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Fatty acids and CHD

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During the last century much evidence has accumulated to suggest that from a public health perspective the type of fat is more important than the amount of fat. Saturated and *trans*-fatty acids increase and both *n*-6 and *n*-3 PUFA decrease the risk of CHD. Most of the knowledge about the effects of dietary fatty acids on CHD risk is based on observational studies and controlled dietary experiments with intermediate end points (e.g. blood lipoprotein fractions). Information from high-quality randomised controlled trials on fatty acids and CHD is lacking. The Netherlands Institute for Public Health has calculated the potential health gain that can be achieved if the fatty acid composition of the current Dutch diet is replaced by the recommended fatty acid composition. The recommendations of The Netherlands Health Council are: saturated fatty acids <10% energy intake; *trans*-fatty acids <1% energy intake; fish consumption (an indicator of *n*-3 PUFA) once or twice weekly. Implementation of this recommendation could reduce the incidence of CHD in The Netherlands by about 25 000/year and the number of CHD-related deaths by about 6000/year and increase life expectancy from age 40 years onwards by 0·5 year. These projections indicate the public health potential of interventions that modify the fatty acid composition of the diet.

CHD: Fat type: Health benefits: Evidence

CHD is a major cause of morbidity and mortality in Europe (De Backer *et al*. 2003). There are well-established risk factors for CHD, including smoking, high blood pressure, raised total cholesterol and HDL-cholesterol, and type 2 diabetes (De Backer *et al*. 2003). In terms of nutrition a diet high in saturated fat has been shown to be associated with the incidence of CHD (Mann, 2002). The observation that Greenland Eskimos (Inuit) have a low incidence of CHD despite a high saturated fat intake (Dyerberg & Bang, 1979) has led to much scientific and public interest in the role of the various fatty acids in the prevention and treatment of disease, and particularly CHD. In the present review the biochemistry and dietary intake of the various fatty acids will be discussed, and the evidence linking them and their food sources with CHD will be reviewed.

Biochemistry of fatty acids

Fatty acids are hydrocarbon chains with terminal methyl and carboxyl groups. A vast number of fatty acids occur in nature and they differ in chain length, number of double bonds and type of double bonds. However, there are probably less than twenty that are quantitatively important in the human diet. Of these twenty, two (palmitic acid and oleic acid) often account for ≥65% of the total fatty acid intake. Table 1 describes the most commonly-occurring fatty acids, grouped as saturated fatty acids (SFA), MUFA and PUFA, depending on the presence and number of double bonds.

Of the total dietary intake of fatty acids >95% is in the form of triacylglycerol. Most natural food sources contain a wide variety of SFA and unsaturated fatty acids, and thus a large number of triacylglycerol molecules of different fatty acid composition. Dietary fatty acids fulfil three major roles: an energy source; structural components of membranes; precursors to other molecules. Dietary fat represents a convenient energy-rich food source, but the role of fatty acids as energy providers can be adequately fulfilled by carbohydrate, while the major fatty acids found in membranes can be manufactured in the body. However, linoleic acid and α-linolenic acid cannot be made by

Abbreviations: MI, myocardial infarction; SFA, saturated fatty acids.
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Table 1. Common dietary fatty acids

Fatty acid	Formula	Common food sources
Saturated		
Lauric	12:0	Coconut oil, palm kernel oil
Myristic	14:0	Coconut oil, palm kernel oil, dairy products
Palmitic	16:0	Dairy products, meat, palm oil
Stearic	18:0	Cocoa butter, meat
MUFA		
Oleic	*Cis*-18:1	Olive oil, rapeseed oil, meat
Elaidic	*Trans*-18:1	Hydrogenated fats
PUFA		
Linoleic	18:2*n*-6	Sunflower, maize and safflower oils
α-Linolenic	18:3*n*-3	Linseed oil, soyabean oil, vegetables
EPA	20:5*n*-3	Fish, marine mammals
DHA	22:6*n*-3	Fish, marine mammals

animals and are thus described as essential fatty acids, apparently as a result of their requirements in membranes and as eicosanoid (such as thromboxanes, prostaglandins, prostacyclins and leukotrienes) precursors.

Biological effects of the various classes of fatty acid

Effect of fatty acids and dietary cholesterol on serum cholesterol: meta-analyses and the Keys equation

It is 40 years since Keys & Parlin (1966) and, working independently, Hegsted *et al*. (1965) developed predictive equations to quantify the effects of fatty acids and dietary cholesterol on plasma cholesterol concentrations. The numerous controlled feeding studies of the effects of different fatty acids on cholesterol levels have been summarised in several meta-analyses (Hegsted *et al*. 1965; Keys & Parlin, 1966; Mensink & Katan, 1992; Hegsted *et al*. 1993; Yu *et al*. 1995). These analyses confirm early reports by Keys & Parlin (1966) and Hegsted *et al*. (1965) that total cholesterol and LDL-cholesterol are increased by SFA and decreased by PUFA. A recent meta-analysis shows that different fatty acids also have a different effect on HDL-cholesterol (Mensink *et al*. 2003).

Saturated fatty acids. SFA increase plasma total cholesterol and LDL-cholesterol levels by decreasing LDL receptor-mediated catabolism (Spady *et al*. 1983; Nicolosi *et al*. 1990). However, not all SFA affect total cholesterol and LDL-cholesterol concentrations in the same manner. Stearic acid has little effect on plasma cholesterol concentrations (Hegsted *et al*. 1965; Grande *et al*. 1970), which has been proposed to be a result of the rapid conversion of stearic acid in the body to oleic acid (Grundy & Denke, 1990). There is also evidence that the chain length of the SFA is related to their effects on HDL-cholesterol, in that the longer the chain length the smaller the effect on HDL-cholesterol. Lauric acid increases HDL-cholesterol and palmitic and stearic acid do not affect HDL-cholesterol (Mensink *et al*. 2003). SFA can also compromise platelet function (Turpeinen *et al*. 1998).

MUFA. The biological effects of MUFA depend on whether the MUFA are in the *cis* or *trans* configuration. *Cis*-MUFA are relatively neutral in relation to their effects on LDL and HDL (Mensink, 2005), but *trans*-MUFA have been shown to increase LDL and decrease HDL (Lichtenstein *et al*. 1993, 1999; Mensink *et al*. 2003; Mensink, 2005). *Trans*-MUFA also increase plasma levels of lipoprotein (a) (Nestel *et al*. 1992; Sundram *et al*. 1997) and triacylglycerols (Katan *et al*. 1995), and may reduce endothelial function by impairing flow-mediated dilation (de Roos *et al*. 2001).

PUFA. Dietary PUFA are sub-classified as *n*-6 or *n*-3, depending on the location of the C atom involved in the first double bond from the methyl end of the chain.

The major *n*-6 fatty acid is linoleic acid. Numerous metabolic studies have shown that linoleic acid has a lowering effect on total cholesterol and LDL-cholesterol (Grundy *et al*. 1982; Sacks, 1994; Mensink *et al*. 2003), while other beneficial effects include improvement in platelet function (Mutanen & Freese, 1996), improved insulin sensitivity (Lovejoy & DiGirolamo, 1992; Lovejoy, 1999) and anti-arrhythmic effects (Abeywardena *et al*. 1991).

n-3 PUFA have wide-ranging biological effects. They have been shown to lower triacylglycerols (Kris-Etherton *et al*. 2002), with a review of human studies reporting that approximately 4 g *n*-3 PUFA from fish oil/d decreases serum triacylglycerols by 25–30%, with an accompanying increase in LDL-cholesterol and HDL-cholesterol of 1–3%. The lowering effect increases as the supplement dose increases (Harris *et al*. 1988). *n*-3 PUFA also reduce VLDL and IDL (Lu *et al*. 1999; Tholstrup *et al*. 2004). They have been associated with a decreased risk of arrhythmias, with studies in cell cultures and animal models, observational studies and human intervention trials all suggesting that *n*-3 PUFA may protect against fatal arrhythmia (Charnock, 1994; Nair *et al*. 1997). The proposed mechanism appears to involve a stabilising effect on the myocardium itself (Nair *et al*. 1997; Kris-Etherton *et al*. 2002; Lee & Lip, 2003). *n*-3 PUFA seem to have a small dose-dependent hypotensive effect (Howe, 1997), and the extent of the reduction in blood pressure appears to be dependent on the initial extent of hypertension (Howe, 1997). A meta-analysis has indicated a marked reduction in blood pressure of 3·4/2·0 mmHg in hypertensive subjects consuming 5·6 g *n*-3 PUFA/d (Morris *et al*. 1993). *n*-3 PUFA have been shown to reduce platelet aggregation (Agren *et al*. 1997; Mori *et al*. 1997), thereby reducing haemostasis. *n*-3 PUFA appear to have an anti-atherogenic action, in that they can inhibit new plaque development (Eritsland *et al*. 1996); for example, EPA and DHA may alter expression of adhesion molecules. Abe *et al*. (1998) have reported a 9% reduction in intercellular adhesion molecule-1 and a 16% reduction in E-selectin but no change in vascular cell adhesion molecule-1 in hypertriacylglycerolaemic subjects receiving *n*-3 PUFA supplementation over 7–12 months, while α-linolenic acid has been proposed to have similar effects (Rallidis *et al*. 2004). However, other studies have failed to confirm these results (Seljeflot *et al*. 1998; Johansen *et al*. 1999). It has been shown in several studies that *n*-3 PUFA improve

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endothelial function (for review, see Chin & Dart, 1995), and they also favourably influence arterial compliance (McVeigh *et al*. 1994). A recent study has shown that *n*-3 PUFA from dietary fish oil supplements are readily incorporated into advanced atherosclerotic plaques and that this process is associated with structural changes consistent with increased plaque stability (Thies *et al*. 2003). *n*-3 PUFA may also be associated with a reduced inflammatory response (de Caterina & Libby, 1996; Endres & von Schackey, 1996; de Caterina *et al*. 2000; Simopoulos, 2002; Trebble *et al*. 2003; Zhao *et al*. 2004).

Dietary measures to reduce LDL-cholesterol

There is no evidence that moderate changes in total fat intake without changes in fatty acid composition have any beneficial effect on LDL-cholesterol. However, a number of dietary measures with the potential to lower LDL-cholesterol have been tested in controlled intervention studies. A reduction in saturated fat, *trans*-fat and dietary cholesterol intake and an increase in soluble dietary fibre and plant sterol or stanol intake have all been shown to independently decrease serum LDL (Krauss *et al*. 2000; Kreisberg & Oberman, 2003), whilst a combined dietary approach, which is low in saturated fat and high in plant sterols, soyabean protein, viscous fibres and almonds (*Amygdalus communis* L.), has been shown to produce a lowering effect on LDL-cholesterol similar to that of a statin (Jenkins *et al*. 2003).

Epidemiological evidence linking consumption of fatty acids with CHD

Serum cholesterol and CHD

Serum total cholesterol concentration is positively related to CHD mortality and is accepted as being a classical risk factor for CHD. The linear relationship between cholesterol and CHD mortality has been confirmed across cultures (Verschuren *et al*. 1995). Thus, the fact that the various fatty acids have different effects on total cholesterol leads to an expectation that they will also have different effects on CHD mortality.

Saturated fatty acids and CHD

Geographic and migration studies show strong positive correlations between saturated fat intake and rates of CHD (Kato *et al*. 1973; Keys, 1980; Kromhout *et al*. 1995*b*). Although these data provide evidence for the importance of environmental factors in the cause of CHD, they are seriously confounded by other dietary, lifestyle and social factors. Prospective studies have also examined the link between saturated fat and CHD (Garcia-Palmieri *et al*. 1980; Gordon *et al*. 1981; Shekelle *et al*. 1981; Kromhout *et al*. 1984; McGee *et al*. 1984; Kushi *et al*. 1985; Ascherio *et al*. 1996; Hu *et al*. 1997; Pietinen *et al*. 1997), but only two studies have found a positive association between saturated fat intake and risk of CHD (McGee *et al*. 1984; Kushi *et al*. 1985). The early studies of fat and CHD were limited by small study size, inadequate dietary assessment and inadequate adjustment for total energy intake, other types of fat or for *trans*-isomer fat intake (Hu *et al*. 2001; Hu & Willett, 2002).

To date, the largest study of fat intake, which also had four repeated dietary assessments, was carried out in the Nurses' Health Study cohort of 80 082 women followed up over 14 years (Hu *et al*. 1997). This study has found a weak positive association between saturated fat intake and risk of CHD.

MUFA and CHD

Ecological studies have suggested an inverse association between MUFA intake and total mortality, as well as CHD-related death (Jacobs *et al*. 1992). In particular, the mortality rate from CHD is very low in the traditional Mediterranean populations that use olive oil as the primary source of fat (Grundy *et al*. 1982). Prospective cohort studies examining MUFA intake and CHD risk are sparse. Two studies (Posner *et al*. 1991; Esrey *et al*. 1996) have found an increased risk of CHD with a higher intake of MUFA in younger, but not older, participants. However, neither study adjusted for intake of other fat types. A more recent study (Pietinen *et al*. 1997) that did adjust for other fat intake has found an inverse association. The Nurses' Health Study (Hu *et al*. 1997) has found an inverse association between MUFA intake and CHD risk.

Trans-fatty acids and CHD

The Nurses' Healthy Study (Hu *et al*. 1997) has found a strong positive association between *trans*-fatty acid intake and CHD risk. In addition to the Nurses' Health Study (Hu *et al*. 1997), three other large prospective studies (Ascherio *et al*. 1996; Pietinen *et al*. 1997; Oomen *et al*. 2001) have found elevated risk from CHD to be associated with higher *trans*-fatty acid intake. The results of these four prospective studies have been combined, and the pooled relative risk of CHD associated with a difference of 2% energy in *trans*-fatty acid intake assessed at baseline is 1·25 (95% CI 1·11, 1·40; Oomen *et al*. 2001).

n-*6 PUFA and CHD*

In prospective cohort studies among men a strong inverse association between CHD and PUFA intake has been shown in the Western Electric Study (Shekelle *et al*. 1981), and borderline inverse associations have been reported in the Ireland-Boston Heart Study (Kushi *et al*. 1985) and the control group of the Multiple Risk Factor Intervention Trial (Dolecek, 1992). An inverse association between PUFA intake and CHD has also been shown in the Nurses' Health Study (Hu *et al*. 1997).

n-*3 PUFA and CHD*

Marine-derived n-*3 PUFA.* Epidemiological studies have consistently shown that consumption of at least one portion of fish weekly may decrease the risk of fatal CHD by approximately 40% compared with consumption of no fish (Kromhout *et al*. 1985, 1995*a*; Shekelle *et al*. 1985;

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Dolecek & Granditis, 1991). More recently, in a 30-year follow-up of the Chicago Western Electric Study men who consumed ≥35 g fish daily compared with those who consumed none had a relative risk of death from CHD of 0·62 (Daviglus *et al*. 1997). The association between marine-derived *n*-3 PUFA and CHD has also been shown for fatal CHD, but not for non-fatal myocardial infarction (MI), in a prospective study in the elderly (Lemaitre *et al*. 2003). A meta-analysis of prospective studies has confirmed the association, but only in high-risk groups (Marckmann & Gronbaek, 1999), while a more recent meta-analysis has also found a protective effect of fish consumption on CHD (relative risk 0·86 (95% CI 0·81, 0·92); $P<0·005$; Whelton *et al*. 2004). A separate meta-analysis has confirmed the association, finding each 20 g/d increase in fish intake to be related to a 7% lower risk of CHD mortality ($P=0·03$; He *et al*. 2004). The inverse association between fish consumption and mortality from CHD has been shown to be consistent across countries in an ecological study of thirty-six countries (Zhang *et al*. 1999).

Fewer studies have examined the effect of tissue *n*-3 PUFA levels rather than dietary intake on CHD risk. In the European Multicentre Case–Control Study on Antioxidants, Myocardial Infarction and Breast Cancer (Guallar *et al*. 1999), a large international case–control study, no association between adipose tissue DHA and MI risk was demonstrated. However, a Finnish study (Erkkila *et al*. 2003), carried out in the context of the EURO-ASPIRE study, has examined the fatty acid composition of serum cholesteryl esters in relation to secondary prevention of CHD. The relative risk of death, adjusted for CVD risk factors, for subjects in the highest tertile of fatty acids compared with those in the lowest tertile was found to be 0·33 for α-linolenic acid, 0·33 for EPA and 0·31 for DHA ($P=0·063$, 0·056 and 0·026 respectively for trend).

Some notable studies have not reported an association between fish consumption and CHD risk. In the Health Professionals Follow-up Study (Ascherio *et al*. 1995) no association between fish intake (and *n*-3 PUFA intake) and risk of CHD was found. Similarly, the Physicians Health Study (Albert *et al*. 1998) has also failed to show an association between fish consumption or *n*-3 PUFA intake and risk of MI, non-sudden cardiac death or total CVD mortality, although a reduced risk of sudden cardiac death and total mortality was reported. The Seven Countries data (Kromhout *et al*. 1996) has also shown a lack of association between fish consumption and both CHD incidence and mortality. In fact, The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Pietinen *et al*. 1997) has found that the estimated *n*-3 PUFA intake from fish is associated with a trend towards increased risk of death from CHD (after adjustment for *trans*-fatty acids, SFA and *cis*-MUFA).

The authors of the American Heart Association scientific statement on fish consumption, fish oil, *n*-3 fatty acids and CVD (Kris-Etherton *et al*. 2002) have summarised the possible reasons for the conflicting data from the epidemiological studies. There have been suggestions that the conflicting data reflect differences in the definition of sudden death and the residual confounding of reference groups that have a less-healthy lifestyle (Kromhout, 1998), variability in end points studied, study design or dietary assessment of fish intake, different study populations (Sheard, 1998) and the possible confounding effect of an increase in haemorrhagic stroke. Albert *et al*. (1998) have attempted to explain the lack of association in their study as being because only a small proportion of their population reported little or no fish consumption, whereas the studies reporting an inverse association between fish consumption and mortality from CHD have had relatively large proportions of the study population that do not eat fish. The European Multicentre Case–Control Study on Antioxidants, Myocardial Infarction and Breast Cancer (Marckmann & Gronbaek, 1999) only examined MI survivors, and it is possible that those who did not survive ate less fish. Another explanation, based on a summary of eleven prospective studies, is that fish is protective in populations at high risk of CHD but not in populations at low risk. Another consideration is the type of fish consumed and how it is prepared; Oomen *et al*. (2000) have reported a lower CHD mortality (relative risk 0·66) only in those eating fatty fish and not in those eating lean fish. Another emerging explanation relates to levels of methylmercury in fish, with several, although not all, studies showing an association between methylmercury exposure and CHD risk (Ahlqwist *et al*. 1999; Salonen *et al*. 2000). Thus, methylmercury in fish may mask the beneficial effects of *n*-3 PUFA on CHD risk. This possibility has been confirmed in an analysis of the European Multicentre Case–Control Study on Antioxidants, Myocardial Infarction and Breast Cancer (Guallar *et al*. 2002).

Plant-derived n-*3 PUFA*. α-Linolenic acid, in contrast to EPA and DHA, is found in plant foods and not marine sources. Evidence from epidemiological studies of α-linolenic acid and CVD indicates that α-linolenic acid is associated with a lower risk of both MI and fatal CHD in both women and men (Kris-Etherton *et al*. 2002). A recent meta-analysis of five prospective studies of α-linolenic acid and mortality from CHD (Brouwer *et al*. 2004) has concluded that high α-linolenic acid intake is associated with a reduced risk of fatal CHD (relative risk 0·79 (95% CI 0·60, 1·04)). In addition, in a recent observational study (Djousse *et al*. 2003) higher consumption of α-linolenic acid has been shown to be associated with a lower prevalence of carotid plaques and with lower segment-specific carotid intima-media thickness. In the same cohort dietary α-linolenic acid has been associated with a lower prevalence of calcified atherosclerotic plaque in the coronary arteries (Djousse *et al*. 2005).

Nut consumption and CHD risk

Dietary recommendations to reduce the risk of CHD have traditionally advised the avoidance of nuts because of their high fat content (≤80% energy from fat). However, epidemiological evidence (Hu & Stampfer, 1999) supports a protective effect of nut consumption and CHD. Intervention studies have confirmed the cholesterol-lowering effects of walnut (*Juglans regia*)-rich (Sabate, 1993), almond-rich (Spiller *et al*. 1992; Abbey *et al*. 1994) and peanut (*Arachis hypogea*)-rich (O'Byrne *et al*. 1997) diets.

A walnut-rich diet has recently been shown to improve endothelium-dependent vasodilation in hypercholesterolaemic subjects, suggesting lipid-independent beneficial effects (Ros *et al*. 2004). These results highlight the importance of fat type, as the fats found in nuts are predominantly mono- and polyunsaturated; however, nuts also contain other CHD-protecting factors such as vegetable protein, Mg, vitamin E, fibre and K.

Fatty acid intervention studies and CHD

The first intervention trial altering fat content of the diet was carried out by Morrison (1951). MI survivors (*n* 100) were randomised to an experimental (dietary cholesterol intake 50–70 mg/d, fat intake 20–25 g/d) or control diet. It was found that the experimental group lost on average 9 kg in weight and cholesterol dropped markedly, while there was no change in the control group. After 3 years of follow-up seven of the fifty subjects in the experimental group had died, compared with fifteen of the fifty subjects in the control group. After 12 years of follow-up nineteen of the fifty subjects in the experimental group had died and all fifty in the control group.

Since that early study a number of dietary trials have examined the effect of alteration in dietary fat and the effect on CHD. They have utilised two different approaches, either replacing saturated fat with polyunsaturated fat but leaving total fat unchanged or lowering total fat. In all the high-PUFA trials serum cholesterol was reported to be reduced (Leren, 1966, 1970; Morris *et al*. 1968; Dayton & Pearce, 1969; Turpeinen *et al*. 1979; Frantz *et al*. 1989). Three of the trials (Dayton & Pearce, 1969; Turpeinen *et al*. 1979; Frantz *et al*. 1989) were primary prevention trials conducted amongst institutionalised patients, which allowed a high extent of control over their diets. In the Los Angeles Veteran Hospital Study (Dayton & Pearce, 1969) CHD rate was found to be reduced by 31 % in the intervention group after 8 years, while in the Finnish Mental Hospital Study (Turpeinen *et al*. 1979) the reduction in CHD risk was reported to be 43 % over 6 years. In contrast, in the Minnesota Coronary Survey (Frantz *et al*. 1989) cardiovascular events were not found to be reduced by a high-PUFA diet, despite a decrease in serum cholesterol, but the duration of the study was short. The two secondary prevention trials carried out in non-institutionalised subjects (Leren, 1966, 1970; Morris *et al*. 1968) have reported contrasting results. In the Oslo Diet-Heart Study (Leren, 1966, 1970) a reduction in major coronary events was found at 5-year follow-up (Leren, 1966), with fatal MI rates still reduced at 11 years (Leren, 1970). In contrast, Morris *et al*. (1968) have shown no effect of soyabean oil on recurrent coronary events after 4 years, despite a 16 % reduction in serum cholesterol at 6 months. The two interventions that tested total fat reduction (Ball *et al*. 1965; Burr *et al*. 1989) have reported no effect on either serum cholesterol or CHD events.

A meta-analysis by Truswell (1994) has shown that there is a direct relationship between the level of reduction in serum cholesterol by PUFA-rich diets and the effect on coronary events and all-cause mortality. The average reduction in serum cholesterol in fourteen trials was found to be 10 %. This reduction was found to be associated with a 13 % reduction in coronary events and a 6 % reduction in all-cause mortality. In the five trials with the largest reduction in serum cholesterol (13 %) a 30 % reduction was observed for coronary events and an 11 % reduction for all-cause mortality.

n-*3 PUFA intervention studies*

Marine-derived n-*3 PUFA intervention studies.* The first randomised controlled trial using *n*-3 PUFA was the Diet and Reinfarction Trial (Burr *et al*. 1989), which examined the effects of increased fatty fish intake on secondary prevention of CHD. A 29 % reduction in all-cause mortality was found over a 2-year period in male MI survivors advised to increase intake of fatty fish by 200–400 g/week (providing an extra 500–800 mg *n*-3 PUFA/d). Analysis of a subset of patients who received fish oil capsules (900 mg EPA + DHA/d) has suggested the effect is associated with these fatty acids (Burr *et al*. 1994). However, after longer-term follow-up this protective effect was not found to persist (Ness *et al*. 2002), although this lack of effect may have been related to only small sustained increases in fish intake in the fish group. The recently-published second Diet and Reinfarction Trial (Burr *et al*. 2003) carried out in angina patients has not found a protective effect on mortality and has even shown a detrimental effect on (sudden) cardiac death.

Trials have also been carried out using fish oil capsules. Singh *et al*. (1997), in the Indian Experiment of Infarct Survival, randomised patients with suspected acute MI to fish oil capsules (1·8 g EPA + DHA/d), mustard-seed oil (20 g/d providing 2·9 g α-linolenic acid/d) or placebo. At follow-up of 1 year it was shown that total cardiac events occurred in 25 % and 28 % of the fish oil and mustard-seed oil groups respectively compared with 35 % of the placebo group, and the difference was significant ($P<0·01$).

To date, the largest randomised control trial carried out using *n*-3 PUFA is the Italian GISSI-Prevention Study (GISSI-Prevenzione Trial Group, 1999). In this secondary prevention study 11 324 patients with pre-existing CHD were randomised to 300 mg vitamin E, fish oil (850 mg EPA + DHA), both vitamin E and fish oil or neither. After 3·5 years follow-up those subjects given *n*-3 PUFA alone were found to have a 15 % reduction in the primary end point of death, non-fatal MI and non-fatal stroke ($P<0·02$), a 20 % reduction in all-cause mortality ($P=0·01$) and a 45 % reduction in sudden death ($P<0·001$) compared with the control group. Vitamin E had no apparent effect on the primary end point, whether given alone or with the *n*-3 PUFA, although *P* values approached significance. This trial was large and carried out in a relatively usual care setting (in that subjects were receiving conventional cardiac therapy). However, it was not placebo controlled (the control group received no intervention) and, therefore, is methodologically weaker than if a placebo control had been utilised. Dropout rates were also high (>25 %).

The last of the intervention studies with a clinical end point has compared maize oil with 3·5 g fish oil

(concentrated in DHA + EPA)/d (Nilsen *et al*. 2001). No effect was seen on cardiac events in post-MI patients (*n* 300) after 1·5 years of intervention. The authors have speculated that this lack of effect may have been related to the high habitual fish intake in western Norway.

No intervention trials have been carried out so far that have examined the effect of *n*-3 PUFA supplementation on primary prevention of CHD, although such trials are underway. However, several studies have examined the effect of supplementation on intermediate CHD end points.

The first study of the effect of *n*-3 PUFA on angiographic progression rates has shown no response to 6 g *n*-3 PUFA or olive oil/d over 2 years (Sacks *et al*. 1995). However, a larger trial of patients presenting for coronary angiography (*n* 223), who were randomised to either placebo or 3 g/d for 3 months followed by 1·5 g/d for 21 months, has shown that *n*-3 PUFA supplementation is associated with less progression, more regression and a trend towards fewer clinical events (seven events *v*. two events; $P = 0{\cdot}1$; von Schacky *et al*. 1999). Supplementation with *n*-3 PUFA (3·4 g/d) has also been shown to lower vein graft occlusion rates from 33 % (control) to 27 % ($P = 0{\cdot}03$; Eritsland *et al*. 1996).

Several trials have examined the effect of *n*-3 fish oils on restenosis (the closing or narrowing of an artery that has previously been opened by a cardiac procedure such as angioplasty) after coronary angioplasty. Although an early meta-analysis (of seven studies; Gapinski *et al*. 1993) has shown a beneficial effect of supplementation, the results of more recent trials (Cairns *et al*. 1996; Johansen *et al*. 1999) do not provide evidence of a beneficial effect. These later trials were large studies using 5–7 g *n*-3 PUFA/d, and therefore further studies are not considered necessary.

Plant-derived n-*3 PUFA intervention studies.* The effect of α-linolenic acid supplementation in CHD prevention has been examined in five trials (Natvig *et al*. 1968; Singh *et al*. 1997, 2002; de Lorgeril *et al*. 1999; Bemelmans *et al*. 2002). The Indian Experiment of Infarct Survival (Singh *et al*. 1997), discussed earlier, has reported a decrease in total cardiac events in the group assigned to mustard-seed oil. In the Lyon Diet Heart Study (de Lorgeril *et al*. 1999) a randomised controlled trial of an α-linolenic acid-rich Mediterranean diet with free-living subjects, the subjects in the intervention group had a 50–70 % reduction in cardiac end points. In the final report of this study de Lorgeril *et al*. (1999) have reported reductions in three composite outcomes (1, cardiac death and non-fatal MI; 2, outcome 1 plus unstable angina, stroke, heart failure and pulmonary or peripheral embolism; 3, outcome 2 plus minor events requiring hospital admission) with adjusted risk ratios ranging from 0·28 to 0·53.

In terms of dietary change, subjects in the control group were reported to average (% energy): 34 from fat; 12 from saturated fat; 11 from monounsaturated fat; 6 from polyunsaturated fat; 312 mg cholesterol/d. In contrast, the values for subjects on the Mediterranean-style diet were reported to be (% energy): 30 from fat; 8 from saturated fat; 13 from monounsaturated fat; 5 from PUFA; 203 mg cholesterol/d. Those subjects on the Mediterranean diet were found to consume less linoleic acid (3·6 % energy *v*. 5·3 % energy), but more oleic acid (12·9 % energy *v*. 10·8 % energy), α-linolenic acid (0·84 % energy *v*. 0·29 % energy) and dietary fibre. Plasma fatty acid analysis conducted after 52 weeks of follow-up confirmed the dietary fatty acid data (de Lorgeril *et al*. 1994). Although the plasma levels of α-linolenic acid were shown to be associated with composite outcome 1, it is impossible to ascribe the benefit unambiguously to α-linolenic acid because of the changes in many other dietary variables.

The Indo-Mediterranean Diet Heart Study was a randomised single-blind trial of 1000 subjects with angina pectoris, MI or surrogate risk factors for coronary artery disease. The intervention group, who consumed a diet rich in α-linolenic acid (rich in whole grains, fruits, vegetables, walnuts and almonds), had fewer total cardiac end points than the control group after 2 years (Singh *et al*. 2002). Also, in this case the intervention effect cannot be ascribed entirely to α-linolenic acid.

These three positive studies of α-linolenic acid are balanced by two negative studies (Natvig *et al*. 1968; Bemelmans *et al*. 2002). In the Norwegian Vegetable Oil Experiment (Natvig *et al*. 1968) 13 000 men aged 50–59 years with no history of MI were randomly assigned to consume either 5·5 g α-linolenic acid (from 10 ml linseed oil)/d or 10 ml sunflower oil/d for 1 year. There were no differences between the groups in sudden death, death from CHD or all deaths. Similarly, the Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention (Bemelmans *et al*. 2002) has examined 282 subjects with multiple CVD risk factors and randomised them to receive margarines rich in either α-linolenic acid or linoleic acid, with a 2-year follow-up. No difference was found between groups in CHD risk, although there was a trend towards reduced CVD events in the α-linolenic acid group ($P = 0{\cdot}20$).

These contradictory studies indicate that further well-designed trials must be carried out in order to determine the role of α-linolenic acid in CHD aetiology. Currently, the effects of plant *n*-3 PUFA as compared with those of marine *n*-3 PUFA are difficult to determine, as few, if any, studies have set out to test this comparison. For example, a meta-analysis of the available randomised control trials has examined all intervention trials whether they used marine or plant sources of *n*-3 PUFA and has found reductions in risk of non-fatal MI, fatal MI and sudden death, but does not distinguish between the two sources of *n*-3 PUFA (Bucher *et al*. 2002).

Public health benefits of an alteration in fatty acid intake

This overview of the relationships between fatty acids and CHD shows that a lot of evidence has been collected in controlled feeding studies, observational studies and clinical trials. However, the results of these studies are equivocal. Thus, a judgment has to be made about the strength of these relationships. An expert committee of the World Health Organization (2003) has judged recently that the relationships between SFA, *trans*-fatty acids and the *n*-3 PUFA EPA and DHA on the one hand and CHD on

the other hand are convincing. For this reason The Netherlands Institute for Public Health and Environment has calculated the potential health gain that can be achieved if the current intake of these fatty acids in the Dutch diet is replaced by the recommended intake.

The recommendations of The Netherlands Health Council are: SFA>10% energy intake; *trans*-fatty acids >1% energy intake; fish consumption (an indicator of *n*-3 PUFA) once or twice weekly. This level of intake could reduce the incidence of CHD in The Netherlands by about 25 000/year and the number of CHD-related deaths by about 6000/year and increase life expectancy from age 40 years onwards by 0·5 years (The Netherlands Institute for Public Health and Environment, 2004). This projection shows the public health potential of interventions that modify the fatty acid composition of the diet.

Conclusions

Evidence from controlled feeding studies, epidemiological studies and clinical trials suggests that an alteration in the fatty acid composition of the diet has the potential to reduce CHD risk. SFA and *trans*-fatty acids increase CHD risk, while *n*-6 and *n*-3 PUFA act to decrease CHD risk. Optimisation of the fatty acid composition of the diet could have major public health benefits.

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