influence of diet. *Phil. Trans. R. Soc. London* **B294**, 373–381.
- Emeis JJ, Houwelingen ACv, Hoogen CmV & Hornstra G (1989): A moderate fish intake increases plasminogen activator inhibitor type-1 in human volunteers. *Blood* **74**, 233–237.
- Fincham JE, Gouws E, Woodroof CW, Wyk MJv, Kruger M, Smuts CM, Jaarsveld PJv, Taljaard JJF, Schall R, Strauss JadW & Benadé AJS (1991): Atherosclerosis. Chronic effects of fish oil and a therapeutic diet in nonhuman primates. *Arterioscler. Thromb.* **11**, 719–732.
- Guallar E, Hennekens CH, Sacks FM, Willett WC & Stampfer MJ (1995): A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. *J. Am. Coll. Cardiol.* **25**, 87–394.
- Harris WS (1989): Fish oils and plasma lipid and lipoprotein metabolism in humans: A critical review. *J. Lipid Res.* **30**, 785–807.
- Hau M-F, Smelt AHM, Bindels AJGH, Sijbrands EJG, Laarse Avd, Onkenhout W, Duyvenvoorde Wv & Princen HMG (1996): Effects of fish oil on oxidation resistance on VLDL in hypertriglyceridemic patients. *Arterioscler. Thromb. Vasc. Biol.* **16**, 1197–1202.
- Hirai A, Terano T, Tamura Y & Yoshida S (1989): Eicosapentaenoic acid and adult disease Japan: Epidemiological and clinical aspects. *J. Intern. Med.* **225**, Suppl 1, 69–75.
- Kang JX & Leaf A (1994): Effects of long-chain polyunsaturated fatty acids on the contraction of neonatal rat cardiac myocytes. *Proc. Natl. Acad. Sci.* **91**, 9886–9890.
- Kromhout D, Bosschieter EB & Coulander Cd (1985): The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N. Engl. J. Med.* **312**, 1205–1209.
- Kromhout D, Feskens EJM & Bowles CH (1995): The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int. J. Epidemiol.* **24**, 340–345.
- Kromhout D, Bloemberg BPM, Feskens EJM, Hertog MG, Menotti A & Blackburn H (1996): Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality. *Int. J. Epidemiol.* **25**, 753–759.
- Lervang H-H, Schmidt EB, Møller J, Svaneborg N, Varming K, Madsen PH & Dyerberg J (1993): The effect of low-dose supplementation with n-3 polyunsaturated fatty acids on some risk markers of coronary heart disease. *Scand. J. Clin. Lab. Invest.* **53**, 417–423.
- Maclure M (1993): Demonstration of deductive meta-analysis: Ethanol intake and risk of myocardial infarction. *Epidemiol. Rev.* **15**, 328–351.
- Mann JI, Appleby PN, Key TJ & Thorogood M (1997): Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* **78**, 450–455.
- Marckmann P, Jespersen J, Leth T & Sandström B (1991): Effect of fish diet versus meat diet on blood lipids, coagulation and fibrinolysis in healthy young men. *J. Intern. Med.* **229**, 317–323.
- Marckmann P, Bladbjerg EM & Jespersen J (1997): Dietary fish oil (4 g daily) and cardiovascular risk markers in healthy men. *Arterioscler. Thromb. Vasc. Biol.* **17**, 3384–3391.
- McLennan PL, Bridle TM, Abeywardena MY & Charnock JS (1993): Comparative efficacy on n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. *Am. J. Clin. Nutr.* **58**, 666–669.
- Morris MC, Manson JE, Rosner B, Buring J, Willett WC & Hennekens CH (1995): Fish consumption and cardiovascular disease in the Physicians' Health Study: A prospective study. *Am. J. Epidemiol.* **142**, 166–175.
- Nordoy A, Hatcher L, Goodnight S, Fitzgerald GA & Connor WE (1994): Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid production and hemostatic parameters in normal men. *J. Lab. Clin. Med.* **123**, 914–920.
- Norell SE, Ahlbom A, Feychting M & Pedersen NL (1986): Fish consumption and mortality from coronary heart disease. *BMJ* **293**, 426.

- Rodriguez BL, Sharp DS, Abbott RD, Burchfiel CM, Masaki K, Chyou PH, Huang B, Yano K & Curb JD (1996): Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. *Circulation* **94**, 952–956.
- Salonen JT, Seppänen K, Nyyssönen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F & Salonen R (1995a): Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* **91**, 645–655.
- Salonen JT, Nyyssönen K & Salonen R (1995b): Fish intake and the risk of coronary disease. *N. Engl. J. Med.* **333**, 937.
- Schacky Cv, Fischer S & Weber PC (1985): Long-term effects of dietary marine w-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *J. Clin. Invest.* **76**, 1626–1631.
- Schechtman G, Boerboom LE, Hannah J, Howard BV, Mueller RA & Kissebah AH (1996): Dietary fish oil decreases low-density-lipoprotein clearance in nonhuman primates. *Am. J. Clin. Nutr.* **64**, 215–221.
- Schmidt EB, Varming K, Møller JM, Pedersen IB, Madsen P & Dyerberg J (1996): No effect of a very low dose of n-3 fatty acids on monocyte function in healthy humans. *Scand. J. Clin. Lab. Invest.* **56**, 87–92.
- Schmidt EB (1997): n-3 fatty acids and the risk of coronary heart disease. *Dan. Med. Bull.* **44**, 1–22.
- Shekelle RB, Shryock AM, Paul O, Lepper M, Stamler J, Liu S & Raynor WJ (1981): Diet, serum cholesterol, and death from coronary heart disease. The Western Electric Study. *N. Engl. J. Med.* **304**, 65–70.
- Shekelle RB, Missell Lv, Paul O, Shryock AM & Stamler J (1985): Fish consumption and mortality from coronary heart disease. *N. Engl. J. Med.* **313**, 820.
- Simonsen T, Värtun Å, Lyngmo V & Nordøy A (1987): Coronary heart disease, serum lipids, platelets and dietary fish in two communities in northern Norway. *Acta Med. Scand.* **222**, 237–245.
- Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, Cobb LA, Copass MK, Psaty BM, Lemaitre R, Retzlaff B, Childs M & Knopp RH (1995): Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* **274**, 1363–1367.
- Vollset SE, Heuch I & Bjelke E (1985): Fish consumption and mortality from coronary heart disease. *N. Engl. J. Med.* **313**, 820–821.
- Weiner BH, Ockene IS, Levine PH, Cuénoud H, Fisher M, Johnson BF, Daoud AS, Jarmolych J, Hosmer D, Johnson MH, Natale A, Vaudreuil C & Hoogasian JJ (1986): Inhibition of atherosclerosis by cod-liver oil in a hyperlipidemic swine model. *N. Engl. J. Med.* **315**, 841–846.