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Dietary Fat and Coronary Heart Disease: Summary of Evidence from Prospective Cohort and Randomised Controlled Trials

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Introduction

This article summarises the evidence from cohort studies and randomised controlled trials for the importance of total fat and dietary fatty acids for risk of coronary heart disease (CHD). Its purpose is to assist the expert consultation group to make evidence-based recommendations about fat, fatty acids and human health.

Ecological studies that compare differences in CHD rates between mean intakes of fatty acids in different populations are uniquely informative, as such associations are virtually unaffected by regression dilution bias. The best known ecological study of diet and CHD is the Seven Countries Study, which consisted of 16 cohorts in 7 different countries involving a total of 12,763 middle-aged men that were examined between 1958 and 1964 [Keys, 1980]. The Seven Countries Study showed that death rates from CHD during 10 and 15 years of follow-up across the 16 cohorts were positively associated with dietary intake of saturated fat (SFA) at baseline and inversely associated with dietary intake of monounsaturated fat (MUFA) [Keys et al., 1986]. The results showed that a substantial proportion of the variation in CHD death rates between geographical regions was explained by differences in intake of SFA and MUFA fat. At 25 years of follow-up only the association with baseline SFA intake remained [Kromhout et al., 1995b]. Moreover, the Seven Countries Study also demonstrated strong associations between mean intakes of SFA and mean levels of serum total cholesterol [Keys, 1980]. The study prompted the 'diet heart' hypothesis that high intakes of SFA and cholesterol and low intakes of polyunsaturated fats (PUFA) increase the level of total cholesterol and ultimately result in the development of CHD. Indeed, the early results of the Seven Countries Study prompted an explosion of epidemiological, clinical, and basic research into the role of dietary fat in CHD.

The results of dietary feeding trials (or 'metabolic ward' studies) which measured blood lipids in healthy volunteers after administration of controlled diets with varying intakes of fats were concordant with the findings of the associations observed between intakes of different fatty acids and changes in blood cholesterol levels observed in the ecological studies. In particular, Keys et al. [1965] and Hegsted et al. [1965] demonstrated that average change in serum cholesterol concentrations could be predicted as equations for the changes in intake of SFA and PUFA and dietary cholesterol. The concordance of the results of the ecological and the metabolic ward studies probably relate to the limited amount of measurement error in both study designs. In view of these findings, some investigators have concluded that use of cholesterol as an intermediary factor is the most rational way of studying the associations between dietary fat and CHD,

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with appropriate correction for measurement error in both study designs. Nevertheless, many investigators have examined the associations of differences in intake of fatty acids directly with CHD risk within populations. The present review summarises the evidence from the cohort studies and dietary intervention trials that examined the effects of differences in diet (or exchanges of particular fats by another or by carbohydrate) on risk of CHD.

In addition to the evidence of the importance of reducing the intake of SFA and dietary cholesterol for prevention of CHD, other sources of evidence have focussed on finding the best replacement for SFA and the relative roles of n–3 and n–6 PUFAs. Based on observations in the mid 1970s of the Greenland Inuit and subsequently in clinical trials, Bang and Dyerberg [Bang et al., 1976; Dyerberg et al., 1978; Dyerberg and Bang, 1979], showed that n–3 long chain polyunsaturated fatty acids (LCPUFA) might have cardio-protective effects independently of their effects on serum cholesterol concentrations.

The articles by Sanders (pp 162–172 of this issue) and Galli and Calder (pp 123–139 of this issue) respectively examine the effects of dietary fats on blood lipids and other biomarkers of inflammation and other factors that may affect CHD risk. The purpose of this article is to summarise the evidence from cohort studies and randomised controlled trials of the relation between dietary fat and risk of CHD.

Methods

Cohort studies and controlled trials of dietary fat and CHD mortality or morbidity were identified by searching the Cochrane Library and examining Cochrane reviews [Hooper et al., 2001, 2004a]; by keyword searches of article databases using Medline, Embase, SCOPUS, Web of Science and PubMed; by examining the tables, figures and list of references in review articles [Hooper et al., 2004b; Mozaffarian et al., 2006; Booker and Mann, 2008; Erkkila et al., 2008], systematic reviews [Wang et al., 2006], meta-analyses [Bucher et al., 2002; Brouwer et al., 2004; He et al., 2004; Whelton et al., 2004; Yzebe and Lievre, 2004; Mozaffarian and Rimm, 2006; Jenkins et al., 2008] and original articles; and by searching for papers that had cited relevant cohort and intervention studies. The present review was limited to English language publications.

Information about study design, methods and key results were extracted from the original source or, in a few instances when the original source was unobtainable, from peer-reviewed articles that had cited the original study results. The cohort study endpoints reviewed were CHD death, CHD events, and non-fatal CHD. The randomised clinical trial endpoints included total mortality. For the n–3 LCPUFA/Fish trials we also examined restenosis/occlusion/revascularization, non-fatal myocardial infarction, and angina.

To summarise the results from published cohort studies, random effects meta-analysis was used to calculate summary estimates of the relative risk (RR) of CHD in high compared with low exposure to dietary fat or its components: *trans* fatty acids (TFA), SFA, MUFA, PUFA, and n–3 LCPUFA. Multiple variable adjusted RRs were extracted from the original sources and used, when available. Table 1 summarises the covariates that were included in the multivariable analysis for each cohort study.

Studies in which dietary fat exposure was assessed using fatty acid biomarkers were included in the meta-analyses of high compared with low fat exposure alongside studies in which fat intake was assessed using traditional methods of dietary assessment. Thus, for example, in the meta-analysis of cohort studies of n–3 LCPUFA and risk of CHD we included studies of dietary fish, fish oil or n–3 LCPUFA intake as well as studies in which exposure was assessed using fatty acid biomarkers. For MUFA we only included studies in which exposure was determined by dietary assessment because blood fatty acids are not good biomarkers of MUFA intake. The dietary assessment methods used in the cohort studies included single 24-hour recall, diet records, diet histories and food frequency questionnaires collected at baseline or from the same participants at various times throughout follow-up (table 2).

Many studies reported the RR of CHD for an incremental change in fat intake. Units of incremental change included 2% or 5% of energy, 1 standard deviation and 100 g of fat. In most studies where the RR associated with an incremental increase in percent energy from fat type was reported, the statistical analysis was adjusted for other types of fat (SFA, MUFA, PUFA and TFA) so that the result represents the RR associated with replacing carbohydrate with the specific type of fat. We included in the results a forest plot of the RRs of CHD for any incremental change, but suppressed the estimate of overall risk because the unit of comparison was markedly different between studies. Separate meta-analyses were performed to generate summary estimates of risk for 2% energy increments for TFA and 5% energy increments for SFA, MUFA and PUFA.

To avoid duplication of data from individual studies that provided multiple reports, reports with the longest duration of follow-up were selected for review. For n–3 LCPUFA and CHD cohort studies we included in the meta-analysis only the risk associated with the n–3 LCPUFA biomarkers in the first instance, or fish consumption if no biomarker was measured.

Cohort studies that did not report a RR associated with intake of dietary fats were excluded from the meta-analyses. The most common alternate measure of association between dietary fat and disease was a test for differences in dietary fat intake or level of fatty acid biomarkers between participants who did or did not develop CHD during follow-up. In all cases the differences were not multivariable-adjusted comparisons and therefore subject to potential confounding; accordingly we have presented the results in the supplementary tables but excluded them from this review. Supplementary materials for this article are available online at www.karger.com/doi/10.1159/000229002.

In the meta-analyses of results from randomised controlled trials of dietary fat and CHD we classified the studies into 4 general categories according to the primary goal of the dietary treatment: (1) diets involving a change in the polyunsaturated to saturated fat (P/S) ratio of the diet, with or without a reduction in total fat intake; (2) diets involving a reduction in total fat; (3) diets

involving an increase in fish or fish oil intake, and (4) diets involving an increase in foods rich in α-linolenic acid. A few studies could not be grouped into these categories and were excluded from the meta-analyses but are reported in the online supplementary tables. Trials that involved multi-factorial interventions (e.g. MRFIT) were excluded from the meta-analysis. Information about the number of participants in the treatment and control groups with or without a coronary disease endpoint during follow-up were extracted from the published trial results. As a sensitivity analysis, trials in which the P/S diet produced a reduction in serum cholesterol relative to the control group were identified and examined separately as a measure of compliance. A separate meta-analysis was performed for trials in which participant compliance with dietary treatment resulted in a reduction in serum cholesterol.

For the meta-analysis of randomised controlled trials of n–3 LCPUFA and CHD risk, we included any trial in which the intervention involved increased consumption of fish, fish oil or an n–3 LCPUFA purified oil.

All the RRs were displayed graphically as Forrest plots with a weighting inversely proportional to the variance of each study or trial. Summary estimates of risk and 95% CI were estimated by means of random effects meta-analysis used in Stata version 10 (Stata Corp., College Station, Tex., USA).

Results

Update of Previous Meta-Analyses

The present meta-analysis excludes 3 trials that were included in the review of dietary fat modification and CHD by Hooper et al. [2001]: the olive oil arm of the study by Rose et al. [1965] was excluded as it did not fit within the low-fat or PUFA-SFA intervention criteria, and the Sydney-diet [Blacket et al., 1979] and Veterans' Diet and Skin Cancer [Black et al., 1994] studies were excluded as they reported only cardiovascular disease and not CHD endpoints. We included 2 additional trials: the Finnish Mental Hospital [Turpeinen, 1979; Miettinen et al., 1983] and the Women's Health Initiative [Howard et al., 2006].

For the fish or n–3 LCPUFA trials, we excluded 3 studies that were included in the meta-analysis by Hooper et al. [2006], as they investigated α-linolenic supplementation rather than n–3 LCPUFA [Borchgrevink et al., 1966; Natvig et al., 1968; Bemelmans et al., 2002] and we excluded 1 trial with methodological concerns [Singh et al., 1997]. Five additional trials were included in the present meta-analysis [Leaf et al., 2005; Raitt et al., 2005; Brouwer et al., 2006; Yokoyama et al., 2007; GISSI-HF Investigators, 2008].

The present meta-analysis updates the review of fish intake and CHD by Mozaffarian and Rimm [2006] with the inclusion of 2 additional trials [Yokoyama et al., 2007; GISSI-HF Investigators, 2008] and 6 cohorts [Norell et al., 1986; Mann et al., 1997; Pietinen et al., 1997; Rissanen et al., 2000; Erkkila et al., 2003; Streppel et al., 2008]. We excluded 1 study that was included in Mozaffarian and Rimm's review [Kromhout et al., 1985] as a report for a longer duration was available [Streppel et al., 2008] and 1 trial with methodological concerns [Singh et al., 1997].

Cohort Studies of Dietary Fat and CHD

Selected characteristics of the 28 individual cohort studies are shown in online supplementary table 1. A few studies (e.g. Nurses' Health Study) have been duplicated because reports from the same study have been published at periodic years of follow-up. Data includes the geographical location, start year, duration of follow-up, number of participants, participant exclusion criteria, method of assessing dietary exposure, type of CHD event assessed, overall event rate, and the method of determining the association between fat exposure and CHD risk; for example, RR of disease in high compared with low consumers.

There were about 6,600 CHD deaths amongst the 280,000 participants in the cohort studies during approximately 3.7 million person-years of follow-up. CHD mortality rates ranged from 45 to 2,300 deaths per 100,000 person-years. The duration of follow-up varied from 4 to 25 years. With few exceptions, the studies were conducted in North America and in Europe. Nineteen of the 28 cohorts included only men, accounting for 1.84 million person-years of follow-up; the Nurses' Health Study was limited to women and accounted for more than 80% of person-years of follow-up amongst women in all cohorts. The age at recruitment varied from 40 to 65 years.

Meta-Analysis of Cohort Studies of Total Fat and CHD

Intake of total fat was not significantly associated with CHD mortality, with a RR for highest compared with the lowest category of 0.94 (95% CI 0.74–1.18, p = 0.583; fig. 1). Intake of total fat was also unrelated to CHD events (RR 0.93, 95% CI 0.84–1.03, p = 0.177). For the analysis that used 5% percent increase in total fat intake, there was no significant association of total fat intake with CHD mortality (RR 1.06, 95% CI 0.88–1.28, p = 0.517) or CHD events (RR 1.02, 95% CI 0.98–1.05, p = 0.404) per 5% total energy (TE) increment in total fat intake (fig. 3). The range of total fat intake (mean or median) varied from 23 to 30% TE in the lowest category to 38 to 47% TE in the highest category (table 3). Overall, the mean or median total fat intake in all cohort studies varied from 27 to 47% TE (online suppl. table 2).

Table 1. Summary of the covariates that were adjusted for in each cohort and nested case-control included in the meta-analyses

Study	Dietary fat investigated	Covariates that were adjusted for in each study												
		energy intake	age	physical activity	smoking	history of hypertension	history of high serum cholesterol	BMI	alcohol	diabetes/ glucose intolerance	other dietary fats	other dietary components	current serum cholesterol/ TAG	other
Norell et al., 1986	fish	•	✓	•	•	•	•	•	•	•	•	•	•	
Framingham Study [Posner et al., 1991]	total fat, SFA, MUFA, PUFA	✓	✓	✓	✓	•	•	•	•	✓	•	•	✓	systolic BP, LVH, metropolitan relative weight
Fraser et al., 1992	fish	•	✓	✓	✓	✓	•	•	•	•	•	•	•	
Esrey et al., 1996	total fat, SFA, MUFA, PUFA	✓	✓	•	✓	•	•	✓	•	✓	•	•	✓	systolic BP
Health Professionals Follow-Up Study [Ascherio et al., 1995, 1996]	fish, total fat, SFA, PUFA, MUFA, TFA	✓	✓	✓	✓	✓	✓	✓	✓	•	•	fibre	•	profession, family history of MI before age 60
ATBC [Pietinen et al., 1997]	fish, total TAG, SFA, MUFA, TFA, PUFA	✓	✓	✓	✓	•	•	•	•	•	✓	cereal fibre, fruits and vegetables	•	treatment group, education
Mann et al., 1997	SFA, fish	•	✓	•	✓	•	•	•	•	•	•	•	•	social class
Chicago Western Electric Study [Daviglus et al., 1997]	fish	•	✓	•	✓	•	•	✓	✓	✓	✓	protein, carbohydrate, vitamins and minerals, cholesterol	✓	education, religion, systolic BP, electrocardiographic abnormalities
Physcians' Health Study [Albert et al., 1998; Morris et al., 1995]	fish	•	✓	✓	✓	✓	✓	✓	✓	•	•	vitamin E, C and multivitamin use (treatment group)	•	evidence of cardiovascular disease
Seven Countries Study [Oomen et al., 2000]	fish	✓	✓	•	✓	•	•	✓	✓	•	•	vegetables and fruits, meat, butter and margarine	•	
FINMONICA [Rissanen et al., 2000]	fish	✓	✓	✓	✓	•	•	✓	•	•	•	•	✓	systolic BP, serum insulin, platelet aggregation, SES, evidence of ischemia, hair mercury content, serum ferritin
Zutphen Elerly Study [Oomen et al., 2001]	ALA, TFA	✓	✓	•	✓	•	•	•	✓	•	✓	fibre, cholesterol, vitamin supplement use	•	profession
Yuan et al., 2001	fish	✓	✓	•	✓	✓	•	✓	✓	✓	•	•	•	education
The Nurses' Health Study [Hu et al., 2002]	fish	•	✓	✓	✓	✓	•	✓	✓	✓	✓	fiber, vitamin E and multivitamin use	•	aspirin use, menopausal status, hormone replacement therapy use

The Health and Lifestyle Survey [Boniface and Tefft, 2002]	total fat, SFA, PUFA	•	✓	✓	✓	•	•	•	•	•	•	•	•	social class
EUROASPIRE [Erkkila et al., 2003]	fish, total fat, SFA, PUFA	✓	✓	•	•	•	•	✓	•	✓	•	•	✓	education, diagnostic category
Cardiovascular Health Study [Lemaitre et al., 2003]	fish	•	✓	•	•	•	•	•	•	•	✓	•	•	systolic BP, weight, education
Iowa Women's Health Study [Folsom et al., 2004]	fish	✓	✓	✓	✓	✓	•	✓	✓	✓	only SFA	wholegrains, fruits and vegetables, red meat, cholesterol, vitamin use	•	education, age at first live birth, waist/hip ratio, menopausal status, hormone replacement use
Nurses' Health Study [Oh et al., 2005]	total fat, SFA, MUFA, PUFA, TFA	✓	✓	✓	✓	✓	•	•	✓	•	✓	cholesterol, protein, vitamin E and multivitamin use	•	aspirin use, family history of MI before age 60, menopausal status, hormone replacement use
Baltimore Longitudinal Study of Aging [Tucker et al., 2005]	SFA	✓	✓	✓	✓	•	•	✓	✓	•	•	supplement use	•	
NIPPON DATA80 [Nakamura et al., 2005]	fish	•	✓	•	✓	✓	•	✓	✓	✓	•	•	✓	
Health Professionals Follow-Up Study [Mozaffarian et al., 2005]	ALA, EPA/DHA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	fibre, protein	•	aspirin use
Strong Heart Study [Xu et al., 2006]	total fat, *trans*, SFA, MUFA, PUFA	✓	✓	•	✓	✓	•	✓	✓	•	•	protein	✓	
Japan Public Health Center-Based Study Cohort I [Iso et al., 2006]	fish	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	fruits and vegetables	•	education
Jarvinen et al., 2006	fish	✓	✓	•	✓	•	•	✓	•	✓	•	•	•	occupation, blood pressure
MONICA I&II [Jakobsen et al., 2004; Osler et al., 2003]	fish, total fat, SFA, MUFA, PUFA	•	•	✓	✓	•	•	✓	✓	•	•	protein, fibre, cholesterol	•	systolic BP, education, family history of MI before age 60
ARIC Study [Yamagishi et al., 2008]	n–3, SFA, MUFA, PUFA	•	✓	•	•	•	•	•	•	•	•	•	•	
Zutphen Study [Streppel et al., 2008]	fish	✓	•	•	✓	•	•	✓	✓	✓	✓	fruits and vegetables, serum cholesterol lowering diet	•	systolic BP, SES

MI = Myocardial infarction; TAG = triacylglyceride; SFA = saturated fat; MUFA = monounsaturated fat; PUFA = polyunsaturated fat; ALA = α-linolenic acid; BP = blood pressure; LVH = left ventricular hypertrophy; SES = socio-economic status.

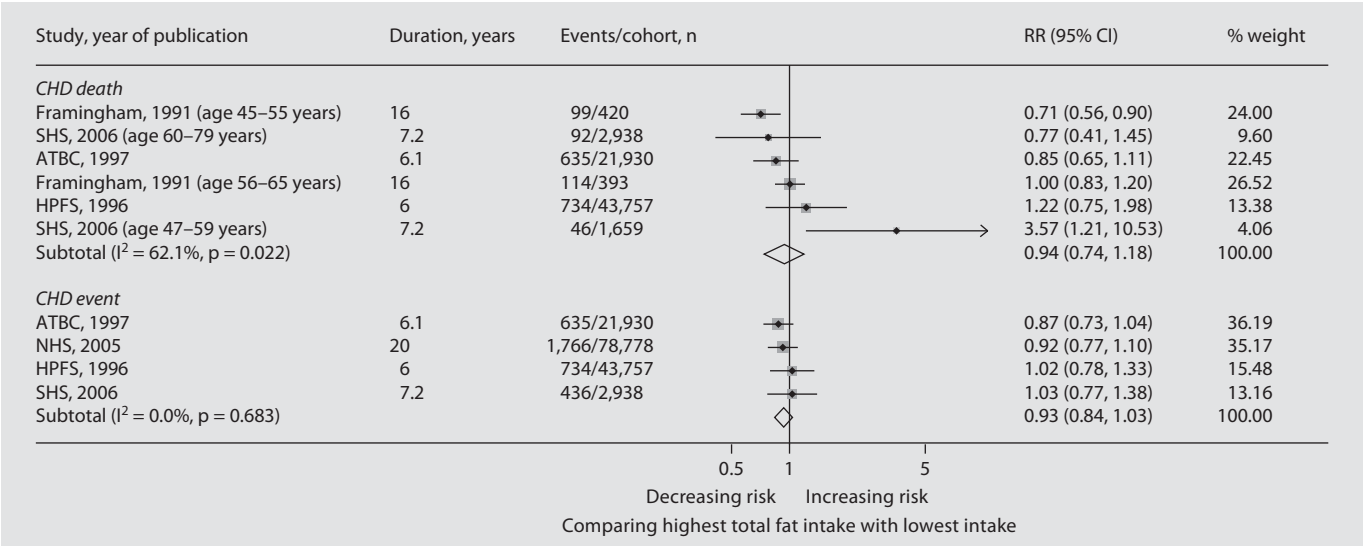
Table 2. Dietary assessment methods used for cohort studies included in the meta-analyses

Study	Diet assessment method	Dietary assessment completed
Norell et al., 1986	food frequency questionnaire	baseline
Framingham Study [Posner et al., 1991]	24-hour recall	baseline
Fraser et al., 1992	food frequency questionnaire	baseline
Esrey et al., 1996	24-hour recall	baseline
Health Professionals Follow-Up Study [Ascherio et al., 1995, 1996]	food frequency questionnaire	baseline
ATBC Study [Pietinen et al., 1997]	food frequency questionnaire	baseline
Mann et al., 1997	food frequency questionnaire	baseline
Physicians' Health Study [Morris et al., 1995; Albert et al., 2002]	food frequency questionnaire	baseline and 1 year later
Seven Countries Study [Kromhout et al., 1995b]	weighed diet records	baseline
Kromhout et al., 1995a (Rotterdam)	cross-check dietary history	baseline
Chicago Western Electric Study [Daviglus et al., 1997]	dietary history	baseline and 1 year later
Yuan et al., 2001	food frequency questionnaire	baseline
Seven Countries Study [Oomen et al., 2000]	dietary history and food frequency checklist	baseline and 1 year later
Health and Lifestyle Survey [Boniface and Tefft 2002]	food frequency questionnaire	baseline
Cardiovascular Health Study [Mozaffarian et al., 2003]	food frequency questionnaire	baseline
EUROASPIRE Study [Erkkila et al., 2003]	4-day estimated food record	baseline
MONICA I&II [Osler et al., 2003; Jakobsen et al., 2004]	7-day weighed diet record	baseline
Iowa Women's Health Study [Folsom and Demissie, 2004]	food frequency questionnaire	baseline
NIPPON DATA80 [Nakamura et al., 2005]	food frequency questionnaire	baseline
Nurses' Health Study [Oh et al., 2005]	food frequency questionnaire	collected 1980, 1984, 1986, 1990, 1994
Baltimore Longitudinal Study of Aging [Tucker et al., 2005]	7-day diet records	4 times throughout follow-up
Health Professionals Follow-Up Study [Mozaffarian et al., 2005]	food frequency questionnaire	baseline and every 4 years
Strong Heart Study [Xu et al., 2006]	24-hour diet recall	4 years after start of study
Jarvinen et al., 2006	dietary history	baseline
Japan Public Health Center-Based Study Cohort 1 [Iso et al., 2006]	food frequency questionnaire	baseline and 5 years later
Zutphen Study [Streppel et al., 2008]	dietary history	baseline

Table 3. Summary estimates of relative risk from random effects meta-analysis of prospective cohort study

Fat	Relative risk (95% CI)				Range of mean fat intake in low and high categories across cohorts, % TE	
	CHD death	p value	CHD events	p value	low	high
High compared with low intake						
Total fat	0.94 (0.74–1.18)	0.583	0.93 (0.84–1.03)	0.177	23–30	38–47
TFA	1.32 (1.08–1.61)	0.006	1.25 (1.07–1.46)	0.007	0.8–2.4	1.6–6.4
SFA	1.14 (0.82–1.60)	0.431	0.93 (0.83–1.05)	0.269	7–11	14–18
MUFA	0.85 (0.60–1.20)	0.356	0.87 (0.74–1.03)	0.110	9–11	16–20
PUFA	1.25 (1.06–1.47)	0.009	0.97 (0.74–1.27)	0.825	3–4	6–10
n–3 LCPUFA[a]	0.82 (0.71–0.94)	0.006	0.87 (0.71–1.10)	0.066	0–0.3 g/day[b] 0–23 g/day[c]	0.37–2.5 g/day[b] 22–180 g/day[c]
Per % TE increment						
Total fat (5% TE)	1.06 (0.88–1.28)	0.517	1.02 (0.98–1.05)	0.404		
TFA (2% TE)	1.21 (0.89–1.65)	0.227	1.22 (1.11–1.35)	<0.001		
SFA (5% TE)	1.11 (0.75–1.65)	0.593	1.03 (0.87–1.22)	0.723		
MUFA (5% TE)	0.92 (0.64–1.34)	0.67	0.93 (0.77–1.12)	0.449		
PUFA (5% TE)	0.94 (0.71–1.25)	0.669	0.84 (0.70–1.00)	0.049		

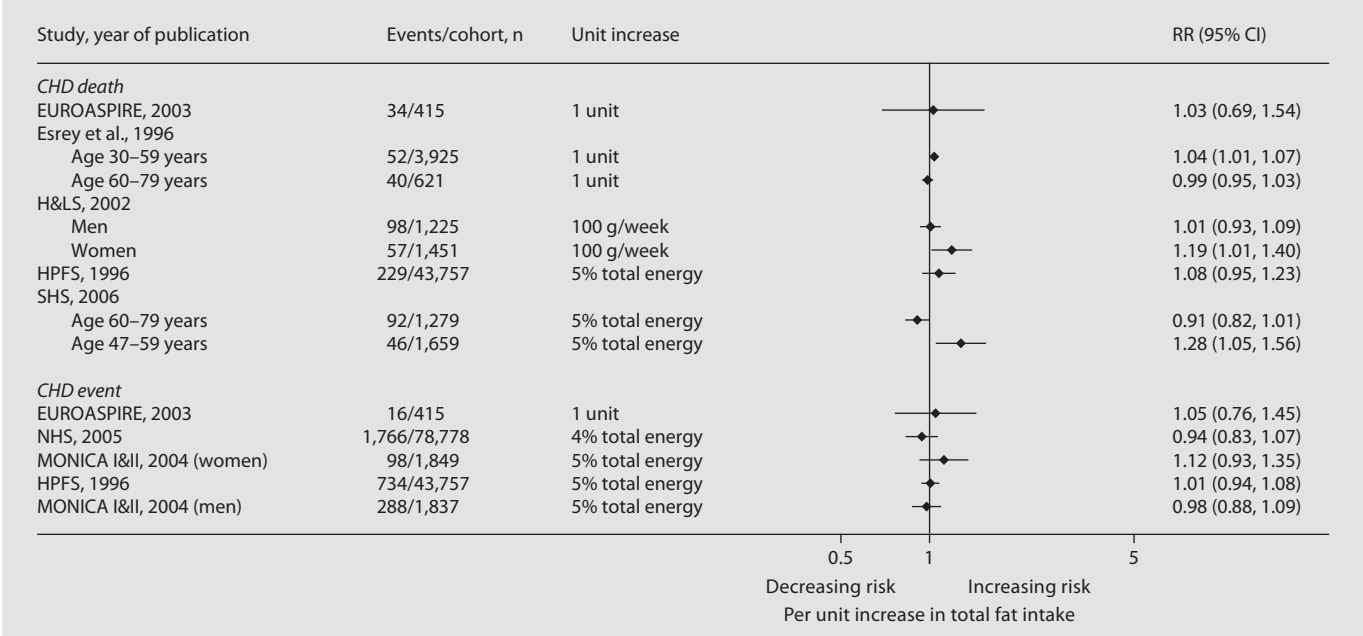
[a] Includes trials of fish consumption, n–3 LCPUFA intake, and biomarkers. [b] Grams of n–3 LCPUFA per day. [c] Grams of fish per day.



p = 0.583 for CHD death subtotal; p = 0.177 for CHD event subtotal. The relative risks correspond to comparisons of the highest total fat intakes with the lowest intakes, except the Framingham Study, which compared the sample mean fat intakes with the National Cholesterol Education Program Recommendations. The relative risks are the fully adjusted, multivariate results for each study.

Framingham = Framingham Study [Posner et al., 1991]; SHS = Strong Heart Study [Xu et al., 2006]; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; NHS = Nurses' Health Study [Oh et al., 2005]. Refer to online suppl. tables 1 and 3 for full study details.

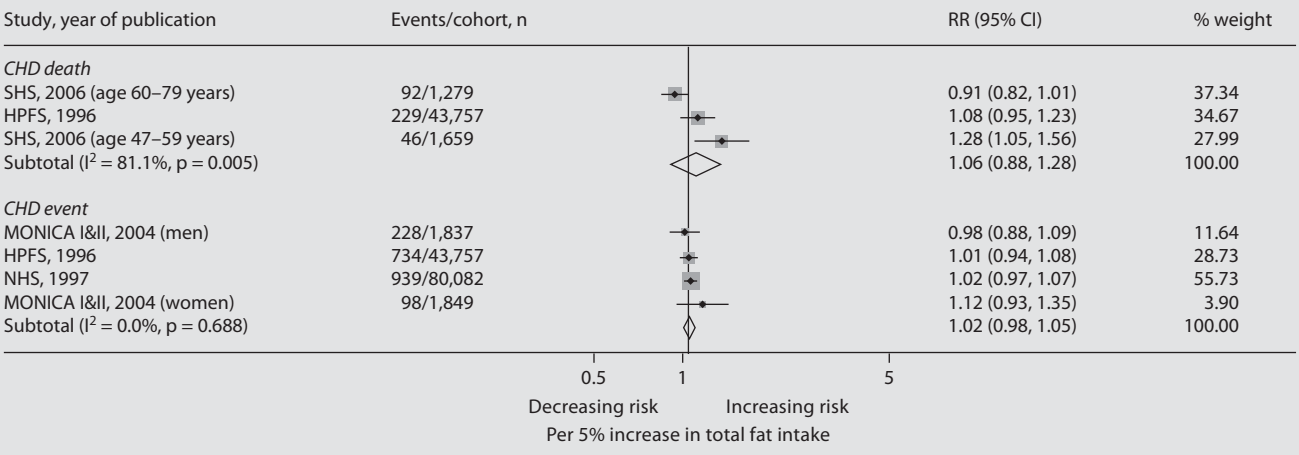
Fig. 1. Meta-analysis of total fat intake and CHD; prospective cohorts.



The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; NHS = Nurses' Health Study [Oh et al., 2005]; EUROASPIRE = Erkkila et al. [2003]; H&LS = Health and Lifestyle Survey [Boniface and Tefft, 2002]; MONICA I&II = Jakobsen et al. [2004]. Refer to online suppl. tables 1 and 4 for full study details.

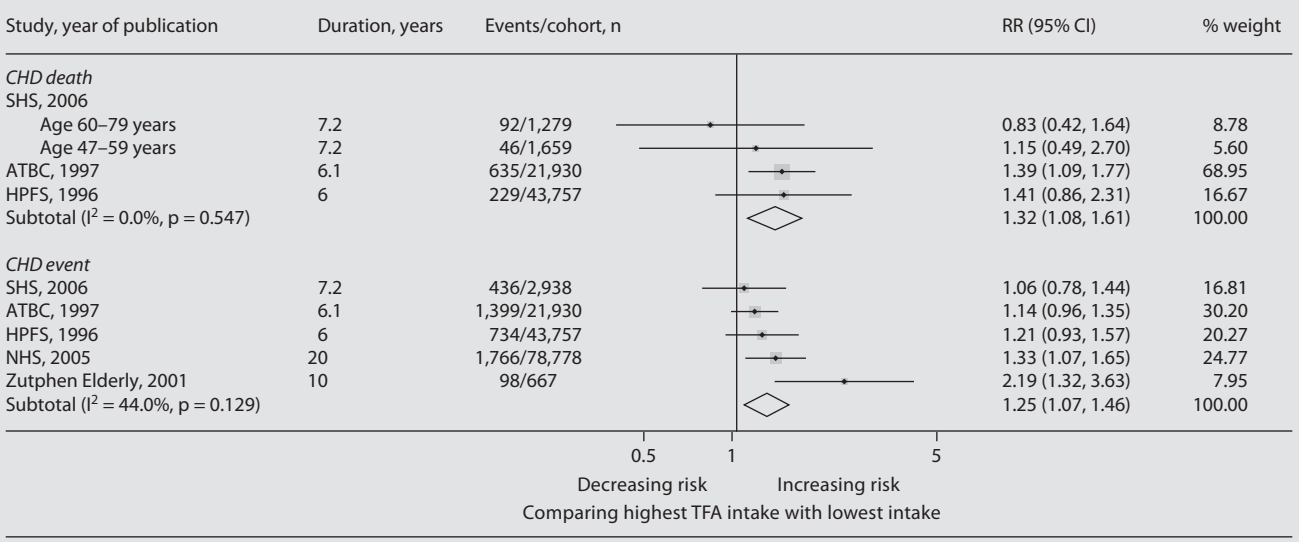
Fig. 2. RRs for CHD per unit increase in total fat intake.



p = 0.517 for CHD death subtotal; p = 0.404 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; NHS = Nurses' Health Study [Hu et al., 1997]; MONICA I&II = Jakobsen et al. [2004]. Refer to online suppl. tables 1 and 4 for full study details.

Fig. 3. Meta-analysis of CHD risk per 5% increase in total fat intake.



p = 0.006 for CHD death subtotal; p = 0.007 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; NHS = Nurses' Health Study [Oh et al., 2005]; Zutphen Elderly = Zutphen Elderly Study [Oomen et al., 2001]. Refer to online suppl. tables 1 and 5 for full study details.

Fig. 4. Meta-analysis of prospective cohorts for TFA and CHD.

Meta-Analysis of Cohort Studies of TFA and CHD

Intake of TFA was strongly associated with CHD mortality, with a RR of CHD death of 1.32 (95% CI 1.08–1.61, p = 0.006) for the highest compared with the lowest category (fig. 4). Similarly, high compared with low TFA intake was associated with a significantly increased risk of CHD events (RR 1.25, 95% CI 1.07–1.46, p = 0.007). A 2% increase in TFA intake was associated with significantly higher risk of CHD events (RR 1.22, 95% CI 1.11–1.35, $p < 0.001$) but not with CHD mortality (RR 1.21, 95% CI 0.89–1.65, p = 0.227; fig. 5). For the cohort studies included in the meta-analysis, mean or median TFA intake varied from 0.8 to 2.4% TE in the lowest category to 1.6 to 6.4% TE in the highest category (table 3). Overall, the mean or median TFA intake varied from 2.0 to 4.3% TE in all cohorts (online suppl. table 5).

Meta-Analysis of Cohort Studies of SFA and CHD

Intake of SFA was not significantly associated with CHD mortality, with a RR of 1.14 (95% CI 0.82–1.60, p = 0.431) for those in the highest compared with the lowest category of SFA intake (fig. 6). Similarly SFA intake was not significantly associated CHD events (RR 0.93, 95% CI 0.83–1.05, p = 0.269 for high vs. low categories). Moreover, there was no significant association with CHD death (RR 1.11, 95% CI 0.75–1.65, p = 0.593) per 5% TE increment in SFA intake (fig. 8). For the cohort studies included in the meta-analysis, mean or median SFA intake varied from 7 to 11% TE in the lowest category to 14 to 18% TE in the highest category (table 3). Overall the mean or median SFA intake in all cohort studies varied from 9 to 20% TE (online suppl. table 7).

Meta-Analysis of Cohort Studies of MUFA and CHD

Intake of MUFA was not significantly associated with CHD mortality, with a RR of 0.85 (95% CI 0.60–1.20, p = 0.356) for those in the highest compared with the lowest category of MUFA intake (fig. 9). Similarly, MUFA intake was not associated with CHD events (RR 0.87, 95% CI 0.74–1.03, p = 0.110, for high compared with low categories). Furthermore, there were no significant associations with CHD death (RR 0.92, 95% CI 0.64–1.34, p = 0.670) or CHD events (RR 0.93, 95% CI 0.77–1.12, p = 0.449) per 5% TE increment in MUFA intake (fig. 11). For the cohort studies included in the meta-analysis, mean or median MUFA intake varied from 9 to 11% TE in the lowest category to 16 to 20% TE in the highest category (table 3). Overall, the mean or median MUFA intakes in all cohort studies varied from 13 to 20% TE (online suppl. table 10).

Meta-Analysis of Cohort Studies of PUFA and CHD

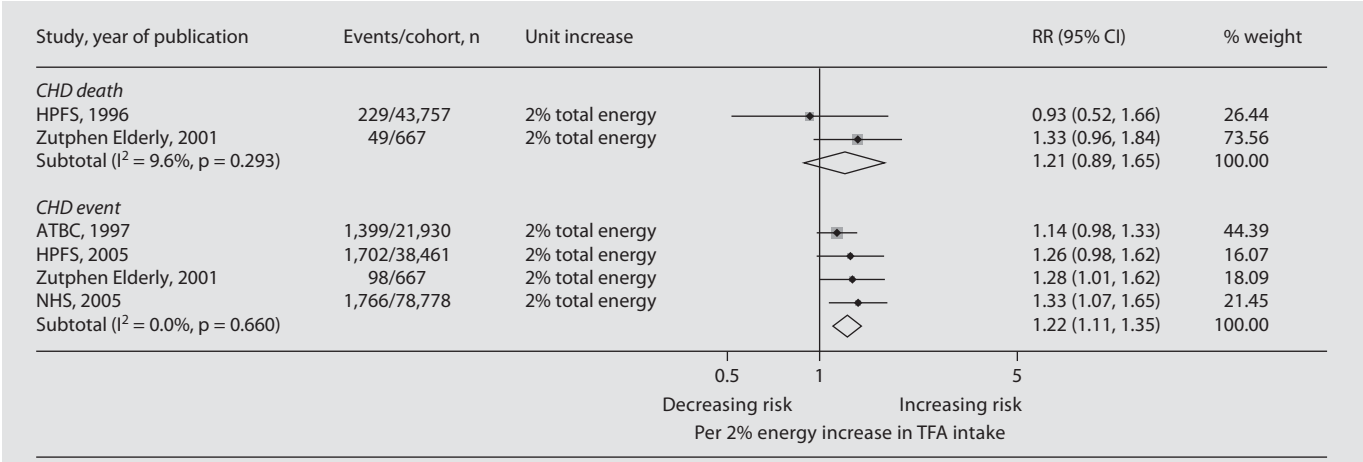
Intake of PUFA was strongly significantly associated with CHD mortality, with a RR of 1.25 (95% CI 1.06–1.47, p = 0.009) for the highest compared with the lowest category (fig. 12). Conversely, high compared with low PUFA intake was not associated with CHD events (RR 0.97, 95% CI 0.74–1.27, p = 0.825, for high compared with low category). A 5% incremental increase in PUFA intake was associated with a significantly lower risk of CHD events (RR 0.84, 95% CI 0.70–1.00, p = 0.049), but not with CHD mortality (p = 0.669; fig. 14). For the cohort studies included in the meta-analysis, mean or median PUFA varied from 3 to 4% TE in the lowest category to 6 to 10% TE in the highest category (table 3). Overall, the mean or median PUFA intake in all cohort studies varied from 3 to 7% TE (online suppl. table 13).

The association between linoleic acid intake and risk of CHD was reported in the ATBC cohort [Pietinen et al., 1997], the Health Professionals Follow-up Study [Ascherio et al., 1996] and the EUROASPIRE study [Erkkila et al., 2003]. The results mirrored those of total PUFA; intake of linoleic acid was significantly associated with CHD mortality for those in the highest category compared with the lowest category of linoleic intake (1.25, 95% CI 1.02–1.52, p = 0.032). Alternatively, linoleic acid intake was not associated with CHD events (RR 1.05, 95% CI 0.92–1.20, p = 0.474, for highest vs. lowest category; fig. 15).

Intake of α-linolenic acid was not associated with CHD death (RR 0.84, 95% CI 0.53–1.31, p = 0.439) or CHD events (RR 1.05, 95% CI 0.78–1.42, p = 0.730) for those in the highest compared with the lowest category of intake (fig. 16). Mean α-linolenic acid intake varied from 0.7 to 0.9 g/day in the lowest category to 1.4 to 2.5 g/day in the highest category (online suppl. table 13). In the Zutphen cohort, α-linolenic acid intake in the lowest category was 0.4% TE and in the highest category 0.67% TE.

Meta-Analysis of Cohort Studies of n–3 LCPUFA and CHD

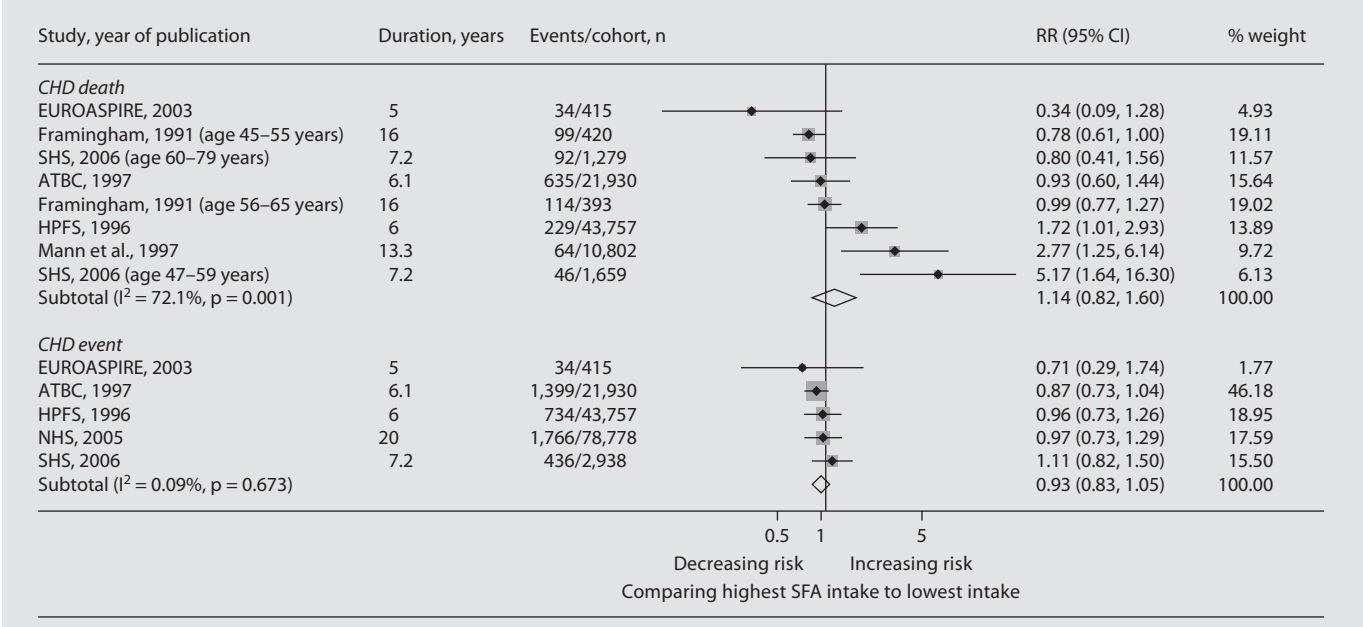
For cohort studies included in the meta-analysis of n–3 LCPUFA and CHD there were about 5,361 CHD deaths amongst the 256,000 participants during approximately 4 million person-years of follow-up. CHD mortality rates ranged from approximately 12 to 1,100 deaths per 100,000 person years. The longest period of follow-up was 40 years and the shortest was 5 years. The studies were conducted in North American and European countries with the exception of 3 studies in Japan. Men accounted for more than 80% of the person-years of follow-up. The age at recruitment varied from 40 to 65 years (online suppl. table 16).



p = 0.227 for CHD death subtotal; p < 0.001 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996; Mozaffarian et al., 2005]; NHS = Nurses' Health Study [Oh et al., 2005]; Zutphen Elderly = Zutphen Elderly Study [Oomen et al., 2001]. Refer to online suppl. tables 1 and 6 for full study details.

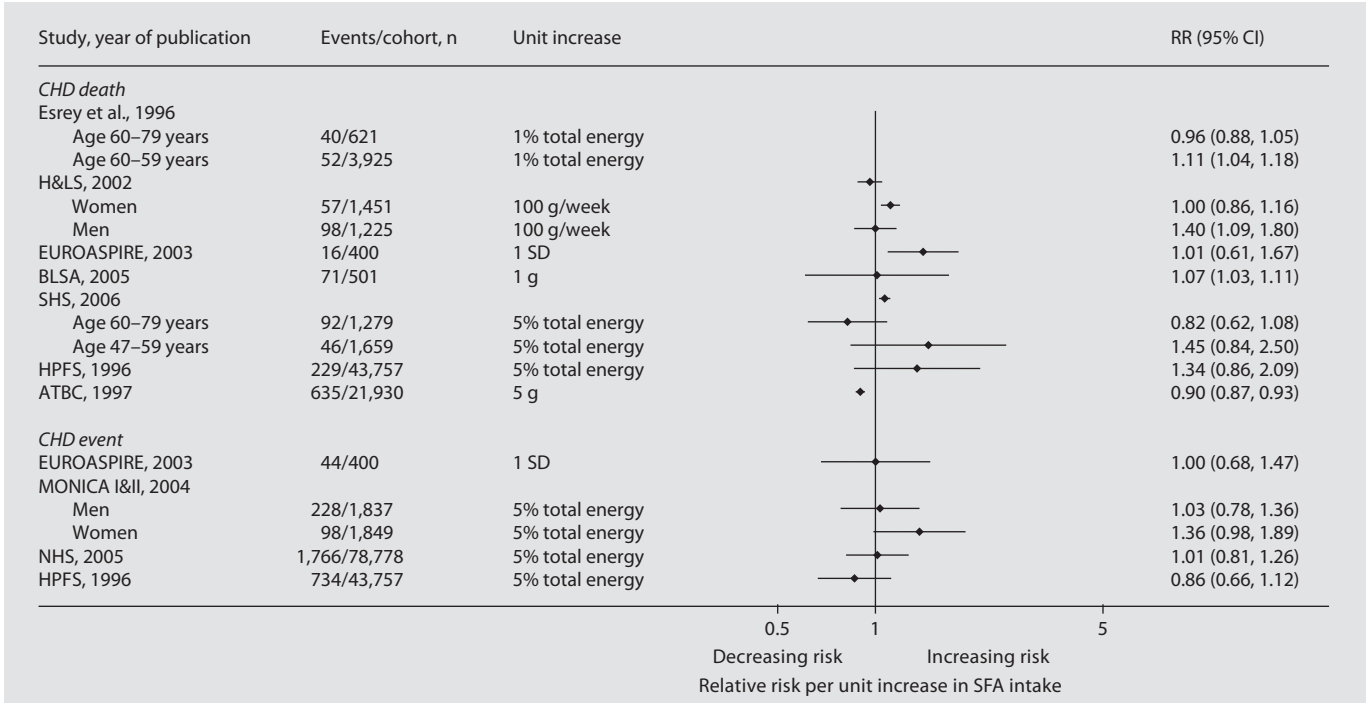
Fig. 5. RR of CHD for a 2% energy increase in TFA.



p = 0.431 for CHD death subtotal; p = 0.269 for CHD event subtotal. The relative risks correspond to comparisons of the highest SFA fat intakes with the lowest intakes, except the Framingham Study, which compared the sample mean SFA intakes with the National Cholesterol Education Program Recommendations. The EUROASPIRE relative risks correspond to comparisons of the highest cholesterol ester SFA fatty acid with the lowest cholesterol ester SFA fatty acid concentrations (mol%). The relative risks are the fully adjusted, multivariate results for each study.

Framingham = Framingham Study [Posner et al., 1991]; SHS = Strong Heart Study [Xu et al., 2006]; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; NHS = Nurses' Health Study [Oh et al., 2005]; EUROASPIRE, 2003 = Erkkila et al. [2003]. Refer to online suppl. tables 1 and 8 for full study details.

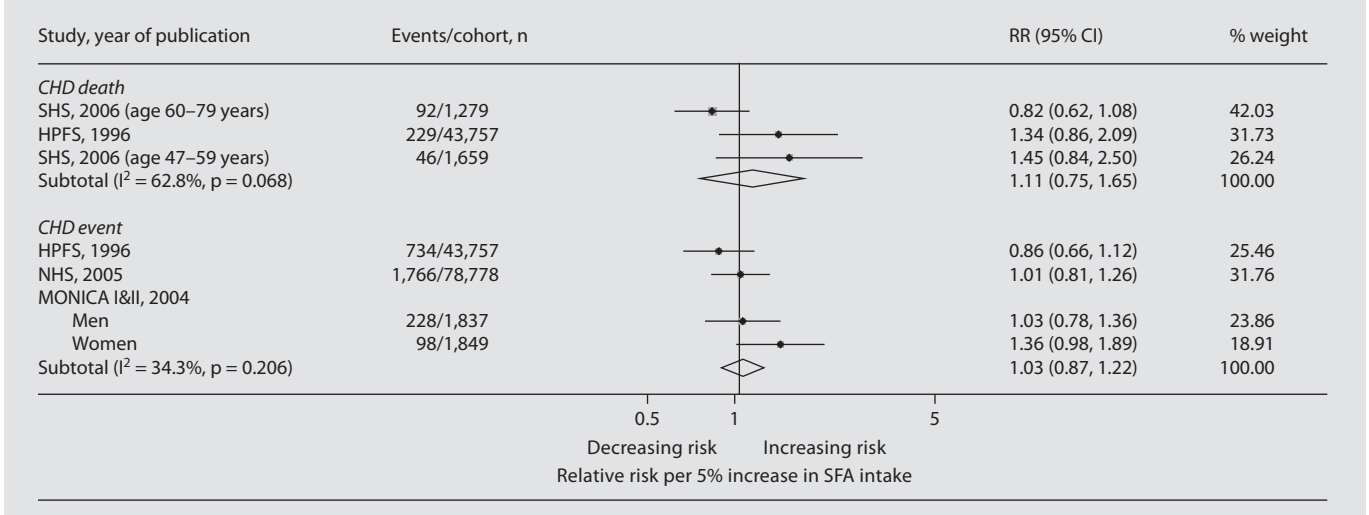
Fig. 6. Meta-analysis of prospective cohorts for saturated fat intake and CHD.



The relative risks are the fully adjusted, multivariate results for each study.

ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; BLSA = Baltimore Longitudinal Study of Aging [Tucker et al., 2005]; H&LS = Health and Lifestyle Survey [Boniface and Tefft, 2002]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; SHS = Strong Heart Study [Xu et al., 2006]; MONICA I&II = Jakobsen et al. [2004]; NHS = Nurses' Health Study [Oh et al., 2005]; EUROASPIRE, 2003 = Erkkila et al. [2003]. Refer to online suppl. tables 1 and 9 for full study details.

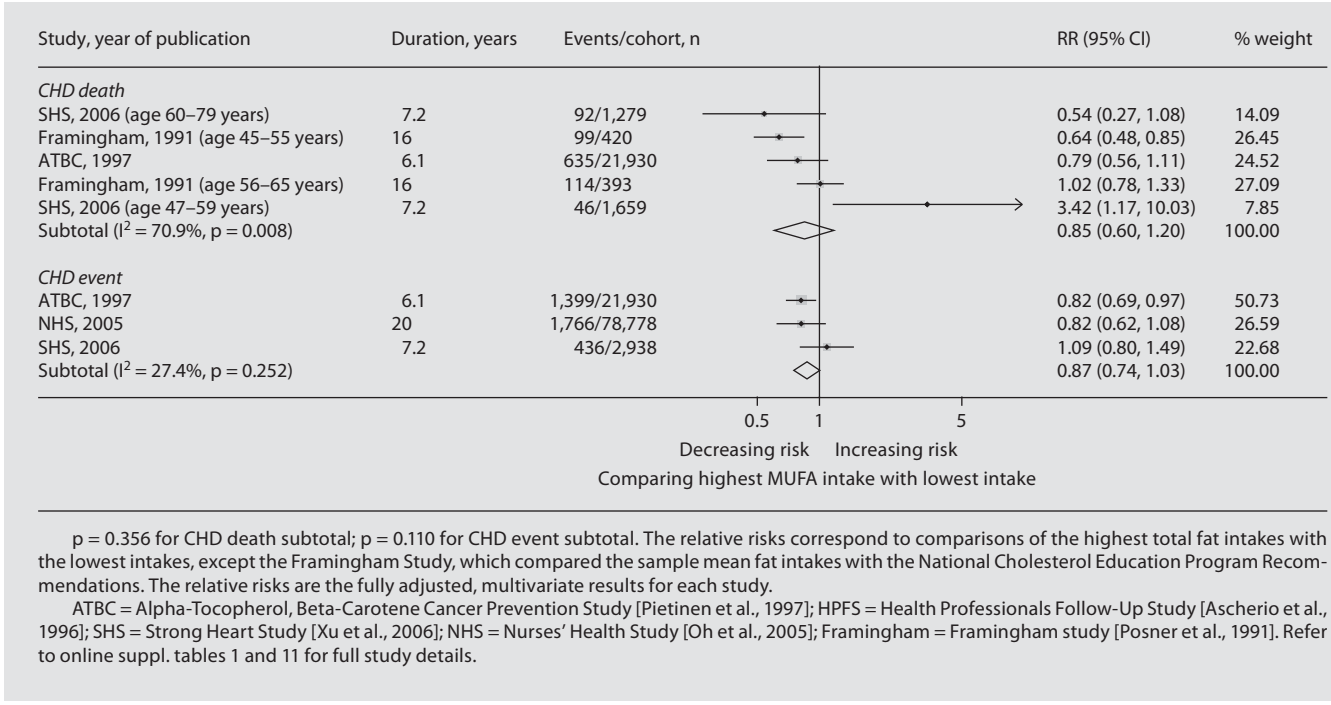
Fig. 7. RR of CHD per unit increase in saturated fat intake.



p = 0.593 for CHD death subtotal; p = 0.723 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; SHS = Strong Heart Study [Xu et al., 2006]; MONICA I&II [Jakobson et al., 2004]; NHS = Nurses' Health Study [Oh et al., 2005]. Refer to online suppl. tables 1 and 9 for full study details.

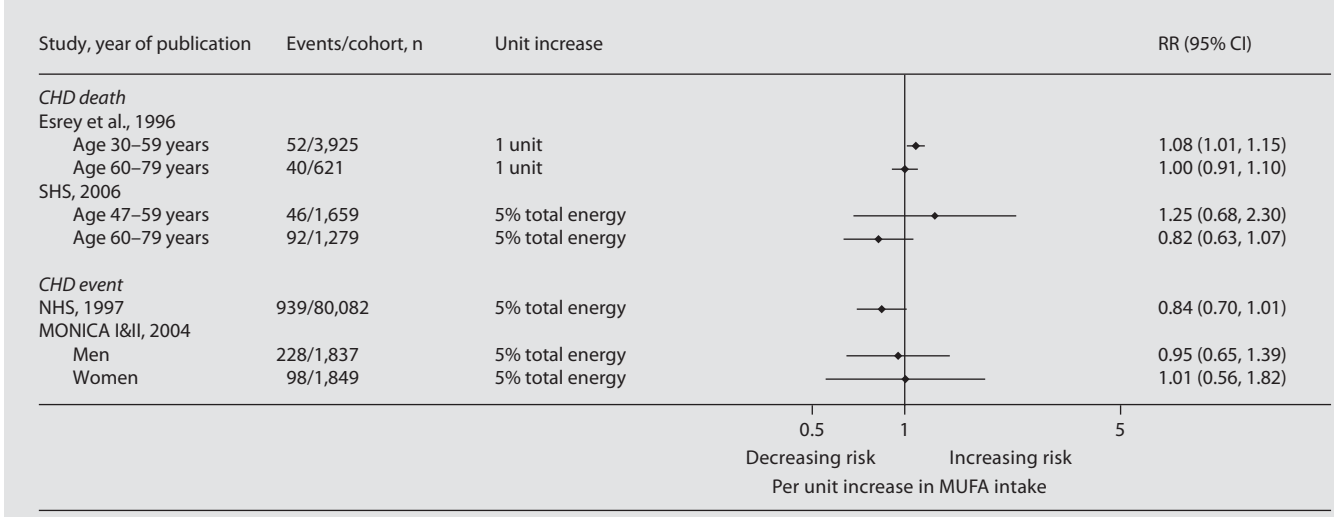
Fig. 8. Meta-analysis of CHD risk per each 5% of energy increase in saturated fat intake.



p = 0.356 for CHD death subtotal; p = 0.110 for CHD event subtotal. The relative risks correspond to comparisons of the highest total fat intakes with the lowest intakes, except the Framingham Study, which compared the sample mean fat intakes with the National Cholesterol Education Program Recommendations. The relative risks are the fully adjusted, multivariate results for each study.

ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; SHS = Strong Heart Study [Xu et al., 2006]; NHS = Nurses' Health Study [Oh et al., 2005]; Framingham = Framingham study [Posner et al., 1991]. Refer to online suppl. tables 1 and 11 for full study details.

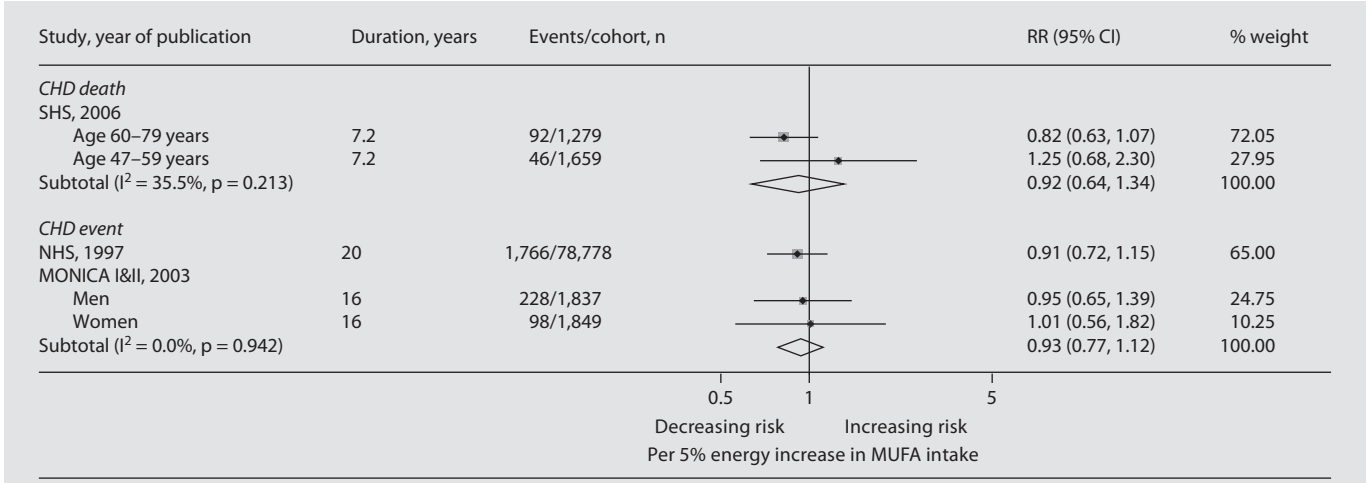
Fig. 9. Meta-analysis of prospective cohorts for MUFA intake and CHD.



The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; MONICA I&II = Jakobsen et al. [2004]; NHS = Nurses' Health Study [Hu et al., 1997]. Refer to online suppl. tables 1 and 12 for full study details.

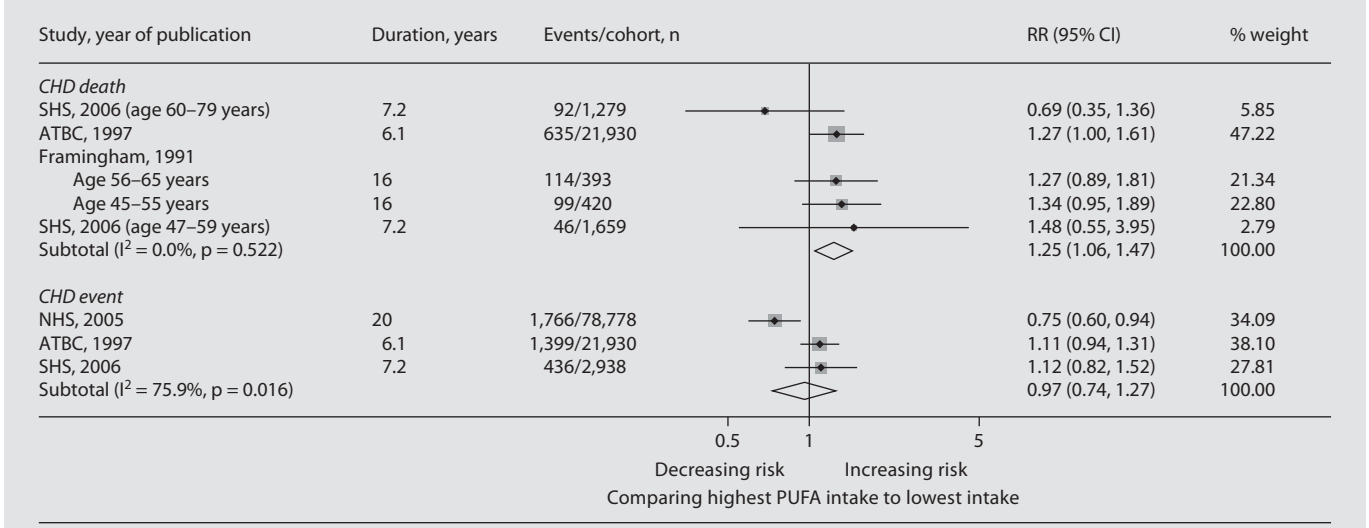
Fig. 10. RR of CHD per unit increase in MUFA intake.



p = 0.670 for CHD death subtotal; p = 0.449 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; MONICA I&II = Jakobsen et al., [2004]; NHS = Nurses' Health Study [Hu et al., 1997]. Refer to online suppl. tables 1 and 12 for full study details.

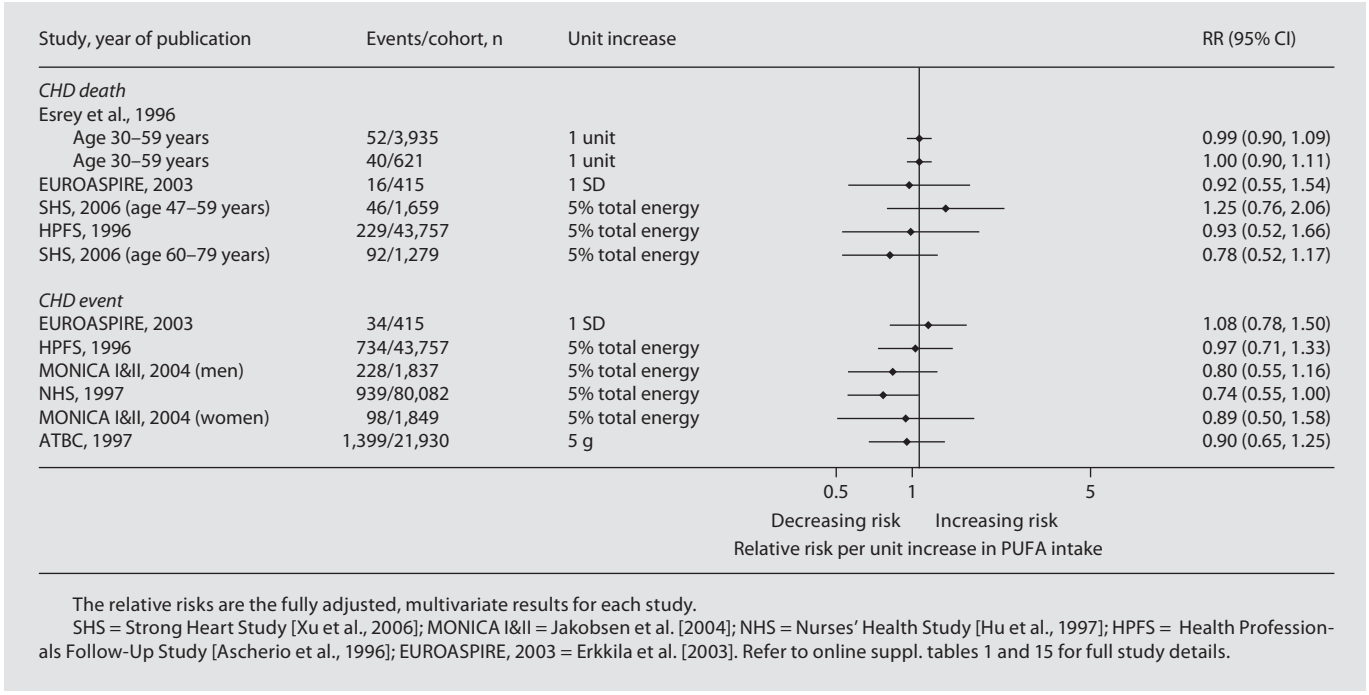
Fig. 11. RR of CHD per 5% energy intake of MUFA intake.



p = 0.009 for CHD death subtotal; p = 0.825 for CHD event subtotal. The relative risks correspond to comparisons of the highest PUFA intake with the lowest intakes, except the Framingham Study, which compared the sample mean fat intakes with the National Cholesterol Education Program Recommendations and risk of CHD. The relative risks are the fully adjusted, multivariate results for each study.

Framingham = Framingham Study [Posner et al., 1991]; SHS = Strong Heart Study [Xu et al., 2006]; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; NHS = Nurses' Health Study [Oh et al., 2005]. Refer to online suppl. tables 1 and 14 for full study details.

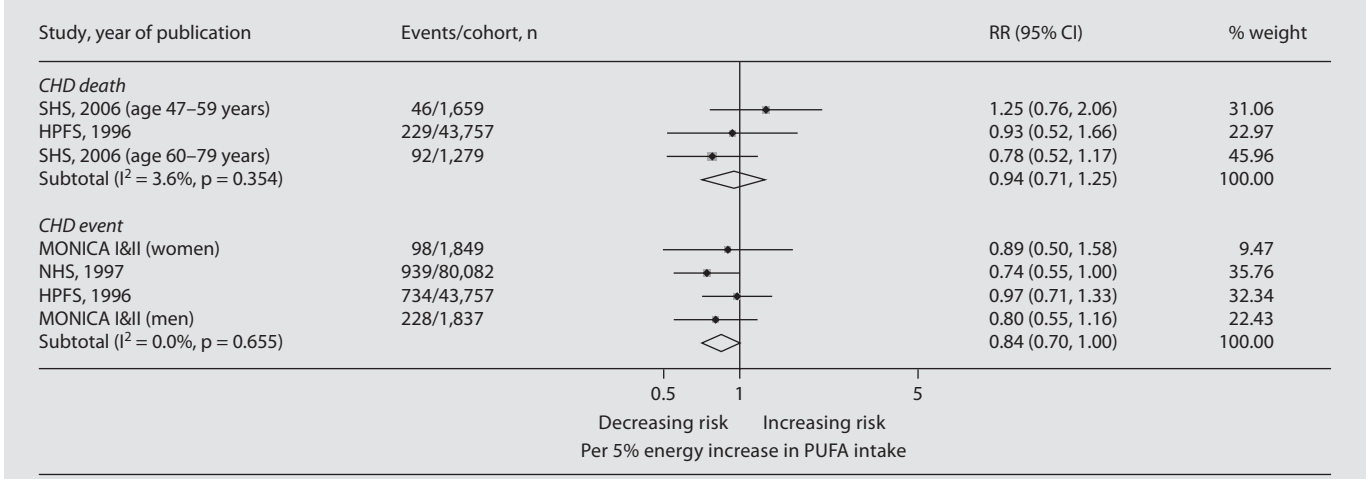
Fig. 12. Meta-analysis of prospective cohorts for PUFA intake and CHD.



The relative risks are the fully adjusted, multivariate results for each study.

SHS = Strong Heart Study [Xu et al., 2006]; MONICA I&II = Jakobsen et al. [2004]; NHS = Nurses' Health Study [Hu et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; EUROASPIRE, 2003 = Erkkila et al. [2003]. Refer to online suppl. tables 1 and 15 for full study details.

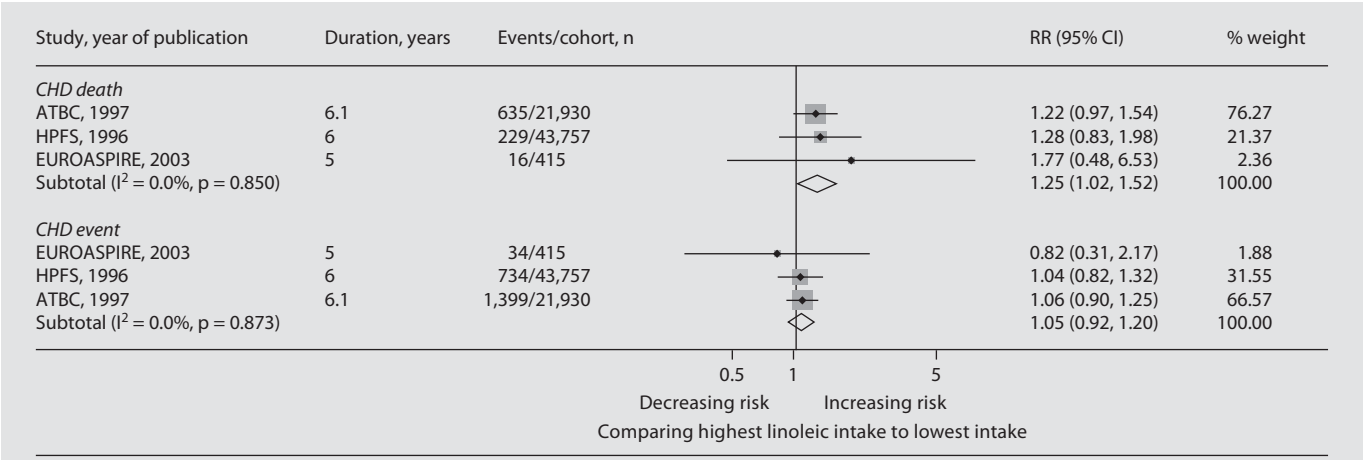
Fig. 13. RR of CHD per unit increase in PUFA intake.



p = 0.669 for CHD death subtotal; p = 0.049 for CHD event subtotal. The relative risks are the fully adjusted, multivariate results for each study.

NHS = Nurses' Health Study [Hu et al., 1997]; MONICA I&II = Jakobsen et al. [2004]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; SHS = Strong Heart Study [Xu et al., 2006]. Refer to online suppl. tables 1 and 15 for full study details.

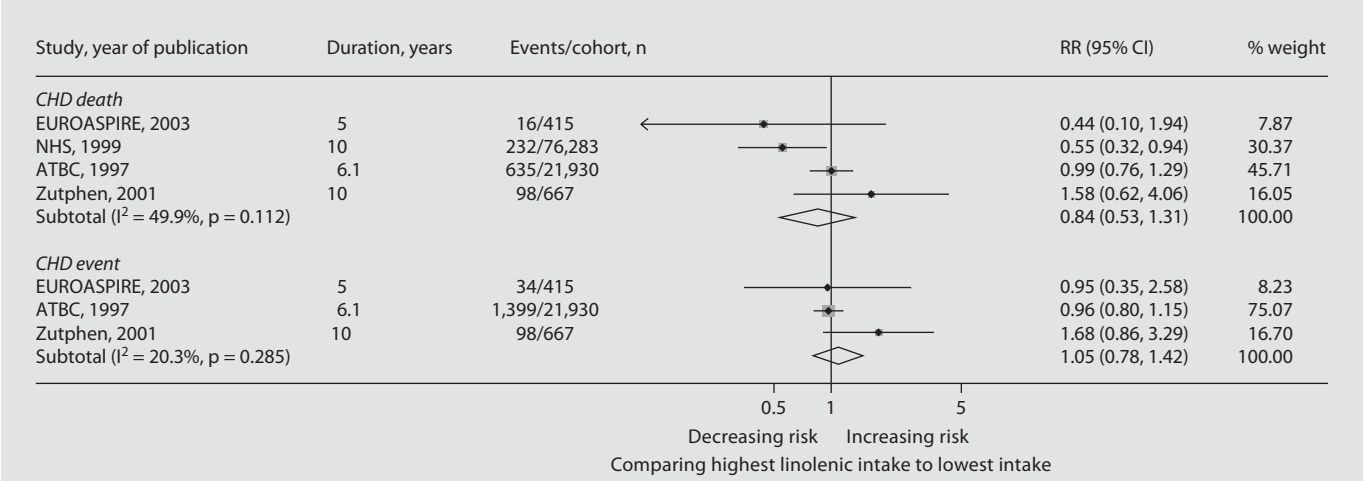
Fig. 14. RR of CHD per 5% energy increase in PUFA intake.



p = 0.032 for CHD death subtotal; p = 0.474 for CHD event subtotal. The relative risks correspond to comparisons of the highest linoleic fat intake with the lowest intake, except the EUROASPIRE Study, which compared the highest cholesterol ester linoleic concentrations with the lowest concentrations (mol%).

ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; HPFS = Health Professionals Follow-Up Study [Ascherio et al., 1996]; EUROASPIRE = Erkkila et al. [2003]. Refer to online suppl. tables 1 and 14 for full study details.

Fig. 15. Meta-analysis of prospective cohorts for linoleic fatty acid intake and CHD.



p = 0.439 for CHD death subtotal; p = 0.730 for CHD event subtotal. The relative risks correspond to comparisons of the highest α-linolenic fat intake with the lowest intake, except the EUROASPIRE Study, which compared the highest cholesterol ester α-linolenic concentrations with the lowest concentrations (mol%).

NHS = Nurses' Health Study [Hu et al., 1999]; Zutphen = Zutphen Elderly Study [Oomen et al., 2001]; EUROASPIRE = Erkkila et al. [2003]; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]. Refer to online suppl. tables 1 and 14 for full study details.

Fig. 16. Meta-analysis of prospective cohorts for α-linolenic fatty acid intake and CHD.

Intake of n–3 LCPUFA or fish consumption were strongly associated with CHD mortality (RR 0.82, 95% CI 0.71–0.94, p = 0.006) for the highest compared with the lowest category (fig. 17). Publication bias was discounted based on rejection of funnel plot asymmetry using the test developed by Begg and Mazumdar [1994]. Intake of n–3 LCPUFA was not associated with decreased risk of CHD events (RR 0.87, 95% CI 0.71–1.06, p = 0.157), non-fatal CHD (RR 0.81, 95% CI 0.59–1.10, p = 0.177) and total myocardial infarction (MI) (RR 0.79, 95% CI 0.53–1.17, p = 0.235), for those in the highest category compared with the lowest category (fig. 18). Moreover, n–3 LCPUFA intake or fish consumption were not associated with sudden cardiac death (RR 0.62, 95% CI 0.32–1.20, p = 0.157, for highest vs. lowest category; fig. 17). For the cohort studies included in the meta-analysis, mean or median n–3 LCPUFA intake varied from 0 to 0.3 g/day in the lowest category to 0.37 to 2.5 g/day in the highest category. The mean or median fish consumption varied from 0 to 23 g/day in the lowest category to 22 to 180 g/day in the highest category (table 3).

Randomised Controlled Trials of Dietary Fat and CHD

Meta-Analysis of Randomised Controlled Trials of Fat-Modified Diets and CHD

The controlled trials included in the present meta-analysis of fat-modified diets and CHD risk were classified into 2 categories: (1) low-fat, and (2) altered P/S ratio. There were 331 CHD deaths in the 2 low-fat trials. The duration of treatment varied from 3 to 8.1 years. There were 284 CHD deaths in the 5 P/S trials. The duration of treatment varied from 2 to 5 years. The studies were conducted in North American and European countries. With the exception of the Womens' Health Initiative [Howard et al., 2006] the participants in the trials were men. The mean age of participants varied from 40 to 65 years. Selected characteristics of the individual trials are provided in online supplementary table 18.

The results of the meta-analyses showed that the RR of fatal CHD was not reduced by either the low-fat diets (1.00, 95% CI 0.80–1.24, p = 0.317) or the high P/S diets (0.84, 95% CI 0.62–1.12, p = 0.867), respectively (fig. 20; 21). There was no evidence of heterogeneity between the trials. High P/S diets reduced the risk of total CHD events (RR 0.83, 95% CI 0.69–1.00, p = 0.050), whereas the low-fat diets did not affect CHD events (RR 0.93, 95% CI 0.84–1.04, p = 0.072; fig. 20; 21). There was evidence of heterogeneity between the low-fat trials but not between the P/S trials. Including results from the MRFIT trial – a trial in which the intervention was not restricted to a P/S diet – did not appreciably alter the pooled RR for CHD events, but the result was no longer statistically significant (RR 0.88, 95% CI 0.77–1.01, p = 0.061).

Restricting the meta-analysis to intervention trials of P/S diets in which mean serum cholesterol concentration was significantly lower in the treatment group showed that the risk of fatal CHD was significantly reduced by the P/S diets (RR 0.52, 95% CI 0.30–0.87, p = 0.014). Similarly, high P/S diets reduced the risk of CHD events (RR 0.68, 95% CI 0.49–0.94, p = 0.020; fig. 22).

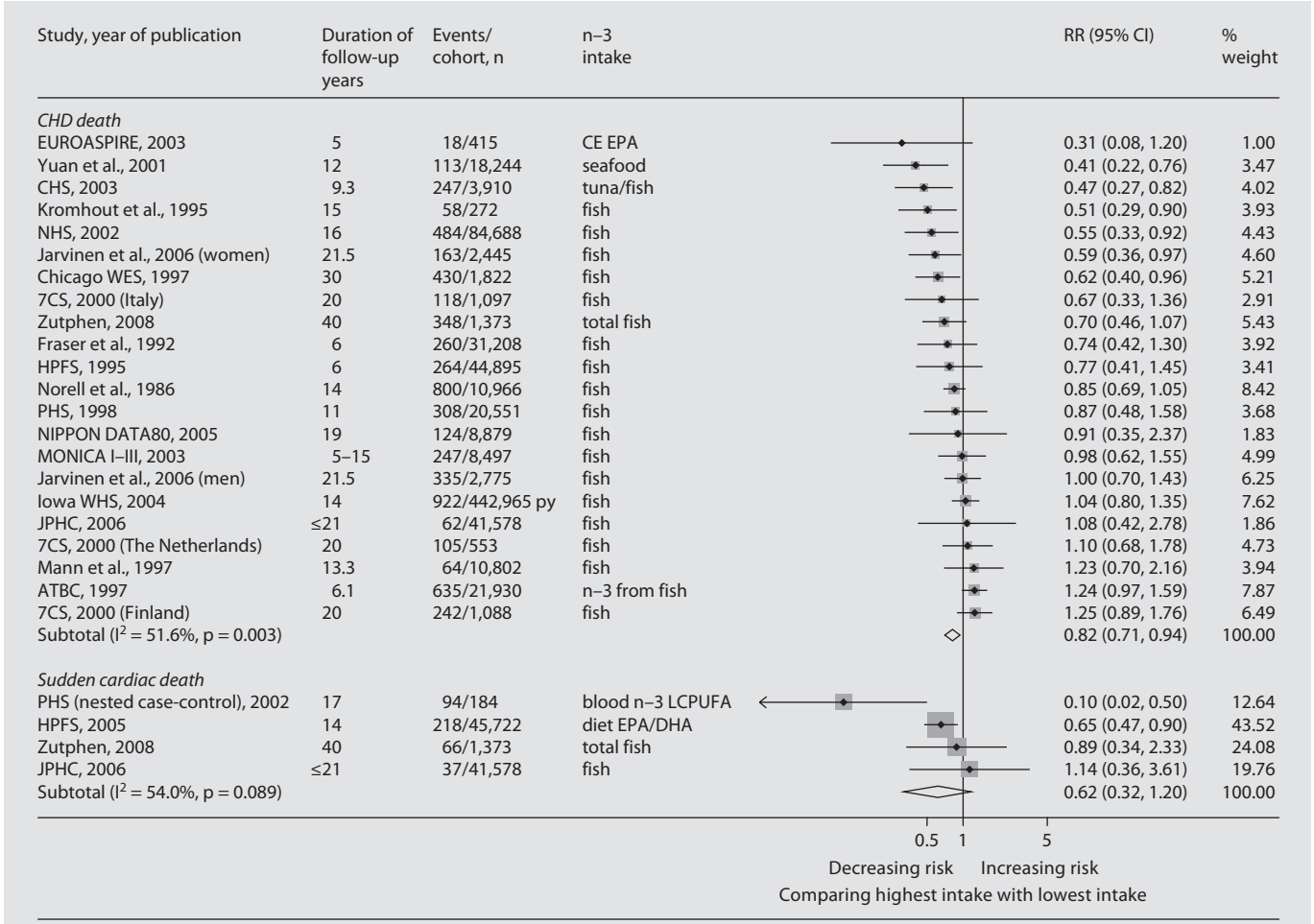
The low-fat diet did not alter the RR of all cause mortality during follow-up (RR 0.98, 95% CI 0.90–1.06, p = 0.590), neither did the P/S diet (RR 0.88, 95% CI 0.76–1.02, p = 0.083; fig. 19).

The Women's Health Initiative [Howard et al., 2006] involved 48,000 postmenopausal women aged 50–79 years, that were randomised to a low-fat (20% TE) high-fruit and vegetable diet or comparison group. The mean duration of follow-up was 8.1 years and total fat intake was 8.2% TE lower in the treatment than comparison group at 6 years. The P/S ratios of the diets in the treatment and comparison groups were not different. Serum and total cholesterol concentrations at 3 years were significantly but marginally lower in the low-fat diet, by 1.5 and 2.7%, respectively. Weight was 1.29 kg lower in the diet group at 3 years. For all participants, the diet had no significant effect on CHD death (RR 1.02, 95% CI 0.84–1.25) or nonfatal MI and CHD death (RR 0.98, 95% CI 0.88–1.09). Similarly, for women with no history of cardiovascular disease the low-fat diet had no effect on CHD death (RR 1.01, 95% CI 0.81–1.27) or nonfatal MI and CHD death (RR 0.93, 95% CI 0.83–1.05). The results suggest that a low-fat diet in postmenopausal women does not reduce CHD risk, but lacked the power to refute this hypothesis.

The Lyon Diet and Heart Study [de Lorgeril et al., 1994] dietary intervention was a quasi Mediterranean diet which could not be classified as either a low-fat or altered P/S intervention. The intervention led to large and significant reductions in the risk of CHD death and CHD events during the 2 years of follow-up, by 65 and 70%, respectively; yet the magnitude of differences in diet composition, established risk factors for CHD, or plasma fatty acids between the treatment and comparison groups were very small, in most cases they were not significant.

Meta-Analysis of Randomised Controlled Trials of n–3 LCPUFA or Fish and CHD

The meta-analysis included results from 16 randomised controlled trials (fig. 25; 26). We include the results from both DART trials [Burr et al., 1989, 2003] but excluded re-



p = 0.006 for CHD death subtotal; p = 0.157 for sudden cardiac death.

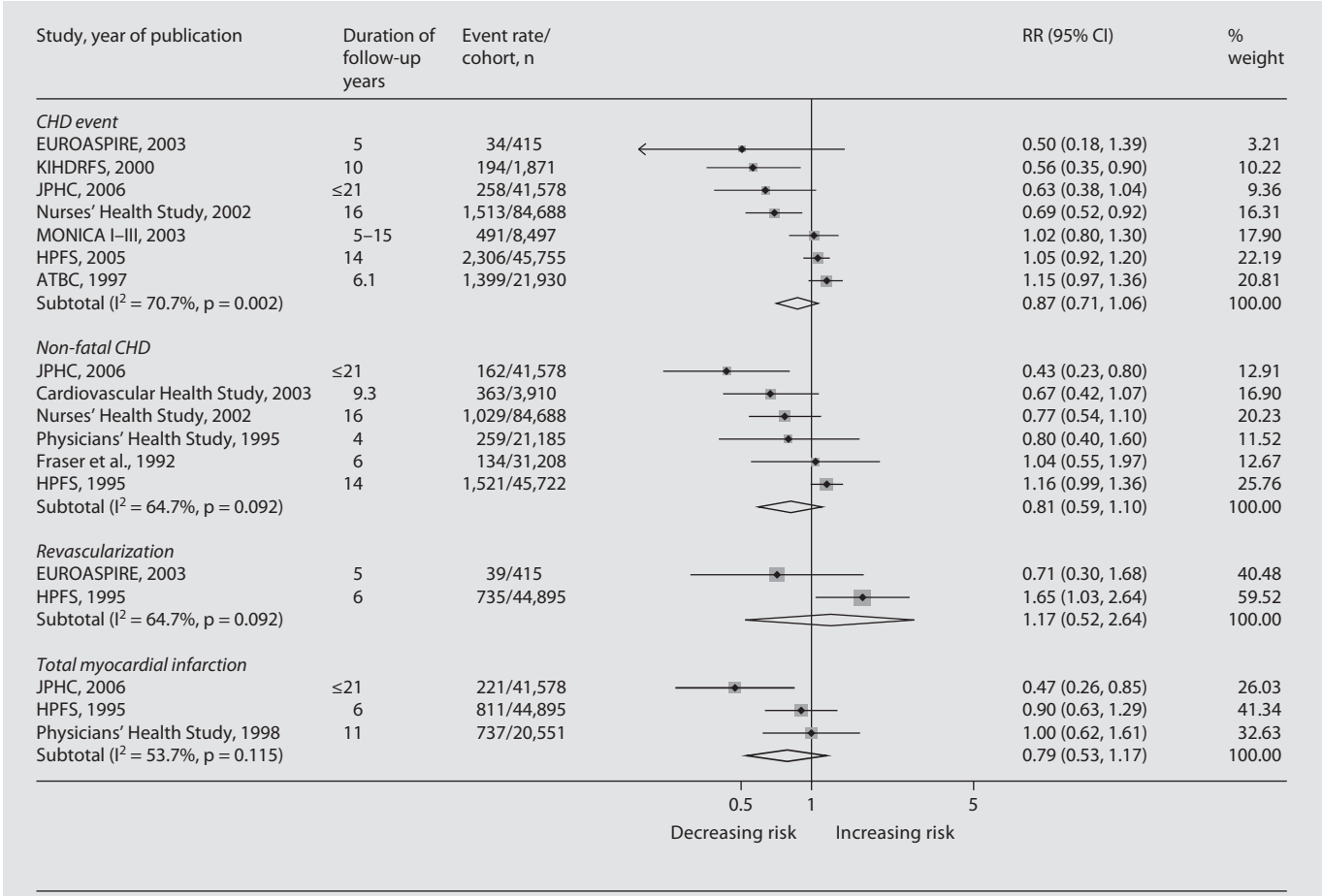
CE = Cholesterol ester; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; py = person-years.

EUROASPIRE = Erkkila et al. [2003]; CHS = Cardiovascular Health Study [Mozaffarian et al., 2003]; NHS = Nurses' Health Study [Hu et al., 2002]; Chicago WES = Chicago Western Electric Study [Daviglus et al., 1997]; 7CS = Seven Countries Study [Oomen et al., 2000]; HPFS = Health Professionals' Follow-Up Study [Ascherio et al., 1995]; PHS = Physicians' Health Study [Albert et al., 1998, 2002]; NIPPON DATA80 = Nakamura et al. [2005]; Iowa WHS = Iowa Women's Health Study [Folsom and Demissie, 2004]; JPHC = Japan Public Health Center-Based Study Cohort I [Iso et al., 2006]; ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; Zutphen, 2008 = Zutphen Study, 2008 [Streppel et al., 2008]; MONICA I–III [Osler et al., 2003]. Refer to online suppl. tables 16 and 17 for full study details.

Fig. 17. Meta-analysis of prospective cohorts for fish or n–3 LCPUFA intake and fatal CHD.

sults from the trial by Singh et al. [Expression of concern, 2005]. There were about 1,300 CHD deaths amongst 37,000 participants during 140,000 person-years of follow-up. Overall CHD mortality rates across the trials ranged from approximately 70 to over 4,000 per 100,000 person-years. Trial duration varied from 6 months to 9 years. The average duration of trials in which CHD death was monitored was 2 years. After excluding the JELIS trial [Yokoyama et al., 2007], men accounted for about 90% of the person-years of follow-up. In the JELIS trial, women made up 70% of the participant population and only 60 CHD deaths occurred during 5 years of follow-up amongst 18,645 patients. The most common form of treatment was fish oil supplements, though a few trials involved increased fish consumption [Burr et al., 1989, 2003]. Total intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ranged from 0.5–6.9 g/day (online suppl. table 18).

The results of the meta-analysis showed that the RR of CHD death was not significantly reduced by n–3 LCPUFA treatment, 0.88 (95% CI 0.76–1.01, p = 0.061;



p = 0.157 for CHD event; p = 0.177 for non-fatal CHD subtotal; p = 0.700 for revascularization; p = 0.235 for total myocardial infarction subtotal. The relative risks correspond to comparisons of the highest intake of fish or marine n–3, or blood biomarker concentrations of EPA or EPA and DHA, with the lowest intakes or concentrations, as indicated on the forest plot. The relative risks are the fully adjusted, multivariate results for each study.

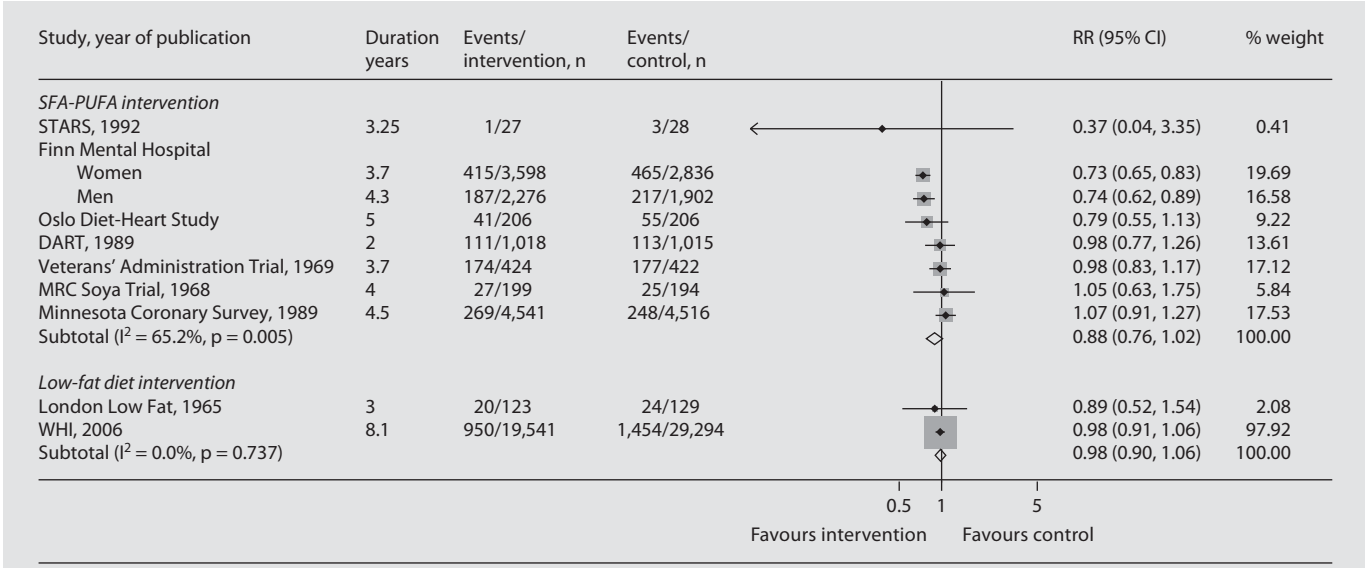
CE = Cholesterol ester; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; py = person-years; n.n. = not noted.

EUROASPIRE = Erkkila et al. [2003]; CHS = Cardiovascular Health Study [Mozaffarian et al., 2003]; NHS = Nurses' Health Study [Hu et al., 2002]; Chicago WES = Chicago Western Electric Study [Daviglus et al., 1997]; HPFS = Health Professionals' Follow-Up Study [Ascherio et al., 1995; Mozaffarian et al., 2005]; PHS = Physicians' Health Study [Albert et al., 1998]; JPHC = Japan Public Health Center-Based Study Cohort I [Iso et al., 2006]; ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study [Pietinen et al., 1997]; KIHDRFS = Kuopio Ischemic Heart Disease Risk Factor Study [Rissanen et al., 2000]; MONICA I–III [Osler et al., 2003]. Refer to online suppl. tables 16 and 17 for full study details.

Fig. 18. Meta-analysis of prospective cohorts for fish or n–3 LCPUFA fat intake and non-fatal or total CHD.

fig. 25). Publication bias was discounted based on rejection of funnel plot asymmetry using the test developed by Begg and Mazumdar [1994]. The risks of fatal MI (RR 0.92, 95% CI 0.65–1.29, p = 0.626) and sudden cardiac death (RR 1.02, 95% CI 0.78–1.33, p = 0.889) were also not decreased by treatment. However, the RR of CHD events was significantly lowered with n–3 LCPUFA treatment (0.89, 95% CI 0.82–0.98, p = 0.012). Non-fatal CHD outcomes such as revascularization events (RR 0.94, 95% CI 0.86–1.04, p = 0.211), non-fatal MI (RR 1.03, 95% CI 0.77–1.37, p = 0.864), and angina (RR 0.89, 95% CI 0.75–1.04, p = 0.149) were not significantly reduced by n–3 LCPUFA treatment (fig. 26).

Meta-analysis of study results after exclusion of the DART II trial considerably altered the summary estimates, such that n–3 LCPUFA significantly reduced the risk of fatal CHD (RR 0.81, 95% CI 0.71–0.92, p = 0.001), fatal MI (RR 0.74, 95% CI 0.57–0.96, p = 0.025), and CHD



p = 0.083 for SFA-PUFA intervention subtotal; p = 0.590 for low-fat diet intervention.

STARS = Watts et al. [1992]; Oslo Diet-Heart Study = Leren [1970]; DART = Burr et al. [1989]; MRC Soya Trial = Medical Research Council, [1968]; Minnesota Coronary Survey = Frantz et al. [1989]; London Low Fat = [Research Committee, 1965]; WHI = Howard et al. [2006]; Finn Mental Hospital (both women and men) = Miettinen et al. [1972]; Veterans' Administration Trial = Dayton and Pearce [1969]. Refer to online suppl. table 18 for full study details.

Fig. 19. Meta-analysis of fat modification trials and total mortality.

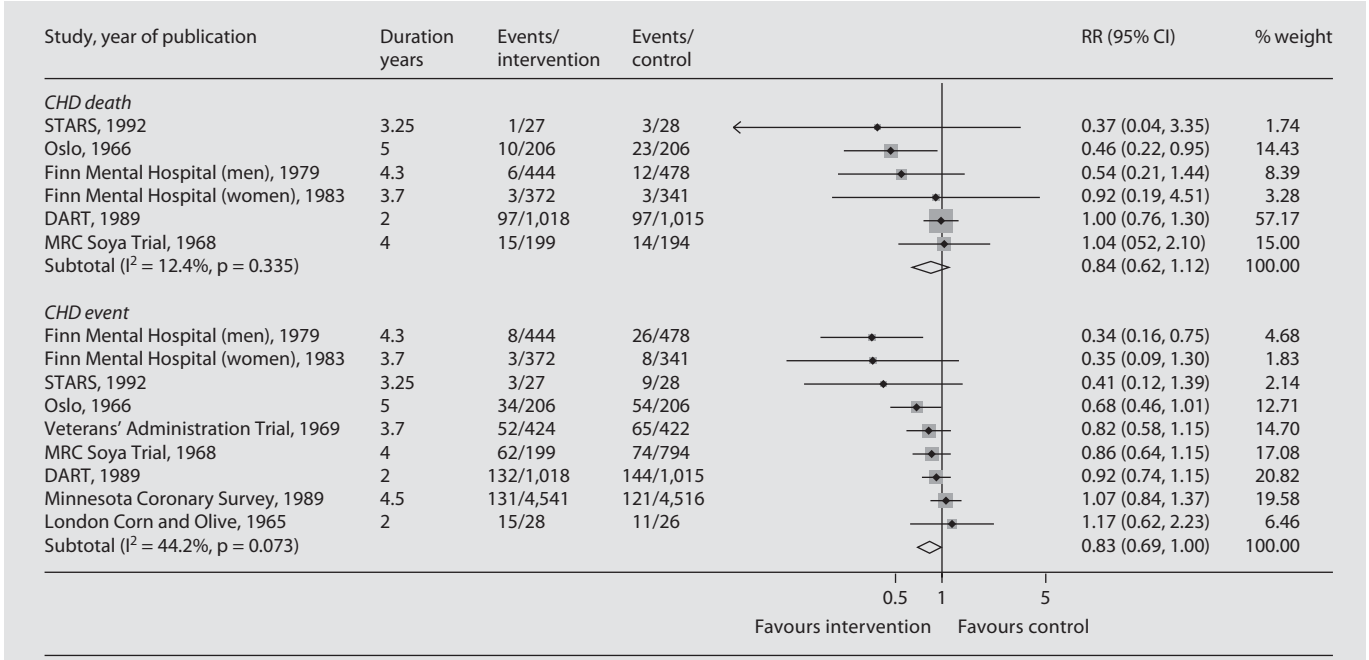
events (RR 0.89, 95% CI 0.82–0.98, p = 0.012; fig. 27). The summary estimate of RR of sudden cardiac death was 0.89 (95% CI 0.72–1.09, p = 0.251).

The RR of all cause mortality during the follow-up periods of the trials was not significantly lower in participants taking n–3 LCPUFA (0.95, 95% CI 0.87–1.03, p = 0.225; fig. 23). Following exclusion of the DART II trial the RR of total mortality was 0.93 (95% CI 0.86–0.99, p = 0.027; fig. 24). Publication bias was discounted based on rejection of funnel plot asymmetry using the test developed by Begg and Mazumdar [1994].

The results of recent meta-analysis [Jenkins et al., 2008] of 3 randomised controlled (1- to 2-year duration) trials of fish oil supplementation in patients with implantable cardioverter defibrillators showed no effect of n–3 LCPUFA on the RR of defibrillator discharge (RR 0.93, 95% CI 0.70–1.24, p = 0.63).

Discussion

Differences between populations in the amount and type of fat consumed explain much of the variation in the incidence of cardiovascular diseases [Keys, 1980]. According to the classic 'diet-heart' hypothesis, high intake of SFAs and cholesterol and low intake of PUFAs increase serum cholesterol levels and risk of CHD. However, few within-population studies have been able to demonstrate consistent associations with any specific dietary lipids, with the exception of *trans* fats and n–3 fatty acids. The available evidence from cohort and randomised controlled trials is unsatisfactory and unreliable to make judgement about and substantiate the effects of dietary fat on risk of CHD. The null results of the observational studies of dietary lipids and CHD do not negate the importance of the underlying associations, but reflect the combined effects of limitations of dietary assessment methods, inadequate numbers of participants studied and the prolonged follow-up of individuals. Furthermore, the evidence from cohort studies of dietary intake of fats and CHD is mostly unreliable (with a few exceptions) because most studies have ignored the effects of measurement error and regression dilution bias. Few studies attempted to measure the within-person variability or reproducibility of the categorizations of dietary fat when assessing these associations. Hence, the null results are very likely to result from regression dilution bias and confounding of 1 nutrient by another. By contrast, CHD risk is moderately



p = 0.867 for CHD death subtotal; p = 0.050 for CHD event subtotal.

STARS = Watts et al. [1992]; Oslo = Leren [1970], 5-year results were used; DART = Burr et al. [1989]; MRC Soya Trial = Medical Research Council [1968]; Minnesota Coronary Survey = Frantz et al. [1989]; Finnish Mental Hospital (men) = Turpeinen [1979]; Finnish Mental Hospital (women) = Miettinen et al. [1983]; Veterans' Administration Trial = Dayton and Pearce [1969]; London Corn and Olive = Rose et al. [1965]. Refer to online suppl. table 18 for full study details.

Fig. 20. Meta-analysis of altered PUFA – SFA modified trials.

Table 4. Summary of the strength of evidence of dietary fat and CHD

Type of fat	Fatal CHD	CHD events
Total fat	C-NR	C-NR
TFA	P↑	C↑
SFA for CHO	P-NR	P-NR
MUFA for SFA		
PUFA for SFA	C↓	C↓
Linoleic		
α-linolenic		
n–3 LCPUFA	P↓	C↓

C↑ = Convincing increase risk; C↓ = convincing decrease risk; C-NR = convincing, no relation; P↑ = probable increase risk; P↓ = probable decrease risk; P-NR = probable no relation.

strongly related to dietary patterns, such as a vegetarian or Mediterranean diet, which are less influenced by misclassification. The null results probably reflect the unreliability of the evidence on dietary fats from cohort studies that differs markedly from the reliability of ecological studies or metabolic ward studies of diet and cholesterol.

One of the exceptions in the body of evidence from prospective cohort studies is n–3 LCPUFA intake or fish consumption and risk of fatal CHD. The evidence is comprehensive in number of studies, duration of follow-up, number of participants and CHD events, geographic location of study populations, homogeneity of association between trials and absence of evidence for publication bias. The observational evidence is convincing that a strong inverse association exists between n–3 LCPUFA or fish intake and risk of CHD. The evidence from randomised controlled trials is concordant, particularly when 2 trials with methodological concerns [Singh et al., 1997; Burr et al., 2003], are excluded from consideration, however, it rests almost entirely on the results from 2 trials (GISSI-P [GISSI-Prevenzione Investigators, 1999], and DART I [Burr et al., 1989]).

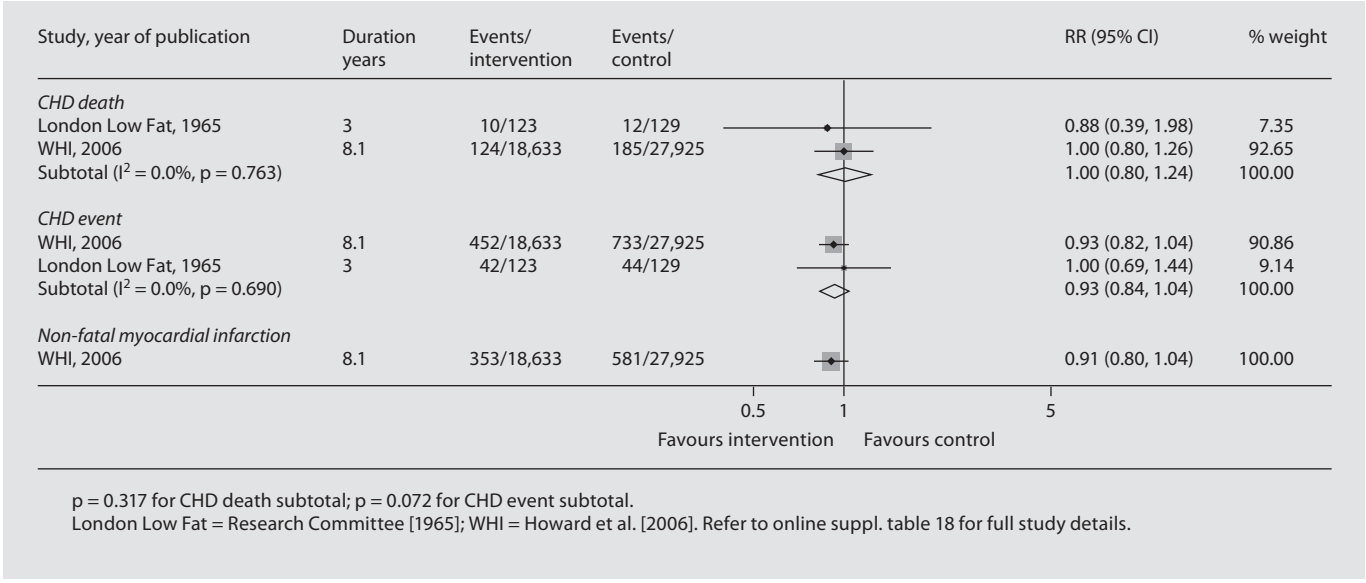


Fig. 21. Meta-analysis of low-fat trials and CHD event.

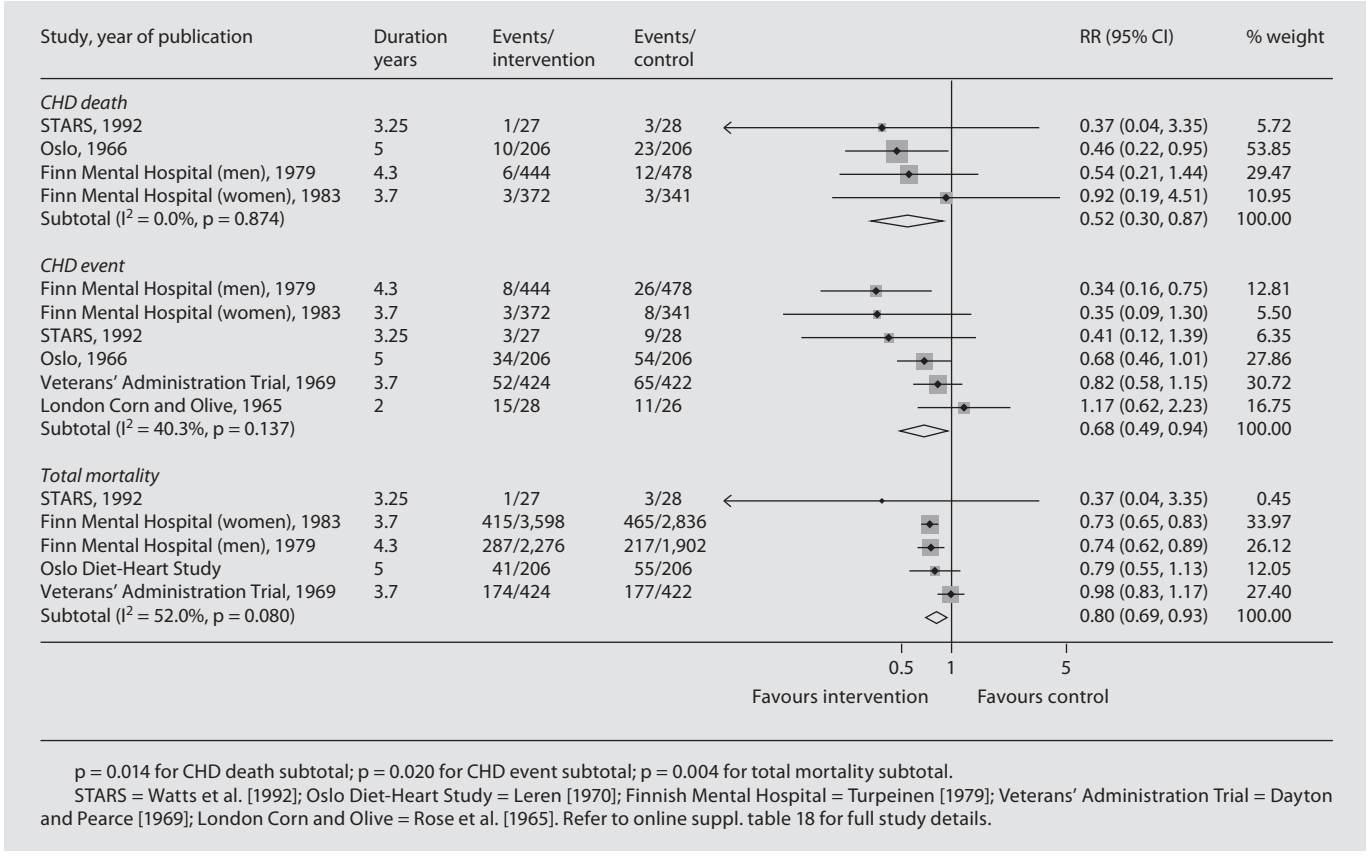
The observational evidence that TFA are independently associated with increased risk of CHD events is convincing, though based on a more limited body of evidence. The evidence of an association with fatal CHD is not as comprehensive. In view of the consistency and strength of the observational evidence, the absence of evidence from randomised controlled trials should not preclude a convincing judgement.

There is probably no direct relation between total fat intake and risk of CHD. The strongest evidence in support of this judgement comes from the Women's Health Initiative that showed that CHD risk was not reduced after 8 years of a low-fat diet. The observational evidence, summarised in the meta-analysis, showed no association between total fat intake and CHD risk, although there was heterogeneity between the study results.

Table 4 summarises the strength of evidence of a link between dietary fat and CHD.

The body of evidence from clinical trials of fat-modified diets – excluding n–3 LCPUFA and fish interventions – is limited. The 10 or so published trials are heterogenous in the nature of the dietary intervention and many of the trials have only a small number of CHD deaths or events; nevertheless, taken together, there were slightly more than 600 CHD deaths and 3,700 CHD events in the intervention trials. The heterogeneous nature of the interventions and lack of compliance may undermine the validity of the summary estimates of risk obtained through meta-analysis of the trial results, as does the small number of trials. Several limitations have been well described [Truswell, 2005] but the use of meta-analysis helps to provide consistent display of all the available evidence together with a summary measure of the overall effects.

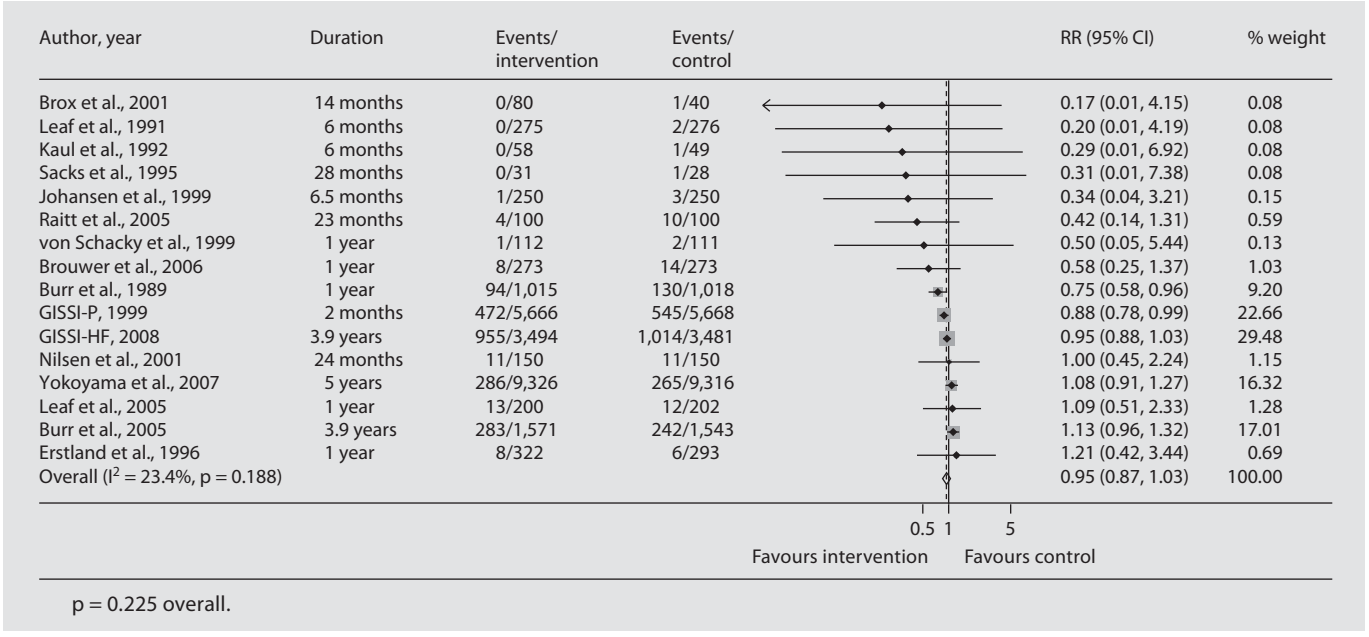
Clinical trials of fat-modified diets, in particular low-fat or high P/S diets, and coronary disease are rarely single factor interventions. Substitution of 1 type of fat for another or reducing total fat intake, invariably results in a range of food substitutions such that intake of other macro- and micronutrients is altered. Many of the early fat intervention trials of CHD required participants to follow a diet lower in cholesterol but with a higher P/S ratio – without a reduction in total fat intake. The results of trials of dietary advice differ from the more reliable evidence from metabolic ward studies. The results of metabolic ward studies [Hegsted et al., 1965; Keys et al., 1965] showed that change in serum cholesterol concentrations could be predicted based on the PUFA, SFA and cholesterol content of the diet. Furthermore, many trials of advice to modify dietary intake of fat have included 1 or more other elements of dietary and non-dietary advice; examples include advice to increase fibre intake, reduce meat consumption, reduce body weight, stop smoking, reduce salt intake, increase fruit and vegetable consumption, increase physical activity, or reduce alcohol consumption. The multifactorial nature of the dietary interventions and accompanying changes in dietary pat-



p = 0.014 for CHD death subtotal; p = 0.020 for CHD event subtotal; p = 0.004 for total mortality subtotal.

STARS = Watts et al. [1992]; Oslo Diet-Heart Study = Leren [1970]; Finnish Mental Hospital = Turpeinen [1979]; Veterans' Administration Trial = Dayton and Pearce [1969]; London Corn and Olive = Rose et al. [1965]. Refer to online suppl. table 18 for full study details.

Fig. 22. Meta-analysis of PUFA – SFA modified trials including studies showing change in serum cholesterol concentrations with intervention.



p = 0.225 overall.

Fig. 23. Meta-analysis of fish or n–3 LCPUFA trials and total mortality, including DART II.

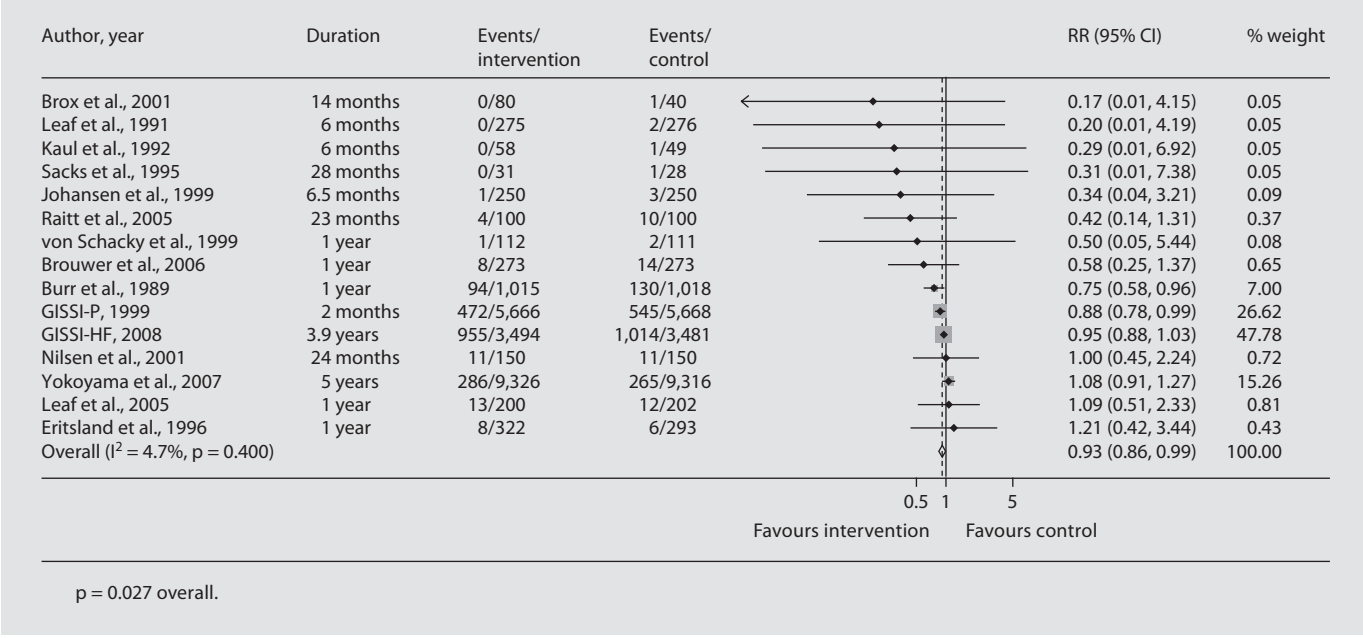


Fig. 24. Meta-analysis of fish or n–3 LCPUFA trials and total mortality, excluding DART II.

terns makes it difficult to disentangle the specific effects of dietary fat from other components of the diet. In effect, the dietary interventions are not homogeneous, and are unreliable. However, in trials of dietary advice to modify intake of dietary lipids where the change in fat intake or in the P/S ratio has been large, and there is good evidence of participant compliance, a meta-analysis of trials, which together provide a large number of endpoint events, should provide more reliable evidence.

In this regard, the meta-analysis of trials in which serum cholesterol concentrations in the high P/S diet group were significantly lower than in the control group, revealed that a diet higher in PUFA and lower in SFA decreased the risk of fatal CHD; however, this was significant only after inclusion of results from the Oslo study which included smoking cessation as part of the treatment. The cholesterol-lowering effect of the high P/S diet is driven largely by the reduction in SFA intake as shown in the metabolic ward studies [Clarke et al., 1997]. The evidence from metabolic ward studies clearly shows that diets low in SFA reduce total cholesterol and should therefore reduce the risk of CHD. However, the meta-analysis of results from cohort studies – albeit from a limited number of studies – showed no association between SFA intake and CHD, demonstrating their unreliability.

The observational evidence for an association between dietary PUFA and CHD risk is inconsistent and is unreliable. The summary estimate from the meta-analysis showed a significant increase in the RR of CHD death in the highest category of dietary PUFA (RR 1.25, 95% CI 1.06–1.47, p = 0.009) in contrast, a 5% increase in PUFA intake was associated with a significant reduction in CHD events (RR 0.84, 95% CI 0.70–1.00, p = 0.049).

The observational evidence for dietary MUFA shows no association with CHD risk.

Clinical trials of n–3 LCPUFA and CHD are better suited to meta-analysis inasmuch as most interventions are single factor, involving consumption of a fish oil or n–3 LCPUFA rich purified oil supplement. However, treatment effects may be modified by the amount and proportions of n–3 LCPUFA consumed during treatment, by the food or supplement form of the LCPUFA, the absolute risk of CHD in the study population, the duration of follow-up, or whether the trial was to prevent recurrence or occurrence of CHD. Several meta-analyses of cohort studies and randomised controlled trials have been published. The meta-analysis by Hooper et al. [2006] was conducted according to the conventions for systematic reviews developed by the Cochrane Collaboration and reviewed the evidence for an effect of n–3 fatty acids on cardiovascular events. The authors limited their re-

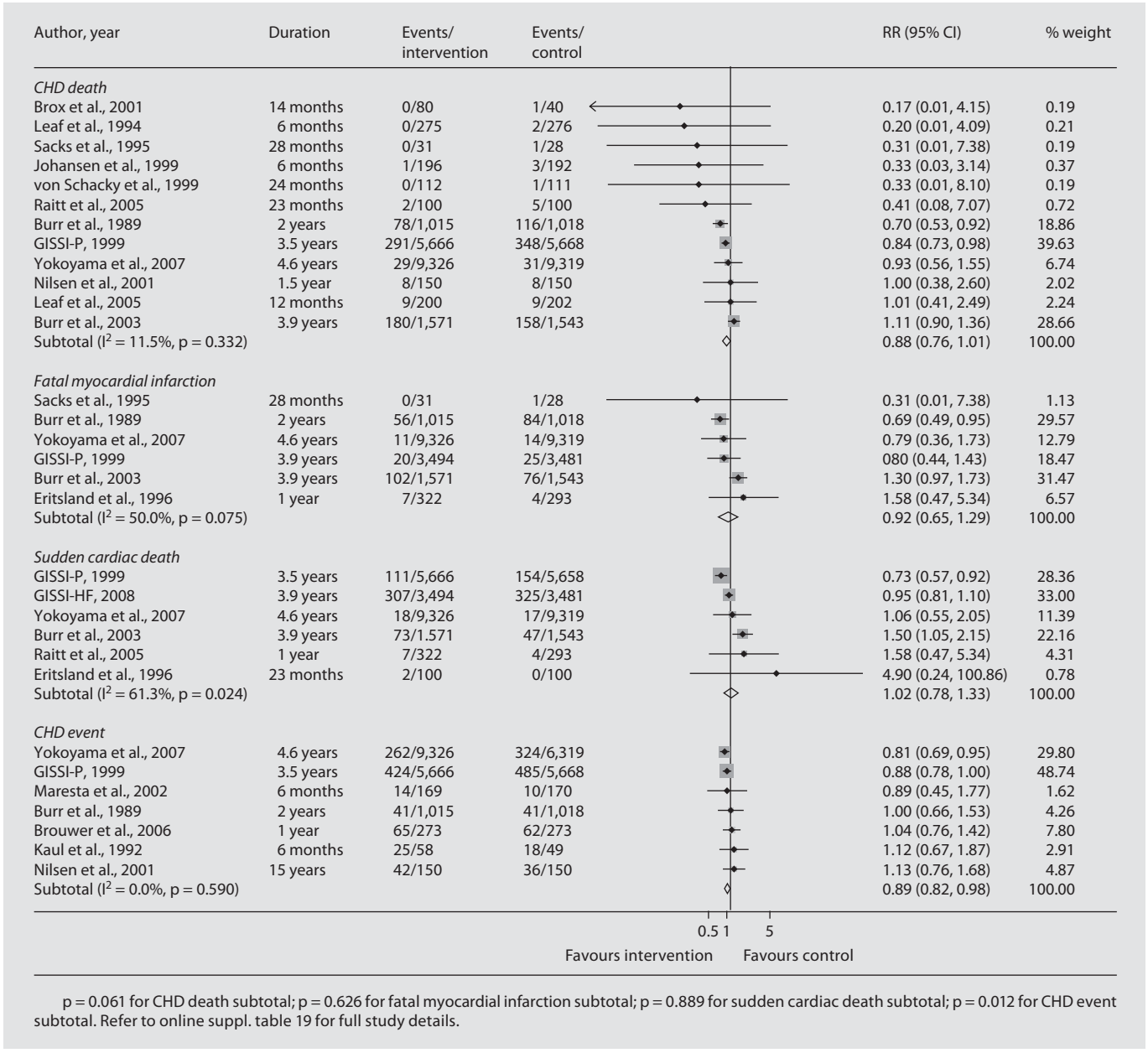
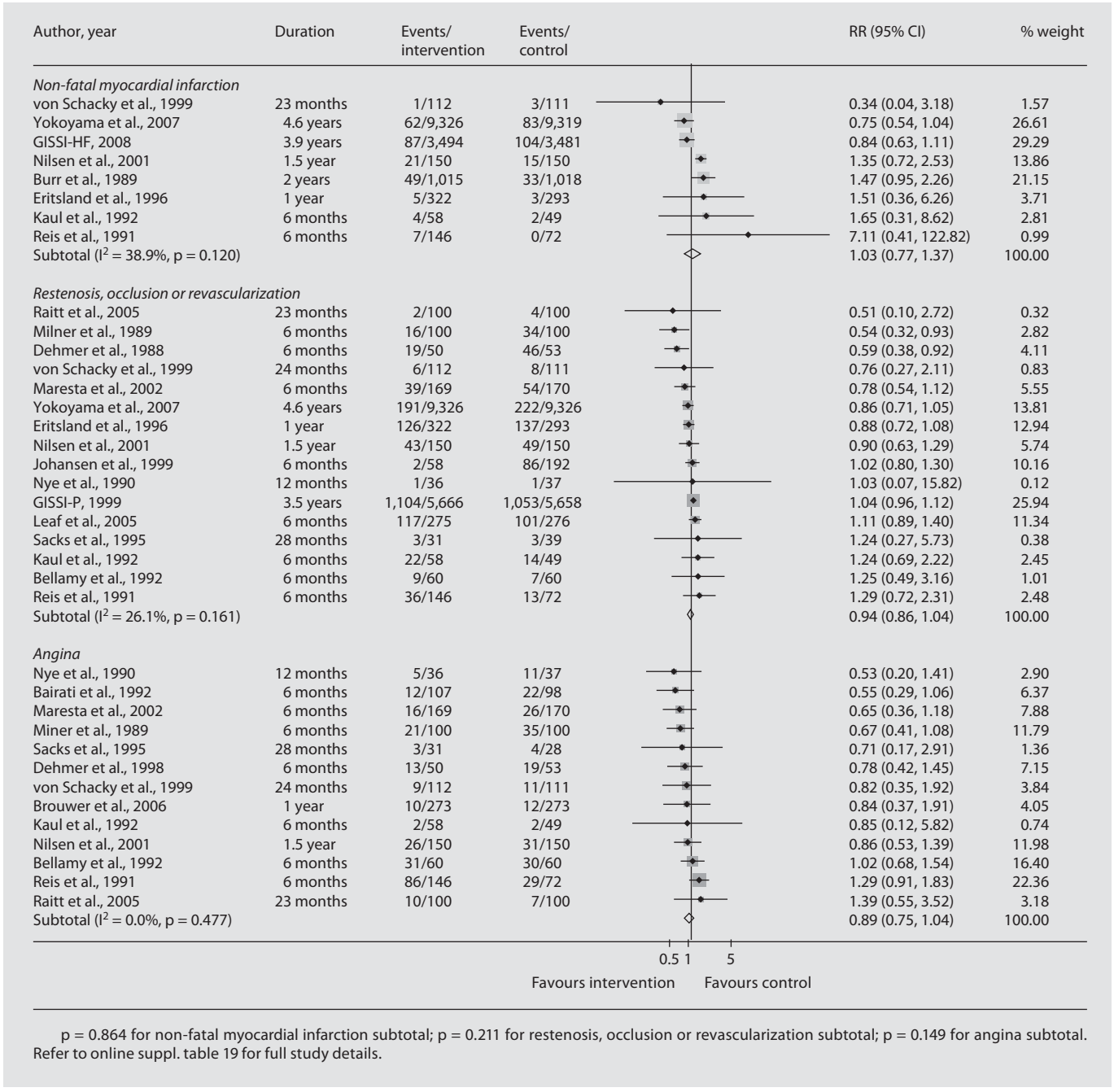


Fig. 25. Meta-analysis of fish or n–3 LCPUFA trials and CHD fatal events, including DART II.

view to studies in which an estimate of n–3 fatty acid intake could be verified because their primary hypothesis was to test the effect of 'long or shorter chain' n–3 fatty acids. Thus, relevant studies were excluded in which exposure to n–3 LCPUFA was assessed by fatty acid biomarkers or in which fish consumption but not n–3 LCPUFA intake was measured. The overall conclusion was an absence of a clear effect of n–3 PUFA on total mortality (RR 0.87, 95% CI 0.73–1.03) or combined cardiovascular events (RR 0.95, 95% CI 0.82–1.12). A number of other critical points have been raised about the systematic review by Hooper et al., to which the authors have given considered and substantiated responses [Twisselmann, 2006].

The meta-analysis by Mozaffarian and Rimm [2006] on n–3 LCPUFA and risk of CHD mortality combined the results from cohort and randomised controlled trials to conclude that 1–2 servings per week of fish reduces the



p = 0.864 for non-fatal myocardial infarction subtotal; p = 0.211 for restenosis, occlusion or revascularization subtotal; p = 0.149 for angina subtotal. Refer to online suppl. table 19 for full study details.

Fig. 26. Meta-analysis of fish or n–3 LCPUFA trials and CHD non-fatal events.

risk of coronary death by 36% (95% CI 20–50%). The risk reduction in total mortality with fish consumption was 17% (95% CI 0–32%). This estimate was calculated using conventional meta-analysis and is quite similar in magnitude to that reported by Hooper et al. [2006] though the CIs are different.

We have updated the meta-analyses with studies published since the work of Hooper et al. [2006] and Mozaffarian and Rimm [2006]. The totality of evidence from observational cohort studies consistently shows that high intake of n–3 LCPUFA or consumption of fish is associated with significantly lower risk of fatal and non-fatal

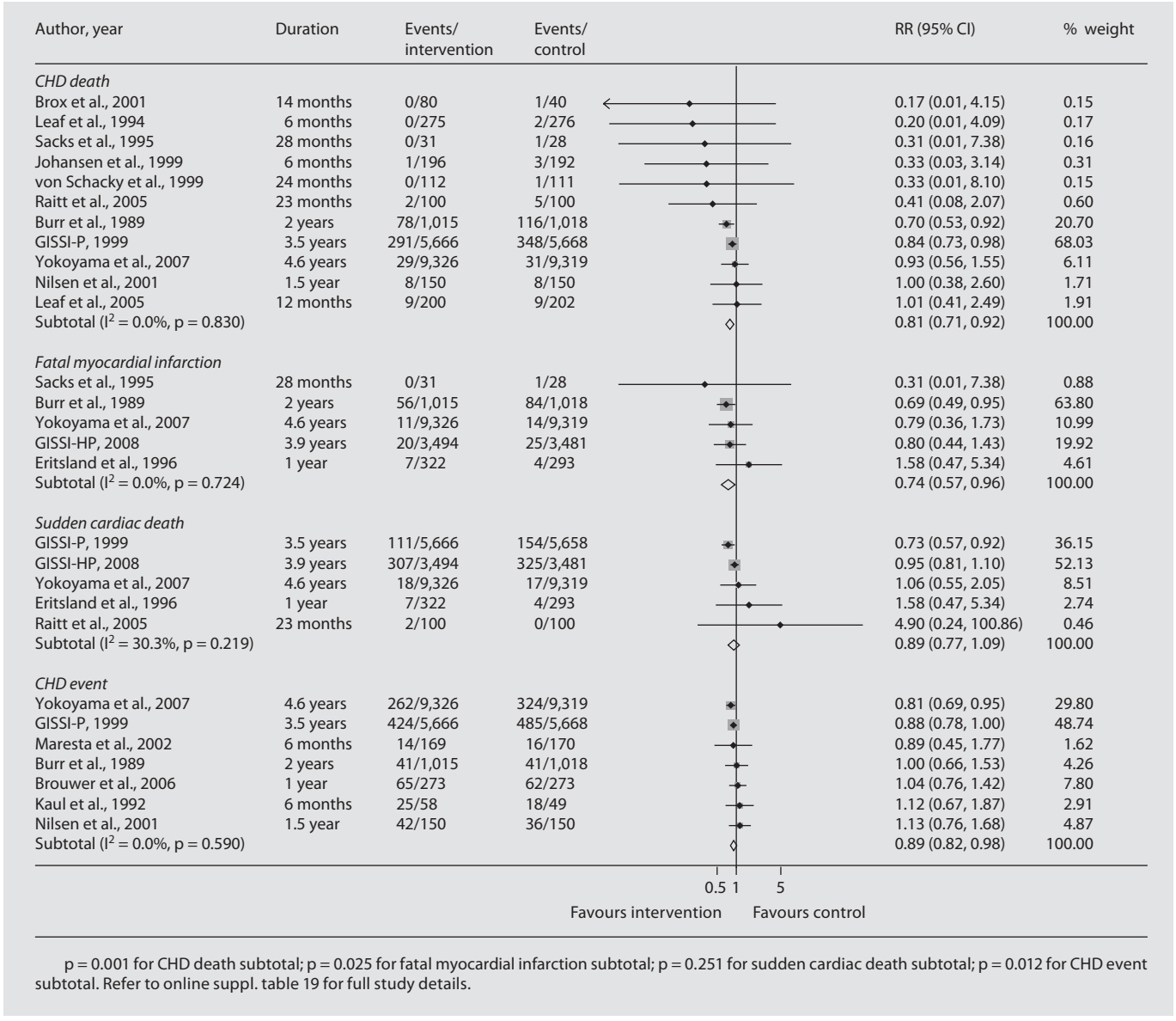


Fig. 27. Meta-analysis of fish or n–3 LCPUFA trials and CHD fatal events, excluding DART II.

CHD as well as combined CHD event. On the other hand, the results of randomised controlled trials, particularly in relation to fatal CHD, fatal MI or sudden cardiac death, do not show a beneficial effect of n–3 LCPUFA, though they do reveal a significant reduction in risk of total CHD events with treatment. To be convinced that n–3 LCPUFA decreases the risk of CHD it is desirable to find concordance of results between observational and cohort studies. The absence of concordance does not preclude a convincing judgement inasmuch as the limitations of study design inherent in cohort or intervention studies may account for some of the discrepancy. One of the most obvious differences between the cohort and intervention trials is the markedly longer duration of follow-up in the cohort studies, 17 years compared with 2 years for CHD death. It is also possible that fish consumers in Europe and North American have a 'healthy' lifestyle, and the inverse association between n–3 LCPUFA intake and fish consumption may be explained by residual confounding. Participants in the intervention trials were generally older at recruitment and at higher initial risk of CHD. Exclusion from the meta-analysis of 1 intervention trial (DART

II) with methodological concerns substantially altered the significance of the summary estimates of RR such that fatal CHD, fatal MI, sudden cardiac death were significantly reduced by n–3 LCPUFA; furthermore, the results of the remaining studies showed no heterogeneity. In the absence of DART II, the GISSI-P and DART I trials contribute 90% of the fatal CHD events on which the summary estimate is based. Thus, the evidence from randomised controlled trials about the protective effects of n–3 LCPUFA on fatal CHD rests on the results of 2 trials, both of which have some methodological limitations which may have introduced bias.

Post-Script

A pooled analysis of 11 cohort studies of dietary fat and coronary disease was presented to the Expert Consultation (Nov, 2008) and the manuscript was published shortly thereafter in May 2009 [Jakobsen et al., 2009]. In the judgement of the Expert Consultation, the results of the 'Pooling Project of Cohort Studies on Diet and Coronary Disease' were a significant advance in quality on the update, undertaken by the Consultation, of the published meta-analyses of observational trials. The Pooling Project combined the results from 11 cohort studies – each meeting criteria for quality of dietary assessment, years of follow-up, and ascertainment of events – to examine the effect on CHD death and CHD events of replacing SFA with MUFA, PUFA or carbohydrate. The main finding was a significantly decreased risk of CHD death and CHD events when PUFA replaces SFA. The multivariate-adjusted hazard ratio for CHD death per 5% TE incremental substitution of PUFA for SFA was 0.87 (95% CI 0.77–0.97); for CHD events, the hazard ratio for the same fat substitution was 0.74 (95% CI 0.61–0.89). This result from the pooling of observational studies, along with supportive evidence from clinical trials of lower CHD risk in high P/S diets, and the effects of PUFA to lower LDL cholesterol and the total:high-density lipoprotein ratio, led the Consultation to conclude there was convincing evidence of lower CHD risk when PUFA replaces SFA.

Disclosure Statement

Ms. Miller has nothing to declare. Dr. Skeaff has conducted clinical research trials which have been funded through the University by Unilever and Fonterra. He has served on governmental and non-governmental advisory groups.

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Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The Western Electric Study Paul *et al.* 1963	US	1957	4 y	1,989	Employees of Western Electric , no previous CHD	100	40-55	Evidence of CHD, permanent disability, special problems in follow-up unrelated to CHD.
Diet and Heart Morris *et al.* 1977	UK	1956	10-20	337	London Transport and Bank employees. All healthy males.	100	30-67	History or clinical evidence of CHD.
The Puerto Rico Heart Health Program Garcia-Palmieri *et al.* 1980 Gordon et al. 1981	Puerto Rico	1965	6	8,218	Urban and rural Puerto Rico men, no previous CHD	100	45-64	Men with CHD
The Framingham Study Gordon *et al.* 1981	US	1966	4	859	Selected from general population, no previous CHD	100	45-64	Men with CHD
The Honolulu Heart Study Gordon *et al*. 1981; McGee *et al.* 1984	Honolulu	1965	6 10	7,272 7,088	Men of Japanese ancestry, no previous CHD	100	45-64	prevalent CHD, stroke, cancer, incorrect 24-hour recall
The Western Electric Study Shekelle *et al.* 1981	US	1957	19	2,107	Employees of Western Electric , no previous CHD	100	40 - 55	evidence of CHD, missing data for diet, height or weight, or serum cholesterol, absence from 2nd examination, and missing data at re-examination
Miettinen *et al.* (nested case-control) 1982	Finland	1974	5 - 7	1,222 (33 cases; 64 controls)	Previous participants of health examinations organised by their employers, no previous CHD	100	40 - 55	Prior IHD

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	*n* of events	Event Rate (%)	Results For:	Table or figure number for results
The Western Electric Study Paul *et al.* 1963	Dietary History - collected at baseline and one-year later	Men examined on a yearly basis for evidence of angina pectoris, MI (clinical history plus ECG findings). Death from CHD assumed on basis of information from family, physicians, hospital records, death certificates and coroners reports.	CHD Event	88	4.4	Comparison of mean intakes of SAFA, unsaturated fat, linoleic acid, linolenic acid, arachidonic acid, for CHD patients compared with non-CHD participants.	Tables S7 and S13
			Angina	47	2.4		
			MI	28	1.4		
			CHD Death	13	0.6		
Diet and Heart Morris *et al.* 1977	7-day weighed diet record	Incidence of CHD ascertained from Personnel records, correspondance with retired men, tagging of the Registrar General's Office, death notification.	CHD Event	45	13	Comparison of CHD incidence rates in tertiles of total fat intake, animal fat, dairy fat, and marine/vegetable fats and oils.	Tables S2,S7 and S13
			CHD Death	26	8		
The Puerto Rico Heart Health Program Garcia-Palmieri *et al.* 1980 Gordon et al. 1981	24-hour recall - completed at baseline	Total coronary heart disease, MI or CHD death, other (angina, coronary insufficiency). Ascertained through hospital systems.	Total CHD	286	3.5	Comparison of mean intakes of total fat, SAFA, MUFA and PUFA for non CHD participants vs Total CHD, MI or CHD death, or Other CHD	Tables S2, S7, S10 and S13
			MI or CHD death	163	2.00		
			Other	123	1.5		
The Framingham Study Gordon *et al.* 1981	24-hour recall - completed at baseline	Routine examinations at regular intervals, and hospital admission surveillance. Endpoints include total CHD fatal and non-fatal), MI or CHD death, and other (angina or coronary insufficiency). No details provided for diagnosis criteria in this report.	Total CHD	79	9.2	Comparison of mean intakes of total fat, SAFA, MUFA and PUFA for non CHD participants vs Total CHD, MI or CHD death, or Other CHD	Tables S2, S7, S10 and S13
			MI or CHD death	51	5.9		
			Other	28	3.2		
The Honolulu Heart Study Gordon *et al*. 1981; McGee *et al.* 1984	24-hour recall - completed at baseline	Total coronary heart disease, MI or CHD death, other (angina, coronary insufficiency). Ascertained through hospital systems.	Total CHD	264	3.6	Comparison of mean intakes of total fat, SAFA, MUFA and PUFA for non CHD participants vs Total CHD, MI or CHD death, or Other CHD	Tables S2, S7, S10 and S13
			MI or CHD death	164	2.2		
			Other	100	1.4		
The Western Electric Study Shekelle *et al.* 1981	Dietary History - collected at baseline and one-year later	ICD definition for fatal & non-fatal CHD events. Review of national registrys and medical records	CHD death	215	10.2	Death rates per tertile of intake of SAFA and PUFA. Logistic Regression for SAFA or PUFA and the relative risks calculated from these.	Tables S7 and S13 Tables S8 and S14
Miettinen *et al.* (nested case-control) 1982	Fatty acid composition of PL, CE & serum TAG	Fatal or non-fatal MI, verified by chest pain, elevated cardiac enzymes and ECG changes, or sudden death.	CHD event	33	2.7	Comparison of serum lipid fatty acid concentrations (SAFA, MUFA, PUFA), cases vs controls.	Tables S7, S10 and S13

Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The Zutphen Study Kromhout & de Lezenne Coulander 1984	Netherlands	1960	10	857	Selected from general population, no previous CHD	100	40-59	none - total *n* was 871, but 2% already had CHD, this table is presenting only the CHD-free men's results
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	Ireland - US	1959	20	1,001	men born & living in Ireland, born in Ireland and immigrated to Boston, born in Boston of Irish immigrants	100	30 - 69	not noted
Salonen *et al.* (nested case-control) 1985	Finland	1977	5	12,155 (92 case and control pairs)	Selected from the general population	75	30 - 64	54 pairs had evidence of CHD
Farchi *et al.* 1989	Italy	1960	15	1,536	Selected from general population	100	45 - 64	only those with missing data
The Framingham Study Posner *et al.* 1991	US	1966	16	813	Participants from the orginal cohort, started in 1948	100	45 - 65	Previous CVD or cancer
MRFIT Dolecek 1992	US	1973	10.5	6,250	Participants in the 'usual care' group of the trial. High risk group (smokers, hypertension, or elevated serum cholesterol)	100	35 - 57	not noted
The Caerphilly Study Fehily *et al.* 1993	South Wales	1979	5	1,881	Rsidents of Caerphilly (89% response rate)	100	45 - 59	This report using only results from men without evidence of preexisting CHD (the reported n in this study varies, and around 64 participants seem to be missing!)
Goldbourt, Yaari & Medalie 1993	Israel	1963	23	10,059	Civil sevants & munipal employees	100	aged ≥ 40	not noted
The Nurses Health Study Willett *et al.* 1993	US	1980	8	85,095	Nurses, no previous CHD	0	34 - 59	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	 *n* of events	 Event Rate (%)	Results For:	Table or figure number for results
The Zutphen Study Kromhout & de Lezenne Coulander 1984	cross-check dietary history method (check with spouse & household groceries) - completed at baseline	CHD death - not defined	CHD death	30	3.5	Comparison of mean SAFA intakes, CHD events compared to Non-CHD events	Table S7
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	diet-history completed at baseline	CHD death ascertained from death certificates	CHD death	110	11	Comparison of mean intakes of SAFA and PUFA for non CHD participants vs CHD death Logistic regression for SAFA and PUFA and the relative risk calcuated from these.	Tables S7 and S13 Tables S8 and S14
Salonen *et al.* (nested case-control) 1985	Serum fatty acid composition	Death information obtained from National death Certificate Register. CAD defined ICD codes 410 to 414.	CHD Death	2,030		Comparison of mean serum concentrations of SAFA.	Table S7
Farchi *et al.* 1989	Diet history completed 5 yr after start of study	Mortality certificates, hospital records, relatives & other witnesses	CHD death	58	3.8	Comparison of mean intakes of Total fat, SAFA, PUFA, MUFA for non CHD participants vs CHD death	Tables S2, S7, S10 and S13
The Framingham Study Posner *et al.* 1991	24-hour recall - completed at baseline	Incident CHD: angina pectoris, coronary insufficiency, MI, sudden death (death within one hour of symptom onset and no other obvious cause) or non-sudden death from CHD. Clinical examinations, ECG and cardiac enzymes used to diagnose MI.	Incident CHD	213	26	Relative risk of CHD Event and sample mean intakes of Total Fat, SAFA, MUFA, PUFA to the National Cholesterol Education Program Recommendations	Tables S2, S7, S10 and S13
MRFIT Dolecek 1992	24-hr recall - completed years 1, 2, 3 and 6	Using National Death Index and death certificates, mortality determined according to ICD codes. Results preseneted as CHD, including deaths and clinical MI.	CHD death	175	2.8	Proportional Hazards Regression for PUFA intake and CHD Death. Relative Risks Quintile 5 compared with Quintile 1 for PUFA intakes.	Tables S13 and S14
The Caerphilly Study Fehily *et al.* 1993	FFQ - completed at baseline (a subsample did 7-day weighed diet rocord)	Ischaemic Heart Disease, determined from ECG and Rose Questionnaire conducted at follow-up. Hopital records used to confirm history acute MI (WHO criteria - ECG only) Notifications of death were used for IHD deaths (ICD codes 410-414).	IHD event	74	3.9	Comparison of mean intakes of Total Fat and Animal Fat for no IHD vs incident IHD. Relative Odds of incident IHD for Quintile 5 cf Qunintile 1 for IHD event and Total Fat and Animal Fat.	Tables S2 and S7 Tables S3 and S8
Goldbourt, Yaari & Medalie 1993	Short dietary questionnaire completed at baseline (not sure if repeated throughout study)	MI base on ECG changes or autopsy findings showing evidence of recent MI an/or coronary thrombosis, sudden death, angina defined by the Rose questionnaire.	CHD mortality	723	7.2	Event rates for Quintile 5 compared to Quintile 1 of SAFA and linoleic intakes.	Tables S7 and S13
The Nurses Health Study Willett *et al.* 1993	FFQ - collected 1980	Medical records, hospital records, autposy or death certificate MI defined as per WHO criteria (symptoms plus elevated cardiac enzymes or ECG changes).	Incident CHD (non-fatal MI & fatal CHD)	431	0.5	Relative Risks for Quintile 5 compared to Quintile 1 for intakes of *trans* fat and CHD Event.	Table S5

Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The Seven Countries Study Kromhout *et al.* 1995	Different Countries	1958	25	12,763	16 Cohorts	100	40 - 59	not noted
Esrey, Joseph & Grover 1996	Canada	1972	12.4	4,546	Selected from general population, no previous CHD	?	30 - 79	taking lipid-lowering medication, history CVD, missing data
The Health Professionals Follow-up Study Ascherio *et al.* 1996	US	1986	6	43,757	Health Professionals, no previous CHD	100	40 - 75	previous MI, angina, coronary artery surgery, stroke, TIA, Peripheral arterial disease, diabetes
Ohrvall *et al.* 1996	Sweden	1970	19	2,016	Men living in Uppsala no previous CHD (82% response rate)	100	50	Presence of CHD (but men with hypertension, hyperlipidemia, or impaired glucose intolerance reamined in study and treatment initiated).
The AT/BC Study Pietnen *et a*l. 1997	Finland	1985	6.1	21,930	High risk group (smokers), no previous CHD	100	50 - 69	history cancer or other serious disease, use of vitamin E, A or beta-carotene supplements in excess of predfined doses, treatment with anticoagulating agents, prior diagnosis of MI, angina, stroke or diabetes, men with typical exercise-related chest chain, and men with missing CV risk factors.
Mann *et al.* 1997	UK	1980	13.3	10,802	Meat eaters and vegetarians	38	34	none
The Nurses Health Study Hu et al. 1997	US	1980	14	80,082	Nurses no previous CHD	0	34 - 59	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	*n* of events	Event Rate (%)	Results For:	Table or figure number for results
The Seven Countries Study Kromhout *et al.* 1995	Weighed Food Records	Mortality from CHD, as per ICD 410-414 classification, as well as classifications developed specifically for this study. CHD death not defined.	CHD death	1,918 (approx)	15	Correlations between Total Fat, SAFA, MUFA, and PUFA and CHD	Tables S2, S7, S10 and S13
Esrey, Joseph & Grover 1996	24-hour recall - completed at baseline	CHD death not defined	CHD death: age 30 - 59 y	52	2	Comparison of mean intakes of Total Fat, SAFA, MUFA and PUFA for CHD patients vs no CHD death.	Tables S2, S7, S10 and S13
			age 60 - 79 y	192		Relative Risks associated with a 1 unit increase in intake of Total Fat, SAFA, MUFA and PUFA	Tables S4, S9, S12 and S15
The Health Professionals Follow-up Study Ascherio *et al.* 1996	FFQ - collected at baseline	Events confirmed with medical records, necropsy reports, death certificates (plus confirmation from other soruces). MI defined as per WHO criteria. Fatal CHD includes sudden death.	Total MI	734	2	Relative Risk for Quintile 5 compared to Quintile 1 for intakes of Total Fat, SAFA, linoleic, linolenic, and *trans* fat.	Tables S3, S5, S8, and S14
			Fatal CHD	229	0.5	Relative Risk for each 5% increase in energy from total fat, SAFA and linoleic, 2% increase in *trans,* and 1% increase in linolenic.	Tables S4, S6, S9 and S15
Ohrvall *et al.* 1996	Serum Fatty Acid concentrations collected from 1,746 subjects (87%)	CHD event described as those suffering MI (fatal or non-fatal) but definition of events not provided.	CHD Event	180	9	Comparison of mean cholesterol ester concentrationsof SAFA, MUFA and PUFA for CHD patients and non-CHD participants.	Tables S7, S10 and S13
The AT/BC Study Pietnen *et a*l. 1997	FFQ - collected at baseline (validated in a pilot study)	Major coronary event (MCE) inlcude first nonfatal MI (alive after 28 days of event), or death due to coronary event. Events ascertained fro death certificates (ICD 9th revision, codes 410-414). Validity of the diagnosis of MCE determined by checking hospital and pathology records in a subgroup.	Major Coronary Event	1,399	6.4	Relative Risk for Quintile 5 compared to Quintile 1 for intakes of Total TAG, SAFA, MUFA, PUFA and *trans* fat.	Tables S3, S5, S8, S11, and S14
			coronary death	635	2.9	Relative Risk for increases in intake of SAFA, MUFA, linoleic, linolenic.	Tables S9, S12 and S15
Mann *et al.* 1997	semiquantitative FFQ - completed at baseline	If CVD noted on death certificate, hospital records were checked	IHD mortality	64	0.6	Standardized Death Rates for Tertile 1 compared to Tertile 3 for animal fat (calculated Relative Risk for this report)	Table S7
The Nurses Health Study Hu et al. 1997	FFQ - collected 1980, 1984, 1986, 1990	Medical records, hospital records, autposy or death certificate MI defined s per WHO criteria (symptoms plus elevated cardiac enzymes or ECG changes).	Incident CHD (non-fatal MI & fatal CHD)	939	1.2	Relative Risk for Quintile 5 compared to Quintile 1 for Total Fat, SAFA, MUFA, PUFA, *trans*.	Tables S3, S5, S8, S11 and S14
						Relative Risk for each 5% increase in energy from total fat, MUFA and SAFA, and 2% increase in *trans*.	Tables S4, S6, S9, S12 and S15

Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The Nurses Health Study Hu *et al.* 1999	US	1980	10	76,283	Nurses no previous CHD	0	30-55	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes
The Zutphen Elderly Study Oomen *et al.* 2001a & 2001b	Netherlands	1985	10	667	Selected from general population	100	mean 71	Previous diagnosis CAD.
The Physicians Health Study (nested case-control) Albert *et al.* 2002	US	1982	17	22,071	Male physicians, no previous CHD	100	40 - 84	History of MI, stroke, transient ischemic attack, cancer
The Health & Lifestyle Survey Bonniface & Teft 2002	UK	1984	16	2,676	Selected from general population, no previous CHD		40 - 75	CHD, diabetes, on antihypertensive treatment, on special diet
The EUROASPIRE Study Erkkila *et al.* 2003	Finland	1995	5	415	Patients with clinically established CAD	67	33 - 74	Included patients with first CABG or PTCA (with no previous CABG) or first or recurrent AMI, or symptoms of acute myocardial ischemia
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	Denmark	1964, 1975, 1980, 1991	16	3,686	Selected from general population, no previous CHD	50	30-71 y	Inmplausible dietary assessment results, previous diagnosis CHD (n=80), diabetes (n=77)
The ARIC Study Wang, Folsom & Eckfeldt 2003	US	1987	10.7	3,594	Probability sample from US Centres	46	45 - 64	Prevalent CHD, stroke, missing Questionnaire, taking cholesterol-lowering medication, non-whites.

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	*n* of events	Event Rate (%)	Results For:	Table or figure number for results
The Nurses Health Study Hu *et al.* 1999	FFQ - collected 1980, 1984	Medical records, hospital records, autposy or death certificate MI defined s per WHO criteria (symptoms plus elevated cardiac enzymes or ECG changes) .	Fatal CHD	232	0.3	Relative Risk for Quintile 5 compared to Quintile 1 for SAFA intakes (including specific SAFAs).	Table S8
			Non-fatal CHD	597	0.8		
The Zutphen Elderly Study Oomen *et al.* 2001a & 2001b	corss-check Dietary History method (cross check with spouse)	Incident cases include fatal CAD plus nonfatal MI. Cause of death obtained from Statistics Netherlands, hospital discharge or GP records. Coded according to ICD codes 410-414. CAD as both primary and secondary cause of death were included. MI diagnosed as specific medical history, ECG changes or cardiac enzymes. Diagnosis confirmed with hospital discharge data.	Incident CAD	98	14.7	Relative Risk for Tertile 3 compared to Tertile 1 for linolenic and *trans* fat intakes and CHD events (fatal and nonfatal).	Tables S5 and S14
						Relative Risk for each 0.13% increase in energy from linolenic, and 2% increase in *trans*.	Tables S6 and S15
The Physicians Health Study (nested case-control) Albert *et al.* 2002	Blood Fatty Acid concentrations, collected at baseline	Sudden cardiac death ascertained from medical records. If cause of death not adequately documented, next-of-kin interviewed. Sudden death defined as death within one hour of onset of symptoms, or witnessed cardiac arrest or collapse within one hour after onset of symptoms, that resulted in death.	Sudden Cardiac Death	94 cases	NA	Comparison of mean wholeblood fatty acid concentrations (SAFA, MUFA, PUFA and *trans*), cases vs controls.	Tables S5, S7, S10 and S13
The Health & Lifestyle Survey Bonniface & Teft 2002	FFQ - collected at baseine	CHD death - not defined	CHD Death: Women	57	3.9	Death rates according to Quartiles of Total Fat, SAFA and PUFA intakes.	Tables S2, S7 and S13
			Men	98	8		
The EUROASPIRE Study Erkkila *et al.* 2003	4-day estimated food record completed at baseline, and Cholesterol Ester Fatty Acids	CAD death ascertained from natioanl death register, and copies of death certificates (ICD codes 120-125). AMI, revascularization obtinaed from hospital and medical records.	CAD death	16	8.5	Relative Risk per 1 SD increment in Total Fat, SAFA, PUFA intake.	Tables S4, S9 and S15
			CAD death or AMI	34	8.5		
			Revascularization	38	9.5		
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	7-day weighed diet record completed at baseline (a subgroup did diet history)	Fatal and non-fatal CHD events defined according to ICD. Identified by flagging National Patient Registry. Review of medical files.	CHD events	326	8.8	Relative Risk per 5% energy increase in Total Fat, SAFA, MUFA, PUFA intake	Tables S4, S9, S12 and S15
The ARIC Study Wang, Folsom & Eckfeldt 2003	Plasma Fatty Acids collected at baseline	Incident CHD events ascertained by hospital records. MI determined from chest pain, medical history, hospital procedures, medications, complications, cardiac enzyme levels, ECG chnages. Non-hospitalised MI by clinic ECGs. CHD deaths from death certificates, confirmed with hospital records or family and physician questionnaireds. CHD defined as death, definite, probably or silent MI or coronary artery revascularization.	CHD incident	282	7.9	Comparison of SAFA, MUFA and PUFA in Cholesterol Esters and Phospholipids of Incident CHD vs no CHD.	Tables S7, S10 and S13

Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The Cardiovascular Health Study, Nested Case-Control Lemaitre *et al.* 2003	US	1989	9	5,201	Community based sample.		≥ 65 y	IHD and stroke at baseline, & use of fish oil supplements at baseline.
The Nurses Health Study Oh *et al.* 2005	US	1980	20	78,778	Nurses, no previous CHD	0	34 - 59	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes
The Baltimore Longitudinal Study of Aging Tucker *et al.* 2005	US	1958	18	501	Not noted	100	34 - 80	Less than 4 completed days of diet record for more than 1 biennial visit, history angina or MI
The Nurses Health Study Albert *et al.* 2005	US	1980	18	76,763	Nurses, no previous CHD	0	34-59	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes
The Health Professional's Follow-up Study Mozaffarian *et al.* 2006	US	1986	14	38,461	Health Professionals, no previous CHD	100	40 - 75	previous MI, angina, coronary artery surgery, stroke, TIA, Peripheral arterial disease, diabetes
The Strong Heart Study Xu *et al.* 2006	US	1989	7.2	2,938	American Indians	36	47 - 79	MI or CHD, implausible energy intakes, under dialysis treatment, kidney transplant or liver cirrhosis
The Nurses Health Study - nested case-control Sun *et al.* 2007	US	1980	6	32,826 blood samples collected	Nurses, no previous CHD	100	30 - 55	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	 *n* of events	 Event Rate (%)	Results For:	Table or figure number for results
The Cardiovascular Health Study, Nested Case-Control Lemaitre *et al.* 2003	Plasma Phospholipid fatty acid concentrations	MI diagnosis based on cardiac enzymes, chest pain & serial ECG changes. IHD deaths were fatal MI or other fatal CHD.	Fatal CHD	54		Comparison of RBC Linolenic and Linoleic acid concentraions between cases and controls	Table S13
			Nonfatal MI	125		Odds Ratios for 1SD increase in PL Linolenic and Linoleic fatty acid concentrations.	Table S15
The Nurses Health Study Oh *et al.* 2005	FFQ - collected 1980, 1984, 1986, 1990, 1994	Medical records, hospital records, autposy or death certificate MI defined as symptoms plus elevated cardiac enzymes or ECG changes (WHO criteria). Fatal CHD ascertained from hospital records or autopsy, and CHD was the most plausible cause of death.	Incident CHD (non-fatal MI & fatal CHD)	1,766	2.2	Relative Risk for Quintile 5 compared to Quintile 1 for Total Fat, SAFA, MUFA, PUFA and *trans* fat intakes.	Tables S3, S5, S8, S11, and S14
						Relative Risk per Unit increases in SFA, MUFA, PUFA, and *trans* intake.	Tables S6, S9, S12 and S15
The Baltimore Longitudinal Study of Aging Tucker *et al.* 2005	7 day diet records during 4 time periods	Casue of death determined by using death certificates, hospital and physician reocrds, autopsy data. CHD mortality includes deaths due to acute MI or sudden coronary death.	CHD death	71	14.2	Comparison of mean SAFA intakes for CHD deaths compared to Survivors	Table S7
						Hazard risk ratio per unit increment in SFA intake	Table S9
The Nurses Health Study Albert *et al.* 2005	FFQ - collected 1980, 1984, 1986, 1990, 1994, 1998	Medical records, hospital records, autposy or death certificate MI defined as symptoms plus elevated cardiac enzymes or ECG changes (WHO criteria). Fatal CHD ascertained from hospital records or autopsy, and CHD was the most plausible cause of death. SCD classified if death occurs within 1 hour of onset of symptoms and autopsy findings consistent with ACD.	Sudden Cardiac Death	206	0.3	Relative Risk for Quintile 4 compared to Quintile 1 for α-linolenic intake.	Table S14
			Other CHD Deaths	641	0.8		
			Nonfatal MI	1,604	2.1		
The Health Professional's Follow-up Study Mozaffarian *et al.* 2006	FFQ, baseline and every 4 years	Events confirmed with medical records, necropsy reports, death certificates (plus confirmation from other soruces). MI defined as per WHO criteria. Fatal CHD includes sudden death.	CHD Event	1,702	4.4	Relative risk per 2% increase in TFA intake	Table 4
The Strong Heart Study Xu *et al.* 2006	24-h diet recall collected around 4 y after start of study	CHD events were first nonfatal or fatal CHD event, nonfatal events included definite MI, definite CHD, ECG-evident MI events. Medical records checked, and fatal CHD events confirmed by review committees.	CHD event	403	13.7	Comparison of mean intakes of Total Fat, *trans* fat, SAFA, MUFA and PUFA for CHD vs no CHD.	Tables S2, S5, S7, S10 and S13
			Nonfatal CHD	298	10.1	Relative Risk for Quintile 4 compared to Qunitile 1, and for incremental change in fat intakes (for all fat fractions)	Tables S3, S4, S6, S8, S9, S11, S12 and S14
The Nurses Health Study - nested case-control Sun *et al.* 2007	Red blood cell fatty acids FFQ - collected 1990	Medical records, hospital records, autposy or death certificate MI defined as symptoms plus elevated cardiac enzymes or ECG changes	cases (CHD event)	166		Comparison of RBC *trans* fatty acids for cases vs controls.	Table S5
			Controls	327		Relative Risk for Qunitile 4 compared to Quintile 1 for *trans* intake.	Table S5

Supplementary Table 1. Prospective Cohorts and Nested Case-Control Studies Investigating Dietary Fat (Total, Saturated. Monunsaturated, Polyunsaturated and *Trans* fats) and Coronary Heart Disease

Study Name **Author, year published**	**Country**	**Start of Study (year)**	**Follow-up (years)**	***n***	**Participants**	**Men (%)**	**Age at Baseline (years)**	**Exclusions**
The ARIC Study Yamagishi *et al.* 2008	UK	1987	14.3	3,592	Probability sample from US Centres	46	45 - 64	History of CHD, stroke or heart failure at baseline, non-white participants, or those without plasma fatty acid data.
MONICA-1 & MONICA-II Jakobsen et al. 2008	Denmark	1964, 1975, 1980, 1991	18	3,686	Selected from general population, no previous CHD	50	30-71 y	Inmplausible dietary assessment results, previous diagnosis CHD, diabetes
The Nurses Health Study - nested case-control Sun *et al.* 2008	US	1980	6	32,826 blood samples collected	Nurses, no previous CHD	100	30 - 55	left > 10 items on questionnaires blank, implausible energy intakes, previous diagnosed cancer, angina, MI, stroke or other CVD, high serum cholesterol or diabetes

Supplementary Table 1.

Study Name Author, year published	Diet Assessment Method	Identification of CHD Casees	CHD Endpoints CHD event	*n* of events	Event Rate (%)	Results For:	Table or figure number for results
The ARIC Study Yamagishi *et al.* 2008	Plasma fatty acid concentrations (CE & PL)	Heart failure defined by first HF hospitalization, ICD code 428 in any position, or any deaths where death certificate included ICD code 428 or 150. Non hospitalized, nonfatal HF not captured.	Incident Heart Failure	195	5.4	Hazard ratios for incident Heart failure and CE and PL SAFA, MUFA and PUFA, highest vs lowest quintiles.	Tables S8, S12 and S11
MONICA-1 & MONICA-II Jakobsen et al. 2008	7-day weighed diet record completed at baseline (a subgroup did diet history)	Fatal and non-fatal CHD events defined according to ICD codes 410-414, and I20-I25 after 1994. Identified by flagging National Patient Registry. Review of medical files.	CHD events	374	10.1	Hazard Ratio for each 0.5 unit (grams or %TE) increase in ruminant *trans* fat intake.	Table S6
The Nurses Health Study - nested case-control Sun *et al.* 2008	Red blood cell fatty acids FFQ - collected 1990	Medical records, hospital records, autposy or death certificate MI defined as symptoms plus elevated cardiac enzymes or ECG changes	Nonfatal MI Controls	146 288		Comparison of plasma and RBC linolenic acids for cases vs controls.	Table S13

Abbreviations: CHD, coronary heart disease; US, United States; UK, United Kingdom; IHD, ischemic heart disease; MI, myocardial infarction; ECG, Electrocardiogram; ICD, The International Statistical Classification of Diseases; SAFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; PL, phospholipid; CE, cholesterol ester; TAG, triacyglyceride; FFQ, food frequency questionnaire; WHO, World Health Organisation; CAD, coronary artery disease; CVD, cardiovascular disease; TIA, transient ischemic attack; MCE, major coronary event; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; AMI, acute myocardial infarction; SCD, sudden cardiac death; HF, heart failure.

Supplementary Table 2. Mean Total Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean Total Fat intake	Endpoint		Comparison of mean intake CHD Event	 No CHD Event	 p-value
Diet and Heart Morris *et al.* 1977	38 - 43%TE (Tertile 2)	CHD death (comparing incidence tertile 1 vs tertile 3)	*Tertile 1:* *Tertile 3:*	*n*=18 *n* = 17		ns
The Framingham Study Gordon *et al.* 1981	115g 39.1%TE	Total CHD MI or CHD Death Other CHD		112g (40.2%TE) 106g (40.0%TE) 119g (40.09%TE)	114g (38.8%TE)	ns ns ns
The Honolulu Heart Study Gordon *et al*. 1981; McGee et al 1984	86.3g 33.4%TE	Total CHD MI or CHD Death Other CHD		86.4g (34.7%TE) 86.9g (35.29%TE) 85.2g (33.7%TE)	86.3 g (33.3%TE)	ns <0.01 (%TE) <0.01 (%TE)
The Puerto Rico Heart Health Program Garcia-Palmieri *et al.* 1980 Gordon et al. 1981	94 g 35.3%TE	Total CHD MI or CHD Death Other CHD		94g (36.6%TE) 92g (36.7%TE) 96g (36.4%TE)	86g (35.3%TE)	<0.01 (%TE) <0.05 (%TE) ns
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	around 38.5%TE	CHD death		39.4%TE	38.5%TE	0.12
Farchi *et al.* 1989	around 84g (27%TE)	CHD death		23.8g 8.0%TE	28.9g 9.0%TE	<0.01 <0.05
The Caerphilly Study Fehily *et al.* 1993	around 101.8g	Incident IHD		100.7g	102.8g	not provided
The Framingham Study Posner *et al.* 1991	118.4 g (39.7%TE) aged 45-55 y 109.3 g (38.3%TE) aged 56 - 65 y			*refer Supplementary Table 3 for results*		
The Seven Countries Study Kromhout *et al.* 1995	not provided	CHD death	*Correlation with total fat r=0.60 (p<0.05)*			
Esrey, Joseph & Grover 1996	around 92g (40%TE)	CHD Death	*age 30 - 59 y* *age 60 - 79 y*	90.26g (42.5%TE) 88.5 (38.0%TE)	98.9g (39.8%TE) 79.19g (38.0%TE)	ns ns
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Q3 - 72g			*refer Supplementary Table 3 for results*		
The AT/BC Study	Total TAG			*refer Supplementary Table 3 for results*		

Supplementary Table 2. Mean Total Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean Total Fat intake	Endpoint		Comparison of mean intake CHD Event	 No CHD Event	 p-value
Pietnen *et a*l. 1997	Q3- 102.4g					
The Nurses Health Study Hu et al. 1997	Q3 - 37.1%TE			*refer Supplementary Table 3 for results*		
The Health & Lifestyle Survey Bonniface & Teft 2002	men - 734 g/w women - 523 g/w	CHD Death Rate (DR)	*Women*	1.40%	5.20%	0.0025
			Men	6.60%	8.20%	0.1928
The EUROASPIRE Study Erkkila *et al.* 2003	33%TE			*refer Supplementary Table 4 for results*		
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	50th percentile women: 46.0%TE men: 46.9%TE			*refer Supplementary Table 4 for results*		
The Nurses Health Study Oh *et al.* 2005	29%TE			*refer Supplementary Table 3 for results*		
The Strong Heart Study Xu *et al.* 2006	around 72g (35.2%TE)	CHD death	*47 - 59 y*	80.6g (36.9%TE)	77.2g (35.8%TE)	ns
			60 - 79 y	64.4g (33.9%TE)	65.6g (34.1%TE)	ns

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; IHD, ischemic heart disease; TE, total energy; PUFA, polyunsaturated fat; ns, not significant; EPA, eicosapentanoic; DHA, docosahexaenoic; PL, phospholipid; CE, cholesterol ester; g, grams; DR, death rate; Q3, quintile 3; TAG, triacylglycerol.

Supplementary Table 3. Relative Risks of Coronary Heart Disease and Total Fat, Comparing Highest Total Fat Intakes to Lowest Intakes.

Study Name Author, year published	Endpoint			Intakes for Relative Risk Lowest Intake	 Highest Intake	Age-adjusted results (Reference intake is the lowest intake) RR	 Lower 95%CI	 Upper 95%CI	 p-trend
The Framingham Study Posner et al. 1991	CHD Death	*grams*	*45-55y*	90g	118.0g	1.00	0.87	0.14	
		%TE		(30%TE) NCEP Recommendations	(39.7%TE) Sample mean for age group	0.75	0.59	0.95	
		grams	*56-65y*	90g	109.3g	1.05	0.95	1.15	
		%TE		(30%TE) NCEP Recommendations	(38.3%TE) Sample mean for age group	0.99	0.83	1.18	
The Caerphilly Study Fehily *et al.* 1993	Incident IHD			<34.1%TE	>45.8%TE	*no age-adjusted results - refer page 2*			
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI			24%TE	39%TE	1.43	1.13	1.81	0.001
	Fatal CHD					1.83	1.19	2.80	0.001
The AT/BC Study Pietnen *et al*. 1997	Major coronary event			83.2g	121.6g	1.05	0.89	1.29	0.303
	coronary death					0.97	0.76	1.24	0.894
The Nurses Health Study Hu *et al*. 1997	Incident CHD		*Total TAG*	29.1%TE	46.1%TE	1.30	1.07	1.58	0.02
The Nurses Health Study Oh *et al.* 2005	Incident CHD			28.3%TE	44.0%TE	1.26	1.07	1.47	0.001
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*		24.8%TE	46.6%TE	*no age-adjusted results - refer page 2*			
	CHD death	*60 - 79 y*		23.0%TE	44.7%TE				
	CHD event	*whole cohort*		24.0%TE	45.9%TE				
	Nonfatal CHD	*whole cohort*							

Supplementary Table 3.

Study Name				Multivariate Results 1 (Reference Intake is the lowest intake)					Multivariate Results 2 (Reference intake is the lowest intake)				
Author, year published	**Endpoint**			**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
The Framingham Study Posner et al. 1991	CHD Death	*grams*	*45-55y*	0.76	0.60	0.96		Energy adjusted	0.74	0.58	0.94		energy intake, physical activity, serum cholesterol, systolic blood pressure, left ventricular hypertophy, smoking, glucose intolerance, Metropolitan relative weight
		%TE		0.74	0.58	0.93			0.71	0.56	0.9		
		grams	*56-65y*	0.99	0.86	1.14			0.99	0.85	1.15		
		%TE		0.98	0.83	1.17	1.17		1.00	0.83	1.19		
The Caerphilly Study Fehily *et al.* 1993	Incident IHD			1.3				age, BMI, smoking					
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI			1.23	0.96	1.57	0.06	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake,history high blood cholesterol, alcohol and profession	1.02	0.78	1.34	0.42	Further adjusteed for fibre
	Fatal CHD			1.59	1.01	2.51	0.02		1.22	0.75	2.00	0.31	
The AT/BC Study Pietnen *et al*. 1997	Major coronary event			0.87	0.73	1.05	0.295	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity					
	coronary death			0.85	0.65	1.12	0.35						
The Nurses Health Study Hu *et al*. 1997	Incident CHD			1.04	0.83	1.28	0.5	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol					
The Nurses Health Study Oh *et al.* 2005	Incident CHD			0.92	0.77	1.09	0.49	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol.					
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*		3.57	1.21	10.49	0.01	gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol consumption, hypertension, protein and total energy intake					
	CHD death	*60 - 79 y*		0.77	0.41	1.45	0.24						
	CHD event	*whole cohort*		1.03	0.77	1.4	0.97						
	Nonfatal CHD	*whole cohort*		1.12	0.79	1.59	0.71						

Abbreviations: CHD, coronary heart disease; IHD, Ischemic Heart Disease; MI, myocardial infarction; y, years; g, grams; CI, confidence interval; TE, total energy intake; NCEP, The National Cholesterol Education Project; Recc, reccomendation; HR, hazard ratio; BMI, Body Mass Index; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TAG, triacylglycerol.

Supplementary Table 4. Relative Risks of Coronary Heart disease and Incremental Change in Total Fat Intake

Study Name				Effect of increasing total fat intake				
Author, year published	**Endpoint**	**Amount of Energy Increase**		**RR**	**lower 95%CI**	**upper 95%CI**	**p-value**	**adjusted for:**
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI	5% energy Increase		1.01	0.94	1.08		Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake,history high blood cholesterol, fibre , alcohol, history high blood cholesterol, profession
	Fatal CHD	5% energy Increase		1.08	0.95	1.22		
Esry, Joseph & Grover 1996	CHD Death	one unit inrease	*age 30 - 59 y*	1.04	1.01	1.08		age, gender, energy inatke, serum lipids, systolic blood pressure, smoking, BMI, glucose intolerance
		one unit increase	*age 60 - 79 y*	0.99	0.95	1.03		
The Nurses Health Study Hu *et al.* 1997	Incident CHD	5% energy Increase		1.02	0.97	1.07	0.32	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.
The Health & Lifestyle Survey Bonniface & Teft 2002	CHD Death Rate (DR)	100g/week increase	*Women*	1.19	1.03	1.37	0.0181	age, alcohol consumption, smoking, exercise and social class.
		100g/week increase	*Men*	1.01	0.93	1.10	0.8547	
The EUROASPIRE Study Erkkila *et al.* 2003	CAD death	1 standard deviation increase		1.03	0.63	1.7	0.902	age, gender, diagnostic category, energy intake, serum cholesterol TAG, diabetes, BMI, education
	CAD death or AMI	1 sandard deviation increase		1.05	0.73	1.52	0.799	
	Revascularization	1 sandard deviation increase		1.31	0.94	1.13	0.113	
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	CHD Event	5% energy Increase	*women*	1.12	0.93	1.36		Total energy intake, cohort identfication, protein, types of fatty acids familial history MI, smoking, physical activity, education, alcohol, fiber, dietary cholesterol, systolic blood pressure, BMI.
			men	0.98	0.87	1.10		
			women < 60y	1.74	1.15	2.64		
			men < 60y	1.15	0.93	1.41		
			women >60 y	1.05	0.86	1.28		
			men >60y	0.93	0.81	1.06		
The Nurses Heathy Study Oh *et al.* 2005	CHD Event	4% energy increase		0.94	0.81	1.08		Age, BMI, smoking, alcohol, parental history MI, history hypertension, menopausal status & hormone use, physical acivity, energy, protein, cholesterol intake.
The Strong Heart Study Xu *et al.* 2006	CHD death	5% energy Increase	*47 - 59 y*	1.28	1.08	1.52		gender, age, study center, diabetes, BMI, HDL, LDL, TAG, smoking alcohol consumption, hypertension, percentage energy from protein, and total energy intake
		5% energy Increase	*60 - 79 y*	0.91	0.81	1.02		

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; DR, death rate; AMI, acute myocardial infarction; CAD, coronary artery disease; %E, percent energy intake; RR, relative risk; CI, confidence interval; BMI, body mass index; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; TAG, triacylglycerol; HDL, HDL-cholesterol; LDL, LDL-cholesterol.

Supplementary Table 5. Relative Risks of Coronary Heart Disease and *Trans* Fat Comparing Highest Intakes to Lowest Intakes, and Comparing Mean Intakes of Participants with a CHD Event and Those Without. Results from the Prospective Cohort Studies

Study Name				**Comparison of mean intake (or concentration)**			**Intakes (or concentrations) for Relative Risk**		**Age-adjusted results (Reference intake is the lowest intake)**			
Author, year published	**Mean *trans* Fat intake**	**Endpoint**		**CHD (or case)**	**No CHD (or controls)**	**p-value**	**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Nurses Health Study Willett *et al*. 1993 *(subgroup - women who have not changed margarine intake in previous 10 years)*	4.0 g (2.2%TE)	Incident CHD	*total trans (whole cohort)* *total trans (subgoup)* *from vegetable fats (subgroup)* *from animal fats (subgroup)*	NR	NR		2.4g (1.3%TE)	5.7g (3.2%TE)	1.50	1.12	2.00	0.001
The Seven Countries Study Kromhout *et al.* 1995	0.05%TE to 1.84%TE	CHD death	*correlation C18:1 trans and CHD* *r = 0.78 (p<0.001)*									
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Q3 - 1.3%TE	Total MI		NR	NR		1.5g (0.8%TE)	4.3g (1.6%TE)	1.57	1.24	1.98	0.0002
		Fatal CHD							1.99	1.27	3.12	0.005
The AT/BC Study Pietnen *et al*. 1997	Q3 - 2.0%TE	Major coronary event	*total trans*	NR	NR		1.3g	6.2g	1.19	1	1.41	0.055
		coronary death	*Total trans*				1.3g	6.2g	1.38	1.08	1.76	0.006
		coronary death	*Elaidic acid*				1.3g	5.6g	1.35	1.06	1.73	0.004
		coronary death	*vegetable trans*				0.1g	5.1g	1.15	0.91	1.44	0.009
		coronary death	*animal trans*				0.6g	2.5g	1.03	0.80	1.31	0.857
The Nurses Health Study Hu *et al*. 1997	2.2%TE	Incident CHD		NR	NR		1.3%TE	2.9%TE	1.34	1.09	1.64	0.002
The Zutphen Elderly Study Oomen *et al.* 2001	1985: 10.9g (4.3%TE) 1995: 4.4g (1.9%TE)	CHD event	*total trans*				2.36%TE	6.38%TE	2.03	1.24	3.34	0.003
The Physicians Health Study (nested case-control) Albert *et al.* 2002	Total Trans Fatty acids 1.78% total fatty acids	Sudden Cardiac Death (wholeblood fatty acid concentrations))	*total trans (% of total fatty acids)*	1.77%	1.79%	0.55						
			18:1 trans isomers (% of total fatty acids)	1.17%	1.18%	0.67						
			18:2 trans isomers (% of total fatty acids)	41.00%	41.00%	0.17						

Supplementary Table 5.

Study Name			Multivariate Results 1 (Reference Intake is the lowest intake)					Multivariate Results 2 (Reference intake is the lowest intake)				
Author, year published	**Endpoint**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
The Nurses Health Study Willett *et al*. 1993 *(subgroup - women who have not changed margarine intake in previous 10 years)*	Incident CHD	*total trans (whole cohort)*	1.35	1.00	1.82	0.009	Age, smoking, BMI, hypertension, alcohol intake, menopausal status and hormone use, energy intake, family history MI before age 60.	1.57	1.05	2.34	0.002	Further adjusted for SAFA, MUFA alpha-linolenic intake
		total trans (subgoup)						1.67	1.05	2.66	0.002	
		from vegetable fats (subgroup)						1.78	1.12	2.83	0.009	
		from animal fats (subgroup)						0.59	0.3	1.17	0.23	
The Seven Countries Study Kromhout *et al.* 1995	CHD death											
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI		1.40	1.10	1.70	0.01	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake,history high blood cholesterol profession	1.21	0.93	1.58	0.20	further adjusted for fibre
	Fatal CHD		1.78	1.11	2.84	0.04		1.41	0.86	2.32	0.42	
The AT/BC Study Pietnen *et al*. 1997	Major coronary event	*total trans*	1.14	0.96	1.14	0.158	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity					
	coronary death	*Total trans*	1.39	1.09	1.78	0.00						
	coronary death	*Elaidic acid*	1.37	1.07	1.75	0.00						
	coronary death	*vegetable trans*	1.23	0.97	1.55	0.00						
	coronary death	*animal trans*	0.83	0.62	1.11	0.04						
The Nurses Health Study Hu *et al*. 1997	Incident CHD		1.27	1.03	1.56	0.02	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol	1.53	1.16	2.02	0.002	Further adjusted for SFA, MUFA PUFA
The Zutphen Elderly Study Oomen *et al.* 2001	CHD event	*total trans*	2.19	1.32	3.62	0.002	age and energy adjusted	2.00	1.26	3.75	0.03	further adjusted for smoking alcohol intake, vitamin supplement use, SFA, PUFA, MUFA, choleserol and fibre intake.
The Physicians Health Study (nested case-control) Albert *et al.* 2002	Sudden Cardiac Death (wholeblood fatty acid concentrations))	*total trans (% of total fatty acids)*										
		18:1 trans isomers (% of total fatty acids)										
		18:2 trans isomers (% of total fatty acids)										

Supplementary Table 5. Relative Risks of Coronary Heart Disease and *Trans* Fat Comparing Highest Intakes to Lowest Intakes, and Comparing Mean Intakes of Participants with a CHD Event and Those Without. Results from the Prospective Cohort Studies

Study Name / Author, year published	Mean *trans* Fat intake	Endpoint		Comparison of mean intake (or concentration)			Intakes (or concentrations) for Relative Risk		Age-adjusted results (Reference intake is the lowest intake)			
				CHD (or case)	No CHD (or controls)	p-value	Lowest Intake	Highest Intake	RR	Lower 95%CI	Upper 95%CI	p-trend
	Q3 - 1.9%TE	Incident CHD	*whole cohort*	NR	NR		1.3%TE	2.8%TE	1.39	1.19	1.63	<0.0001
The Nurses Health Study		Incident CHD	*age < 65 y*	NR	NR		NR	NR				
Oh *et al.* 2005		Incident CHD	*age > 65y*	NR	NR		NR	NR				
		Incident CHD	*BMI < 25*	NR	NR		NR	NR				
		Incident CHD	*BMI >25*	NR	NR		NR	NR				
		CHD event	*whole cohort*	NR	NR		0.9%TE	3.9%TE				
The Strong Heart Study	around 4.9g (2.4%TE)	Nonfatal CHD	*whole cohort*									
Xu *et al.* 2006		CHD death	*47 - 59 y*	5.1g (2.4%TE)	5.3g (2.3%TE)	ns						
		CHD Death	*60 - 79 y*	4.6g (2.4%TE)	4.6g (2.5%TE)	ns						
			Dietary trans intake	3.1 g/d	3.0 g/d	0.53						
			RBC -total trans	1.78%	1.66%	<0.01	1.17%	2.23%	2.7	1.5	5.0	<0.01
			t16:1n-7	0.13%	0.14%	0.53						
	1.72 % total fatty acids		*t18:1n-12*	0.33%	0.30%	<0.001						
The Nurses Health Study - nested case-control	3.0 %TE	Incident CHD	*t18:1n-9*	0.52%	0.48%	<0.01						
Sun *et al.* 2007			*t18:1n-7*	0.40%	0.38%	0.05						
			total trans 18:1 isomers	1.25%	1.16%	<0.01	0.77%	1.62%	2.4	1.4	4.3	<0.01
			9t 12t 18:-2n-6	0.13%	0.12%	0.05						
			9t 12c 18:-2n-6	0.15%	0.14%	<0.01						
			9t 12c 18:-2n-6	0.10%	0.10%	0.22						
			total 18:2 trans isomers	0.38%	0.36%	0.02	0.25%	0.50%	2.2	1.2	4.1	<0.01

Supplementary Table 5.

Study Name			Multivariate Results 1 (Reference Intake is the lowest intake)					Multivariate Results 2 (Reference intake is the lowest intake)				
Author, year published	**Endpoint**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
	Incident CHD	*whole cohort*	1.33	1.07	1.66	0.01						
The Nurses Health Study	Incident CHD	*age < 65 y*	1.5	1.13	2	0.01	Age, BMI, smoking, alcohol intake, parental history MI					
Oh *et al.* 2005	Incident CHD	*age > 65y*	1.15	0.8	1.66	0.49	hisotry hypertension, menopausal status and hormone use					
	Incident CHD	*BMI < 25*	1.53	1.09	2.15	0.02	aspirin use, multivitamin and vitamin E use, physical activity					
	Incident CHD	*BMI >25*	1.19	0.88	1.6	0.29	energy, protein, cholesterol intake (not clear if adjusted for other fats)					
	CHD event	*whole cohort*	1.06	0.78	1.44	0.88						
The Strong Heart Study	Nonfatal CHD	*whole cohort*	1.21	0.85	1.74	0.41	gender, age, study centre, diabetes, BMI, HDL, LDL, TAG,					
Xu *et al.* 2006	CHD death	*47 - 59 y*	1.15	0.49	2.68	0.66	smoking, alcohol consumption, hypertension, protein and total energy intake					
	CHD Death	*60 - 79 y*	0.83	0.42	1.66	0.54						
		Dietary trans intake										
		RBC -total trans	2.7	1.3	5.6	<0.01		3.3	1.5	7.2	<0.01	
		t16:1n-7										
		t18:1n-12										
The Nurses Health Study - nested case-control	Incident CHD	*t18:1n-9*					Matching factors: age at blood draw, smoking, fasting status, time of blood darw					as per MV1 plus long chain n-3,
Sun *et al.* 2007		*t18:1n-7*					BMI, postmenopausal status and hormone use, physical					total n-6, in red blood cells
		total trans 18:1 isomers	2.5	1.2	5	<0.01	activity, alcohol intake, parental hisotry MI, history	3.1	1.5	6.7	<0.01	
		9t 12t 18:-2n-6					hypertension, hypercholesterolemia, diabetes.					
		9t 12c 18:-2n-6										
		9t 12c 18:-2n-6										
		total 18:2 trans isomers	2.2	1	4.8	0.03		2.8	1.2	6.3	<0.01	

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; NR, not recorded; Q3, qunitile 3; TE, total energy; g, grams; RR, relative risk; CI, confidence interval; BMI, body mass index; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TAG, triacylglycerol.

Supplementary Table 6. Relative Risks of Coronary Heart Disease and Incremental Change in *Trans* Fat Intake

Study Name				Effect of increasing *trans* intake				
Author, year published	**Endpoint**	**Type of *trans* fat**	**Amount of Energy Increase**	**RR**	**lower 95%CI**	**upper 95%CI**	**p-value**	**adjusted for:**
The Nurses Health Study Hu *et al*. 1997	Incident CHD	*total trans*	Each 2%E increase	1.62	1.23	2.13	<0.001	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol
The Nurses Health Study Oh *et al.* 2005	Incident CHD	*total trans*	Each 2%E increase	1.33	1.07	1.66	0.01	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.
The Health Professionals Follow-up Study Ascherio *et al.* 1996; Mozaffarian *et al.* 2006	Total MI	*total trans*	For each 2%E increase	1.13	0.70	1.5	ns	Age, BMI, smoking, physical activity, history of hypertension or high blood cholesterol, family history MI before age 60, energy intake, profession, fibre, total fat
	CHD Event (14 y update)			1.26	0.98	1.62	ns	
The AT/BC Study Pietnen *et al*. 1997	Major coronary event	*total trans*		1.14	0.98	1.3		calculated by Oomen et al. 2001
The Zutphen Elderly Study Oomen *et al.* 2001	CHD event	*total trans*	Each 2%E increase	1.28	1.01	1.61		age, energy, smoking alcohol intake, vitamin supplement use, SFA, profession, fibre, total fat PUFA, MUFA, choleserol and fibre intake.
	Fatal CHD	*total trans*	Each 2%E increase	1.33	0.96	1.86		
	CHD event	*ruminant trans*	Each 0.5%E increase	1.17	0.69	1.98		
	CHD event	*manufactured C18:1 trans*	Each 0.5%E increase	1.05	0.94	1.07		
	CHD event	*other manufactured trans*	Each 0.5%E increase	1.07	0.99	1.15		
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*	Increase of 5%TE	1.73	0.57	5.25		gender, age, study center, diabetes, BMI, HDL, LDL, TAG, smoking alcohol consumption, hypertension, percentage energy from protein, and total energy intake
		60 - 79 y	Increase of 5%TE	1.34	0.48	2.46		
MONICA I & II Jakobsen *et al* . 2008	CHD Event	*whole cohort*	Increase of 0.5g ruminant trans	0.98	0.92	1.05		Gender, systolic blood pressure, family history MI, education, smoking, BMI, physical activity alcohol, protein, SFA, MUFA, PUFA, fiber, cholesterol intakes, and weightedintake of foods containing high amounts of industrially produced trans fats.
		whole cohort	Increase of 0.5%TE ruminant trans	1.05	0.92	1.19		

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; %E, percent of energy; RR, relative risk; CI, confidence interval; BMI, body mass index; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; ALA, alpha-linolenic fatty acid; SFA, saturated fat; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TAG, triacylglycerol.

Supplementary Table 7. Mean Saturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean SAFA Intake (or concentration)	Endpoint			Comparison of mean intake CHD Event	 No CHD Event	 p-value	
The Western Electric Study Paul *et al.* 1963	59g	CHD Event			59g	59g	ns	
Diet and Heart Morris *et al.* 1977	12-18%TE from animal fat (second tertile)	CHD Event	number of events in tertile 1 vs tertile 3	*T1 = 18* *T2 = 14*	ns			
	11-17%TE from dairy fat (second tertile)		number of events in tertile 1 vs tertile 3	*T1 = 13* *T2 = 18*	ns			
The Western Electric Study Shekelle *et al.* 1981	16.7%TE	CHD Death	Logistic Regression Coefficient	*0.031* *p=0.131*	NR	NR		
The Honolulu Heart Study Gordon *et al*. 1981; McGee et al 1984	32g 12.3%TE	Total CHD			32g (12.7%TE)	32 g (12.3%TE)	ns	
		MI or CHD Death			31g (12.9%TE)		<0.05 for %TE	
		Other CHD			31g (12.2%TE)		ns	
The Framingham Study Gordon *et al.* 1981	44g 15.1%TE	Total CHD			43g (15.3%TE)	44g (14.9%TE)	ns	
		MI or CHD Death			39g (14.8%TE)		ns	
		Other CHD			47g (15.9%TE)		ns	
The Puerto Rico Heart Health Program Garcia-Palmieri *et al.* 1980 Gordon et al. 1981	35 g 13.2%TE	Total CHD			35g (13.5%TE)	36g (13.3%TE)	ns	
		MI or CHD Death			33g (13.4%TE)		ns	
		Other CHD			36g (13.6%TE)		ns	
Miettinen *et al.* (nested case-control) 1982	Serum lipids	CHD Event	*Serum Lipids, % of total fatty acids up to 18:3*	*TAG 14:0*	1.76%FA	2.29%FA	<0.05	(other serum lipid fractions not significantly different)
				PL 16:0	36.54%FA	35.17%FA	<0.05	
				PL 18:0	20.04%FA	19.3%FA	<0.05	

Supplementary Table 7. Mean Saturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean SAFA Intake (or concentration)	Endpoint			Comparison of mean intake CHD Event	 No CHD Event	 p-value	
The Zutphen Study Kromhout & de Lezenne Coulander 1984	57g 18%TE	CHD Death			17.7%TE 54.6g	17.6%TE 59.8g	0.82 0.094	
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	17.5%TE	CHD Death			17.4%TE	16.9%TE	0.12	
Salonen *et al.* (nested case-control) 1985	not measured	CHD Death	*Serum fatty acid concentration, mg/L*	*SAFA*	1,026 mg/L	945 mg/L	<0.05	*parital coefficient = 0.00197, p<0.05*
Farchi *et al.* 1989	around 26.5g 8.5%TE	CHD Death			23.8g (8.0%TE)	28.9g (9.0%TE)	<0.05	
The Framingham Study Posner *et al.* 1991	45.3 g (15.2%TE) aged 45-55 y 42.3 g (14.8%TE) aged 56 - 65 y				*refer Supplementary Table 8 for results*			
The Caerphilly Study Fehily *et al.* 1993	74g animal fat	IHD Event			72.1g	76.1g	ns	
Goldbourt, Yaari & Medalie 1993	not noted	CHD Mortality	*event rate / 10,000 person years*	*SFA by grams* *SFA by %TE*	Q1 - 61 Q1 - 48	Q 5 - 49 Q5 - 58		
The Seven Countries Study Kromhout *et al.* 1995	10.1 - 88.6g 3.8 - 22.7%TE	CHD Death	*Correlation*	*r=0.88* *(p<0.01)*				
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Q3 - 24.8 g/day 10.9%TE				*refer Supplementary Table 8 for results*			
Esrey, Joseph & Grover 1996	around 35g (15%TE)	CHD Death		*age 30 - 59 y* *age 60 - 79 y*	40.8g (16.8%TE) 32.7 (13.8%TE)	37.7g (15.1%TE) 29.9g (14.3%TE)		
Ohrvall *et al.* 1996	Serum Lipids	CHD	Serum Lipids, % of total fatty acids	*Myristic* *Palmitic* *Stearic*	1.19%FA 11.94%FA 1.2%FA	1.13%FA 11.65%FA 1.15%FA	0.0065 0.0006 0.0755	
The AT/BC Study Pietnen et al. 1997	Q3 - 50.3 g				*refer Supplementary Table 8 for results*			

Supplementary Table 7. Mean Saturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean SAFA Intake (or concentration)	Endpoint		Comparison of mean intake CHD Event	 No CHD Event	 p-value
Mann *et al.* 1997	women:26.3g/d men: 27.4 g/d	CHD Death	Standardized death Rate (reference intake is tertile 1)	T1 - 100	T3 - 277 (95%CI 125-613)	<0.01
The Nurses Health Study Hu et al. 1997	15.6 %TE (intakes are the cumulative updated averages)			*refer Supplementary Table 8 for results*		
The Physicians Health Study (nested case-control) Albert *et al.* 2002	Total SFA 19.6% total fatty acids	Sudden Cardiac Death	*Serum Lipids, % of total fatty acids* *total SFA*	31.60%	31.30%	0.21
			Palmitic	19.20%	18.80%	0.16
			Stearic	10.60%	10.60%	0.75
The Health & Lifestyle Survey Bonniface & Teft 2002	men - 329 g/w women - 241 g/w	CHD Death Rate	*Women*	Q1 - 2.4%	Q5 - 5.8%	0.0018
			Men	Q1 -7.4%	Q5 - 8.2%	0.4706
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	women: 19.5%TE men: 19.7%TE			*refer Supplementary Table 9 for results*		

Supplementary Table 7. Mean Saturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean SAFA Intake (or concentration)	Endpoint			Comparison of mean intake CHD Event	 No CHD Event	 p-value
The ARIC Study Wang, Folsom & Eckfeldt 2003	Serum Lipids	Incident CHD	*Serum Lipids, % of total fatty acids*	*CE SFA*	11.90%	11.60%	<0.05
				CE Palmitic	10.2	10.00%	<0.05
				CE Stearic	0.96%	0.89%	<0.05
				PL SFA	40.9%	40.60%	<0.05
				PL Palmitic	25.5%	25.40%	ns
				PL Stearic	13.5%	13.30%	<0.05
The Nurses Health Study Oh *et al.* 2005	9.4%TE at 1998				*refer Supplementary Table 8 for results*		
The Baltimore Longitudinal Study of Aging Tucker *et al.* 2005	around 13%TE	CHD death			13.8%TE	12.3%TE	<0.05
The Strong Heart Study Xu *et al.* 2006	11.9%TE	CHD death		*47 - 59 y*	27.7 g (12.6%TE)	26.1 g (12.1%TE)	ns
				60 - 79 y	21.9g (11.5%TE)	2.4g (11.6%TE)	ns
The ARIC Study Yamagishi *et al.* 2008	Serum Lipids (Hazard Ratio)				*refer Supplementary Table 8 for results*		

Abbreviations CHD, coronary heart disease; SFA, saturated fat; MI, myocardial infarction; TE, total energy; TAG, triacylglycerol; PL, phospholipid; CE,cholesterol ester; Q1, Quintile 1; Q3, Quintile 3; Q5, Quintile 5; T1, Tertile 1; T3, Tertile 3; g/w, grams per week.

Supplementary Table 8. Relative Risks of Coronary Heart Disease and Saturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Western Electric Study Shekelle *et al.* 1981	CHD Death	RR calculated from logistic regression		NR	NR	1.03 (p=0.144)			
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	CHD Death	RR calculated from logistic regression		NR	NR	1.07 (p=0.05)			
The Framingham Study Posner *et al.* 1991	CHD Death		*45-55y - grams*	30g	45.3g	0.81	0.64	1.03	
		lowest intake: NECP Recommendations	*%TE*	(10%TE) NCEP Recommendations	(15.2%TE) Sample mean for age group	0.79	0.63	1.00	
		Highest intake: sample mean intake	*56-65y - grams*	30g	42.3g	1.01	0.84	1.22	
			%TE	(10%TE) NCEP Recommendations	(14.8%TE) Sample mean for age group	1.02	0.83	1.26	
The Caerphilly Study Fehily *et al.* 1993	Incident IHD		*animal fat*	≤ 22.3%TE	≥ 36.2%TE	*no age-adjusted results, refer page 2*			
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI			7.2%TE	14.8%TE	1.44	1.14	1.81	0.002
	Fatal CHD					2.55	1.65	3.95	<0.0001
The AT/BC Study Pietnen *et al*. 1997	MACE	*Total SFA*		34.7 g	67.5g	0.99	0.84	1.16	0.672
	coronary death	*Total SFA*				0.83	0.66	1.06	0.329
	CHD Event	C_{12} - C_{16} *SFA*		21.7 g	42.2 g	1.01	0.86	1.18	0.644
	Coronary death	C_{12} - C_{16} *SFA*				0.85	0.67	1.08	0.349
Mann *et al.* 1997	IHD Death			Tertile 1	Tertile 3	2.77	1.25	6.13	<0.01
The Nurses Health Study Hu *et al*. 1997	Incident CHD			10.7%TE	18.8%TE	1.38	1.13	1.68	<0.001

Supplementary Table 8.

Study Name Author, year published	Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The Western Electric Study Shekelle *et al.* 1981	CHD Death												
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	CHD Death												
The Framingham Study Posner *et al.* 1991	CHD Death	*lowest intake: NECP Recommendations* *Highest intake: sample mean intake*	*45-55y grams* *%TE* *56-65y grams* *%TE*	0.82 0.78 1.04 1.06	0.64 0.61 0.86 0.86	1.04 1.00 1.26 1.30		Energy intake, physical activity, serum cholesterol, systolic blood pressure, left ventricular hypertorphy, smoking, glucose intolerance, Mteropolitan Life Insurance Company relative weight.					
The Caerphilly Study Fehily *et al.* 1993	Incident IHD		*animal fat* *OR*	0.9			ns	Age, BMI, smoking, evidence IHD at baseline					
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI Fatal CHD			1.22 2.21	0.96 1.38	1.56 3.54	0.14 0.0016	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity	0.96 1.72	0.73 1.01	1.27 2.9	0.69 0.09	as per MV1 plus fibre
The AT/BC Study Pietnen *et al*. 1997	MACE coronary death CHD Event Coronary death	*Total SFA* *Total SFA* C_{12} - C_{16} *SFA* C_{12} - C_{16} *SFA*		0.87 0.73 0.88 0.74	0.73 0.56 0.74 0.57	1.03 0.95 1.04 0.96	0.189 0.04 0.18 0.045	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity	NR 0.93	NR 0.6	NR 1.44	NR 0.909	as per MV1 plus *trans*, MUFA, linoleic acid
Mann *et al.* 1997	IHD Death												
The Nurses Health Study Hu *et al*. 1997	Incident CHD			1.16	0.93	1.44	0.04	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol	1.07	0.77	1.48	0.37	as per MV 1, plus *trans* fatty acid intake

Supplementary Table 8. Relative Risks of Coronary Heart Disease and Saturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Nurses Health Study Hu *et al*. 1999 (report for individual SFA's)	Incident CHD	*C 4:0 - 10:0*		0.87 %TE	2.00 %TE	1.03	0.85	1.25	0.99
		C12:0 + 14:0		0.98 %TE	2.14 %TE	1.5	1.23	1.83	0.0001
		C16:0		5.82 %TE	10.31 %TE	1.71	1.4	2.08	0.0001
		C18:0		2.61 %TE	4.91 %TE	1.97	1.61	2.42	0.0001
		Sum of 12:0 - 18:0		9.5 %TE	17.2 %TE	1.79	1.47	2.18	0.0001
The ARIC Study Wang, Folsom & Eckfeldt 2003	Incident CHD	*Cholesterol Ester FA*	*SFA*	NR	NR	1.42			0.026
		Cholesterol Ester FA	*Palmitic*	NR	NR	no association			ns
		Cholesterol Ester FA	*Stearic*	NR	NR	increased risk			0.004
		Phospholipid FA	*SFA*	NR	NR	increased risk			0.12
		Phospholipid FA	*Palmitic*	NR	NR	no association			ns
		Phospholipid FA	*Stearic*	NR	NR	increased risk			0.02
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA*	*Palmitic*						
	CAD Death or AMI	*Cholesterol Ester FA*	*Palmitic*	≤ 12.81mol%	≥13.87 mol%				
	Revascularization	*Cholesterol Ester FA*	*Palmitic*						
The Nurses Health Study Oh *et al.* 2005	Incident CHD			10.1%TE	17.6%TE	1.52	1.30	1.79	<0.0001
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*		7.8%TE	16.7%TE				
	CHD Death	*60 - 79 y*		7.2%TE	16.1%TE				
	CHD event	*whole cohort*		7.5%TE	16.5%TE				
	Nonfatal CHD	*whole cohort*							

Supplementary Table 8.

Study Name				Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
The Nurses Health Study Hu *et al*. 1999 (report for individual SFA's)	Incident CHD	*C 4:0 - 10:0*		1.07	0.89	1.3	0.78	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol	1.00	0.82	1.21	0.6	MFUA, PUFA, *Trans* fat, protein, dietary cholesterol, dietary fiber, total energy
		C12:0 + 14:0		1.15	0.94	1.40	0.07		1.05	0.83	1.32	0.46	
		C16:0		1.09	0.89	1.33	0.04		1.03	0.71	1.50	0.45	
		C18:0		1.24	1.01	1.53	0.009		1.16	0.81	1.66	0.30	
		Sum of 12:0 - 18:0		1.14	0.93	1.39	0.03		1.04	0.72	1.48	0.47	
The ARIC Study Wang, Folsom & Eckfeldt 2003	Incident CHD	*Cholesterol Ester FA*	*SFA*	ncreased risk			0.07	Age, gender, smoking, alcohol intake, sports index, special diet, dietary cholesterol, percent energy intake from fat.					
		Cholesterol Ester FA	*Palmitic*	o association			ns						
		Cholesterol Ester FA	*Stearic*	ncreased risk			0.12						
		Phospholipid FA	*SFA*	o association			ns						
		Phospholipid FA	*Palmitic*	o association			ns						
		Phospholipid FA	*Stearic*	ncreased risk			0.04						
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA*	*Palmitic*	0.34	0.09	1.26	0.072	Age, gender, diagnotic category, energy intake, serum choleserol, serum TAG, diabetes, BMI, education.					
	CAD Death or AMI	*Cholesterol Ester FA*	*Palmitic*	0.71	0.29	1.76	0.06						
	Revascularization	*Cholesterol Ester FA*	*Palmitic*	0.77	0.32	1.85	0.347						
The Nurses Health Study Oh *et al.* 2005	Incident CHD			0.97	0.73	1.27	0.93	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.					
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*		5.17	1.64	16.36	0.01	gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol consumption, hypertension, protein and total energy intake gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol consumption, hypertension, protein and total energy intake					
	CHD Death	*60 - 79 y*		0.8	0.41	1.54	0.22						
	CHD event	*whole cohort*		1.11	0.82	1.51	0.45						
	Nonfatal CHD	*whole cohort*		1.15	0.81	1.63	0.24						

Supplementary Table 8. Relative Risks of Coronary Heart Disease and Saturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)					
Author, year published	Endpoint			Lowest Intake	Highest Intake		RR	Lower 95%CI	Upper 95%CI	p-trend	Endpoint
		Cholesterol Ester FA	*SFA*	NR	NR	HR	3.68	2.11	6.4	<0.0	
		Cholesterol Ester FA	*Myristic*	NR	NR	HR	1.7	1.06	2.71	0.005	
		Cholesterol Ester FA	*Pentadecanoic*	NR	NR	HR	0.8	0.5	1.28	0.39	
		Cholesterol Ester FA	*Palmitic*	NR	NR	HR	4.02	2.24	7.21	<0.001	
		Cholesterol Ester FA	*Margaric*	NR	NR	HR	0.81	0.52	1.26	0.38	
The ARIC Study Yamagishi *et al.* 2008	Heart Failure	*Cholesterol Ester FA*	*Stearic*	NR	NR	HR	1.63	1.01	2.62	0.05	
		Phospholipid FA	*SFA*	NR	NR	HR	2.71	1.64	4.45	<0.001	
		Phospholipid FA	*Myristic*	NR	NR	HR	1.29	0.8	2.08	0.42	
		Phospholipid FA	*Pentadecanoic*	NR	NR	HR	0.62	0.38	1.02	0.04	
		Phospholipid FA	*Palmitic*	NR	NR	HR	2.16	1.36	3.43	<0.001	
		Phospholipid FA	*Margaric*	NR	NR	HR	0.55	0.35	0.85	0.008	
		Phospholipid FA	*Stearic*	NR	NR	HR	1.01	0.64	1.58	0.9	

ABBREVIATIONS: SFA, saturated fat; CHD, coronary heart disease; MI, myocardial infarction; IHD, Ischemic Heart Disease; CI, confidence interval; RR, relative risk; TE, total energy; BMI, Body Mass Index; PUFA, polyunsaturated fat; MUFA, monounsaturated fat; LDL, LDL-cholesterol; HDL, HDL-cholesterol; ALA, alpha-linolenic; TAG, triacylglycerol; FA, fatty acid; HDL, HDL-cholesterol; LDL, LDL-cholesterol, CE, cholesterol ester; PL, phospholipid.

Supplementary Table 8.

Study Name	Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The ARIC Study Yamagishi *et al.* 2008										

ABBREVIATIONS: SFA, saturated fat; CHD, LDL-cholesterol; HDL, HDL-cholesterol; ALA

Supplementary Table 9. Relative Risks of Coronary Heart Disease and Incremental Change in Saturated Fat Intake

Study Name				Effect of increasing SAFA intake				
Author, year published	**Endpoint**			**RR**	**lower 95%CI**	**upper 95%CI**	**p-value**	**adjusted for:**
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI		Increase by 5%	0.86	0.66	1.12		age, BI, smoking, alcohol, physical activity, history hypertension or high blood cholesterol, family history MI, energy intake
	Fatal CHD			1.34	0.86	2.08		
Esry, Joseph & Grover 1996	CHD Death	*age 30 - 59 y*	one unit increase SAFA	1.11	1.04	1.18		age, gender, energy intake, serum lipids, systolic blood pressure, smoking, BMI glucose intolerance
		age 60 - 79 y	one unit increase SAFA	0.96	0.88	1.05		
The AT/BC Study Pietnen *et al*. 1997	Coronary death		Increase of 5g	0.90	0.87	0.94		Not noted
The Nurses Health Study Hu *et al*. 1997	Incident CHD		Each 5%E increase	1.14	0.97	1.34	0.12	Fully adjusted
The Nurses Health Study Hu et al. 1999 (report for individual SAFA's)	Incident CHD	*C 4:0 - 10:0*	For 1% energy increase: C 4:0 - 10:0	1.07	0.94	1.23	0.30	Fully adjusted
		C12:0 + 14:0	C12:0 + 14:0	1.14	1.01	1.29	0.03	
		C16:0	C16:0	1.03	0.99	1.07	0.14	
		C18:0	C18:0	1.09	1.02	1.17	0.02	
		Sum of 12:0 - 18:0	For 5% energy increase: Sum of 12:0 - 18:0	1.10	1.00	1.23	0.05	
The Health & Lifestyle Survey Bonniface & Teft 2002	CHD death	*Women*	100g/week increase	1.00	0.86	1.18	0.959	age, alcohol, smoking, exercise, social class
		Men	100g/week increase	1.40	1.09	1.79	0.0074	
The EUROASPIRE Study Erkkila *et al.* 2003	CAD death		1 standard deviation increase	1.01	0.61	1.69	0.966	age, gender, diagnostic category, energy intake, serum cholesterol TAG, diabetes, BMI, education
	CAD death or AMI		1 sandard deviation increase	1.00	0.68	1.46	0.993	
	Revascularization		1 sandard deviation increase	1.19	0.85	1.66	0.304	
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	CHD Event		increase by 5% women	1.36	0.98	1.88		fiber, dietary cholesterol, systolic blood pressure, BMI, cohort, fat intake, energy intake protein intake, family history MI, smoking, physical activity, education, alcohol
			increase by 5%: men	1.03	0.78	1.37		
The Baltimore Longitudinal Study of Aging Tucker *et al.* 2005	CHD death		gram increase in SAFA	1.07	1.03	1.11	<0.001	age at first visit, total energy intake, BMI, smoking, alcohol intake, physical activity score, supplement use.
The Nurses Health Study Oh *et al.* 2005	CHD Event		Increase by 5%	1.01	0.81	1.26	0.93	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.
The Strong Heart Study Xu *et al.* 2006 (results by age)	CHD death	*47 - 59 y*	Increase of 5%TE	HR1.66	1.15	2.42		gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, hypertension, percent energy from protein, total energy intake, all other fats.
		60 - 79 y	Increase of 5%TE	HR 1.45	0.84	2.51		

ABBREVIATIONS: SAFA, saturated fat; MI, Myocardial Infarction; AMI, acute myocardial infarction; CHD, coronary heart disease; RR, relative risk; CI, confidence interval;BMI, Body Mass Index.

Supplementary Table 10. Mean Monounsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes of Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	**Mean MUFA intake**		**Comparison of mean intake (or concentration) between cases and controls**				
Author, year published	**(or concentration) for whole cohort**		**Endpoint**		**CHD Events**	**No CHD Event**	**p-value**
The Honolulu Heart Study	33g		Total CHD		33g (13.2%TE)	33 g (12.8%TE)	ns
Gordon *et al*. 1981;	(12.8%TE)		MI or CHD Death		32g (13.69%TE)		<0.01 for %TE
McGee *et al*. 1984			Other CHD		32g (12.6%TE)		ns
The Framingham Study	47g		Total CHD		45g (14.1%TE)	46g (13.8%TE)	ns
Gordon *et al.* 1981	(16%TE)		MI or CHD Death		43g (14.2%TE)		ns
			Other CHD		48g (14.0%TE)		ns
The Puerto Rico Heart Health Program	37g		Total CHD		35g (16.2%TE)	36g (15.8%TE)	ns
Garcia-Palmieri *et al.* 1980	(13.7%TE)		MI or CHD Death		33g (16.3%TE)		ns
Gordon *et al.* 1981			Other CHD		36g (15.9%TE)		ns
		serum lipid		*TAG 18:1*	43.63%FA	41.96%FA	<0.05
Miettinen *et al.* (nested case-control)	NR	*concentrations*	CHD Event	*CE 18:1*	25.69%FA	25.31%FA	ns
1982		*(% of total fatty acids)*		*PL 18:1*	18.29%FA	17.52%FA	ns
The Zutphen Study	around 59g		CHD Death		56.7g	62.0g	0.094
Kromhout & de Lezenne Coulander 1984	(18.2%TE)				(18.2%TE)	(18.2%TE)	0.997
Farchi *et al.* 1989	around 48g		CHD Death		43.9g	49.5g	<0.05
	(15.4%TE)				14.9%TE	15.9%TE	ns
The Framingham Study	around 46g						
Posner *et al.* 1991	(15.8%TE)						
	M/S ratio		CHD Death Rates (per 10,000 person years)		58	50	
Goldbourt, Yaari & Medalie 1993			Q1 vs Q5				

Supplementary Table 10. Mean Monounsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes of Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	Mean MUFA intake		Comparison of mean intake (or concentration) between cases and controls				
Author, year published	(or concentration) for whole cohort		Endpoint		CHD Events	No CHD Event	p-value
The Seven Countries Study	C18:1cis		Correlation between MUFA intake and CHD:		r= -0.08 (ns)		
Kromhout *et al.* 1995	not noted						
Esrey, Joseph & Grover 1996	around 36g		CHD Death	*age 30 -59 y*	40.9g (16.9%TE)	38.6g (15.5%TE)	
	(15.5%TE)			*age 60 - 79 y*	35.1 (15.1%TE)	30.6g (14.7%TE)	
Ohrvall *et al.*	not measured	*Fatty acid in cholesterol esters*	MI	*CE 18:1 n-9*	19.8%FA	19.5%FA	0.72
1996				*CE 16: 1n-7*	4.11%FA	3.83%FA	0.0163
The AT/BC Study	Q3 - 31.8g						
Pietnen et al. 1997							
The Nurses Health Study	16.0%TE						
Hu et al. 1997							
The Physicians Health Study (nested case-control)	Total MUFA	*Blood fatty acid*	Sudden Cardiac Death	*Total MUFA*	19.8%FA	19.5%FA	0.72
Albert *et al.* 2002	19.6% total fatty acids			*Oleic*	17.2%FA	17.0%FA	0.89
MONICA-1 & MONICA-II	50th percentile						
Jakobsen *et al.* 2003	15.5%TE						
				CE MUFA	18.8%FA	18.6%FA	ns
		serum lipid		*CE Palmitoleic*	2.53%FA	2.58%FA	ns
The ARIC Study		*concentrations*	Incident CHD	*CE Oleic*	16.2%FA	16%FA	<0.1
Wang, Folsom & Eckfeldt 2003		*(% of total fatty*		*PL MUFA*	9.96%FA	9.97%FA	ns
		acids)		*PL Palmitoleic*	0.62%FA	0.64%FA	ns
				PL Oleic	8.62%FA	8.6%FA	ns

Supplementary Table 10. Mean Monounsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes of Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	Mean MUFA intake	Comparison of mean intake (or concentration) between cases and controls				
Author, year published	(or concentration) for whole cohort	Endpoint		CHD Events	No CHD Event	p-value
The Nurses Health Study	Q3 - 13.8%TE					
Oh *et al.* 2005						
The Strong Heart Study	around 28g	CHD death	*47 - 59 y*	30.8 g (14.0%TE)	29.6g (13.7%TE)	ns
Xu *et al.* 2006	(13.5%TE)	CHD Death	*60 - 79 y*	25.2g (13.2%TE)	25.0g (13.0%TE)	ns

Abbreviations: CHD, coronary heart disease; MUFA, monounsaturated fat; MI, myocardial infarction; TE, total energy; TAG, triacyglycerol; CE, cholesterol ester; PL, phospholipid; M/S, monounsaturated fat / saturated fat; Q1, quintile 1; Q3, quintile 3; Q5, quintile 5; ns, not significant; y, years

Supplementary Table 11. Relative Risks of Coronary Heart Disease and Monounsaturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name / Author, year published	Endpoint			Intakes for Relative Risk: Lowest Intake	Intakes for Relative Risk: Highest Intake	Age-adjusted results (Lowest Intake is Comparison Group): RR	Lower 95%CI	Upper 95%CI	p-trend
The Framingham Study Posner *et al.* 1991	CHD Death	*lowest intake: NECP Recommendations* *Highest intake: sample mean intake*	*45-55y*	30g (10%TE) NCEP Recommendations	48.5g (16.2%TE) Sample mean for age group	0.68 0.69	0.50 0.56	0.94 0.94	
			56-65y	30g (10%TE) NCEP Recommendations	44.3g (15.5%TE) Sample mean for age group	1.01 1.15	0.84 0.76	1.22 1.73	
The AT/BC Study Pietnen *et al*. 1997	Major coronary event		*MUFA*	26.0g	37.8g	0.96	0.81	1.13	0.658
	coronary death		*MUFA*	26.0g	37.8g	0.88	0.69	1.11	0.504
	Major coronary event		*Oleic acid*	22.7g	33.1g	0.98	0.83	1.16	0.644
	Coronary death		*Oleic acid*	22.7g	33.1g	0.87	0.69	1.11	0.581
The Nurses Health Study Hu *et al*. 1997	Incident CHD			11.0%TE	19.3%Te	1.30	1.07	1.59	0.004
The ARIC Study Wang, Folsom & Eckfeldt 2003	Incident CHD	*Cholesterol Ester FA*	*MUFA*	NR	NR	no association			ns
		Cholesterol Ester FA	*Palmitoleic*	NR	NR	no association			ns
		Cholesterol Ester FA	*Oleic*	NR	NR	no association			ns
		Phospholipid FA	*MUFA*	NR	NR	no association			ns
		Phospholipid FA	*Palmitoleic*	NR	NR	no association			ns
		Phospholipid FA	*Oleic*	NR	NR	no association			ns
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA*	*Oleic*						
	CAD Death or AMI	*Cholesterol Ester FA*	*Oleic*	≤ 20.05mol%	≥ 22.31 mol%				
	Revascularization	*Cholesterol Ester FA*	*Oleic*						

Supplementary Table 11.

Study Name				Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
The Framingham Study Posner *et al.* 1991	CHD Death	*lowest intake: NECP Recommendations* *Highest intake: sample mean intake*	*45-55y*	0.64	0.47	0.88		Energy intake, physical activity, serum cholesterol, systolic blood pressure, left ventricular hypertorphy, smoking, glucose intolerance, Mteropolitan Life Insurance Company relative weight.					
				0.64	0.48	0.87							
			56-65y	0.99	0.77	1.27							
				1.02	0.78	1.34							
The AT/BC Study Pietnen *et al*. 1997	Major coronary event		*MUFA*	0.82	0.69	0.99	0.186	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity	0.79	0.56	1.1	0.429	as per MV1 plus *trans*, MUFA, linoleic acid
	coronary death		*MUFA*	0.77	0.59	1.00	0.15						
	Major coronary event		*Oleic acid*	0.84	0.70	1.01	0.22						
	Coronary death		*Oleic acid*	0.76	0.59	0.99	0.213						
The Nurses Health Study Hu *et al*. 1997	Incident CHD			1.18	0.95	1.46	0.14	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol	0.95	0.64	1.39	0.57	as per MV 1, plus *trans* fatty acid intake
The ARIC Study Wang, Folsom & Eckfeldt 2003	Incident CHD	*Cholesterol Ester FA*	*MUFA*				ns	Age, gender, smoking, alcohol intake, sports index, special diet, dietary cholesterol, percent energy intake from fat.					
		Cholesterol Ester FA	*Palmitoleic*				ns						
		Cholesterol Ester FA	*Oleic*				ns						
		Phospholipid FA	*MUFA*				ns						
		Phospholipid FA	*Palmitoleic*				ns						
		Phospholipid FA	*Oleic*				ns						
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA*	*Oleic*	1.37	0.35	5.42	0.834	Age, gender, diagnotic category, energy intake, serum choleserol, serum TAG, diabetes, BMI, education.					
	CAD Death or AMI	*Cholesterol Ester FA*	*Oleic*	1.57	0.57	4.39	0.44						
	Revascularization	*Cholesterol Ester FA*	*Oleic*	0.95	0.37	2.45	0.907						

Supplementary Table 11. Relative Risks of Coronary Heart Disease and Monounsaturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name Author, year published	Endpoint			Intakes for Relative Risk Lowest Intake	 Highest Intake		Age-adjusted results (Lowest Intake is Comparison Group) RR	 Lower 95%CI	 Upper 95%CI	 p-trend
The Nurses Health Study Oh *et al.* 2005	Incident CHD			10.6%TE	18.0%TE		1.30	1.11	1.53	0.0003
The Strong Heart Study Xu *et al.* 2006	CHD event	*whole cohort*	*HR*	8.5%TE	18.2%TE					
	non-fatal CHD	*whole cohort*	*HR*	8.5%TE	18.2%TE					
		age 47-59 y	*HR*	8.7%TE	18.6%TE					
		age 60-79y	*HR*	8.2%Te	17.7%TE					
The ARIC Study Yamagishi *et al.* 2008	Heart Failure	*Cholesterol Ester FA*	*MUFA*	NR	NR	HR	2.37	1.47	3.82	0.001
		Cholesterol Ester FA	*Palmitoleic*	NR	NR	HR	2.26	1.39	3.68	<0.001
		Cholesterol Ester FA	*Oleic*	NR	NR	HR	1.8	1.13	2.85	0.004
		Phospholipid FA	*MUFA*	NR	NR	HR	1.36	0.88	2.11	0.32
		Phospholipid FA	*Palmitoleic*	NR	NR	HR	1.67	1.1	2.52	0.01
		Phospholipid FA	*Oleic*	NR	NR	HR	1.38	0.9	2.11	0.17

Supplementary Table 11.

Study Name Author, year published	Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The Nurses Health Study Oh *et al.* 2005	Incident CHD			0.82	0.62	1.10	0.19	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.					
The Strong Heart Study Xu *et al.* 2006	CHD event	*whole cohort*	*HR*	1.09	0.8	1.48	0.64	gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol consumption, hypertension, protein and total energy intake					
	non-fatal CHD	*whole cohort*	*HR*	1.23	0.86	1.76	0.32						
		age 47-59 y	*HR*	3.43	1.17	10.04	0.01						
		age 60-79y	*HR*	0.54	0.27	1.06	0.07						
The ARIC Study Yamagishi *et al.* 2008													

ABBREVIATIONS: SAFA, saturated fat; CHD, coronary heart disease; MI, myocardial infarction; CI, confidence interval; RR, relative risk; HR, Hazard Ratio; TE, total energy; BMI, Body Mass Index; PUFA, polyunsaturated fat; MUFA, monounsaturated fat; NCEP, The National Cholesterol Education Programme; ALA, alpha-linolenic; TAG, triacylglycerol; LDL, LDL-cholesterol; HDL, HDL-cholesterol.

Supplementary Table 12. Relative Risks of Coronary Heart Disease and Incremental Change in Monosaturated Fat Intake

Study Name					Effect of increasing MUFA intake				
Author, year published	**Endpoint**				**RR**	**lower 95%CI**	**upper 95%CI**	**p-value**	**adjusted for:**
Esry, Joseph & Grover 1996	CHD Death	*age 30 - 59 y*	one unit increase MUFA		1.08	1.01	1.16	<0.05	age, gender, energy intake, serum lipids, systolic blood pressure, smoking, BMI.
		age 60 - 79 y	one unit increase MUFA		1.00	0.91	1.08	ns	
The Nurses Health Study Hu *et al*. 1997	Incident CHD		Each 5%E increase		0.84	0.7	1.01	0.06	Fully adjusted
AT/BC Pietinen *et al.* 1997	CHD death		11.8g increase		0.79	0.56	1.10	0.429	age, treatment group, smoking, BMI, blood pressure, intakes of energy, alcohol, fiber, education, physical activity, trans, SAFA & linoleic intake.
MONICA-1 & MONICA-II Jakobsen *et al.* 2004	CHD Event	*women*	increase by 5%	HR	1.01	0.56	1.83		fiber, dietary cholesterol, systolic blood pressure, BMI, cohort, fat intake, energy intake protein intake, family history MI, smoking, physical activity, education, alcohol
		men	increase by 5%	HR	0.95	0.65	1.40		
		women <60y	increase by 5%	HR	2.56	1.15	5.73		
		men >60y	increase by 5%	HR	0.75	0.4	1.41		
		men <60y	increase by 5%	HR	1.37	0.78	2.40		
		men >60y	increase by 5%	HR	0.85	0.57	1.28		
The Nurses Health Study Oh *et al.* 2005	CHD Event		Increase by 5%		0.91	0.72	1.16	0.19	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*	Increase of 5%TE	HR	1.68	1.11	2.53		gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, hypertension, percent energy from protein, total energy intake, all other fats.
		60 - 79 y	Increase of 5%TE	HR	0.82	0.63	1.07		

ABBREVIATIONS: MUFA, monounsaturated fat; SAFA, saturated fat; MI, Myocardial Infarction; CHD, coronary heart disease; RR, relative risk; CI, confidence interval;BMI, Body Mass Index; TE, total energy; HR, hazard ratio; TAG, triacylglycerol.

Supplementary Table 13. Mean Polyunsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name Author, year published	Mean PUFA intake	Endpoint			Comparison of mean intake or serum fatty acid concentration CHD Patiens	Non CHD Participants	p-value	
The Western Electric Study Paul *et al.* 1963	82g	CHD Event		*Unsaturated fat* *Linoleic acid* *Linolenic acid* *Arachidonic Acid*	80g 11.57g 0.66g 0.97	83g 12.28g 0.69g 0.98	ns	
Diet and Heart Morris *et al*. 1977	8.5 - 12% TE marine and vegetable fats and oils (tertile 2) 0.13 - 0.18 P/S ratio (second tertile)	CHD Event	oils: tertile 1 vs tertile 3 P/S: tertile 1 vs tertile 3 (first 5 years)	*T1 = 19* *T2 = 11* *T1 = 20* *T3 = 7*	ns p<0.05			
The Western Electric Study Shekelle *et al.* 1981	not noted	CHD Death	logistic regression:	*-0.258* *p=0.010*				
The Honolulu Heart Study Gordon *et al.* 1984 McGee *et al* 1984	15g (6.0%TE)	Total CHD MI or CHD Death Other CHD			16g (6.7%TE) 16g (6.7%TE) 17g (6.6%TE)	16g (6.0%TE)	<0.01 (%TE) <0.01 (%TE) ns	
The Framingham Study Gordon *et al.* 1981	16g (5.3%TE)	Total CHD MI or CHD Death Other CHD			16g (5.8%TE) 16g (6.0%TE) 16g (5.4%TE)	16g (5.4%TE)	ns ns ns	
The Puerto Rico Heart Health Program Garcia-Palmieri *et al.* 1980 Gordon et al. 1981	14g (5.3%TE)	Total CHD MI or CHD Death Other CHD			15g (6.0%TE) 15g (6.2%TE) 14g (5.7%TE)	14g (5.3%TE)	<0.01 (%TE) <0.01 (%TE) ns	
Miettinen *et al.* (nested case-control) 1982		CHD Event	*% of total fatty acids up to 18:3*	*PL 18:2* *PL 18:3* *PL total PUFA*	23.40% 0.20% 14.63%	26.15% 0.23% 17.74%	<0.05 <0.05 <0.05	(other fractions not significantly different)
The Zutphen Study Kromhout & de Lezenne Coulander 1984	around 19.2g (5.9%TE)	CHD Death			18.3g (5.9%TE)	20.1g (5.9%TE)	0.132 0.979	
The Ireland-Boston Diet-Heart Study	around 2.7%TE	CHD Death	logistic regression:	*-0.069 (p=0.52)*	2.6%TE	2.7%TE	0.73	

Supplementary Table 13. Mean Polyunsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	**Mean PUFA intake**				**Comparison of mean intake or serum fatty acid concentration**		
Author, year published		**Endpoint**			**CHD Patiens**	**Non CHD Participants**	**p-value**
Kushi *et al.* 1985			Proportional Hazards regression:	*-0.070 (p=0.45)*			
Farchi *et al.* 1989	around 11.1g (3.6%TE)	CHD Death			9.2g (3.2%TE)	11.5g (3.7%TE)	<0.01 ns
The Framingham Study Posner *et al.* 1991	15.8g (5.5%TE)				*refer table 14 for results*		
MRFIT	16.8g	All CHD	*Linoleic*	*%TE*	-0.0724 (p<0.1)		<0.1
			α-linolenic	*%TE*	-0.8493 (p<0.05)		<0.05
Dolecek 1992			*18:3n-3 / 18:2n-6*	*ratio*	0.2764		ns
			total n-3 / n-6	*ratio*	-0.5447		ns
Goldbourt, Yaari & Medalie 1993	not noted	CHD Mortality	*Linoleic Acid (not noted if grams or %TE)*	*Age adjusted rates per 10,000 person-years of follow-up*	63	47	
The Seven Countries Study Kromhout *et al.* 1995	lowest 3.4%TE highest 8.6%TE	CHD Death	C18:2CC	Correlation: 0.00	0.36		ns
			EPA + DHA	Correlation: -0.36 (ns)			

Supplementary Table 13. Mean Polyunsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	Mean PUFA intake				Comparison of mean intake or serum fatty acid concentration		
Author, year published		Endpoint			CHD Patiens	Non CHD Participants	p-value
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Linoleic Q3 - 11.0g/d				*refer table 14 for results*		
Esrey, Joseph & Grover 1996	around 14.4g (6.3%TE)	CHD Death	*age 30 - 59 y*		14.3g (6.0%TE)	15.8g (6.5%TE)	ns
			age 60 - 79 y		14.5g (6.4%TE)	12.9g (6.2%TE)	ns
Ohrvall *et al.* 1996	Not measured	MI	*CE 18:2 n-6*	*% of cholesterol ester fatty acids*	52.9%FA	54.1%FA	0.0065
			CE 18:3 n-6		0.74%FA	0.70%FA	0.1091
			CE 18:3 n-3		0.68%FA	0.66%FA	0.2977
			CE 20:3 n-6		0.60%FA	0.57%FA	0.0028
			CE 20:4 n-6		4.73%FA	4.77%FA	0.6158
The AT/BC Study Pietnen et al. 1997	Q3 - 9.6g				*refer table 14 for results*		
The Nurses Health Study Hu et al. 1997	Q3 - 4.6%TE				*refer table 14 for results*		
The Nurses Health Study Hu *et al.* 1999	α-linolenic 1.10g (0.57%TE)				*refer table 14 for results*		
The Zutphen Elderly Study Oomen *et al.* 2001	Linoleic 5.0%TE				*refer table 14 for results*		
The Physicians Health Study (nested case-control) Albert *et al.* 2002	Total PUFA 38.2% total fatty acids	Sudden Cardiac Death	*% of total fatty acids*	*total PUFA*	38.1%FA	38.3%FA	0.65
				linoleic	24%FA	24.2%FA	0.56
				ALA	0.39%FA	0.37%FA	0.28
The Health & Lifestyle Survey Bonniface & Teft 2002	men: 93.7g/week women: 63.1g/week	CHD Death Rate		*Death rates: Women*	2.40%	4.40%	0.4613
				Men	7.40%	9.00%	0.6611
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	6.5%TE				*refer table 14 for results*		

Supplementary Table 13. Mean Polyunsaturated Fat Intakes for All Participants, and Comparison of Mean Intakes Between Participants With a CHD Event and Those Without. Results from the Prospective Cohort Studies.

Study Name	**Mean PUFA intake**				**Comparison of mean intake or serum fatty acid concentration**			
Author, year published		**Endpoint**			**CHD Patiens**	**Non CHD Participants**	**p-value**	
The ARIC Study Wang, Folsom & Eckfeldt 2003	not measured		*Cholesterol Ester FA* *Serum lipid concentrations (% of total fatty acids)*	*CE PUFA*	65.2%FA	65.7%FA	<0.1	(other fractions not significantly different)
				CE n-6	63.7%FA	64.2%FA	<0.05	
				CE 20:3n6	0.78%FA	0.76%FA	<0.05	
				CE arachidonic	7.99%FA	8.25%FA	<0.05	
				PL PUFA	42.5%FA	42.7%FA	<0.1	
				PL α-linolenic	0.14%FA	0.15%FA	<0.05	
				PL n-6	38%FA	38.2%FA	<0.1	
				PL 20:3n6	3.45%FA	3.32%FA	<0.05	
				PL arachidonic	11.2%FA	11.5%FA	<0.05	
The Cardiovascular Health Study, Nested Case-Control Lemaitre *et al.* 2003	not measured	IHD Death	*fatty acid concentrationsof plasma Phospholipids*	*Linoleic*	0.16%FA	0.17%FA	ns	
		Nonfatal MI		*Linolenic*	0.17%FA	0.17%FA	ns	
		IHD Death		*Linoleic*	20.1%FA	19.2%FA	<0.05	
		Nonfatal MI		*Linolenic*	20.3%FA	20%FA	ns	
The Nurses Health Study Oh *et al.* 2005	Q3 - 5.6%TE				*refer table 14 for results*			
The Nurses Health Study, Nested Case-Control Sun et al. 2008	NR	Nonfatal MI	*Plasma Fatty acids*	*Linolenic*	0.55%FA	0.51%FA	0.01	
			Erythrocyte Fatty acids	*Linolenic*	0.19%FA	0.18%FA	0.00	
The Strong Heart Study Xu *et al.* 2006	around 13.1g (6.4%TE)	CHD death	*47 - 59 y*		14.6g (6.8%TE)	14.6g (6.7%TE)	ns	
		CHD Death	*60 - 79 y*		11.2g (5.9%TE)	12.1g (6.3%TE)	ns	

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; TE, total energy; PUFA, polyunsaturated fat; ns, not significant; EPA, eicosapentanoic; DHA, docosahexaenoic; PL, phospholipid; CE, cholesterol ester.

Supplementary Table 14. Relative Risks of Coronary Heart Disease and Polyunsaturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Western Electric Study Shekelle *et al.* 1981	CHD Death		RR calculated from logistic regression	NR	NR	0.77 (p=0.010)			
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	CHD Death		RR calculated from logistic regression	NR	NR	0.93 (p=0.52)			
The Framingham Study Posner *et al.* 1991	CHD Death		*45-55y*	30g	16.5g	1.33	0.92	1.91	
		lowest intake: NECP Recommendations		(10%TE) NCEP Recommendations	(5.5%TE) Sample mean for age group	1.31	0.92	1.85	
		Highest intake: sample mean intake	*56-65y*	30g	15g	1.20	0.85	1.69	
				(10%TE) NCEP Recommendations	(5.4%TE) Sample mean for age group	0.90	0.77	1.05	
MRFIT Dolecek 1992	All CHD	*Linoleic*	*grams*	7.04	25.07	*no age-adjusted results*			
		Linoleic	*%TE*	3.3%TE	8.8%TE				
		ALA	*grams*	0.87g	2.8g				
		ALA	*%TE*	0.4%TE	0.98%TE				
		ALA/linoleic ratio	*ratio*	0.08	0.17				
		total n-3 / n-6 ratio	*ratio*	0.086	0.199				
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI	*Linoleic*		7.6g/d	15.4g/d	1.08	0.85	1.36	0.89
	Fatal CHD					1.28	0.84	1.97	0.41
The AT/BC Study Pietnen *et al*. 1997	MACE	*Total PUFA*		6.6 g	20.7g	1.09	0.93	1.29	0.524
	coronary death	*Total PUFA*				1.15	0.91	1.45	0.156
	MACE	*linoleic*		4.4g	17.6g	1.04	0.89	1.23	0.544
	Coronary death	*linoleic*				1.22	0.97	1.55	0.032
	MACE	*ALA*		0.9g	2.5g	0.94	0.8	1.11	0.716
	Coronary death	*ALA*				0.97	0.68	1.12	0.423
The Nurses Health Study Hu *et al*. 1997	Incident CHD			2.9%TE	6.4%TE	0.89	0.73	1.09	0.28

Supplementary Table 14.

Study Name Author, year published	Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The Western Electric Study Shekelle *et al.* 1981	CHD Death		RR calculated from logistic regression										
The Ireland-Boston Diet-Heart Study Kushi *et al.* 1985	CHD Death		RR calculated from logistic regression										
The Framingham Study Posner *et al.* 1991	CHD Death	*lowest intake: NECP Recommendations*	*45-55y*	1.34	0.93	1.93		Energy intake, physical activity, serum cholesterol, systolic blood pressure, left ventricular hypertorphy, smoking, glucose intolerance, Mteropolitan Life Insurance Company relative weight.					
				1.34	0.95	1.90							
		Highest intake: sample mean intake	*56-65y*	1.26	0.82	1.93							
				1.27	0.89	1.81							
MRFIT Dolecek 1992	All CHD	*Linoleic*	*grams*	0.63				age, race, smoking, blood pressure, HDL, LDL, alcohol					
		Linoleic	*%TE*	0.58	(p<0.1)								
		ALA	*grams*	0.66									
		ALA	*%TE*	0.58	(p<0.05)								
		ALA/linoleic ratio	*ratio*	0.96									
		total n-3 / n-6 ratio	*ratio*	0.90									
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI	*Linoleic*		1.05	0.83	1.34	0.97	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, history high blood cholesterol, profession	1.04	0.82	1.33	0.89	as per MV1 plus fibre
	Fatal CHD			1.30	0.85	2.00			1.28	0.83	1.98	0.41	
The AT/BC Study Pietnen *et al*. 1997	MACE	*Total PUFA*		1.11	0.94	1.31	0.47	(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, educatio and physical activity(age-adjusted results also adjusted for treatment group) smoking, BMI, blood pressure, intakes of energy, alcohol and fiber, education and physical activity					as per MV1 plus *trans*, MUFA, linoleic acid
	coronary death	*Total PUFA*		1.27	1.00	1.61	0.03						
	MACE	*linoleic*		1.06	0.90	1.25	0.48						
	Coronary death	*linoleic*		1.22	0.97	1.55	0.032						
	MACE	*ALA*		0.96	0.80	1.14	0.911						
	Coronary death	*ALA*		0.99	0.76	1.28	0.770						
The Nurses Health Study Hu *et al*. 1997	Incident CHD			0.83	0.67	1.02	0.07	Age, BMI, smoking, physical activity, history of hypertension, family history MI before age 60, energy intake, time period, menopausal status and hormone use, multivitamin use, vitamin E supplement use, alcohol intake, energy from protein, dietary cholesterol	0.68	0.53	0.88	0.003	as per MV 1, plus SFA, MUFA and trans fat

Supplementary Table 14. Relative Risks of Coronary Heart Disease and Polyunsaturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name / Author, year published	Endpoint			Intakes for Relative Risk: Lowest Intake	Intakes for Relative Risk: Highest Intake	Age-adjusted results (Lowest Intake is Comparison Group): RR	Lower 95%CI	Upper 95%CI	p-trend
The Nurses Health Study Hu *et al*. 1999	Fatal CHD	*ALA*		0.71 g/d	1.36 g/d	*no age-adjusted results*			
	Nonfatal CHD								
The Zutphen Elderly Study Oomen *et al.* 2001	Incident CAD	*ALA*		0.4%TE	0.67%TE	2.23	1.32	3.76	0.003
	Fatal CAD	*ALA*		0.4%TE	0.67%TE	1.95	0.96	3.94	0.05
	Incident CAD	*ALA from sources with trans fats*		<0.40%TE	>0.52%TE	2.20	1.30	3.71	0.004
	Incident CAD	*ALA from sources without trans fats*		<0.04%TE	>0.06%TE	0.97	0.58	1.63	0.90
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA*	*Linoleic*						
	CAD Death or AMI	*Cholesterol Ester FA*	*Linoleic*	<46.74	>50.69				
	Revascularization	*Cholesterol Ester FA*	*Linoleic*						
	CAD Death	*Cholesterol Ester FA*	*ALA*						
	CAD Death or AMI	*Cholesterol Ester FA*	*ALA*						
	Revascularization	*Cholesterol Ester FA*	*ALA*						
The Nurses Health Study Albert *et al.* 2005	Sudden Cardiac Death					0.70	0.45	1.07	0.06
	Other CHD Death	*ALA*		0.37%TE	0.74%TE	1.04	0.81	1.33	0.89
	Nonfatal MI					1.14	0.98	1.34	0.11
The Nurses Health Study Oh *et al.* 2005	Incident CHD	*whole cohort*		4.1 %TE	7.4 %TE	0.80	0.69	0.94	0.002
		age < 65 y		NR	NR				
		age > 65 y		NR	NR				
		BMI < 25		NR	NR				
		BMI > 25		NR	NR				

Supplementary Table 14.

Study Name			Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
The Nurses Health Study Hu *et al*. 1999	Fatal CHD	*ALA*	0.71	0.47	1.08	0.03	age and smoking	0.55	0.32	0.94	0.01	as per MV1, plus time period, BMI, smoking, history hypertension, hypercholesterolemia menopausal status, hormone use, parental history MI, vitamin use, alcohol, aspirin use, exercise, SFA, linoleic, vitamin C and E intake, total energy.
	Nonfatal CHD		0.84	0.64	1.08	0.29		0.85	0.61	1.19	0.50	
The Zutphen Elderly Study Oomen *et al.* 2001	Incident CAD	*ALA*	1.68	0.86	3.29	0.17	age, BMI, smoking, vitamin supplement use, SFA, trans fat, linoleic, EPA,DHA other cis unPolyunsaturated fatty acids, protein, energy, dietary cholesterol, fiber, Vitamin E, vitamin C, B-carotene, alcohol intake.					
	Fatal CAD	*ALA*	1.59	0.62	4.08	0.26						
	Incident CAD	*ALA from sources with trans fats*	2.20	1.30	3.71	0.004		1.51	0.75	3.04	0.31	as per MV1, plus *trans* fat intake
	Incident CAD	*ALA from sources without trans fats*	1.17	0.63	2.15	0.63		1.15	0.63	2.11	0.67	
The EUROASPIRE Study Erkkila *et al.* 2003	CAD Death	*Cholesterol Ester FA Linoleic*	1.77	0.48	6.53	0.496	Age, gender, diagnotic category, energy intake, serum choleserol, serum TAG, diabetes, BMI, education.					
	CAD Death or AMI	*Cholesterol Ester FA Linoleic*	0.82	0.31	2.16	0.435						
	Revascularization	*Cholesterol Ester FA Linoleic*	0.98	0.4	2.4	0.939						
	CAD Death	*Cholesterol Ester FA ALA*	0.44	0.1	1.93	0.304						
	CAD Death or AMI	*Cholesterol Ester FA ALA*	0.95	0.35	2.57	0.94						
	Revascularization	*Cholesterol Ester FA ALA*	1.56	0.6	4.09	0.495						
The Nurses Health Study Albert *et al.* 2005	Sudden Cardiac Death		0.63	0.41	0.98	0.02	Age, calories, smoking, BMI, alcohol, menopausal status, hormone use, physical activity, multivitamin use, vitamin E supplement use, history hypertension, hypercholesterolemia, family history MI, history prior CVD.	0.6	0.37	0.96	0.02	further adjusted for trans fat, PUFA to SAFA ratio, omega-3 fatty acids.
	Other CHD Death	*ALA*	0.93	0.73	1.19	0.74		1.01	0.77	1.33	0.74	
	Nonfatal MI		1.05	0.9	1.23	0.62		1.09	0.92	1.29	0.38	
The Nurses Health Study Oh *et al.* 2005	Incident CHD	*whole cohort*	0.75	0.6	0.92	0.004	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin andvimtain E supplement use, physical activity, energy, protein, cholesterol, SFA, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.					
		age < 65 y	0.66	0.5	0.85	0.002						
		age > 65 y	0.96	0.66	1.39	0.60						
		BMI < 25	0.91	0.67	1.26	0.43						
		BMI > 25	0.63	0.47	0.84	0.002						

Supplementary Table 14. Relative Risks of Coronary Heart Disease and Polyunsaturated Fat, Comparing Highest Intakes to Lowest Intakes.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*		3.5%TE	10.4%TE	*no age-adjusted results*			
	CHD Death	*60 - 79 y*		3.4%TE	9.5%TE				
	CHD event	*whole cohort*		3.5%TE	9.9%TE				
	Nonfatal CHD	*whole cohort*		3.5%TE	9.9%TE				
The ARIC Study Yamagishi *et al.* 2008	Heart Failure	*HR for*	*CE n-6 PUFA*			0.34	0.2	0.57	<0.001
			CE linoleic			0.54	0.34	0.88	0.00
			PL n-6 PUFA			0.54	0.34	0.88	0.001
		fatty acid concentrations	*PL linoleic*			0.57	0.36	0.92	0.009
			CE ALA			0.99	0.63	1.53	0.81
			PL ALA			0.97	0.61	1.54	0.88

Supplementary Table 14.

Study Name Author, year published	Endpoint		Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The Strong Heart Study Xu *et al.* 2006	CHD death	*47 - 59 y*	1.47	0.55	3.96	0.78						
	CHD Death	*60 - 79 y*	0.69	0.35	1.36	0.30	gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol					
	CHD event	*whole cohort*	1.12	0.82	1.54	0.69						
	Nonfatal CHD	*whole cohort*	1.18	0.81	1.71	0.55						
The ARIC Study Yamagishi *et al.* 2008												

ABBREVIATIONS: PUFA, Polyunsaturated fat; CHD, coronary heart disease; MI, myocardial infarction; CI, confidence interval; RR, relative risk; TE, total energy; BMI, Body Mass Index; SAFA, saturated fat; PUFA, polyunsaturated fat; MUFA, monounnsaturated fat; LDL, LDL-cholesterol; HDL, HDL-cholesterol; ALA, alpha-linolenic; TAG, triacylglycerol; NECP, National Cholesterol Education Project; CE, cholesterol Ester; PL, phospholipid.

Supplementary Table 15. Relative Risks of Coronary Heart Disease and Incremental Change in Polyunsaturated Fat Intake.

Study Name				Effect of increasing PUFA intake				
Author, year published	**Endpoint**			**RR**	**lower 95%CI**	**upper 95%CI**	**p-value**	**adjusted for:**
The Health Professionals Follow-up Study Ascherio *et al.* 1996	Total MI	*Linoleic*	Increase by 5%	0.97	0.71	1.32	ns	age, BMI, smoking, alcohol, physical activity, history hypertension or high blood cholesterol, family history MI, energy intake , fibre, total fat
	Fatal CHD			0.93	0.52	1.69	ns	
Esry, Joseph & Grover 1996	CHD Death	*age 30 - 59 y*	one unit increase PUFA	0.99	0.9	1.08	ns	age, gender, energy intake, serum lipids, systolic blood pressure, smoking, BMI glucose intolerance
		age 60 - 79 y	one unit increase PUFA	1.00	0.90	1.10	ns	
The Nurses Health Study Hu *et al*. 1997	Incident CHD		Each 5%E increase	0.74	0.55	1.00	0.05	Fully adjusted
AT/BC Pietinen *et al.* 1997	Incident CHD	*Linoleic*	5g increase	0.90	0.65	1.26	0.67	Age, treatment group, smoking, BMI, blood pressure, intakes of energy, alcohol, fiber, education, physical activity.
		Linolenic	1.6g increase	0.75	0.52	1.1	0.05	
The Zutphen Elderly Study Oomen *et al.* 2001	CHD Event	*linolenic*	0.13%E increase	0.90	0.65	1.26	0.67	Age, BMI, smoking, alcohol, vitamin supplement use, SAFA, trans, linoleic, EPA and DHA and other unsaturated fat intake, protein and energy and dietary cholesterol intakes, fiber, vitamin E, C and β-carotene.
	CHD Death	*linolenic*	0.13%E increase	0.75	0.52	1.1	0.05	
The EUROASPIRE Study Erkkila *et al.* 2003	CAD death		1 standard deviation increase	0.92	0.55	1.54	0.758	age, gender, diagnostic category, energy intake, serum cholesterol TAG, diabetes, BMI, education
	CAD death or AMI		1 sandard deviation increase	1.08	0.78	1.51	0.642	
	Revascularization		1 sandard deviation increase	1.1	0.83	1.44	0.516	
The Cardiovascular Health Study, Nested Case-Control Lemaitre *et al.* 2003	IHD Death	*Linoleic*	1 SD increase in PL concentration	0.48	0.24	0.96	0.04	gender, age, clincal site, entry cohort, systoclic bloodpressure, weight, educaiton, fasting plasma glucose
	Nonfatal MI	*Linolenic*	1 SD increase in PL concentration	1.07	0.81	1.41	0.60	
	IHD Death	*Linoleic*	1 SD increase in PL concentration	2.42	1.07	5.43	0.03	
	Nonfatal MI	*Linolenic*	1 SD increase in PL concentration	1.10	0.83	1.46	0.50	
MONICA-1 & MONICA-II Jakobsen *et al.* 2003	CHD Event	*women*	5% Increase	0.89	0.5	1.57		fiber, dietary cholesterol, systolic blood pressure, BMI, cohort, fat, intake, energy intake, protein intake, family history MI, smoking, physical activity, education, alcohol
		men	5% Increase	0.8	0.55	1.15		
The Nurses Health Study Albert *et al.* 2005	Sudden Cardiac Death Other CHD Death Nonfatal MI	*ALA*	0.1% Increase	0.88	0.8	0.98		not clear
The Health Professional's Follow-up Study (Mozaffarian et al. 2005)	Sudden Cardiac Death	*ALA*	1g /day	1.15	0.69	1.93		Age, BMI, physical activity, smoking, history diabetes, hypertension, hypercholesterolemia, aspirin use, alcohol intake, protein SFA fiber MUFA ALA or EPA/DHA
	Nonfatal MI	*ALA*	1g /day	0.82	0.67	1.02		
	CHD Event	*ALA*	1g /day	0.84	0.71	1.00		
	Sudden Cardiac Death	*n-6 PUFA*	5g / day	0.82	0.63	1.06		
	Nonfatal MI	*n-6 PUFA*	5g / day	1.00	0.91	1.11		
	CHD Event	*n-6 PUFA*	5g / day	0.96	0.89	1.04		
The Nurses Health Study Oh *et al.* 2005	CHD Event		Increase by 3%	0.75	0.6	0.92	0.004	Age, BMI, smoking, alcohol intake, parental history MI, history hypertension,menopausal status and hormone use, aspirin, multivitamin and vimtain E supplement use, physical activity, energy, protein, cholesterol, MUFA, PUFA, trans fat, ALA, marine n-3, cereal fiber and fruits and vegetables.

The Strong Heart Study Xu *et al.* 2006 (results by age)	CHD death	*47 - 59 y*	Increase of 5%TE	1.25	0.76	2.06	Gender, age, study centre, diabetes, BMI, HDL, LDL, TAG, smoking, alcohol, hpertension, percent energy from protein, total energy intake.
		60 - 79 y	Increase of 5%TE	0.78	0.52	1.16	

ABBREVIATIONS: PUFA, polyunsaturated fat; MUFA, monounsaturated fat; SAFA, saturated fat; TE, total energy; TAG, triacylglycerol; ALA, alpha linolenic; DHA, docosahexaenoic acid; EPA, eicosapentaenoic; MI, Myocardial Infarction; CHD, coronary heart disease; RR, relative risk; CI, confidence interval;BMI, Body Mass Index; AMI, acute MI.

Supplementary Table 16. Prospective Cohorts and Nested Case-Control Studies Investigating Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intakes and Coronary Heart Disease.

Study Name Author, year published	Country	Start of Study (year)	Follow-up (years)	*n*	Participants	Men (%)	Age at Baseline (years)	Exclusions	Diet assessment method	CHD Endpoint	*n* events	Event Rate (%)
The Zutphen Study Kromhout *et al.* 1985	Netherlands	1960	20	852	Community based sample	100	40-59	Previous CHD	Dietary history	CHD Death	78	9.2
Norell et al. 1986	Sweden	1967	14	10,966	Community based sample		40 - 80	Previous symptoms of CVD.	FFQ	CHD Death	800	7.3
The Health Professionals Follow-up Study Asherio et al. 1995	USA	1986	6y	44,895	Male health workers	100	40-75	CVD at baseline, inadequate completion of FFQ, unlikely Energy intake	FFQ	Total MI Fatal CHD	734 229	1.6 0.5
Physicians' Health Study Morris et al.1995	USA	1982	4y	21,185	Male Physicians	100	40-84	History of MI, stroke, TIA, cancer, liver or renal disease, peptic ulcer, gout, current use of aspirin, other platelet active drugs or NSAIDs, reported CV event or died in rst year, incomplete completion of FFQ	Semi-quantitative FFQ	Total MI	284	1.3
The Seven Countries Study Kromhout *et al.* 1995	7 countries	1958	25y	12,763	Various	100	40-59	Not provided.	Weighed diet records.	CHD Death		5 - 28%
Ohrvall *et al.* 1996	Sweden	1970	19	2,016	Men living in Uppsala no previous CHD (82% response rate)	100	50	Presence of CHD (but men with hypertension, hyperlipidemia, or impaired glucose intolerance reamined in study and treatment initiated).	Serum Fatty Acid concentrations collected from 1,746 subjects (87%)	MI	180	9
The AT/BC Study Pietenen et al. 1997	Finland	1985	6.1	21,930	Male smokers	100	50-69	Previous cancer, serious disease, use of anti-coagulants, excess use of vit E, b-carotene or vit A, prior MI, DM, angina, or missing data on CV risk factors	FFQ completed at baseline	Major Coronary Events Coronary Death	1,399 581	6.4 2.6
The Chicago Western Electric Study Daviglus et al. 1997	US	1957	30	1,822	Employees of the Chicago Western Electric		40-55	Did not attend second follow-up (one year after starting), prior history CHD, missing data.	Dietary History completed at baseline and one year later.	Fatal MI CHD Death	293 430	
Mann *et al.* 1997	UK	1981	13.3	10,802	Vegetarians and non-vegetarian friends and relatives	38	mean 34y	not clear	FFQ completed at baseline	IHD Death	64	0.6
Physicians' Health Study, Nested Case-Control Albert et al. 1998	USA	1982	17y	22,071	Male Physicians	100	40-84	History of MI, stroke, TIA, cancer	Blood fatty acid concentrations	Sudden Cardiac Death	94 cases, 184 controls	

Supplementary Table 16. Prospective Cohorts and Nested Case-Control Studies Investigating Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intakes and Coronary Heart Disease.

Study Name Author, year published	Country	Start of Study (year)	Follow-up (years)	*n*	Participants	Men (%)	Age at Baseline (years)	Exclusions	Diet assessment method	CHD Endpoint	*n* events	Event Rate (%)
The Seven Countries Study	Italy	1960	20y	1,097	Men aged 40-59	100	40-59	Unclear	dietary, cross-checked dietetic interview (habitual food consumption) and food frequency checklist	CHD Death	116	10.6
Oomen *et al.* 2000	Netherlands	1960	20y	553	Men aged 40-59	100	40-59	Unclear			105	20
	Finland	1959	20y	1,088	men agen 40-59	100	40-59	Unclear			242	22
The Kuopio Ischaemic Heart Disease Risk Factor Study Rissanen *et al.* 2000	Finland	1984	10	1,871	Males, otherwise unclear	100	42-60	Unclear	Serum fatty acids.	Acute coronary event	194	10.4
Yuan et al. 2001	China	1986	9.8y	18,037	Community based sample.	100	45-64	History of cancer	FFQ - validated in subgroup from 24-hr recall	Fatal CHD	113	0.6
Swedish Nested Case-Control Hallgren *et al.* 2001	Sweden	1985	9 y	405	Community based sample.	79	mean 55	Cancer, inadequate amount of blood collected for FA analysis. Controls - previous AMI or stroke.	Erythrocyte Fatty Acid Concentrations	MI	78 cases 156 controls	
The Nurses Health Study Hu et al. 2002	USA	1976	16y	84,688	Nurses	0	30-55	Excluded those with previous cancer, CVD or poor completion of FFQ	Semi-quantitative FFQ	CHD Event Fatal CHD Nonfatal MI	1,513 484 1,029	1.8 0.6 1.2
The Physcian's Heath Study Ablert *et al.* 2002	USA	1982	17 y	22,071	Male physicians, no previous CHD	100	40 - 84	History of MI, stroke, transient ischemic attack, cancer	Blood Fatty Acid concentrations, collected at baseline	Sudden cardiac death	94 cases	NA
The Cardiovascular Health Study, Nested Case-Control Lemaitre *et al.* 2003	US	1989		5,201	Community based sample.		≥ 65 y	IHD and stroke at baseline, & use of fish oil supplements at baseline.	Plasma Phospholipid fatty acid concentrations	Fatal CHD Nonfatal MI	54 cases 125 cases	
EUROASPIRE Erkkila *et al.* 2003	Finland	1991	5	415	Patients with clinically established CAD	68	<71	18% declined to participate	Serum cholesterol ester and serum phospholipids fatty acids	CAD Death CAD Death or AMI Revascularization	16 34 38	4 8.5 9.5
MONICA I, II & III Osler *et al.* 2003	Denmark	1982	5 - 15	7,610	Community based sample.	53	30-70	Incomplete data. No other exclusions reported.	FFQ	CHD Event	491	6.4

Supplementary Table 16. Prospective Cohorts and Nested Case-Control Studies Investigating Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intakes and Coronary Heart Disease.

Study Name Author, year published	Country	Start of Study (year)	Follow-up (years)	*n*	Participants	Men (%)	Age at Baseline (years)	Exclusions	Diet assessment method	CHD Endpoint	*n* events	Event Rate (%)
The Cardiovascular Health Study Mozaffarian et al. 2003	US	1989	9.3y	3,910	Community based sample.		≥ 65 y	CVD at baseline, incomplete dietary data.	FFQ, and plasma phospholipid fatty acid concentrations.	IHD Death	247	6.3
										Arrhythmic IHD Death	148	3.8
										Nonfatal MI	363	9.3
The Atherosclerosis Risk in Communities Study Wang *et al.* 2003	US	1987	10.7y	3,591	Community based sample.	46		Prevalent CHD.	Cholesterol Ester & Phospholipid fatty acid concentrations	CHD Event	282	7.8
The Iowa Women's Health Study Folsom & Demissie 2004	US	1986	around 11 y	41,836	Community based sample.	0	55-69	Previous CVD or cancer.	FFQ	CHD Death	922	2.2
The Health Professionals Follow-up Study Mozaffarian et al. 2005	USA	1986	14 y	45,722	Male health workers	100	40-75	CVD at baseline, inadequate completion of FFQ, unlikely Energy intake	FFQ	Nonfatal MI	1,521	3.3
										Sudden Cardiac Death	218	0.5
										CHD Event	2,306	5
NIPPON DATA80 Nakamura et al. 2005	Japan	1980	19	8,879	Community based sample.	44	30 years and over	Past history CAD, stroke, cancer or significant comorbidities, missing information and loss to follow-up.	FFQ	CHD Death	124	1.4
Jarvinen et al. 2006	Finland	1966	21.5	5,220	Community based sample.	53	30-79	No CHD.	Dietary History	CHD Death men	335	12
										CHD Death women	163	6.7
The Japan Public Health Center-Based Study Cohort 1 Iso *et al.* 2006	Japan	1990	11	41,578	Community based sample.		40-59	Previous diagnosis cancer or CVD.	FFQ completed baseline at 5 years later	CHD Event	258	0.6
										MI	221	0.5
										Sudden Cardiac Death	37	0.1
The Nurses Health Study, Nested case-control Sun *et al.* 2008	US	1976	6	32,826	Nurses		30-55	Previous CHD.	Plasma fatty acid concentrations	Nonfatal MI	146 cases 288 controls	
Zutphen Study Steppel *et al*. 2008	Netherlands	1960	40	1,373	Community based sample.		40-59	No previous CHD	Dietary History	CHD Death	348	25
The ARIC Study Yamagishi *et al.* 2008	US	1987	14.3	3,592	Community based sample.	46	45 - 64	History CHD, stroke, or heart failure, or those without plasma fatty acid data, and non-white subjects.	Plasma Fatty Acids	Heart Failure	195	5.4

Supplementary Table 16. Prospective Cohorts and Nested Case-Control Studies Investigating Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intakes and Coronary Heart Disease.

Study Name		Start of Study	Follow-up			Men	Age at Baseline	Exclusions	Diet assessment method	CHD Endpoint	*n* events	Event Rate (%)
Author, year published	**Country**	**(year)**	**(years)**	***n***	**Participants**	**(%)**	**(years)**					

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; DM, diabetes melitis; TIA, transient ischemic attack; IHD, ischemic heart disease; AMI, acute myocardial infarction; CAD, coronary artery disease; FFQ, food frequency questionnaire.

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The Zutphen Study Kromhout *et al.* 1985	CHD Death	*fish consumption*		0	≥ 45 g/day	*age adjusted RR not reported*			
Norrel *et al.* 1986	CHD Death	*fish intake*		low	high	0.85	0.69	1.06	
	Fatal MI					0.7	0.5	0.98	
The Adventist Health Study Fraser et al. 1992	Nonfatal MI Fatal CHD	*fish intake* *fish intake*		Never	≥ 1 serve/week				
The Health Professionals Follow-up Study Ascherio *et al.* 1995	CABG	*Fish intake*		<1 / month	≥ 6/wk	1.73	1.1	2.72	0.01
	Nonfatal MI	*Fish intake*		<1 / month	≥ 6/wk	0.95	0.63	1.42	0.97
	Fatal CHD	*Fish intake*		<1 / month	≥ 6/wk	0.82	0.45	1.52	0.19
	any MI	*Fish intake*		<1 / month	≥ 6/wk	0.91	0.64	1.28	0.47
	Any CHD	*Fish intake*		<1 / month	≥ 6/wk	1.16	0.89	1.53	0.17
	CABG	*Omega 3 intake*		0.01 - 0.11 g/day	0.42 - 6.52 g/day	1.27	1.01	1.6	0.01
	Nonfatal MI	*Omega 3 intake*		0.01 - 0.11 g/day	0.42 - 6.52 g/day	1.13	0.89	1.45	0.69
	Fatal CHD	*Omega 3 intake*		0.01 - 0.11 g/day	0.42 - 6.52 g/day	1.06	0.72	1.55	1.00
	any MI	*Omega 3 intake*		0.01 - 0.11 g/day	0.42 - 6.52 g/day	1.13	0.91	1.39	0.65
	Any CHD	*Omega 3 intake*		0.01 - 0.11 g/day	0.42 - 6.52 g/day	1.19	1.02	1.39	0.03
The Physicians Health Study Morris *et al.* 1995	Total MI	*fish consumption*		< 1 serve/week	≥ 5 serves/week	1.2	0.6	2.2	0.34
	Nonfatal MI					1.1	0.6	2.2	0.79
The Seven Countries Study Kromhout *et al.* 1995	CHD Death	*correlation EPA + DHA*	*r= -0.36 (ns)*						
Ohrvall *et al.* 1996	CHD Death	*comparison of mean cholesterol ester fatty acids*	*EPA*	Healthy: 1.35%FA	MI: 1.45%FA	p=0.0778			
			DHA	Healthy: 0.70%FA	MI: 0.72%FA	p=0.32988			

Supplementary Table 17.

Study Name Author, year published	Endpoint		Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The Zutphen Study Kromhout *et al.* 1985	CHD Death	*fish consumption*	0.39	0.13	1.15	nr	age, systolic blood pressure, serum total cholesterol, smoking, subscapular skinfold, physical activity, energy intake, dietary cholesterol, prescribed diet, occupation					
Norrel *et al.* 1986			no multivariate results									
The Adventist Health Study Fraser et al. 1992			1.04 0.74	0.55 0.42	1.96 1.33		Age, gender, smoking, exercise, relative weight, high blood pressure.					
The Health Professionals Follow-up Study Ascherio *et al.* 1995	CABG	*Fish intake*	1.65	1.03	2.64	0.02	Age, energy, BMI, smoking, alcohol, hypertension, diabetes, hypercholesterolemia, family history MI, profession.					
	Nonfatal MI	*Fish intake*	0.96	0.63	1.47	0.62						
	Fatal CHD	*Fish intake*	0.77	0.41	1.44	0.14						
	any MI	*Fish intake*	0.9	0.63	1.28	0.7						
	Any CHD	*Fish intake*	1.14	0.86	1.51	0.19						
	CABG	*Omega 3 intake*	1.16	0.92	1.47	0.09						
	Nonfatal MI	*Omega 3 intake*	1.09	0.85	1.41	0.44						
	Fatal CHD	*Omega 3 intake*	1.03	0.7	1.52	0.94						
	any MI	*Omega 3 intake*	1.09	0.88	1.35	0.48						
	Any CHD	*Omega 3 intake*	1.12	0.96	1.31	0.09						
The Physicians Health Study Morris *et al.* 1995	Total MI	*fish consumption*	0.9	0.4	1.8	0.72	Age, group assignment, smoking, alcohol, obesity, diabetes, vigorous exercise, parental history MI, history hypertension or hypercholesterolemia, vitamin supplement use, SFA intake.					
	Nonfatal MI		0.8	0.4	1.7	0.79						
The Seven Countries Study Kromhout *et al.* 1995			no multivariate results									
Ohrvall *et al.* 1996			no multivariate results									

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
AT/BC Pietinen *et al.* 1997	CHD Event	*omega-3 fish fatty acids*		0.2g	0.8g	1.10	0.94	1.30	0.298
	CHD Death	*omega-3 fish fatty acids*		0.2g	0.8g	1.23	0.97	1.56	0.130
	CHD Event	*ALA*		0.9g	2.5g	0.94	0.8	1.11	0.716
	CHD Death	*ALA*		0.9g	2.5g	0.97	0.68	1.12	0.423
The Chicago Western Electric Study Daviglus *et al.* 1997	CHD Death	*Fish intake*		0	≥ 35 g/day				
	Fatal MI								
Mann *et al.* 1997	CHD Death	*Fish intake*		0	≥1 serve/week				
The Physicians Health Study Albert et al. 1998	Sudden Cardiac Death	*Fish intake*		<1 serve / month	≥ 1 serve / week	0.44	0.22	0.86	0.006
	Sudden Cardiac Death	*Dietary omega-3*		< 0.3 g/m	≥ 7.4 g/m	0.4	0.19	0.85	0.13
	Nonsudden Cardiac Death	*Fish intake*		<1 serve / month	≥ 1 serve / week				
	CHD Death	*Fish intake*		<1 serve / month	≥ 1 serve / week				
	MI	*Fish intake*		<1 serve / month	≥ 1 serve / week	1.02	0.64	1.62	0.75
The Kuopio Ischaemic Heart Disease Risk Factor Study Rissanen *et al.* 2000	Acute Coronary Events	*serum DHA + DPA*		<2.38%	3.08% to 3.58%				
The Seven Countries Study Oomen *et al.* 2000	CHD Mortality	*Fish intake*	*Finland*	0-19 g/day	≥ 40 g/day	1.39	1.00	1.92	0.05
			Italy	0	≥ 40 g/day	0.56	0.27	1.13	0.11
			The Netherlands	0	≥ 20 g/d	1.13	0.71	1.8	0.6

Supplementary Table 17.

Study Name / Author, year published	Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
AT/BC Pietinen *et al.* 1997	CHD Event	*omega-3 fish fatty acids*		1.15	0.97	1.35	0.12	age, treatment group, smoking, BMI, blood pressure, intakes of energy, alcohol, fiber, education and physical activity.					
	CHD Death	*omega-3 fish fatty acids*		1.24	0.97	1.58	0.12		1.30	1.01	1.67	0.06	further adjusted for trans, cis-MUFA, SFA
	CHD Event	*ALA*		0.99	0.76	1.28	0.77						
	CHD Death	*ALA*							0.75	0.52	1.1	0.05	
The Chicago Western Electric Study Daviglus *et al.* 1997	CHD Death	*Fish intake*		0.62	0.4	0.94	0.04	age, education, religion, systolic pressure, serum cholesterol, smoking, BMI, diabetes, ECG abnormalities, energy, cholesterol, SFA, MUFA, PUFA, total protein, vitamins and minerals, alcohol.					
	Fatal MI			0.56	0.33	0.93	0.017						
Mann *et al.* 1997	CHD Death	*Fish intake*		1.23	0.7	2.17	ns	age, gender, smoking and social class					
The Physicians Health Study Albert et al. 1998	Sudden Cardiac Death	*Fish intake*		0.48	0.24	0.96	0.03	age, aspirin and beta carotene treatment assignment, evidence of CVD prior to 12-month questionnaire, BMI, smoking, diabetes, history hypertension or hypercholesterolemia, alcohol, vigorous exercise, vitamin E, vitamin C and multivitamin use.					
	Sudden Cardiac Death	*Dietary omega-3*		0.43	0.2	0.93	0.21						
	Nonsudden Cardiac Death	*Fish intake*		1.25	0.46	3.43	0.31						
	CHD Death	*Fish intake*		0.87	0.48	1.56	0.26						
	MI	*Fish intake*		1.00	0.62	1.6	0.67						
The Kuopio Ischaemic Heart Disease Risk Factor Study Rissanen *et al.* 2000	Acute Coronary Events	*serum DHA + DPA*		0.56	0.35	0.89	0.014	age, examination years, BMI, maximal oxygen uptake, hair mercury content, serum ferritin, serum LDL, blood pressure, serum insulin, ADP-induced platelet aggregation, SES, ischemic findings in exercise test, smoking, place of residence, energy intake.					
The Seven Countries Study Oomen *et al.* 2000	CHD Mortality	*Fish intake*	*Finland*	1.31	0.94	1.84	0.12	Age, BMI, smoking, energy intake.	1.25	0.89	1.76	0.2	further adjsuted for vegetable and fruit, alcohol, meat, butter, margarine
			Italy	0.69	0.34	1.42	0.38		0.67	0.33	1.39	0.33	
			The Netherlands	1.16	0.72	1.86	0.55		1.1	0.68	1.79	0.69	

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
	Acute MI	*Fish / Shellfish*		< 50 g/w	≥ 200 g/w					
	Acute MI	*Fish only*		< 30 g/w	≥ 150 g /w					
Yuan et al. 2001	Acute MI	*Shellfish only*		< 10 g/w	≥ 100 g/w					
	Other Ischemic Heart Disease	*Fish / Shellfish*		< 50 g/w	≥ 200 g/w					
	Other Ischemic Heart Disease	*Fish only*		< 30 g/w	≥ 150 g /w					
	Other Ischemic Heart Disease	*Shellfish only*		< 10 g/w	≥ 100 g/w					
	Acute MI	*Omega 3 from seafood*		< 0.27 g/w	≥ 1.10 g/w					
	Other Ischemic Heart Disease	*Omega 3 from seafood*		< 0.27 g/w	≥ 1.10 g/w					
Zutphen Elderly Study Oomen *et al.* 2001	CHD Event	*ALA*		<0.45%TE	>0.58%TE		2.23	1.32	3.76	0.003
	CHD Death	*ALA*		<0.45%TE	>0.58%TE		1.95	0.96	3.94	0.05
Swedish Nested Case-Control Hallgren *et al.* 2001	MI	*fatty fish consumption*		< 1 / week	≥ 1 / week	OR	0.85	0.45	1.62	nr
		Erythrocyte EPA + DHA		≤5.5%FA	> 6.5%FA	OR	0.43	0.21	0.88	0.02
The Nurses' Health study Hu *et al.* 2002	CHD Event	*Fish intake*		<1 / month	≥ 5 times / week		0.64	0.48	0.86	<0.001
	Fatal CHD	*Fish intake*		<1 / month	≥ 5 times / week		0.55	0.33	0.91	0.01
	Nonfatal MI	*Fish intake*		<1 / month	≥ 5 times / week		0.77	0.54	1.11	0.1
	CHD Event	*Omega 3 intake*		0.03%TE	0.27%TE		0.52	0.43	0.62	<0.001
	Fatal CHD	*Omega 3 intake*		0.03%TE	0.27%TE		0.63	0.45	0.88	<0.001
	Nonfatal MI	*Omega 3 intake*		0.03%TE	0.27%TE		0.69	0.55	0.88	<0.001
The Physicians' Health Study - nested case-control Albert *et al.* 2002	Sudden Cardiac Death	*Total LCPUFA*	*% blood fatty acids*	3.58%	6.87%					

Supplementary Table 17.

Study Name				Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
Yuan et al. 2001	Acute MI	*Fish / Shellfish*		0.41	0.22	0.78	0.03	age, smoking, total energy intake, education, BMI, alcohol, history hypertension or diabetes					
	Acute MI	*Fish only*		0.35	0.17	0.72	0.02						
	Acute MI	*Shellfish only*		0.4	0.14	1.12	0.02						
	Other Ischemic Heart Disease	*Fish / Shellfish*		0.68	0.32	1.46	0.37						
	Other Ischemic Heart Disease	*Fish only*		0.92	0.41	2.06	0.34						
	Other Ischemic Heart Disease	*Shellfish only*		0.58	0.17	1.92	0.99						
	Acute MI	*Omega 3 from seafood*		0.43	0.23	0.81	0.02						
	Other Ischemic Heart Disease	*Omega 3 from seafood*		0.71	0.32	1.57	0.68						
Zutphen Elderly Study Oomen *et al.* 2001	CHD Event	*ALA*		1.68	0.86	3.29	0.17	Age, BMI, ex-smoking, alcohol intake, use of vimtamin supplements, SFA, *trans* fatty acids, linoleic acid, EPA, DHA, *cis* MUFA, protein, energy, fiber, vitamin E, vitamin C, beta-carotene.					
	CHD Death	*ALA*		1.59	0.62	4.08	0.26						
Swedish Nested Case-Control Hallgren *et al.* 2001				no multivariate results									
The Nurses' Health study Hu *et al.* 2002	CHD Event	*Fish intake*		0.66	0.5	0.89	0.001	age, time periods, smoking, BMI, alcohol, menopausal status & postmenopausal hormone use, physical activity, aspirin use, vitamin E supplement use, history hypertension, hypercholesterolemia and diabetes.	0.69	0.52	0.93	0.007	
	Fatal CHD	*Fish intake*		0.55	0.33	0.9	0.01		0.55	0.33	0.91	0.01	
	Nonfatal MI	*Fish intake*		0.73	0.51	1.04	0.03		0.77	0.54	1.11	0.1	further adjusted for *trans* fat, P/S, dietary fiber
	CHD Event	*Omega 3 intake*		0.67	0.55	0.81	<0.001		0.69	0.57	0.84	<0.001	
	Fatal CHD	*Omega 3 intake*		0.63	0.45	0.88	<0.001		0.62	0.44	0.88	<0.001	
	Nonfatal MI	*Omega 3 intake*		0.69	0.55	0.88	<0.001		0.73	0.57	0.93	0.003	
The Physicians' Health Study - nested case-control Albert *et al.* 2002	Sudden Cardiac Death	*Total LCPUFA*	*% blood fatty acids*	0.31	0.13	0.75	0.004	age and smoking	0.19	0.05	0.71	0.007	further adjusted for treatment group, BMI, diabetes, hypertension, hypercholesterolemia, alcohol, exercise, parental history MI

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk			Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
	CAD Death	*fish intake*		0	> 57 g/day					
	CAD death or AMI	*Fish intake*		0	> 57 g/day					
The EUROASPIRE Study	Revascularization	*Fish intake*		1	> 57 g/day					
Erkkila *et al.* 2003	CAD Death	*EPA*	*mol% serum cholesteryl esters*	<1.34%	>2.11%					
	CAD death or AMI	*EPA*		<1.34%	>2.11%					
	Revascularization	*EPA*		<1.34%	>2.11%					
The Cardiovascular Health Study, Nested Case-Control	IHD Death	*Plasma PL*	*DHA + EPA*	cases: 3.3%FA	controls: 3.8%FA	p<0.05				
Lemaitre *et al.* 2003	Nonfatal MI	*Plasma PL*	*DHA + EPA*	cases: 3.6%FA	controls: 3.7%FA	ns				
MONICA I, II & III Osler *et al.* 2003	CHD Event		*fish consumption*	1 serve week	≥ 2 serves / week					
	CHD Death									
The Atherosclerosis Risk in Communities Study	Incident CHD	*CE*	*EPA*	CHD: 0.57%FA	NonCHD: 0.54%FA	ns				
		CE	*DHA*	CHD: 0.44%FA	NonCHD: 0.44%FA	ns				
Wang *et al.* 2003		*PL*	*EPA*	CHD: 0.58%FA	NonCHD: 0.56%FA	ns				
		PL	*DHA*	CHD: 2.81%FA	NonCHD: 2.80%FA	ns				
The Iowa Women's Health Study Folsom & Demissie 2004	CHD Death		*fish consumption*	<0.5 serves/week	≥ 2.5 serves /week		0.95	0.76	1.2	0.02
The Health Professional's Follow-up Study Mozaffarian et al. 2005	Sudden Cardiac Death			n-6 <11.2g/d & EPA/DHA <250mg/d	n-6<11.2g/d & EPA/DHA >250mg/d					
	Nonfatal MI						1.08	0.94	1.25	
	Total CHD						0.96	0.86	1.08	
NIPPON DATA80 Nakamura *et al.* 2005	Fatal CHD	*Fish intake*		1 - 2 /week	2+ /day		0.8	0.31	2.06	0.42

Supplementary Table 17.

Study Name Author, year published		Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
		CAD Death	*fish intake*		1.04	0.25	4.31	0.731						
		CAD death or AMI	*Fish intake*		0.49	0.17	1.41	0.209						
The EUROASPIRE Study		Revascularization	*Fish intake*		1.09	0.37	3.17	0.226	age, gender, diagnostic category, energy intake, serum cholesterol, serum TAG, diabetes, BMI, education.					
Erkkila *et al.* 2003		CAD Death	*EPA*	*mol% serum cholesteryl esters*	0.31	0.08	1.14	0.034						
		CAD death or AMI	*EPA*		0.5	0.18	1.38	0.307						
		Revascularization	*EPA*		0.71	0.3	1.68	0.251						
The Cardiovascular Health Study, Nested Case-Control	OR	IHD Death	*Plasma PL*	*DHA + EPA*	0.3	0.12	0.76	0.01	RR ARE FOR 1 SD INCREASE IN INTAKE; Gender, clinical site, entry cohort, age, BP, weight, education fasting plasma glucose.					
Lemaitre *et al.* 2003	OR	Nonfatal MI	*Plasma PL*	*DHA + EPA*	0.97	0.71	1.33	0.8						
MONICA I, II & III Osler *et al.* 2003		CHD Event		*fish consumption*	0.93	0.68	1.27	0.55	familial predisposition, smoking status, physical activity, alcohol, education, healthy diet score, total cholesterol, BMI.					
		CHD Death			0.98	0.62	1.52	0.74						
The Atherosclerosis Risk in Communities Study Wang *et al.* 2003					no multivariate results									
The Iowa Women's Health Study Folsom & Demissie 2004		CHD Death		*fish consumption*	1.04	0.8	1.34	0.31	age, energy intake, education, physical activity, alcohol, smoking, vitmain use, BMI, WHR, diabetes, hypertension, intake whole grains, fruit & vegetables, red meat, cholesterol, SAFA.					
The Health Professional's Follow-up Study Mozaffarian et al. 2005					0.65 1.16 1.05	0.47 0.99 0.92	0.88 1.36 1.19		BMI, smoking, physical activity, history of diabetes, hypertension or hypercholesterolemia, aspirin use, alcohol use, protein, SFA, fiber, MUFA, trans, energy intake, ALA.					
NIPPON DATA80 Nakamura *et al.* 2005		Fatal CHD	*Fish intake*		0.86	0.33	2.23	0.51	age, gender, smoking, alcohol, hypertension, BMI, diabetes.	0.91	0.35	2.35	0.54	further adjusted for serum cholesterol

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk			Age-adjusted results (Lowest Intake is Comparison Group)			
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
		Fish intake	*men*	≤ 11 g/day	≥ 63 g/day		1.24	0.88	1.75	0.23
	CHD Death	*seawater fish*	*men*	≤ 1 g/day	≥ 23 g/day		1.29	0.93	1.79	0.3
		lake fish	*men*	≤ 3 g/day	≥ 42 g/day		1.43	1.02	1.99	0.46
Jarvinen *et al.* 2006		*LCPUFA*	*men*	≤ 0.17 g/day	≥ 0.60 g/day		1.21	0.87	1.69	0.16
		Fish intake	*women*	≤ 8 g/day	≥ 41 g/day		0.63	0.39	1.02	0.04
	CHD Death	*seawater fish*	*women*	≤ 1 g/day	≥ 19 g/day		0.73	0.44	1.18	0.52
		lake fish	*women*	≤ 1 g/day	≥ 23 g/day		0.8	0.49	1.3	0.28
		LCPUFA	*women*	≤ 0.11 g/day	≥ 0.37 g/day		0.83	0.52	1.31	0.63
	CHD	Fish intake		23 g/day	180 g/day	HR	0.47	0.32	0.69	0.001
	Total MI	*Fish intake*		23 g/day	180 g/day		0.5	0.22	0.56	< 0.001
	Sudden Cardiac Death	*Fish intake*		23 g/day	180 g/day		1.6	0.63	4.06	0.04
	Nonfatal CHD	*Fish intake*		23 g/day	180 g/day		0.31	0.19	0.51	< 0.001
JPHC Study	Fatal CHD	*Fish intake*		23 g/day	180 g/day		1.4	0.65	3.01	0.09
Iso *et al.* 2006	CHD	*Omega 3 intake*		0.3 g/day	2.1 g/day		0.46	0.32	0.68	0.001
	Total MI	*Omega 3 intake*		0.3 g/day	2.1 g/day		0.35	0.22	0.55	<0.001
	Sudden Cardiac Death	*Omega 3 intake*		0.3 g/day	2.1 g/day		1.65	0.65	4.19	0.03
	Nonfatal CHD	*Omega 3 intake*		0.3 g/day	2.1 g/day		0.28	0.17	0.46	<0.001
	Fatal CHD	*Omega 3 intake*		0.3 g/day	2.1 g/day		1.79	0.82	3.87	0.03
	CHD Death	*Fish intake*		0	22g / day (1-2 serves / week)		0.7	0.46	1.06	
	CHD Death	*EPA + DHA*		0	> 250 mg		0.64	0.4	1.02	0.33
The Zutphen Study	CHD Death	*Fatty Fish*		0	7 g / day		0.87	0.64	1.16	
Streppel *et al.* 2008	CHD Death	*Lean fish*		0	yes		0.98	0.71	1.37	
	Sudden Cardiac Death	*Fish intake*		0	22g / day (1-2 serves / week)		0.94	0.37	2.36	
	Sudden Cardiac Death	*EPA + DHA*		0	> 250 mg		0.72	0.26	2.05	
	Sudden Cardiac Death	*Fatty Fish*		0	7 g / day		0.44	0.27	0.74	
	Sudden Cardiac Death	*Lean fish*		0	yes		1.14	0.59	2.19	

Supplementary Table 17.

Study Name				Multivariate Results 1 (Lowest intake is comparison group)					Multivariate Results 2 (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**	**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**	**Adjusting for:**
		Fish intake	*men*	1.00	0.7	1.43	0.83						
	CHD Death	*seawater fish*	*men*	1.09	0.77	1.54	0.93						
		lake fish	*men*	1.21	0.85	1.73	0.7						
Jarvinen *et al.* 2006		*LCPUFA*	*men*	0.96	0.68	1.38	1.00	Age, energy intake, area, BMI, serum cholesterol, blood pressure, smoking, occupation, diabetes.					
		Fish intake	*women*	0.59	0.36	0.99	0.02						
	CHD Death	*seawater fish*	*women*	0.7	0.41	1.18	0.39						
		lake fish	*women*	0.75	0.45	1.26	0.37						
		LCPUFA	*women*	0.73	0.44	1.19	0.31						
	CHD	Fish intake		0.63	0.38	1.04	0.25						
	Total MI	*Fish intake*		0.47	0.26	0.85	0.03						
	Sudden Cardiac Death	*Fish intake*		1.14	0.36	3.63	0.15						
	Nonfatal CHD	*Fish intake*		0.43	0.23	0.81	0.02						
JPHC Study	Fatal CHD	*Fish intake*		1.08	0.42	2.76	0.31	age, gender, smoking, alcohol, BMI, hypertension, diabetes, hypercholesterolemia, education, sports at leisure time, fruit, vegetable. SFA, MFUA, n-2 PUFA, choelsterol & total energy intake,.					
Iso *et al.* 2006	CHD	*Omega 3 intake*		0.58	0.35	0.97	0.18						
	Total MI	*Omega 3 intake*		0.43	0.24	0.78	0.02						
	Sudden Cardiac Death	*Omega 3 intake*		1.24	0.39	3.98	0.12						
	Nonfatal CHD	*Omega 3 intake*		0.33	0.17	0.63	0.003						
	Fatal CHD	*Omega 3 intake*		1.54	0.6	3.99	0.1						
	CHD Death	*Fish intake*		0.73	0.47	1.13							
	CHD Death	*EPA + DHA*		0.65	0.40	1.06	0.270						
The Zutphen Study	CHD Death	*Fatty Fish*		0.88	0.65	1.19							
Streppel *et al.* 2008	CHD Death	*Lean fish*		1.03	0.73	1.45		Energy, alcohol, wine use, fruit and vegetable consumption, SFA, trans, cis MUFA, PUFA, serum cholesterol lowering diet, smoking, BMI, diabetes, blood pressure, SES					
	Sudden Cardiac Death	*Fish intake*		0.89	0.34	2.3							
	Sudden Cardiac Death	*EPA + DHA*		0.68	0.23	2.02							
	Sudden Cardiac Death	*Fatty Fish*		0.46	0.27	0.78							
	Sudden Cardiac Death	*Lean fish*		1.29	0.65	2.59							

Supplementary Table 17. Results from the Prospective Cohorts Investigating Coronary Heart Disease and Fish Consumption or n-3 Long Chain Polyunsaturated Fat Intake.

Study Name				Intakes for Relative Risk		Age-adjusted results (Lowest Intake is Comparison Group)				
Author, year published	**Endpoint**			**Lowest Intake**	**Highest Intake**		**RR**	**Lower 95%CI**	**Upper 95%CI**	**p-trend**
The ARIC Study Yamagishi *et al.* 2008	Heart Failure	*Cholesterol Ester FA*	*LCPUFA men*	NR	NR	HR	1.49	0.84	2.63	0.4
		Cholesterol Ester FA	*LCPUFA women*	NR	NR	HR	0.42	0.19	0.92	0.09
		Cholesterol Ester FA	*EPA*	NR	NR	HR	1.37	0.85	2.2	0.26
		Cholesterol Ester FA	*DHA men*	NR	NR	HR	1.3	0.73	2.32	0.47
		Cholesterol Ester FA	*DHA women*	NR	NR	HR	0.21	0.1	0.44	<0.001
		Phospholipid FA	*LCPUFA men*	NR	NR	HR	0.99	0.55	1.77	0.43
		Phospholipid FA	*LCPUFA women*	NR	NR	HR	0.24	0.11	0.54	<0.001
		Phospholipid FA	*EPA*	NR	NR	HR	1.61	0.98	2.64	0.06
		Phospholipid FA	*DHA men*	NR	NR	HR	1.17	0.66	2.07	0.51
		Phospholipid FA	*DHA women*	NR	NR	HR	0.16	0.07	0.4	<0.001
The Nurses Health Study, Nested Case-Control Sun *et al.* 2008	Nonfatal MI	*Plasma FA*	*Total LCPUFA*	Cases: 2.74%FA	Controls: 3.04%FA	p=0.0004				
		Plasma FA	*EPA*	Cases:0.41%FA	Controls: 0.44%FA	p=0.0006				
		Plasma FA	*DPA*	Cases: 0.41%FA	Controls: 0.44%FA	p=0.001				
		Plasma FA	*DHA*	Cases: 1.43%FA	Controls: 1.58%FA	p=0.006				
		Erythrocyte FA	*Total LCPUFA*	Cases: 8.99%FA	Controls: 9.36%FA	p=0.0.05				
		Erythrocyte FA	*EPA*	Cases: 3.66%FA	Controls: 3.77%FA	p=0.16				
		Erythrocyte FA	*DPA*	Cases: 1.76%FA	Controls: 1.85%FA	p=0.002				
		Erythrocyte FA	*DHA*	Cases: 3.57%FA	Controls: 3.74%FA	P=0.09				

Supplementary Table 17.

Study Name Author, year published	Endpoint			Multivariate Results 1 (Lowest intake is comparison group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:	Multivariate Results 2 (Lowest Intake is Comparison Group) RR	Lower 95%CI	Upper 95%CI	p-trend	Adjusting for:
The ARIC Study Yamagishi *et al.* 2008				no multivariate results									
The Nurses Health Study, Nested Case-Control Sun *et al.* 2008	Nonfatal MI	*Plasma FA*	*Total LCPUFA*	0.38	0.16	0.92	0.03	age at blood draw, smoking, fasting status, BMI, postmenopausal status and hormone use, physical activity, alcohol intake, total fat intake, parental history MI, history hypertension or hypercholesterolemia or diabetes, ALA in blood and matching factors.					
		Plasma FA	*EPA*	0.23	0.09	0.55	0.00						
		Plasma FA	*DPA*	0.40	0.20	0.82	0.00						
		Plasma FA	*DHA*	0.46	0.18	1.16	0.07						
		Erythrocyte FA	*Total LCPUFA*	0.86	0.28	2.58	0.34						
		Erythrocyte FA	*EPA*	0.97	0.28	3.28	0.84						
		Erythrocyte FA	*DPA*	0.46	0.21	1.01	0.06						
		Erythrocyte FA	*DHA*	0.65	0.27	1.57	0.27						

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass graft; ns, not significant; wk, week; RR, relative risk; CI, confidence interval; FA, fatty acids; BMI, body mass index; SFA, saturated fat; ALA, alpha-linolenic; DPA, Docosapentaenoic acid; ECG, electrocardiogram; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; CVD, cardiovascular disease; SES, socio-economic status; LCPUFA, long chain polyunsaturated fat; P/S; polyunsaturated to saturated fat ratio; CE, cholesterol ester; PL, phospholipid.

Supplementary Table 18. Randomized Controlled Trials of Fat Modified Diets and Coronary Heart Disease

Study Name Author, Year Country	Country	Start of Study	Follow-up (years)	Primary or Secondary Prevention	Endpoint	*n* events / *n* at risk Intervention,	 Control	Men (%)	Age at Baseline (years)	Physician/Reviewer Blinding	Goals of Intervention
London Corn & Olive Rose, Thomson, Williams 1965	UK	?1960	2	Secondary	CHD Event: corn	15 / 28	11 / 24	not noted	mean 56y	Unclear if pysician blinded	80g of either corn oil or olive oil per day. Instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes. Milk, butter and eggs restricted.
					CHD Event: olive	11 / 26	11 / 24				
London Low Fat Ball *et al.* 1965	UK	1957	3.0	Secondary	Reinfarction	42 / 123	44 / 129	100	mean 45	physician blinded	14g butter, 84g meat, 1 egg, 56g cottage cheese and skimmed milk. Given dietary advice to reduce fat to 40g/day. Overweight participants (15% of group) given weight-loss diets.
					CHD Death	10 / 123	22 / 129				
The Oslo Diet-Heart Study Leren 1966	Norway	1956	4.3	Secondary	Fatal MI	10 / 206	23 / 206	100	30 - 64	not clear	Cholesterol lowering diet: low in SFA and cholesterol, high in PUFA (details not provided in this report)
					Sudden Death	27 / 206	27 / 206				
					Non-Fatal MI	24 / 206	31 / 206				
					Major CHD relapse (above events combined)	61 / 206	81 / 206				
MRC Soya trial Morris *et al.* 1968	UK	1960	4	Secondary	CHD Death	15 / 199	14 / 194	100		Physicians may not have been blinded, but review committee were.	Saturated fats removed from diet as far as possible, and replaced with 85g soya-bean oil daily.
					CHD Event	62 / 199	74 / 194				
The Veterans Administration trial Dayton *et al.* 1969	US	1959	3.7	Primary	Sudden Cardiac Death	18 / 422	27 / 424	100	over 55y	double-blinded	Keep total fat the same, but decrease SFA and increase unsaturated fat, so that iodine value of fat was 100.
					Fatal MI	23 / 422	23 / 424				
					Non-Fatal MI	19 / 422	28 / 424				
					Combined total events (# of men with event)	52 / 422	65 / 424				
The Finnish Mental Hospital Study Turpeinen *et al.* 1979	Finland	1959	6 yr then cross-over	Primary	CHD Death	3.0 / 1,000 person year	6.1 / 1,000 person years	100	34-64y	? Not blinded	Total fat to remain unchanged, replace saturated fats (mainly diary) with unsaturated fat (soybean oil in skim milk, and replacing butter
					CHD Event	4.2 / 1,000 person years	12.7 / 1,000 person years				
The Finnish Mental Hospital Study Miettinen *et al*. 1983	Finland	1959	6 yr then cross-over	Primary	CHD Death	3 / 372	3 / 341	0	34-64y	? Not blinded	Total fat to remain unchanged, replace saturated fats (mainly diary) with unsaturated fat (soybean oil in skim milk, and replacing butter

Supplementary Table 18.

Study Name		Estimated Fat Intakes During Study for Interveniton Group and Controls						Diet assessment
Author, Year Country		Total Fat	SFA	MUFA	PUFA	P/S ratio	Goals of Control	method used
London Corn & Olive Rose, Thomson, Williams 1965	Intervention - corn	50g	-	-	-	-	no advice	Self-administered questionnaire
	Intervention - olive	45g	-	-	-	-		
	control	70g	-	-	-	-		
London Low Fat Ball *et al.* 1965	at year 1: Intervention:	45g	-	-	-	-	Overweight patients (20% of group) given weight-loss diet (reduced CHO rather than fat).	Weighed diet records completed throughout the trial
	control:	112g	-	-	-	-		
The Oslo Diet-Heart Study Leren 1966	Intervention:	39%TE	8.5%TE	10.1%TE	20.7%TE	2.4	not provided	subgroup did 7-day weighed diet record
	control:	not provided	-	-	-			
MRC Soya trial Morris *et al.* 1968		Dietary details not provided					Usual diet	Weighed 7-day diet records taken at various times during study
The Veterans Administration trial Dayton *et al.* 1969	Intervention:	10.7g (38.9%TE)		iodine value of fat ➔	102.4		Keep fat at 40%TE and iodine value at 55.	Food provided to participants.
	control:	111.2g (40.1%TE)		iodine value of fat ➔	53.5			
The Finnish Mental Hospital Study Turpeinen *et al.* 1979	Intervention:	110g	27.3g	36.8g	40.5g	1.48	Usual institution diet	food provided
	Control:	107g	54.7g	33.3g	13.6g	0.25		
The Finnish Mental Hospital Study Miettinen *et al*. 1983	Intervention:	110g	27.3g	36.8g	40.5g	1.48	Usual institution diet	food provided
	Control:	107g	54.7g	33.3g	13.6g	0.25		

Supplementary Table 18.

Study Name Author, Year Country	Compliance Measured by:	Serum Cholesterol Changed in Treatment Group
London Corn & Olive Rose, Thomson, Williams 1965	Changes in serum cholesterol. No change in control or olive oil group, and decrease in corn oil group.	Yes for corn No for Olive
London Low Fat Ball *et al.* 1965	Changes in serum cholesterol. At year 4, intervention decreased serum chol by 44 mg/100ml, control group by 25 mg/100ml (not signifcantly different to intervention)	No
The Oslo Diet-Heart Study Leren 1966	serum cholesterol, which decreased by 17.6% in intervention group, cf control group (3.7% decrease)	Yes
MRC Soya trial Morris *et al.* 1968	Serum cholesterol & adipose fatty acids Cholesterol was lower in intervention group at 6 motnhs, but started to rise again. Authors advise adipose fatty acid concentrations were more unsaturated in the intervention group (data not provided)	No
The Veterans Administration trial Dayton *et al.* 1969	Greater decrease in serum cholesterol compared with controles (mean difference 12.7%) Serum and adipose fatty acid changes consistent with change in diet.	Yes
The Finnish Mental Hospital Study Turpeinen *et al.* 1979	During intervention phases, mean serum cholesterols were lower in intervention group (lower by 41.4 mg/dl) Subcutaneous linoleic fatty acid concentrations reflected changes in diet.	Yes
The Finnish Mental Hospital Study Miettinen *et al*. 1983	During intervention phases, mean serum cholesterols were lower in intervention group (lower by 35.2 mg/dl)	

Supplementary Table 18. Randomized Controlled Trials of Fat Modified Diets and Coronary Heart Disease

Study Name Author, Year Country	Country	Start of Study	Follow-up (years)	Primary or Secondary Prevention	Endpoint	*n* events / *n* at risk Intervention,	 Control	Men (%)	Age at Baseline (years)	Physician/Reviewer Blinding	Goals of Intervention
DART Burr *et al.* 1989	UK		2		IHD Events IHD Deaths Non-fatal MI	132 97 35	144 97 47	100	56	Physican blinded	Fat advice (reduce fat intake to 30%TE and increase P/S to 1;0
The Minnesota Coronary Survey Frantz Jr *et al.* 1989	US		4.5		CHD Event	27.2 / 1,000 person years	25.7 / 1,000 person years	49	around 30 - 60 y	double-blinded	
The STARS Study Watts *et al.* 1992	UK		3.25		CHD Event	3 / 27	10 / 28	100	50 - 54 y	not clear	Total fat reduced to 27%TE, SFA to 8·10%TE, dietary cholesterol to 100mg/1,000 kcal, PUFA to 8%TE.
The Lyon Diet Heart Study de Lorgeril *et al.* 1999	France		3.8		CHD Death Non-Fatal MI CHD Event	6 / 302 8 / 302 14 / 302	19 / 303 25 / 303 44 / 303	90	53 y	single-blinded (physician blinded)	Mediterranean-type diet: more bread, root and green vegetables, fish and less meat. Daily serves of fruit. Butter and cream to be swapped with margarine supplied by the study (to use instead of olive oil)
The Women's Health Initiative Howard *et al.* 2006	US		8.1		CHD Event Non-Fatal MI CHD Death Revascularization Composite of all	559 / 19541 435 / 19541 158 / 19541 717 / 19541 1000 / 19541	863 / 29294 671 / 29294 234 / 29294 1113 / 29294 1549 / 29294	0	50 - 79 y	physician blinded	Decrease total fat to 20%TE, increase vegetable, frruits and grains.
THIS-DIET Tuttle *et al.* 2008	US		6-24 mo		Cardiac Death MI Heart Failure Unstable Angina	0 / 51 3 / 51 0 / 51 4 / 51	3 / 101 8 / 101 3 / 101 20 / 101	70 - 80	58 y	unclear	Decrease total fat to <30%TE, SFA ≤ 7%TE

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; IHD, ischemic heart disease; SFA, saturated fat; PUFA, polyunsaturated fat; ALA, alpha-linolenic; MUFA, monounsaturated fat; TE, total dietary energy; CHO, carbohydrate.

Supplementary Table 18.

Study Name		Estimated Fat Intakes During Study for Interveniton Group and Controls						Diet assessment
Author, Year Country		Total Fat	SFA	MUFA	PUFA	P/S ratio	Goals of Control	method used
DART Burr *et al.* 1989	Intervention:	32.3%TE				0.78	No fat advice	25% of sample did weighed food records (7-days)the rest did 'dietary questionnaire'
	Control:	35.0%TE				0.44		
The Minnesota Coronary Survey Frantz Jr *et al.* 1989	Intervention:	37.8%TE	9.2%TE		14.7%TE	1.6	Usual institution diet.	Food provided.
	control:	39.1%TE	18.3%TE		5.2%TE	0.3		
The STARS Study Watts *et al.* 1992	Intervention:	26%TE	8.9%TE	9.1%TE	7.2%TE	0.9	Usual diet	Diet history at baseline, and at least one other time during study
	Control:	36%TE	17%TE	16.8%TE	4.7%TE	0.3		
The Lyon Diet Heart Study de Lorgeril *et al.* 1999	Intervention:		8.0%TE	12.9%TE (Oleic)	5.6% (PUFA) 3.6%TE (Linoleic) 0.84%TE (ALA)		Usual diet	"dietary survey"
	control:		11.7%TE	10.8%TE (Oleic)	6.10%TE (PUFA) 5.3%TE (Linoleic) 0.29%TE (ALA)			
The Women's Health Initiative Howard *et al.* 2006	Intake at year 6: Intervention:	28.8%TE	9.5%TE	10.8%TE	6.1%TE	0.7	Usual diet.	FFQs completed throughout study
	control:	37%TE	12.4%TE	14.2%TE	7.5%TE	0.6		
THIS-DIET Tuttle *et al.* 2008	Intervention at 24 mth:	29.7%TE	8.0%TE	10.3%TE	5.7%TE		Usual diet	3-day diet record
	Control:	not provided						

Supplementary Table 18.

Study Name Author, Year Country	Compliance Measured by:	Serum Cholesterol Changed in Treatment Group
DART Burr *et al.* 1989	A subgroup had blood fatty acids measured. Mean % of linoleic for intervention group significantly higher than control group. Blood Cholesterol measured. At 2 yr total cholesterol decreased by 0.18mml/l in fat group, and increased by 0.08 mmol/l in control group (not significantly different).	No
The Minnesota Coronary Survey Frantz Jr *et al.* 1989	Food provided. Serum cholesterol decreased by 32 mg/dl in treatment group, and 4 mg/dl in control group (not statistically significant).	No
The STARS Study Watts *et al.* 1992	Plasma cholesterol (total and LDL) decreased significantly in the intervention group, baseline compared to follow-up. Plasma TAGs also decreased significantly. No changes observed in the control group.	yes
The Lyon Diet Heart Study de Lorgeril *et al.* 1999	Plasma fatty acid concentrations were obtained, but not reported. Cholesterol did not appear any different between intervention group and controls in this final analysis.	No
The Women's Health Initiative Howard *et al.* 2006	Serum total cholesterol and LDL decreased significantly at year 3 (intervention group compared to control). Intervention group lost weight.	Yes
THIS-DIET Tuttle *et al.* 2008	Plasma fatty acid composition - suggested SFA decreased in intervention group (control not monitored)	

Supplementary Table 19. Randomized Controlled Trials of Omega 3 Long Chain Polyunsaturated Fat and Coronary Heart Disease

Study Name Author, Year	Country	Start of Study	Follow-up	Endpoint	*n* Events / *n* at Risk Intervention	 Control	Participant Characteristics	Men (%)	Mean Age (years)
				Restenosis	19 / 50	46 / 53			
Dehmer et al. 1988		1986		Angina	13 / 50	19 / 53	PTCA patients	100	56
				IHD Death	78 / 1,015	116 / 1,018			
Burr et al. 1989	UK	unclear	24 mo	Nonfatal MI	49 / 1,015	33 / 1,018	Hospitalized with AMI	100	56.5
				IHD Event	127 / 1,015	149 / 1,018			
				Angina	21 / 100	35 / 100			
Milner et al. 1989	US	1987	6 mo	Clinical Restenosis	16 / 100	35 / 100	PTCA patients	72	59
				Nonfatal MI	7 / 146	0 / 72			
Reis et al. 1991	US	1997	6 mo	Angina	86 / 146	29 / 72	PTCA patients	74	unclear
				Revascularization	36 / 146	13 / 72			
				Clinical Restenosis	22 / 58	14 / 49			
Kaul et al. 1992	India	1990	6 mo	Revascularization	18 / 58	12 / 49	PTCA patients	85	57.5
				Nonfatal MI	4 / 58	2 / 49			
				Angina	2 / 58	2 / 49			
				CHD Event	25 / 58	18 / 49			
Bairati et al. 1992	Quebec	1992	6 mo	Angina	12 / 107	22 / 98	Patients scheculed for elective PTCA	81	55

Supplementary Table 19.

Study Name Author, Year	Participant Blinding?	Outcome assessors masked	Intervention Type of Intervention	Intervention Total EPA+DHA	Control	Dropouts
Dehmer et al. 1988	no	no	MaxEPA capsules, 18/day	5.4g daily	nil	3 int, 5 control
Burr et al. 1989	no	yes	dietary advice or Max EPA capsules (3/day)	400g Fatty fish /week 0.5g EPA/day	No dietary advice or capsules	
Milner et al. 1989	no	yes	Promega capsules, 9 per day	3.15g EPA, 1.35g DHA	no placebo given	none, but 11% did not take capsules after 1 week
Reis et al. 1991	yes	yes	Super EPA or Promega capsules, 12 per day	6.0-7.0 g/day (inlcuding ALA)	olive oil capsules	22 int, 10 control
Kaul et al. 1992	no	yes	MaxEPA capsules, 10/day	3g/d EPA + DHA	nil	unclear
Bairati et al. 1992	yes	yes	MaxEPA capsules 15g/day	2.7g EPA, 1.8gDHA	15g olive oil capsule	48 int, 38 control

Supplementary Table 19. Randomized Controlled Trials of Omega 3 Long Chain Polyunsaturated Fat and Coronary Heart Disease

Study Name Author, Year	Country	Start of Study	Follow-up	Endpoint	*n* Events / *n* at Risk Intervention	 Control	Participant Characteristics	Men (%)	Mean Age (years)
Leaf et al. 1994	USA	1989	6 mo	Restenosis	117 / 275	101 / 276	Patients scheduled for elective PTCA	70-80	around 50-60y
				CHD Death	0/ 275	2 / 276			
Sacks et al. 1995	USA	unclear	29 mo	Nonfatal MI	1 / 31	2 / 28	Angiographically confirmed CAD	93.5	62
				Revascularization	3 / 31	3/ 28			
				Unstable Angina	3 / 31	4 / 28			
				CHD Death	0 / 31	1 / 28			
				Fatal MI	0 / 31	1 / 28			
Eritsland et al. 1996	Norway	1989	12 mo	Fatal MI	7 / 322	4 / 293	CABG patients	87	59.7
				Nonfatal MI	5 / 322	3 / 293			
				SCD	7 / 322	4 / 293			
				Vein graft occlusion	196 / 322	172 / 293			
Singh et al. 1997	India	unclear	12 mo	Angina	22 / 122	50 / 118	Patients with AMI	94	48.6
				Arrhythmia	16 / 122	34 / 118			
				SCD	2 / 122	2 / 118			
				CHD Death	14 / 122	26 / 118			
				CHD Event	30 / 122	41 / 118			
Johansen et al. 1999	Norway	1992	6.5 mo	Restenosis	90 / 196	86 / 192	Patients scheduled for elective PTCA	78	59.7
				CHD Death	1 / 250	3 / 250			

Supplementary Table 19.

Study Name Author, Year	Participant Blinding?	Outcome assessors masked	Type of Intervention	Intervention Total EPA+DHA	Control	Dropouts
Leaf et al. 1994	yes	yes	Fish oil capsule: 10x1g/d	6.9g/d	corn oil capsules with fish oil 10x1g/d with 0.4% fish oil (0.003g/d EPA + DHA)	69 int, 69 control
Sacks et al. 1995	yes	yes	Promega supplement, 6 /day	3.0 (including DPA)	olive oil capsules 6x1g/d OR cellulose tablets, 3/d	10 int, 11 control
Eritsland et al. 1996	no	yes	Omacor capsules 4/day	3.3g / day	nil	15 int, 14 control
Singh et al. 1997	no	yes	MaxEPA capsules 6/day	1.8g/day	aluminium hydroxide 100 mg/d	4 fish oil, 6 placebo
Johansen et al. 1999	yes	yes	Omacor capsule 6/day	5g/day	corn oil capsules 6/d	54 int, 58 control

Supplementary Table 19. Randomized Controlled Trials of Omega 3 Long Chain Polyunsaturated Fat and Coronary Heart Disease

Study Name Author, Year	Country	Start of Study	Follow-up	Endpoint	*n* Events / *n* at Risk Intervention	 Control	Participant Characteristics	Men (%)	Mean Age (years)
von Schacky et al. 1999	Germany	1992	24 mo	Fatal MI	0 / 112	1 / 111	Patients with angiographically confirmed stenosis	80.5	58.3
				Non-Fatal MI	1 / 112	3 / 111			
				Revascularization	6 / 112	8 / 111			
				Angina	9 / 112	11 / 111			
GISSI-P 1999	Italy	1993	40 mo	Cardiac Death	520 / 5,666	292 / 5,668	Patients with recent MI	85.3	59.4
				Coronary death	214 / 5,666	265 / 5,668			
				CHD Death and nonfatal MI	424 / 5,666	485 / 5,668			
Nilsen et al. 2001	Norway	1995	24 mo	CHD Event	42 / 150	36 / 150	Patients with first AMI	79.5	64
				CHD Death	8 / 150	8 / 150			
				Resuscitation	1 / 150	2 / 150			
				Nonfatal CHD	39 / 150	31 / 150			
				Angina	26 / 150	31 / 150			
				Nonfatal MI	21 / 150	15 / 150			
Brox et al. 2001	Norway	?	14 mo	Fatal MI	0 / 80	1/40	Clinically healthy volunteers, with blood cholesterol levels 7.0-9.5mmol/L	50	54.6
Maresta et al. 2002	Italy	1993	7 mo	Acute MI	0 / 169	5 / 169	Patients scheduled for elective PTCA	84.5	58.7
				Angina	16 / 169	26 / 170			
				CHD Event	14 / 169	16 / 169			

Supplementary Table 19.

Study Name Author, Year	Participant Blinding?	Outcome assessors masked	Intervention Type of Intervention	Intervention Total EPA+DHA	Intervention Control	Intervention Dropouts
von Schacky et al. 1999	yes	yes	Fish oil capsule: 6/d first 3mth, then 3/d	First 3mth: 4g/d (incl DPA and ALA) Rest of Study: 2g/day	capsules containing fat replicating average European diet, 6/d for first 3 mo, 3/d for rest of study	unclear
GISSI-P 1999	no	yes	Omacour capsule 1g/day	0.9g/d EPA + DHA daily (half group also took vitamin E)	control or vitamin E alone	unclear
Nilsen et al. 2001	yes	yes	Omacor capsules 4/day	3.5g/day	Corn oil capsules 4/d	unclear
Brox et al. 2001	No placebo given - oils only were blinded	yes	Seal Oil: 15 ml/d Cod Liver Oil: 15ml/d	2.6g 3.3g	nil, no supplement	8 seal, 2 cod liver, 1 control
Maresta et al. 2002	yes	yes	Esapent capsules, 6 / day for 2 mo, then 3/d	5.1g/d EPA + DHA initially, then 2.6g/d	Olive oil capsules 6/d for 2 mo, then 3/d	44 int, 38 control

Supplementary Table 19. Randomized Controlled Trials of Omega 3 Long Chain Polyunsaturated Fat and Coronary Heart Disease

Study Name Author, Year	Country	Start of Study	Follow-up	Endpoint	*n* Events / *n* at Risk Intervention	 Control	Participant Characteristics	Men (%)	Mean Age (years)
Burr et al 2003	UK	1990	36-108 mo	Cardiac Death	180 / 1,571	158 / 1,543	Patients being treated for angina	100	61.1
				SCD	47 / 1,571	73 / 1,543			
Raitt et al. 2005	US	1999	23 mo	CHD Death	2 / 100	5 / 100	Patients with implantable cardioverter defibrillators and recent episode of VT or VF	86	62
				SCD	2 / 100	0 / 100			
				Angina	10 / 100	7 / 100			
				Arrthythmia	21 / 100	16 / 100			
				Revascularization	2 / 100	4 / 100			
				Total MI	1 / 100	3 / 100			
Leaf et al. 2005	US	1999	12 mo	CHD Death	9 / 200	9 / 202	Patients with implantable cardioverter defbrillators	83	65
Brouwer et al. 2006	Europe	2001	356 days	CHD event	65 / 273	62 / 273	Patients with ventricular tachycardia or ventricular fibrillation, & had received, or were about to receive an ICD	85	61
				Angina	10 / 273	12 / 273			
				Cardiac Death	6 / 273	13 / 273			
				ICD intervention	75 / 273	81 / 273			
				MI	1 / 273	3 / 273			
				Heart Failure	22 / 273	19 / 273			
				Arrythmia	36 / 273	34 / 273			

Supplementary Table 19.

Study Name Author, Year	Participant Blinding?	Outcome assessors masked	Type of Intervention	Intervention Total EPA+DHA	Control	Dropouts
Burr et al 2003	no	yes	1109 dietary advice to eat 2 weekly portions fatty fish or MaxEPA capsules 3/day; 462 only MaxEPA capsules	0.5g EPA	no dietary advice or capsules	none
Raitt et al. 2005	yes	yes	Fish oil 1.8g/day	42%EPA, 30%DHA	73%o oleic, 12% palmitic	2 int, 6 control
Leaf et al. 2005	yes	yes	Fish oil capcules, 4/day	2.6g	Olive oil capsule	35% dropped out, not clear how many per group.
Brouwer et al. 2006	yes	yes	Fish capsules, 4 / day	464mg EPA, 335mg DHA, 162 other n-3	Oil capsule containing sunflower oil (high oleic)	33 int, 32 control

Supplementary Table 19. Randomized Controlled Trials of Omega 3 Long Chain Polyunsaturated Fat and Coronary Heart Disease

Study Name Author, Year	Country	Start of Study	Follow-up	Endpoint	*n* Events / *n* at Risk Intervention	 Control	Participant Characteristics	Men (%)	Mean Age (years)
Yokoyama et al. 2007	Japan	1996	55 mo	CHD Event	262 / 9,326	324 / 9,319	All patients with hypercholesterolemia (total chol ≥ 6.5mmol/L, LDL ≥4.4 mmol/L) with or without CAD.	31	61
				SCD	18 / 9,326	17 / 9,319			
				Fatal MI	11 / 9,326	14 / 9,319			
				Nonfatal MI	62 / 9,326	83 / 9,319			
				Unstable Angina	147 / 9,326	193 / 9,319			
				Revascularization	191 / 9,326	222 / 9,319			
				CHD Death	29 / 9,326	31 / 9,319			
GISSI-HF, 2008	Italy	2002	3.9 y	SCD	307 / 3,494	325 / 3,481	Patients with clinical evidence of heart failure of any cause	78	67
				Fatal/nonfatal MI	107 / 3,494	129 / 3,481			
				AMI	20 / 3,494	25 / 3,481			
Tuttle et al. 2008	US	2000	6 - 24 mo	Cardiac Death	0 / 51	3 / 101	patients with first AMI	around 70-80	58
				MI	1 / 51	8 / 101			
				Heart failure	0 / 51	3 / 101			
				Unstable Angina	4 / 51	20 / 101			

Abbreviations: IHD, ischemic heart disease; MI, myocardial infarction; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; PTCA, percutaneous transluminal coronary angioplasty; AMI, acute myocardial

Supplementary Table 19.

Study Name Author, Year	Participant Blinding?	Outcome assessors masked	Type of Intervention	Intervention Total EPA+DHA	Control	Dropouts
Yokoyama et al. 2007	no	yes	EPA capsles 3/ day (with statin)	1,800mg EPA	statin only, no placebo given	
GISSI-HF, 2008	yes	yes	n-3 capsure, 1g/day, with normal treatment	850-882 EPA/DHA (ratio 1:1.2)	placebo	69 int, 82 ctrl
Tuttle et al. 2008	no	yes	Dietary Advice to eat fish, olive canola or syobean oil	Omega-3 fats 0.67%TE (plasma n-3, EPA & DHA fatty acids increased significantly from baseline to 6 months)	usual care (plasma fatty acids not measured)	5 int, 3 control