Clinical review

Science, medicine, and the future

Omega 3 fatty acids and cardiovascular disease–fishing for a natural treatment

Jehangir N Din, David E Newby, Andrew D Flapan

Omega 3 fatty acids from fish and fish oils can protect against coronary heart disease. This article reviews the evidence regarding fish oils and coronary disease and outlines the mechanisms through which fish oils might confer cardiac benefits

Cardiovascular Research, University of Edinburgh, Edinburgh EH16 4SB
Jehangir N Din *research fellow*
David E Newby *reader*
Royal Infirmary of Edinburgh, Edinburgh EH16 4SA
Andrew D Flapan *consultant cardiologist*
Correspondence to: J N Din jehangirdin@hotmail.com

BMJ 2004;328:30–5

Omega 3 fatty acids from fish and fish oils can protect against coronary heart disease. Both health professionals and the public are increasingly interested in their role in the prevention and management of coronary heart disease. In this era of multiple pharmacological treatments for cardiovascular disease many believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

Several areas of uncertainty remain. The optimal intake of omega 3 fatty acids is not firmly established, nor is their mechanism of action fully understood. Some studies have produced conflicting results, and concerns have been increasing about environmental contamination of certain fish. This article reviews the current evidence regarding fish oils and cardiovascular disease, their possible mechanism of action, and potential future developments and research strategies.

Summary points

- Coronary heart disease is still the most common cause of death in the United Kingdom
- Omega 3 fatty acids from fish and fish oils can protect against coronary heart disease
- There is evidence to support the use of fish or fish oil supplements after myocardial infarction
- The mechanisms by which fish oils confer their benefits are not fully understood
- Unravelling these mechanisms may identify novel therapeutic targets and could help guide the development of future treatments for coronary heart disease
- Future trials may identify other patients who could benefit, such as those with stable angina, risk factors for coronary heart disease, or left ventricular dysfunction

Sources and selection criteria

We searched PubMed for relevant articles by using the key words "fish," "fish oils," "omega 3 fatty acids," and "cardiovascular disease." References identified in the search are on bmj.com

Fig 1 Greenland Inuit gutting a seal in the early 1900s. Their diet consisted largely of fish, whale, seal, and walrus, resulting in a high intake of omega 3 fatty acids. *Copyright Arctic Institute, used with permission from Leif Vanggaard, Arctic Institute*

Omega 3 polyunsaturated fatty acids

The association between omega 3 fatty acids and cardiovascular disease was established following the observation that the Greenland Inuit had low mortality from coronary heart disease despite a diet that is rich in fat. In the 1970s the Danish investigators Bang and Dyerberg proposed that this could be because of the high content of omega 3 fatty acid in the Inuit diet,[1] which consisted largely of fish, seal, and whale (fig 1).

P+ *Additional references (w1-w15) are on bmj.com*

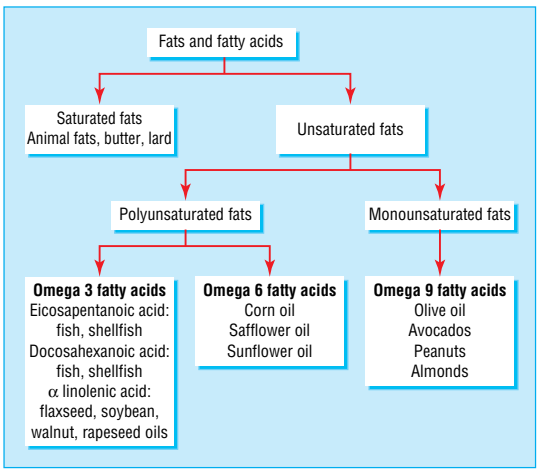

Fig 2 Fatty acids are saturated, monounsaturated, or polyunsaturated. Two types of polyunsaturated fatty acid exist—the omega 6 and the omega 3 fatty acids. The omega 6 fatty acids are available mainly from vegetable oils. Three types of omega 3 fatty acid exist: α linolenic acid is available from certain plants but eicosapentanoic acid and docosahexanoic acid must be obtained from marine sources

Omega 3 fatty acids, along with omega 6 fatty acids, are essential polyunsaturated fatty acids (fig 2 and fig 3). The Western diet is abundant in omega 6 fatty acids, mainly from vegetable oils rich in linoleic acid.[2] However, humans lack the necessary enzymes to convert omega 6 fatty acids to omega 3 fatty acids, and the latter must be obtained from separate dietary sources. While α linolenic acid (ALA) is available from certain plants, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are derived from fish and fish oils. This review is limited to the two marine derived omega 3 fatty acids.

Epidemiological and observational studies

Most studies have shown an inverse association between fish consumption and the risk of coronary heart disease.[3–5] Furthermore, both consumption of fish[6] and higher blood concentrations of omega 3 fatty acids[7] are associated with a reduced risk of sudden death. However, some studies[8 w1] have not found a relation between intake of fish and coronary heart disease. These inconsistencies could be due to differences in methods, study populations, or fish. Importantly, most studies showing no association were in populations with an already moderate fish intake, potentially masking any relation. Overall, fish consumption seems to be beneficial, and a systematic review of 11 prospective cohort studies concluded that fish intake notably reduced mortality due to coronary heart disease in populations at increased risk.[9]

Clinical intervention trials

Several trials have assessed the effects of fish and fish oil supplements on coronary heart disease, mainly after myocardial infarction (table 1). The diet and reinfarction trial (DART) randomised 2033 men with a recent myocardial infarction to three dietary interventions.[10] Patients who received advice on fish had a relative reduction in total mortality of 29% during the two year follow up ($P<0.05$), mainly because of a reduction in deaths from coronary heart disease. The open label Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI-Prevenzione) trial randomised 11 324 patients after myocardial infarction to either a daily capsule of about 850 mg omega 3 fatty acid, 300 mg vitamin E, both, or neither.[11] After 3.5 years participants randomised to fish oil capsules had a reduction in relative risk of 15% in the composite primary end point of total mortality, non-fatal myocardial infarction, and stroke ($P=0.023$). The relative risk of cardiovascular death was also reduced, by 30% ($P=0.024$), and of sudden death by 45% ($P=0.01$). These benefits were apparent within just four months of randomisation.[w2]

Two smaller secondary prevention trials have also assessed the effects of omega 3 fatty acids. In an Asian population patients with a suspected myocardial infarction randomised to fish oil capsules experienced a significant reduction in mortality from coronary heart disease after one year compared with placebo.[12] However, a Norwegian study reported no benefit in patients after myocardial infarction who were given fish oil capsules compared with placebo after 1.5 years.[13] This may have been because of the high habitual fish consumption among the general population in that area, with omega 3 supplementation conferring no additional benefit.

A recent trial of 3114 men with angina unexpectedly found that individuals advised to eat oily fish, and particularly those given fish oil capsules, had a higher risk of cardiac death than people not given advice to eat fish (11.5% *v* 9%, $P=0.02$).[14] The investigators speculated that this may have arisen from risk compensation or other changes in patients' behaviour. Several flaws in this study weakened the validity of the results, and they should be viewed with caution until more evidence becomes available.

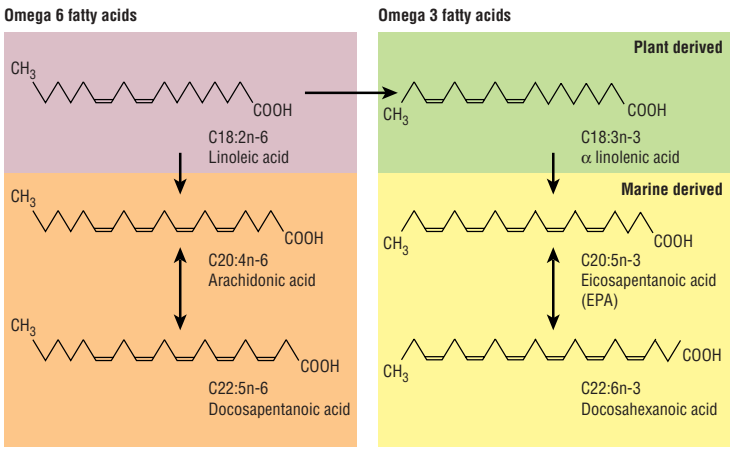

Fig 3 Structures of the two classes of polyunsaturated fatty acids. The omega 3 fatty acids have their first double bond at the third carbon molecule from the methyl (CH_3) end of the fatty acid, whereas the omega 6 fatty acids have their first double bond at the sixth carbon molecule. The chemical names for each fatty acid are also given: the number of carbon atoms is given first, followed by the number of double bonds and the position of the first double bond. Omega 6 linoleic acid can be desaturated in certain plants to form omega 3 α linolenic acid. Whereas linoleic acid is mainly converted into arachidonic acid, α linolenic is elongated and desaturated into eicosapentanoic acid and then docosahexanoic acid

Box 1: Possible mechanisms of action of omega 3 fatty acids

- Antiarrhythmic
- Antithrombotic
- Antiatherosclerotic
- Anti-inflammatory
- Improves endothelial function
- Lowers blood pressure
- Lowers triglyceride concentrations

Mechanism of action

Although the weight of evidence outlined above supports a protective effect of omega 3 fatty acids on coronary heart disease, the mechanisms through which they confer these benefits remain unclear. Omega 3 fatty acids have several potentially cardioprotective effects (box 1), although the relative contribution of each of these is not fully understood.

Arrhythmias

The benefits of fish oils were originally thought to be due to their antithrombotic effects, but recent evidence has indicated that the predominant effect may be antiarrhythmic. In the GISSI-Prevenzione trial the decrease in mortality was largely due to a reduction in sudden death,[11] and, as in DART,[10] no reduction in the rate of non-fatal myocardial infarction occurred. Fish oil supplementation increases heart rate variability in patients after myocardial infarction, which correlates with a lower risk of mortality and malignant arrhythmia.[15] In animal models fish oil protects against ventricular fibrillation after surgical occlusion of a coronary artery.[16] The addition of eicosapentanoic acid or docosahexanoic acid can prevent or terminate pharmacologically induced arrhythmias in cultured cardiomyocytes from newborn rats.[16] However, studies are necessary to show a direct antiarrhythmic effect in humans and trials are currently under way in patients with implantable defibrillators.

Thrombosis

Activation of platelets and their deposition at sites of unstable plaque rupture promotes thrombus formation, and these critical events have become a common therapeutic target in acute coronary syndromes. However, the effects of omega 3 fatty acids on platelet function and thrombosis are controversial. Large doses reduce platelet aggregation, but smaller amounts have modest platelet inhibitory effects.[17] Omega 3 fatty acids have inconsistent effects on fibrinolysis and little effect on blood coagulability.[18] Therefore, although omega 3 fatty acids have an antithrombotic effect, its relevance to the mortality reduction seen with lower doses is unclear.

Atherosclerosis

Omega 3 fatty acids may also influence the atherosclerotic process. Fish oil fed to experimental animals protects against progression of atherosclerotic plaques.[w3 w4] In humans with coronary heart disease omega 3 fatty acid supplementation versus placebo for two years resulted in modest improvements in atherosclerosis as assessed by angiography.[w5] These effects may be due to a reduction in lipids, inflammation, production of growth factor, or suppression of smooth muscle cell proliferation.[w6] An important recent study randomised patients awaiting carotid endarterectomy to fish oil capsules, sunflower oil capsules, or control until surgery and then assessed morphology of the plaque.[19] Omega 3 fatty acids were readily incorporated into atherosclerotic plaques in the fish oil group, and these plaques were more likely to have thick fibrous caps and less inflammatory infiltrate. These features imply a plaque that is less vulnerable to rupture and indicate that fish oils may be important in establishing stability of the plaque.

Inflammation

Inflammation has a central role in the development and progression of coronary artery disease. Omega 3

Table 1 Effect of marine derived omega 3 fatty acids on death from coronary heart disease in secondary prevention of myocardial infarction

Study	Design	Intervention	Intervention events (%)	Control events (%)	Absolute risk reduction (%)	Relative risk reduction (%)	No needed to treat	Comments
Diet and reinfarction trial[10]	Randomised, controlled, two year follow up, 2033 men after myocardial infarction	Fish meal twice weekly or fish oil capsules if unable to tolerate fish (1.5 g/d)	7.7*	11.4	3.7	32.5	27	Before routine use of secondary prevention treatment such as aspirin, β blockers, statins
Indian experiment of infarct survival[12]	Randomised double-blind placebo controlled, one year follow up, 360 patients after myocardial infarction	Fish oil (EPA+DHA 1.8 g/d) or mustard seed oil (ALA 2.9 g/d)	11.4*	22	10.6	48.2	10	Small size, high mortality, may not be applicable to Western populations
GISSI-Prevenzione trial, Italy[11]	Randomised, controlled, 3.5 year follow up, 11 324 patients after myocardial infarction	Fish oil (EPA+DHA 0.85 g/d)	4.8**	6.8	2	29.7	50	Not blinded, no placebo
Nilsen et al[13]	Randomised double-blind placebo controlled, 1.5 year follow up, 300 patients after myocardial infarction	Fish oil (EPA+DHA 3.5 g/d)	5.3	5.3	—	—	—	Small size, reasonable intake of fish among general population

*P<0.01 between control and intervention groups.
**P=0.024 between control and intervention groups.
EPA=eicosapentanoic acid, DHA=docosahexanoic acid, ALA=α linolenic acid.

fatty acids have recognised anti-inflammatory actions that may contribute to their beneficial cardiac effects. Omega 6 fatty acids can be converted into arachidonic acid and then metabolised into the omega 6 eicosanoids (fig 4).[20] These cellular mediators enhance platelet aggregation and are generally pro-inflammatory. Consumption of omega 3 fatty acids increases eicosapentanoic acid in the cell membrane. This competes with arachidonic acid for enzymatic conversion into its own metabolites, the omega 3 derived eicosanoids. These are less active and can partly oppose or antagonise the pro-inflammatory actions of the omega 6 eicosanoids.

Independent of the effects on the metabolism of eicosanoids fish oils suppress pro-inflammatory cytokines and reduce expression of cell adhesion molecules.[21] These are critical in recruiting circulating leucocytes to the vascular endothelium, an important event in the pathogenesis of atherosclerosis and inflammation. These effects may be mediated through actions on intracellular signalling pathways, leading to reduced activation of transcription factors such as NF-κB.[21] However, the precise effects of omega 3 fatty acids on these fundamental cellular processes and their potential impact on coronary heart disease are yet to be delineated completely.

Endothelial function

Abnormal endothelial function is found in individuals with cardiovascular risk factors or established coronary heart disease. Omega 3 fatty acids have direct effects on endothelial vasomotor function. Higher concentrations are associated with improved dilation of the brachial artery in young adults with cardiovascular risk factors, which implies a protective effect on endothelial function.[w7] In hyperlipidaemic men omega 3 fatty acid supplementation improved systemic arterial compliance[w8] and supplementation with docosahexanoic acid increased vasodilator responses in the human forearm.[w9]

Blood pressure

Fish oils can produce modest reductions in blood pressure, possibly through their effects on endothelial function discussed above. A recent meta-analysis of 36 randomised trials found a reduction in systolic blood pressure of 2.1 mm Hg and in diastolic blood pressure of 1.6 mm Hg.[22] However, most trials used relatively high doses of fish oils (3.6 g/day), and the effects of lower intakes of omega 3 fatty acids, such as those in the secondary prevention trials, remain to be established.

Triglyceride lowering

Omega 3 fatty acids reduce triglyceride concentrations in a dose dependent manner, with intakes of about 4 g per day lowering serum triglycerides by 25-30%.[w10] Their effect on cholesterol is small and of uncertain clinical importance. Higher doses (3-5 g/day) can be used in the treatment of hypertriglyceri-

Box 2: Recommendations for intake of omega 3 fatty acid

- Patients without documented coronary heart disease: Eat a variety of (preferably oily) fish at least twice weekly. Include oils and foods rich in α linolenic acid
- Patients with documented coronary heart disease: Consume 1 g of eicosapentanoic and docosahexanoic acid daily, preferably from oily fish. Supplements could be considered in consultation with a doctor
- Patients with hypertriglyceridaemia: Take 2-4 g of eicosapentanoic acid and docosahexanoic acid daily, provided as capsules under a doctor's care

These are the recommendations of the American Heart Association.[23]

Box 3: Consumption and sources of marine derived omega 3 fatty acids

- Current consumption of marine derived omega 3 fatty acids is low, at 0.1-0.2 g/day. An expert US panel of nutrition scientists has recommended an intake of 0.65 g/day whereas the British Nutrition Foundation's recommendation is 1.2 g/day.[2] Secondary prevention trials after myocardial infarction indicate that consumption of 0.5-1.8 g/day of eicosapentanoic and docosahexanoic acid from fish or fish oil supplements may be beneficial. Intake of marine derived omega 3 fatty acids can be increased through diet or with fish oil supplements. Oily fish such as mackerel, herring, tuna, salmon, sardines and trout are rich sources of eicosapentanoic and docosahexanoic acid (table 2), and two to three servings per week should provide approximately 1 g/day omega 3 fatty acids. Lean fish such as cod or haddock have smaller amounts, and fried fish (for example, from fast food establishments or frozen products) contains minimal amounts of omega 3 fatty acids.
- Concerns about the depletion of fish stocks will become more pressing if the benefits of fish oils are confirmed beyond the population after myocardial infarction, as this may result in an unsustainable increase in demand. Alternative strategies to increase omega 3 intake include supplementing animal feed with fish oil to augment the omega 3 content of eggs, meat, and milk.[2] Available foods can also be enriched in eicosapentanoic and docosahexanoic acid, although they may impart a fishy aroma or flavour. A different approach independent of an adequate supply of fish oil would involve using modern biotechnology to genetically modify certain plants species, thereby producing plants and plant oils rich in eicosapentanoic and docosahexanoic acid.[2]

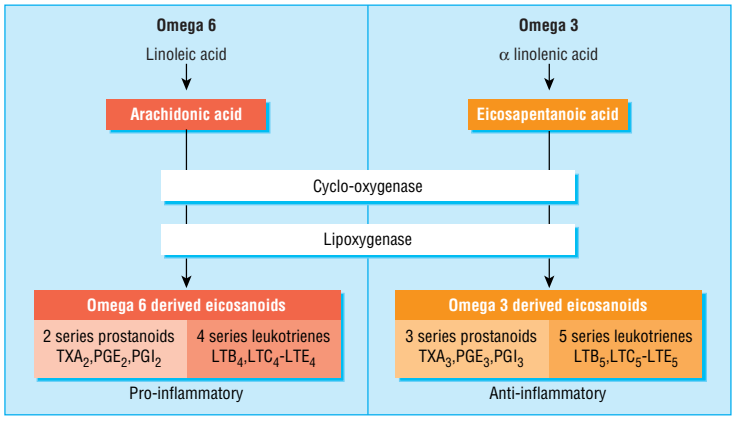

Fig 4 Synthesis of eicosanoids from omega 6 and omega 3 fatty acids. Arachidonic acid and eicosapentanoic acid compete for the cyclo-oxygenase and lipoxygenase enzymes for conversion into eicosanoids. Those derived from arachidonic acid are pro-inflammatory and pro-aggregatory, whereas those derived from omega 3 fatty acids are anti-inflammatory and inhibit platelet aggregation

Table 2 Content of omega 3 fatty acids of selected fish and seafood (adapted from the guidelines of the American Heart Association[23])

	EPA+DHA content (g) per 100 g serving of fish (edible portion)	Amount of fish (in g) required to provide 1 g EPA+DHA
Tuna (fresh)	0.28-1.51	66-357
Atlantic salmon	1.28-2.15	42.5-70.9
Mackerel	0.4-1.85	54-250
Atlantic herring	2.01	50
Rainbow trout	1.15	87
Sardines	1.15-2	50-87
Halibut	0.47-1.18	85-213
Tuna (canned)	0.31	323
Cod	0.28	357
Haddock	0.24	417
Catfish	0.18	556
Flounder or sole	0.49	204
Oyster	0.44	227
Shrimp	0.32	313
Scallop	0.2	500
Cod liver oil capsule	0.19	5
Omacor (Pronova)	0.85	1

EPA=eicosapentanoic acid, DHA=docosahexanoic acid.
Omega 3 content varies markedly depending on species, season, diet, and packaging and cooking methods, and the figures above are therefore rough estimates.

daemia. Only a small reduction in triglycerides occurred at the lower doses used in the GISSI-Prevenzione trial[11] (about 1 g/day), and it therefore seems unlikely that this effect alone could be responsible for the cardiovascular benefits.

Clinical implications

Omega 3 fatty acids from fish or fish oil supplements should be considered in the secondary prevention regimen of patients after myocardial infarction. Patients should consume about 1 g/day of eicosapentanoic acid and docosahexanoic acid, preferably by increasing their intake of oily fish to at least two servings per week. Fish oil capsules may be considered for those unable to tolerate fish or change their diet effectively. Approved pharmaceutical grade capsules should be prescribed rather than encouraging over the counter supplements.

Recent guidelines from the American Heart Association (box 2) have gone further, supporting the use of fish oil supplements for patients with "documented" coronary heart disease.[23] However, we believe that more evidence is required before considering fish oil supplements for patients with coronary heart disease outside the specific indication of myocardial infarction. Others have argued that fish oil supplements should not be recommended routinely for patients after myocardial infarction until more definitive evidence is available.[w11]

No trial has assessed the effects of fish oils on risk of coronary heart disease in primary prevention, and therefore explicit recommendations for this group cannot be made currently. Such a trial may prove impractical in terms of the numbers required. However, on the basis of evidence from epidemiological and observational studies the consumption of (preferably oily) fish at least twice weekly should be encouraged as part of a balanced diet. Box 3 and table 2 show current consumption and dietary sources of eicosapentanoic and docosahexanoic acid.

Any recommendations regarding fish and fish oils should be balanced against safety issues. Side effects such as fishy aftertaste are uncommon, and gastrointestinal upset is infrequent at moderate intakes.[23] Some reports show that fish oil may worsen glycaemic control in diabetes, but two meta-analyses found no adverse effect.[w12] [w13] Furthermore, a recent prospective cohort study found that a higher consumption of omega 3 fatty acids was associated with a lower incidence of coronary heart disease and mortality in diabetic women.[w14] Concerns have been raised regarding adverse effects on low density lipoprotein (LDL) cholesterol and oxidative stress, but increases in LDL cholesterol are modest and studies into oxidative stress have been contradictory.[w15] Overall these effects are unlikely to be dominant given the apparent cardiac benefits of omega 3 fatty acids. More specific concerns regarding dietary fish relate to environmental contaminants, and a recent study showed that mercury in fish may attenuate their cardioprotective effects.[24] Contaminants accumulate in larger, predatory fish, and consumption of a variety of fish should minimise any possible adverse effects.[23]

Future directions

Despite advances in our understanding of the cardioprotective effects of fish oils in the past three decades, many issues remain unresolved. A double blind, placebo controlled trial of fish oil capsules in patients after myocardial infarction is required, and further trials are needed in individuals with risk factors for coronary heart disease or with heart failure. The specific effects of eicosapentanoic acid versus docosahexanoic acid on risk of coronary heart disease and the relative merits of oily fish compared with fish oil

Additional educational resources

Websites
www.nal.usda.gov/fnic/foodcomp/—USDA Nutrient Data Laboratory, a database with online search function to find the omega 3 content of various foods
www.foodstandards.gov.uk/multimedia/pdfs/fsis40_2003.pdf—Food Standards Agency UK, provides data on mercury content of various fish and advice on safe consumption for pregnant women and women of childbearing potential.

Reviews
Hu FB, Willett WC. Optimal diets for the prevention of coronary heart disease. *JAMA* 2002;288:2569-78
Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr* 2002;56(suppl 3):S14-9.
Davis BC, Kris-Etherton PM. Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications. *Am J Clin Nutr* 2003;78(suppl 3):S640-6.
American Journal of Clinical Nutrition 2000;71(suppl 1)—dedicated to fish oils and omega 3 fatty acids. Twenty articles covering a range of subjects from current intake and biological actions through to effects on a wide range of medical conditions.

For patients
Omega 3 Information Service. A wealth of well balanced information about omega 3 fatty acids; including their effects on medical conditions apart from coronary heart disease (www.omega-3info.com/)
British Nutrition Foundation. Charitable organisation promoting healthy eating through impartial interpretation of nutritional knowledge and advice (www.nutrition.org.uk/)

capsules also require further investigation. In addition to trials with clinical end points, research efforts should be focused on understanding the mechanisms by which fish oils might confer cardiac benefits. This will allow us not only to refine the clinical applications of fish oils but hopefully also to identify other therapeutic targets and help guide the development of future treatments for coronary heart disease.

Contributors: JD researched and drafted the original manuscript. All authors jointly contributed to the final paper. JD is the guarantor.

Funding: JD is funded by a project grant from the British Heart Foundation. DEN is funded by the British Heart Foundation. ADF is employed by the National Health Service.

Competing interests: None declared.

1 Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr* 1975;28:958-66.
2 Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, et al. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 2000;71(suppl):S179-88.
3 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.
4 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.
5 Hu FB, Bronner L, Willett WC, Stampfer 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.
6 Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998;279:23-8.
7 Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002;346:1113-8.
8 Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett 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.
9 Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *Eur J Clin Nutr* 1999;53:585-90.
10 Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-61.
11 Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1999;354:447-55.
12 Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival—4. *Cardiovasc Drugs Ther* 1997;11:485-91.
13 Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001;74:50-6.
14 Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57:193-200.
15 Christensen JH, Gustenhoff P, Korup E, Aaroe J, Toft E, Moller J, et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomised controlled trial. *BMJ* 1996;312:677-8.
16 Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 2003;107:2646-52.
17 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. *Arterioscler Thromb Vasc Biol* 1997;17:279-86.
18 Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids* 2001;36(suppl):S79-82.
19 Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;361:477-85.
20 Heller A, Koch T, Schmeck J, van Ackern K. Lipid mediators in inflammatory disorders. *Drugs* 1998;55:487-96
21 De Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. *Am J Clin Nutr* 2000;71(suppl):S213-223.
22 Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens* 2002;20:1493-9.
23 Kris-Etherton PM, Harris WS, Appel LJ for the Nutrition Committee. AHA scientific statement. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2747-57.
24 Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, et al. Mercury, fish oils, and the risk of myocardial infarction. . Heavy Metals and Myocardial Infarction Study Group. *N Engl J Med* 2002;347:1747-54.

(Accepted 6 November 2003)

Corrections and clarifications

Editor's Choice and the filler "An extreme failure of concordance"
In his Editor's Choice of 11 October, Richard Smith wrote about the failure of communication between a Hmong family in California with a daughter with severe epilepsy and the Californian healthcare system—as described in a book from which we published an extract in the same issue (as a "filler," p 867). Unfortunately, Smith said that Lia had now died. He was wrong to say this; she is still alive. Anne Fadiman, the author of the book (*The Spirit Catches You and You Fall Down*) has asked us to make clear that "Lia suffered profound neurological damage after an episode of status epilepticus and that the parents thought that the doctors and their drugs had injured her rather than helped." In the filler, we also misspelt the first name of the book's author and introduced a rogue apostrophe into the word "fractions." We apologise for these errors to all concerned.

Communicating risks at the population level: application of population impact numbers
Richard F Heller and colleagues have reported an error in their Education and Debate article (15 November, pp 1162-5) that was due to a little recognised problem in calculating population attributable risk for multiple levels of exposure. This led to an overestimation of population attributable risk in table 2, which shows the impact of blood cholesterol concentration on premature death from coronary heart disease (p 1164). However, this does not alter the general conclusion drawn from the table (that the population impact of cholesterol concentrations of 5.2-6.5 mmol/l and of 6.5-7.8 mmol/l is larger than that of concentrations above 7.8 mmol/l) or the substance of the article. Full details of the correct calculations and the corrected table 2 appear on bmj.com (http://bmj.bmjjournals.com/cgi/content/full/327/7424/1162/DC1).

Submitting articles to the *BMJ*

We are now inviting all authors who want to submit a paper to the *BMJ* to do so via the web (http://submit.bmj.com).

Benchpress is a website where authors deposit their manuscripts and editors go to read them and record their decisions. Reviewers' details are also held on the system, and when asked to review a paper reviewers will be invited to access the site to see the relevant paper. The system is secure, protected by passwords, so that authors see only their own papers and reviewers see only those they are meant to.

Anyone with an internet connection and a web browser can use the system.

The system provides all our guidance and forms and allows authors to suggest reviewers for their paper. Authors get an immediate acknowledgement that their submission has been received, and they can watch the progress of their manuscript. The record of their submission, including editors' and reviewers' reports, remains on the system for future reference.

The system itself offers extensive help, and the *BMJ*'s editorial office will help authors and reviewers if they get stuck.

Benchpress is accessed via http://submit.bmj.com or via a link from bmj.com