

Dietary oils, serum lipoproteins, and coronary heart disease¹⁻⁴

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ABSTRACT Variable amounts of olive oil rather than hard fats were used in classic Mediterranean diets. We review the effects of replacing hard fats with olive oils or starchy foods on blood lipoprotein concentrations. The saturated fatty acids lauric, myristic, and palmitic acids raise both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) somewhat compared with oleic acid. If any fat is replaced by carbohydrates, fasting triglyceride values rise and HDL concentrations fall; effects on LDL depend on the type of fat that is being replaced. *Trans* isomers of oleic acid lower HDL and raise LDL and lipoprotein(a). The fatty acids in unhydrogenated fish oil potentially lower triglycerides but may raise LDL somewhat. When body weight is forcibly kept constant, substitution of unsaturated oils such as olive oil for hard fats rich in saturated or *trans* fatty acids will produce a more favorable lipoprotein profile than replacement of fat by carbohydrates. However, high-oil diets might lead to obesity, which would undo their favorable effects. *Am J Clin Nutr* 1995;61(suppl):1368S-73S.

KEY WORDS Dietary fatty acids, serum lipoproteins, cholesterol, oils, fats, humans

INTRODUCTION

Classic Mediterranean diets included olive oil rather than hard fats. In most regions, total fat intake was low, with starchy foods providing most of dietary energy; however, on the isle of Crete, fat intake mainly in the form of olive oil exceeded 40% of dietary energy, and this high fat intake was associated with a remarkably low rate of coronary mortality.

Dietary fats and oils differ in the chain lengths of their constituent fatty acids and the number and geometry of their double bonds. These differences markedly affect concentrations of lipids in plasma (1) and, therefore, risk of coronary heart disease; differences in amount and type of fat in the diet can induce differences of 30-40% in serum concentrations of low-density-lipoprotein (LDL) cholesterol (2). Although the mechanisms through which dietary fats affect serum lipoprotein concentrations are still being clarified (3, 4), empirical data allow us to predict how plasma lipids and lipoproteins in humans will change with changes in amount and quality of fat in the diet. We review the effects of various fatty acids and fatty acid classes, the effects of replacing hard fats by carbohydrate-rich foods or oils on blood lipids and lipoproteins, and

the implications of such dietary changes for risk of coronary heart disease.

EFFECTS OF FATTY ACIDS ON SERUM LIPIDS AND LIPOPROTEINS

The fatty acids that occur most commonly in the human diet are listed in **Table 1**. Most information regarding effects of dietary fat on plasma lipids and lipoproteins derives from studies of these fatty acids. Each will be discussed further in the next section.

We previously summarized in a meta-analysis the results of 27 trials on dietary fatty acids and serum lipoproteins that met certain criteria (1). **Figure 1** indicates changes in serum lipids and lipoproteins that take place when 1% of dietary energy in the form of carbohydrate is replaced by a particular class of fatty acids. In metabolic studies of this type, addition of a particular fatty acid to the diet requires removal of an equivalent amount of some other energy-yielding food component to avoid weight gain in study subjects. For this reason, it is only possible to express the effect of a certain amount of energy provided by a specific fatty acid in terms of a similar quantity of energy provided by another dietary component that serves as a reference. The choice of "reference currency" is arbitrary. In **Figure 1**, we calculated the effects of fatty acids for the case in which they replace carbohydrates, as is customary. The choice of a reference can be a major source of confusion. For example, the effect of olive oil on total serum cholesterol is neutral when it replaces carbohydrates, but cholesterol-lowering when it replaces saturated fatty acids.

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TABLE 1

Daily intake of the major dietary fatty acids in middle-aged men in Finland, the Netherlands, the United States, and on the isle of Corfu, Greece¹

	Intake ²			
	Finland	Netherlands	United States	Corfu
	<i>g/d</i>			
Saturated fatty acids				
Lauric acid (12:0)	4	2	2	0.3
Myristic acid (14:0)	12	8	6	1.1
Palmitic acid (16:0)	38	30	30	16
Stearic acid (18:0)	20	15	14	3
Monounsaturated fatty acids				
Oleic acid (18:1n-9)	40	29	37	56
<i>Trans</i> 16:1 + 18:1 ³	5	8	4	0.2
Polyunsaturated fatty acids				
Linoleic acid (18:2n-6)	8	12	17	13
α -Linolenic acid (18:3n-3)	2	2	2	1
Eicosapentaenoic acid (20:5n-3)	0.4	0.3	0.1	0.2
Docosahexaenoic acid (22:6n-3)	0.3	0.1	0.1	0.6

¹ Duplicates of the diets reported in the early 1960s by men participating in the Seven Countries Study (5) were collected retrospectively in 1987 and chemically analyzed (D Kromhout et al, unpublished observations, 1994).

² Kromhout et al, unpublished measurements. Data on Finland are means of two regions.

³ Not including *trans* isomers with chain lengths of 20 and 22 carbon atoms as found in hydrogenated fish oils.

Evidence from feeding trials

As shown in Figure 1, replacement of carbohydrates by any type of fat raises concentrations of high-density-lipoprotein (HDL) cholesterol, with the effect being more pronounced with increasing saturation. Paradoxically, increasing fat intake at the expense of carbohydrates decreases the fasting concentration of triglycerides in blood plasma; dietary saturates, monounsaturates, and n-6 polyunsaturates all produce this effect to about the same extent. Effects on LDL cholesterol are markedly different, however, with saturates strongly raising its concentration and n-6 polyunsaturates, ie, linoleic acid, slightly lowering it. As a result, oils high in linoleic acid produce the highest ratio of HDL to LDL, but the difference between their effects and those of monounsaturated oils rich in oleic acid is small.

Epidemiologic evidence

Epidemiologic studies tend to confirm the effects of dietary fatty acids on blood cholesterol and lipoprotein concentrations observed in controlled trials. Studies within just one population are handicapped by difficulties in reliable estimation of small differences in fatty acid intakes in individuals over time. Nevertheless, most studies of these effects reported correlations in the same direction as seen in controlled trials (6, 7).

Comparisons of population means offer the advantage of large, stable differences in intake, but the disadvantage of confounding by other lifestyle factors that accompany differences in fat consumption. For example, Keys and coworkers selected 16 cohorts each of up to 1000 men in 7 countries in which populations exhibited large differences in serum cholesterol concentrations. They found that differences in mean blood cholesterol concentrations among cohorts could be predicted from dietary intake (8), and that differences in coronary heart disease rates were consistent with differences in diet and in blood cholesterol concentrations. The absolute extent of the differences in blood cholesterol associated with dif-

ferences in diet was larger in the Seven Countries Study than has been observed in controlled metabolic-ward studies. Evidently, other factors or long-term effects of diet played an additional role in influencing blood cholesterol concentrations in this study.

The effects of dietary fats relative to effects of carbohydrates on HDL and triglyceride concentrations that have been observed in controlled trials also have been confirmed by epidemiologic studies of free-living individuals (9-12). Such studies have been reviewed (13) and have revealed significant differences in population means (11, 14).

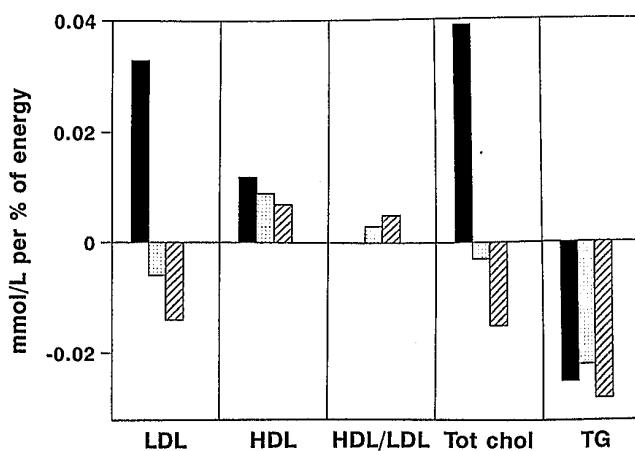


FIGURE 1. Predicted changes in serum lipids and lipoproteins when 1% of dietary carbohydrate is replaced by saturated (■), monounsaturated (▨), or n-6 polyunsaturated (▧) fatty acids under isoenergetic, metabolic-ward, or equivalent conditions. Effects of carbohydrates are set to zero. Tot chol, total cholesterol; TG, triglyceride.

SPECIFIC FATTY ACIDS

Interest in and information on the effects on blood cholesterol of specific fatty acids is now rapidly accumulating. Various fatty acids of interest are discussed below and recent findings on individual fatty acids are summarized in **Figure 2**.

Palmitic, lauric, and myristic acids

As shown in Table 1, the principal saturated fatty acid in most human diets is palmitic acid (16:0), followed by stearic, myristic, and lauric acids. In mixed diets, lauric, myristic, and palmitic acids together usually make up some 60–70% of all saturated fatty acids; they are responsible for the cholesterol-raising effect of saturated fat. The relative cholesterol-raising potential of these fatty acids has proved controversial (1, 15, 16, 21–26).

Some investigators have reported that palm oil, which is rich in palmitic acid, has less of a cholesterol-raising effect than does coconut oil, which is rich in lauric and myristic acid (23, 24, 26). For this reason, Ng et al (25) suggested that palmitic acid may be neutral in its effects on raising cholesterol, just as are stearic and oleic acids. This view, however, is contradicted by the results of several well-controlled studies in which palmitic acid was shown to raise LDL cholesterol relative to the effects of oleic acid (15–18, 27). Therefore, it appears that palmitic acid from palm oil as well as other sources is indeed a cholesterol-raising saturated fatty acid.

The effect of lauric acid (12:0) has been reevaluated recently. Denke and Grundy (15) found that the cholesterol-raising potential of dietary lauric acid was about two-thirds that of palmitic acid, whereas Temme et al (28) concluded that a diet enriched in lauric acid caused higher concentrations of HDL, LDL, and total cholesterol than did a diet rich in palmitic acid.

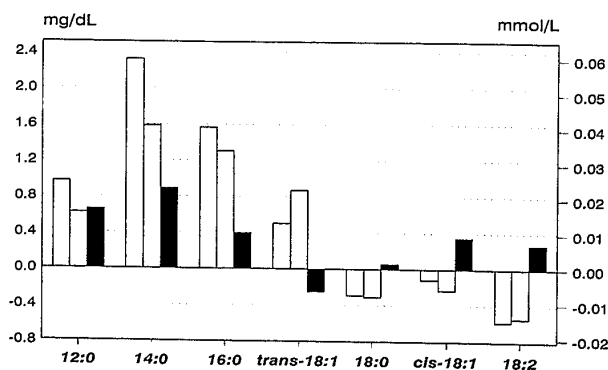


FIGURE 2. Effects of individual dietary fatty acids on serum total (□), LDL (▣), and HDL (■) cholesterol, when 1% of energy from carbohydrates in the diet is replaced by 1% of energy from the fatty acid in question. References for these values are as follows: lauric acid (12:0), (15); myristic acid (14:0), (16); palmitic acid (16:0), (15–18); stearic acid (18:0), (18, 19), and monounsaturated *trans* fatty acids (*trans*-18:1), (19, 20). Data for oleic acid (*cis*-18:1) and linoleic acid (18:2) are based on regression coefficients derived from a meta-analysis of 27 trials (1); these latter values were also used to calculate the effects of the fatty acids observed in each trial relative to carbohydrates. Reprinted with permission (16).

Myristic acid has long been suspected of being the most cholesterol-raising of all the fatty acids. Hegsted et al (21) drew this conclusion from a multiple-regression analysis of a series of controlled trials; our own meta-analysis also suggested that myristic acid may be four to six times more cholesterol-raising than is palmitic acid (1). Zock et al (16) addressed the question directly; they produced a special fat rich in myristic acid and fed it to a large number of volunteers in a well-controlled trial. They found myristic acid to be ≈ 1.5 times as cholesterol-raising as palmitic acid, which is much less than the factor of 4–6 that was suggested by our meta-analysis (1) and by the work of others (21). Zock et al also reported that about half of the effect of myristic acid on cholesterol was due to its effects on HDL. Thus, differences in cholesterol-raising potential among lauric, myristic, and palmitic acids appear modest. All three clearly raise LDL cholesterol compared with unsaturated fatty acids.

Stearic acid

The studies of Ahrens et al (29), Keys et al (30), and Hegsted et al (21), as well as more recent studies, have demonstrated that the effect of stearic acid in raising total blood cholesterol concentrations is much less than that of lauric, myristic, and palmitic acids, and more closely approximates the effect of oleic acid. More recent trials also have reported a modest fall in HDL in response to dietary stearic acid relative to dietary unsaturated fatty acids (18, 19, 31). Thus, stearic and oleic acids are equivalent in their effects on LDL-cholesterol concentrations, but might be somewhat different in their effects on HDL-cholesterol concentrations.

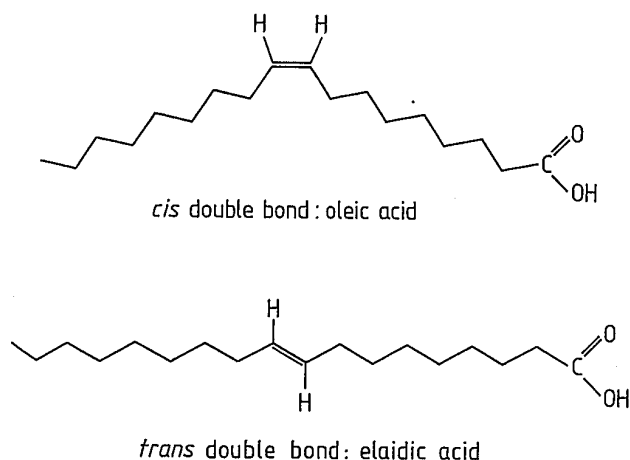
Trans saturated fatty acids

Trans and *cis* isomers of oleic acid are produced during hydrogenation of linoleic and α -linolenic acids, either in the rumen of cows or in oil-hardening factories. The structures of these isomers are illustrated in **Figure 3**. The effect of such *trans* fatty acids on serum lipoproteins markedly differs from those of the natural *cis* isomer, oleic acid. *Trans* fatty acids have been shown to raise LDL-cholesterol concentrations and, although less consistently, to decrease plasma HDL-cholesterol concentrations (19, 20, 32, 33). In addition, *trans* fatty acids raise plasma concentrations of lipoprotein(a) (32, 34), an atherogenic lipoprotein (35) that was hitherto thought impervious to dietary effects. Thus, the overall effect of *trans* 18:1 fatty acids on plasma lipoproteins is unfavorable. However, many people eat no more than a few grams of *trans* fatty acids per day, and such quantities produce only modest effects on lipoprotein concentrations.

In addition to partially hydrogenated vegetable oils, partially hydrogenated fish oils are an important source of *trans* fatty acids in the Netherlands, Norway, the United Kingdom, and South Africa. Such hardened fish oils contain mainly *trans* isomers with chain lengths of 20 or 22 rather than 18 carbon atoms. The effects of hydrogenated fish oils on lipoproteins in humans have not been studied in depth, and could be quite different from those of fats rich in *trans* isomers of oleic acid (*trans* 18:1).

Eicosapentaenoic and docosahexaenoic acids

Eicosapentaenoic acid (EPA, 20:5n-3, n-6, n-9, n-12, n-15) and docosahexaenoic acid (DHA, 22:6n-3, n-6, n-9,

STRUCTURE OF *CIS* AND *TRANS* FATTY ACIDS.FIGURE 3. Structure of *cis* and *trans* 18:1.

n-12, n-15, n-18) typically occur in fatty fish and unhydrogenated fish oil. These very-long-chain (n-3) polyunsaturates do not share the LDL-lowering effect of linoleic acid (18:2n-6, n-9). On the contrary, several studies have shown that fish oils raise LDL and apoprotein B (36-40), and similar results have been reported for fatty fish (41). Fish oil and fatty fish do, however, have favorable effects on serum triglycerides and very-low-density lipoprotein (VLDL), which can be reduced by intake of a few grams of fish oil per day. Whether this effect is responsible for the lower incidence of coronary heart disease observed in fish-eating populations in epidemiologic studies (42) remains uncertain; fish oils also can modulate many other physiological processes, including blood platelet function. One study reporting that fish oil lowers lipoprotein(a) (43) has not been confirmed.

PREDICTED EFFECTS OF VARIOUS FATS AND OILS ON PLASMA LIPIDS

Commercially available oils can be ranked according to their cholesterol-raising effects on plasma lipids and lipoproteins. To accomplish such a ranking, we chose as a reference diet the average intakes of 5898 subjects in the Dutch National Nutrition Surveillance in 1987 (44). Similar dietary patterns have been reported from other affluent Western populations (45), and diets in developing populations are also moving in a similar direction. Figure 4 depicts predicted changes in plasma lipoproteins when all of the fat in the average Dutch diet plus the associated 150 mg cholesterol is replaced by a particular fat or oil. Note that such total replacement is of course not a realistic situation, but it suffices for the present ranking of oils. Lauric, myristic, and palmitic acids were assumed to be equally hypercholesterolemic, whereas saturated fatty acids with chain lengths of < 12 or > 16 carbon atoms were considered neutral (ie, equivalent to carbohydrates) in their effects on both HDL- and LDL-cholesterol concentrations.

As shown in Figure 4, tropical and ruminant fats (including butter) induce increases in serum LDL-cholesterol concentrations, whereas unsaturated oils induce decreases.

Thus, an increase in consumption of butter would raise average values of blood cholesterol in the Netherlands to concentrations typical in Finland, for example, whereas an increase in intake of unmodified oils would reduce the present high concentrations of LDL cholesterol closer to those observed in southern Italy. Replacement of the average dietary fat by lard would have little effect because the overall composition of dietary fat in the Netherlands is already close to that of lard.

These points are relevant to discussions of the effects of Mediterranean diets. If the diet of Crete in the 1960s was used as a reference, then the zero level for LDL in Figure 4 would have been reduced by ≈ 0.5 mmol/L. In this situation, all animal fats would have been observed to be cholesterol-raising compared with fat in the average Cretan diet, which was largely olive oil.

OILS, LIPOPROTEINS, AND CORONARY RISK

Lowering the concentration of LDL cholesterol in plasma lowers the risk of coronary heart disease. In high-risk groups, total mortality rates are also reduced by cholesterol-lowering treatment. In low-risk groups, side effects of drugs sometimes outweigh benefits on mortality of cholesterol-lowering treatment; however, side effects of dietary treatment appear to be minimal (47). It is probable that dietary changes combined with other lifestyle interventions contributed heavily to the striking fall in coronary death rates in the

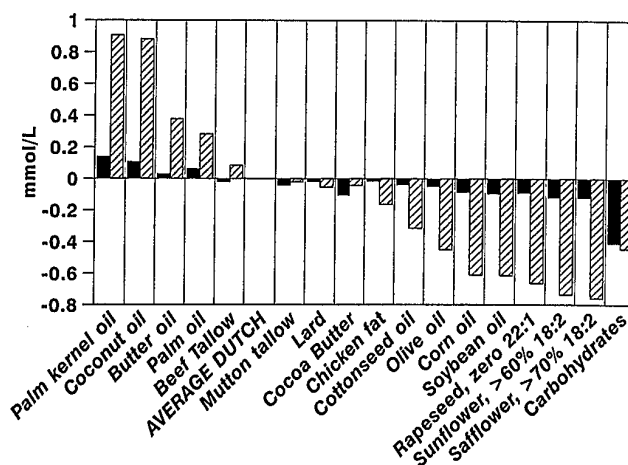


FIGURE 4. Predicted changes in concentrations of HDL cholesterol (■) or LDL cholesterol (▨) when all the fat in an average Dutch diet is replaced by a particular fat or oil. These effects were calculated from the equations of Mensink and Katan (1), modified to take into account that only lauric, myristic, and palmitic acids raise cholesterol whereas other saturated fatty acids do not. Therefore, saturated fatty acid was replaced by $1.5 \times (12\text{-carbon} + 14\text{-carbon} + 16\text{-carbon fatty acids})$. The effect of dietary cholesterol on total plasma cholesterol was calculated by using the equation of Keys et al (30). The reference diet is close to the average diet reported by 5898 Dutch men and women aged 1-74 y in the Dutch National Nutrition Surveillance 1987-1988. It provides 100 g fat, 290 mg cholesterol, and 9628 kJ/d (2300 kcal/d). Of the 290 mg cholesterol, 150 mg was estimated to be provided by fats, and is eliminated when fat is replaced; 140 mg is provided by eggs, lean meats, etc, and is not removable (44). Fat compositions were derived from US Department of Agriculture handbook 8-4 (46).

United States since 1968. Whether manipulations of HDL-cholesterol concentrations will affect cardiovascular risk is uncertain, but many types of behavior that lower coronary risk—such as smoking cessation, physical activity, and moderate alcohol use—are known to raise HDL-cholesterol concentrations (48). In controlled clinical trials, drugs that raise HDL cholesterol tended to reduce coronary events (49, 50). Therefore, observations that high-carbohydrate, low-fat diets reduce HDL-cholesterol concentrations are of some concern. In metabolic-ward studies, diets that are high in oils, ie, not low-fat diets, produced the most favorable plasma lipoprotein profiles. In such studies, however, body weight is forced to remain constant. In clinical practice, on the other hand, allowing patients to consume dietary oils without restraint entails the risk of energy overconsumption and weight gain, which could reverse the beneficial effects of high-oil diets on HDL cholesterol and triglycerides. Obesity also increases blood pressure and diabetes risks. In the 1950s and 1960s, the population of Crete had an unusually high intake of olive oil and, at the same time, enjoyed a remarkable immunity from coronary events. However, now that mechanization has eliminated the need for heavy physical labor, the prevalence of obesity in Crete has increased drastically (51, 52), and, as a result, coronary risk may soon start to rise. Thus, unsaturated oils such as olive oil are probably the replacement of choice for hard fats rich in saturated or *trans* fatty acids, but they should be used in moderation, as they have been in most of the Mediterranean area for centuries. ■

REFERENCES

- Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins—a meta-analysis of 27 trials. *Arterioscler Thromb* 1992;12:911–9.
- Lewis B, Hammet F, Katan MB, et al. Towards an improved lipid-lowering diet: additive effects of changes in nutrient intake. *Lancet* 1981;2:1310–3.
- Spady DK, Dietschy JM. Dietary saturated triacylglycerols suppress hepatic low density lipoprotein receptor activity in the hamster. *Proc Natl Acad Sci U S A* 1985;82:4526–30.
- Woollett LA, Spady DK, Dietschy JM. Saturated and unsaturated fatty acids independently regulate low density lipoprotein receptor activity and production rate. *J Lipid Res* 1992;33:77–88.
- Kromhout D, Keys A, Aravanis C, et al. Food consumption patterns in the 1960s in seven countries. *Am J Clin Nutr* 1989;49:889–94.
- Kesteloot H, Geboers J, Joossens JV. On the within-population relationship between nutrition and serum lipids: the BIRNH Study. *Eur Heart J* 1989;10:196–202.
- Berns MAM, De Vries JHM, Katan MB. Dietary and other determinants of lipoprotein levels within a population of Dutch males aged 28 and 29. *Eur J Clin Nutr* 1990;44:535–44.
- Keys A, Menotti A, Karvonen MJ, et al. The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol* 1986;124:903–15.
- Ernst ND, Fisher M, Smith W, et al. The association of plasma high-density lipoprotein cholesterol with dietary intake and alcohol consumption. *Circulation* 1980;62(suppl IV):41–52.
- Knuiman JT, Westenbrink S, Van der Heijden L, et al. Determinants of total and high density lipoprotein cholesterol in boys from Finland, the Netherlands, Italy, The Philippines and Ghana with special reference to diet. *Hum Nutr Clin Nutr* 1983;37C:237–54.
- Knuiman JT, West CE, Katan MB, Hautvast JGAJ. Total cholesterol and high density lipoprotein cholesterol levels in populations differing in fat and carbohydrate intake. *Arteriosclerosis* 1987;7:612–9.
- Fehily AM, Yarnell JWG, Bolton CH, Butland BK. Dietary determinants of plasma lipids and lipoproteins: the Caerphilly Study. *Eur J Clin Nutr* 1988;42:405–13.
- Katan MB. Diet and HDL. In: Miller NE, Miller G, eds. *Clinical aspects of high density lipoproteins*. Amsterdam: Elsevier, 1985: 103–31.
- West CE, Sullivan DR, Katan MB, Halferkamp IL, Van der Torre HW. Boys from populations with high carbohydrate intake have higher fasting triglycerides than boys from populations with high fat intake. *Am J Epidemiol* 1990;131:271–82.
- Denke MA, Grundy SM. Comparison on effects of lauric acid and palmitic acid on plasma lipids and lipoproteins. *Am J Clin Nutr* 1992;56:895–8.
- Zock PL, De Vries JHM, Katan MB. Impact of myristic versus palmitic acid on serum lipid and lipoprotein levels in healthy women and men. *Arterioscler Thromb* 1994;14:567–75.
- Mattson FH, Grundy SM. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res* 1985;26:194–202.
- Bonanome A, Grundy SM. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. *N Engl J Med* 1988;318: 1244–8.
- Zock PL, Katan MB. Hydrogenation alternatives: effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 1992;33:399–410.
- Mensink RP, Katan MB. Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol in healthy subjects. *N Engl J Med* 1990;323:439–45.
- Hegsted DM, McGandy RM, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 1965;17: 281–95.
- McGandy RB, Hegsted DM, Myers ML. Use of semisynthetic fats in determining effects of specific dietary fatty acids on serum lipids in man. *Am J Clin Nutr* 1970;23:1288–98.
- Sundram K, Hassan AH, Siru OH, Hayes KC. Dietary palmitate lowers cholesterol relative to laurate and myristate in humans. *Arterioscler Thromb* 1991;11:1614a(abstr).
- Ng TKW, Hassan K, Lim JB, Lye MS, Ishak R. Nonhypercholesterolemic effects of a palm-oil diet in Malaysian volunteers. *Am J Clin Nutr* 1991;53(suppl):1015–20.
- Ng TKW, Hayes KC, DeWitt GF, et al. Dietary palmitic and oleic exert similar effects on serum cholesterol and lipoprotein profiles in normocholesterolemic men and women. *J Am Coll Nutr* 1992;11: 383–90.
- Hayes KC, Pronczuk A, Lindsey S, Diersen-Schade D. Dietary saturated fatty acids (12:0, 14:0, 16:0) differ in their impact on plasma cholesterol and lipoproteins in nonhuman primates. *Am J Clin Nutr* 1991;53:491–8.
- Derr J, Kris-Etherton PM, Pearson TA, Seligson FH. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: II. The plasma total and low-density lipoprotein cholesterol response of individual fatty acids. *Metabolism* 1993;42:130–4.
- Temme EHM, Mensink RD, Hornstra G. Effects of lauric and palmitic acid on serum lipids. (Effecten van laurinezuur en palmitinezuur op serumlipiden.) *Voeding* 1994;55:32(in Dutch).
- Ahrens EH, Hirsch J, Insull W, Tsaltas TT, Blomstrand R, Peterson ML. The influence of dietary fats on serum-lipid levels in man. *Lancet* 1957;1:943–53.
- Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. IV: Particular saturated fatty acids in the diet. *Metabolism* 1965;14:776–87.
- Kris-Etherton PM, Derr J, Mitchell DC, et al. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. *Metabolism* 1993;42:121–9.

32. Nestel PJ, Noakes M, Belling GB, et al. Plasma lipoprotein lipid and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res* 1992;33:1029-36.
33. Judd JT, Clevidence BA, Muesing RA, Wittes J, Sunkin ME, Podczasy JJ. Dietary *trans* fatty acids: effects on plasma lipids and lipoproteins of healthy men and women. *Am J Clin Nutr* 1994;59:861-8.
34. Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein[a] levels in humans. *J Lipid Res* 1992;33:1493-501.
35. Lawn RM. Lipoprotein(a) in heart disease. *Sci Am* 1992;266:26-32.
36. Sullivan DR, Sanders TAB, Trayner IM, Thompson GR. Paradoxical elevation of LDL apoprotein B levels in hypertriglyceridaemic patients and normal subjects ingesting fish oil. *Atherosclerosis* 1986;61: 129-34.
37. Harris WS, Zucker ML, Dujovne CA. Omega-3 fatty acids in type IV hyperlipidemia: fish oils vs methyl esters. *Am J Clin Nutr* 1987;45: 858(abstr).
38. Harris WS, Dujovne CA, Zucker ML, Johnson B. Effects of a low saturated fat, low cholesterol fish oil supplement in hypertriglyceridemic patients. *Ann Intern Med* 1988;109:465-70.
39. Glauber H, Wallace P, Griver K, Brechtel G. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1988;108:663-8.
40. Wilt TJ, Lofgren RP, Nichol KL, et al. Fish oil supplementation does not lower plasma cholesterol in men with hypercholesterolemia. Results of a randomized, placebo-controlled crossover study. *Ann Intern Med* 1989;111:900-5.
41. Gerhard GT, Patton BD, Lindquist SA, Wander RC. Comparison of three species of dietary fish: effects on serum concentrations of low-density-lipoprotein cholesterol and apolipoprotein in normotriglyceridemic subjects. *Am J Clin Nutr* 1991;54:334-9.
42. Kromhout D, Bosschieter EB, De Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985;312:1205-9.
43. Beil FU, Terres W, Orgass M, Greten H. Dietary fish oil lowers lipoprotein(a) in primary hypertriglyceridemia. *Atherosclerosis* 1991; 90:95-7.
44. Hospers JJ, Katan MB, Van Oosten-van der Goes GJC, Van Staveren WA. Intake of fat, fatty acids and cholesterol from different food groups and different social-economic classes in the Dutch Nutrition Survey of 1987-1988. (Consumptie van vet, vetzuren en cholesterol naar voedingsmiddelengroep en naar sociale klasse in de voedselconsumptiepeiling 1987-1988.) *Voeding* 1992;53: 9-14(in Dutch).
45. Anonymous. The lipid research clinics population studies data book. Vol II. The prevalence study—nutrient intake. Bethesda, MD: National Institutes of Health, 1982:82-2014.
46. US Department of Agriculture. Composition of foods: fats and oils. Agriculture handbook no. 8-4. Washington, DC: US Government Printing Office, 1990.
47. Davey Smith G, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. *Br Med J* 1993;306:1367-73.
48. Heiss G, Johnson NJ, Reiland S, Davis CE, Tyroler HA. High-density lipoprotein cholesterol levels. The Lipid Research Clinics Program Prevalence Study. *Circulation* 1980;62(suppl IV):116-36.
49. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. *Circulation* 1989;79: 8-15.
50. Frick MH, Elo O, Haapa K, et al. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk-factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.
51. Aravanis C, Mensink RP, Corcondilas A, Ioannidis P, Feskens EJM, Katan MB. Risk factors for coronary heart disease in middle-aged men in Crete as of 1982. *Int J Epidemiol* 1988;17:779-83.
52. Aravanis C, Mensink RP, Karalias N, Christodoulou B, Kafatos A, Katan MB. Serum lipids, apoproteins and nutrient intake in rural Cretan boys consuming high-olive-oil diets. *J Clin Epidemiol* 1988; 41:1117-23.