Effects of fats and fatty acids on blood lipids in humans: an overview[1-4]

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ABSTRACT Differences in dietary fatty acid structure induce marked differences in lipid and lipoprotein concentrations in plasma from fasting subjects. Under metabolic-ward conditions, replacement of carbohydrates by lauric, myristic, and palmitic acids raise both low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol whereas stearic acid has little effect. Oleic and linoleic acids raise HDL and slightly lower LDL; all fatty acids lower fasting triglycerides when substituted for carbohydrates. *Trans* monounsaturates lower HDL and raise LDL and lipoprotein(a). The fatty acids in unhydrogenated fish oil potently lower triglycerides, with variable effects on LDL. Of the commercial fats, palm-kernel and coconut oil are the most hypercholesterolemic, followed by butter and palm oil. Repacement of hard fats rich in lauric, myristic, or palmitic acids or *trans* fatty acids by unsaturated oils will lower LDL, but replacement by carbohydrates will in addition decrease HDL and increase triglycerides. In free-living subjects, high-oil diets could lead to obesity, undoing the favorable effects on HDL and triglycerides. *Am J Clin Nutr* 1994;60(suppl):1017S–22S.

KEY WORDS Dietary fatty acids, serum cholesterol, serum HDL, serum triglycerides, dietary carbohydrates.

Introduction

Dietary triglycerides may differ from each other in many aspects: the chain lengths of their constituent fatty acids, the number and position of double bonds, the geometry (*cis* or *trans*) of these double bonds, and the distribution of fatty acids over the three possible attachment sites on the glycerol molecule. Plasma lipid concentrations from fasting subjects are quite susceptible to the nature and amount of dietary lipid (1, 2). This may be contrasted with the concentration of plasma proteins, which remains constant over a wide range of protein intakes; also, people eating high- or low-carbohydrate diets have roughly similar fasting blood sugar concentrations as long as their body mass index and physical activity level are comparable.

Although the mechanisms through which dietary fats affect serum lipoprotein concentrations are still in the process of being clarified (3, 4), there are sufficient empirical data to allow us to predict how plasma lipid and lipoproteins in humans will change when the amount and quality of fat in the diet are changed. This paper reviews the effects of various fatty acids and food fats on blood lipids and lipoproteins.

Saturates, oleic acid, and linoleic acid

The fatty acids that occur most commonly in human diets are listed in **Table 1.** It is for these fatty acids that most of the information regarding effects on plasma lipids and lipoproteins is available. We previously summarized, in a meta-analysis, the results of 27 well-controlled trials on dietary fatty acids and plasma lipoproteins (2). This analysis resulted in equations that predict the effect of the major classes of fatty acids on plasma lipoprotein concentrations in man under controlled conditions. Fat provides energy, and if a particular fatty acid is added to the diet, an equivalent amount of some other energy-yielding food component must be removed or the subject will gain weight. Thus the effect of a certain amount of energy provided by a specific fatty acid can only be expressed relative to a similar quantity of energy provided by another dietary component that serves as a reference. The choice of the reference component is arbitrary; in **Figure 1** the effects of fatty acids are calculated for when they replace carbohydrates, as is customary, and in **Figure 2** they are calculated relative to saturated fatty acids. Figure 1 represents the changes that may occur when people habitually consuming a low-fat diet, such as the rural Chinese, are switched to diets higher in fat, whereas Figure 2 represents the average US diet in which over the past 30 y part of the saturated fatty acids have been replaced by other fatty acids or carbohydrates. The choice of a reference can be a major source of confusion; thus the effect of olive oil on total serum cholesterol is neutral when it replaces carbohydrates (Fig 1) but cholesterol lowering when it replaces saturated fatty acids (Fig 2).

As shown in Figure 1, replacement of carbohydrates by fat raises high-density lipoprotein (HDL), the effect being more marked the more saturated the fat. Increasing the dietary fat intake also decreases the fasting concentration of neutral fat (triglycerides) in blood plasma; dietary saturates, monounsaturates,

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TABLE 1
Daily intake of the major dietary fatty acids in middle-aged men in four countries[1]

	Intake[2]			
	Finland	Netherlands	United States	Japan
	g/d			
Saturated fatty acids				
Lauric acid (12:0)	4	2	2	0.1
Myristic acid (14:0)	12	8	6	0.9
Palmitic acid (16:0)	38	30	30	8
Stearic acid (18:0)	20	15	14	3
Monounsaturated fatty acids				
Oleic acid (18:1n−9)	40	29	37	10
Trans 16:1 and 18:1[4]	5	8	4	0.2
Polyunsaturated fatty acids				
Linoleic acid (18:2n−6)	8	12	17	8
α-Linolenic acid (18:3n−3)	2	2	2	1
EPA (20:5n−3)	0.4	0.3	0.1	0.7
DHA (22:6n−3)	0.3	0.1	0.1	0.9

[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, unpublished observations, 1994). EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] D Kromhout, unpublished measurements. Data on Finland and Japan are each means of two regions.
[4] Does not include *trans* isomers with chain lengths of 20 and 22 carbon atoms as found in hydrogenated fish oils.

and (n−6) polyunsaturates all produce this effect to about the same extent.

Effects on low-density lipoprotein (LDL) are markedly different, with saturates raising LDL 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 with monounsaturated oils (oils rich in oleic acid) is relatively small.

Epidemiologic evidence

Data from metabolic-ward studies lasting several weeks should ideally be consistent with observations on free-living subjects who have been eating their customary diets for a long time period. Comparisons of individuals within one population are handicapped by the problem of reliably estimating small differences in true long-term fatty acid intakes between individuals. Still, most published studies do report correlations in the same direction as seen in controlled trials [eg, (6); for a review *see* Berns et al (7)]. Specifically, the HDL-lowering effect of high-carbohydrate diets is seen quite regularly when comparing individuals within affluent populations [(8–10); for a review *see* (12)].

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 dietary fat consumption. Keys et al (13) selected 16 cohorts of ≤ 1000 men, from seven countries, with large differences in cholesterol concentrations. They found that the differences in mean cohort cholesterol concentration could be predicted from the men's diets and that differences in coronary heart disease rates agreed with

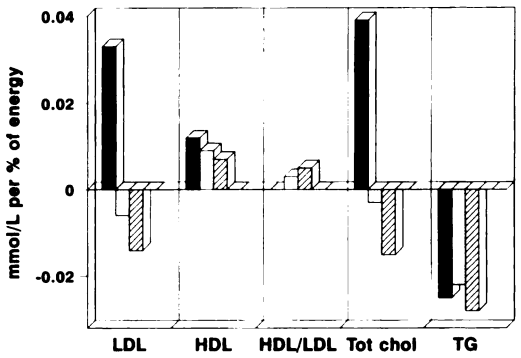

FIG 1. Predicted changes in serum lipids and lipoproteins when 1% of dietary carbohydrates is replaced by fatty acids of a particular class (carb to sat, mono, or poly) under isoenergetic metabolic-ward or equivalent conditions (2). ■, Saturated; □, monounsaturated; ▨, polyunsaturated; □, carbohydrate. Regression equations for the different lipoproteins (mmol/L) are as follows: ΔLDL cholesterol = 0.033 × (carb to sat) − 0.006 × (carb to mono) − 0.014 × (carb to poly); ΔHDL cholesterol = 0.012 × (carb to sat) + 0.009 × (carb to mono) + 0.007 × (carb to poly); Δ ratio of HDL to LDL cholesterol = 0.000 × (carb to sat) + 0.003 × (carb to mono) + 0.005 × (carb to poly); Δtotal cholesterol (chol) = 0.039 × (carb to sat) − 0.003 × (carb to mono) − 0.015 × (carb to poly); and Δtriglycerides (TG) = −0.025 × (carb to sat) − 0.022 × (carb to mono) − 0.028 × (carb to poly).

contrasts in diet and in cholesterol concentrations. However, the absolute extent of differences in cholesterol associated with differences in diet was much larger in the Seven Countries Study (14) than those seen in controlled metabolic-ward studies (2). Evidently other factors or long-term effects of diet played an additional role in shaping cholesterol concentrations.

The effects of dietary fats vs carbohydrates on HDL and triglyceride concentrations seen in controlled trials have also been confirmed by epidemiologic studies of population means (10, 15). In children, high-carbohydrate diets are associated not only with lower LDL but also with lower HDL concentrations than are high-fat diets (10, 16). In adults the effects on HDL, and presumably also on triglycerides, are attenuated by the higher body fatness associated with affluent diets and lifestyles (10, 16).

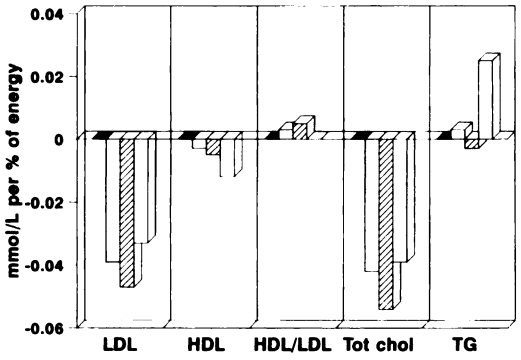

FIG 2. Predicted changes in serum lipids and lipoproteins when 1% of dietary saturated fatty acids is replaced by fatty acids of a particular class or by carbohydrates under isoenergetic metabolic-ward or equivalent conditions. ■, saturated; □, monounsaturated; ■, polyunsaturated; □, carbohydrate. Chol, cholesterol; TG, triglyceride.

Weight gain and obesity

In metabolic-ward studies in which body weight is forcibly kept constant, diets high in oils produce more favorable plasma lipoprotein profiles than do high-carbohydrate, low-fat diets. In clinical practice, however, allowing patients the unrestrained consumption of dietary oils entails a risk of energy overconsumption and weight gain, which would reverse the beneficial effects of high-oil diets on HDL and triglycerides. Obesity will also increase blood pressure and diabetes risk. In population comparisons, high-fat diets and obesity often go hand in hand. However, such associations do not prove causality, and differences in activity could be an important confounder. Controlled trials of fat-restricted diets have produced only modest losses in body weight (17), and long-term effects are uncertain.

Particular fatty acids

Most publications on the effects of fats on plasma lipids and lipoproteins have not reported the intakes of individual dietary fatty acids. However, interest in and information on individual 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 3.**

Lauric, myristic, and palmitic acids

The major saturated fatty acids in most human diets are palmitic acid (16:0) followed by stearic, myristic, and lauric acids (Table 1). In mixed diets, lauric, myristic, and palmitic acids combined usually are 60–70% of all saturates, and they are the fatty acids responsible for the cholesterol-raising effect of saturates. Their relative cholesterol-raising potential has been controversial (2, 18, 24–29). Some investigators reported that palm oil, which is rich in palmitic acid, causes remarkably lower cholesterol concentrations than does coconut oil, which is rich in lauric and myristic acid (26, 27, 29). Ng et al (28) therefore suggested that myristic acid is the major contributor to the cholesterol-raising effect of saturated fatty acids and that palmitic acid may be neutral, just like stearic and oleic acid. This is, however, contradicted by the results of many well-controlled studies in which palmitic acid was shown to raise LDL cholesterol relative to oleic acid (18–21, 30). It thus appears that palmitic acid from palm oil is indeed a cholesterol-raising saturated fatty acid.

The effect of lauric acid (12:0) was reevaluated recently. Denke and Grundy (18) found that the cholesterol-raising potential of dietary lauric acid was about two-thirds that of palmitic acid, whereas Temme et al (31) concluded that a diet rich in lauric acid caused higher HDL-, LDL-, and total cholesterol concentrations than did a diet rich in palmitic acid.

Myristic acid has long been suspected of being the most cholesterol raising of all fatty acids. Hegsted et al (24), who pioneered this field, drew this conclusion from a multiple-regression analysis of a series of controlled trials; our recent meta-analysis (2) also suggested that myristic acid may be four to six times more cholesterol raising than palmitic acid is. However, in edible fats, high concentrations of myristic acid are invariably associated with high concentrations of either lauric acid, such as in coconut oil, or palmitic acid, such as in butter. These associations may invalidate multiple-regression analyses through collinearity, which causes spuriously high or low regression coefficients. McGandy et al (25) studied the effect of myristic acid directly by using specifically synthesized fats but did not reach a conclusion. Recently we fed a special fat rich in myristic acid to a large number of volunteers in a well-controlled trial (19). We found that myristic acid is about 1.5 times as cholesterol-raising as palmitic acid, which is much less than the factor of four to six suggested by meta-analysis (2, 24). In addition, half of the effect of myristic acid on cholesterol was due to HDL.

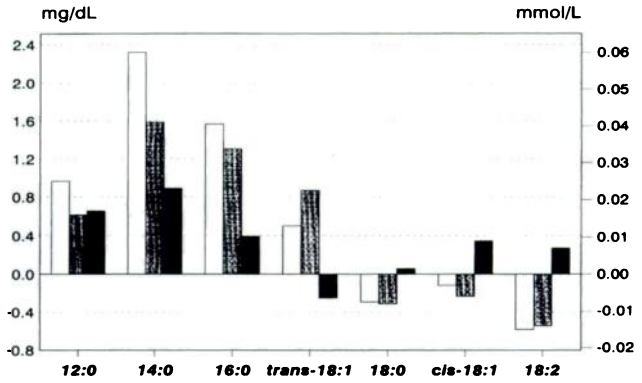

FIG 3. Effects of individual dietary fatty acids on serum total (□) and LDL (▩) and HDL (■) cholesterol when 1% of energy from carbohydrates in the diet is replaced by 1% of energy from the fatty acid in question. The values for lauric acid (12:0) are based on reference 18; myristic acid (14:0) on reference 19; palmitic acid (16:0) on references 18–21; stearic acid (18:0) on references 21 and 22; and monounsaturated *trans*-fatty acids (18:1-*trans*) on references 22 and 23. Data for oleic acid (18:1-*cis*) and linoleic acid (18:2) are based on regression coefficients derived from a meta-analysis of 27 trials (2). These latter values were also used to calculate the effects of the fatty acids observed in each trial relative to carbohydrates. Figure reproduced from reference 19 with permission (copyright 1994, American Heart Association).

These data suggest that there may be differences in the cholesterol-raising potential among lauric, myristic, and palmitic acids but that these differences are modest; all three clearly raise LDL cholesterol compared with unsaturated fatty acids.

Stearic acid

The studies of Ahrens et al (32), Keys et al (33), and Hegsted et al (24) as well as more recent studies (21, 22, 34) showed that the effect of stearic acid on total cholesterol is much less than that of lauric, myristic, and palmitic acids and more closely approximates the effect of oleic acid. The more recent trials also reported a modest decrease in HDL for stearic acid relative to unsaturates (21, 22, 34). Thus, stearic and oleic acids have similar effects on total and LDL cholesterol, but they might not be completely equivalent regarding HDL.

Trans *fatty acids*

Trans and *cis* isomers of oleic acid (**Fig 4**) are produced during the hydrogenation of linoleic and α-linolenic acid, either in the rumen of the cow or in oil-hardening factories. Such *trans* fatty acids have effects on serum lipoproteins markedly different from those of their natural *cis* isomer, oleic acid. *Trans* fatty acids raise LDL concentrations and, less consistently, decrease plasma *HDL* concentrations (22, 23, 35, 36). In some (35, 37) but not all (36) studies they also raised the plasma concentrations of lipoprotein(a), an atherogenic lipoprotein (38) that was hitherto thought to be impervious to dietary effects. Thus the overall effect of

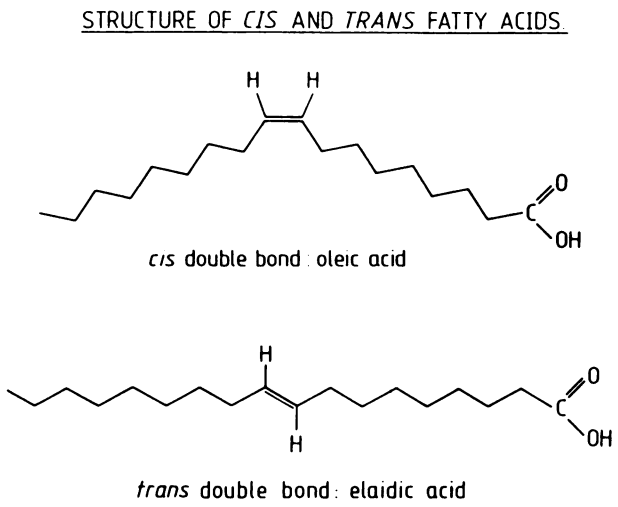

FIG 4. Structure of *cis* and *trans* 18:1n−9. Partially hydrogenated fats contain a mixture of positional isomers of which 18:1n−9 (elaidic acid) is one.

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 have 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 a chain length of 20 or 22 rather than 18 carbon atoms. Their effects on lipoproteins in humans have not been studied in depth and could conceivably be quite different from those of elaidic acid (*trans* 18:1n−9/Δ^9) and its isomers.

Eicosapentaenoic acid and docosahexaenoic acid

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,n−12, n−15,n−18) typically occur in fatty fish and unhydrogenated fish oil. The effects of these very-long-chain (n−3) polyunsaturates on LDL concentrations are controversial. Some studies find LDL to be lowered but several other studies show that fish oils raise LDL and apoprotein B (39–43), and similar results were reported for fatty fish (44). Fish oil and fatty fish do, however, have a favorable effect on serum triglycerides and very-low-density lipoprotein (VLDL), which are lowered by intakes of only a few grams of fish oil per day. Whether this effect is responsible for the lower incidence of coronary heart disease that has been seen in fish-eating people in epidemiologic studies (45) remains unclear; fish oils can also modulate many other physiological processes, including blood platelet function. A report that fish oil lowers lipoprotein(a) (46) has not been confirmed.

Predicted effects of individual fats and oils on plasma lipids

We applied the predictive formulas (2) described above (Fig 1) to rank commercially available oils by their effect on plasma lipids and lipoproteins. As a reference diet we chose one that provided 9600 kJ/d (2300 kcal/d), 100 g fat/d (41 g saturated, 38.5 g monounsaturated, and 17.3 g polyunsaturated fatty acids), and 290 mg cholesterol/d (of which 150 mg was associated with animal fats and another 140 mg was provided by foods such as eggs and lean meat). These values are close to the average intakes of the 5898 subjects in the Dutch National Nutrition Surveillance (47). Similar intakes were reported in other affluent Western populations (48, 49) and the diet in developing populations is moving in the same direction. We calculated the predicted average changes in the plasma lipoproteins of healthy Dutch men when all 100 g fat in this diet plus its associated 150 mg cholesterol were to be replaced by a particular fat. Such total replacement is of course not a realistic situation, but it elucidates the calculations; the effects of more realistic degrees of replacement can be easily derived from those of total replacement because effects of fats on serum lipids and lipoproteins appear to be roughly linear with dose (2).

The effects of saturated, monounsaturated, and polyunsaturated fatty acids were calculated with the equations of Mensink and Katan (2) and the effect of dietary cholesterol on total plasma cholesterol was calculated with the Keys equation (33); values for the composition of fats were derived from the US food table (50). The equations of Mensink and Katan (2) used total saturates as the dietary variable because not enough information was available on the amounts of lauric, myristic, and palmitic acids fed in the various trials. In mixed diets such as used in the studies on which the equations were based (2), the sum of the cholesterol-raising fatty acids lauric, myristic, and palmitic acids usually is ≈0.67 times the sum of all saturated fatty acids. In contrast, for individual fats and oils this ratio can range from 0.43 for cocoa butter to 0.91 for palm and cottonseed oil; as a result, using total saturates would give incorrect predictions for the effects of individual fats and oils on plasma cholesterol. In calculating effects of individual fats and oils on lipoprotein concentrations we there-

TABLE 2
Predicted effect on serum lipids when 100 g of a particular fat replaces all the fat plus fat-associated cholesterol (150 mg) in an average Dutch diet[1]

	ΔHDL	ΔLDL	ΔTC	ΔTG
	mmol/L [mg/dL]			
Palm-kernel oil	0.1 [5]	0.9 [35]	1.0 [39]	−0.2 [−21]
Coconut oil	0.1 [4]	0.9 [34]	1.0 [37]	−0.2 [−15]
Butter oil	0.0 [1]	0.4 [15]	0.4 [17]	0.1 [5]
Palm oil	0.1 [2]	0.3 [11]	0.3 [12]	−0.2 [−14]
Menhaden oil	−0.1 [−2]	0.2 [7]	0.2 [8]	—[2]
Beef tallow	0.0 [−1]	0.1 [3]	0.1 [4]	0.1 [8]
Average Dutch diet	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]
Mutton tallow	0.0 [−2]	0.0 [−1]	0.0 [−1]	0.1 [10]
Lard	0.0 [−1]	−0.1 [−2]	−0.1 [−2]	0.0 [4]
Cocoa butter	−0.1 [−4]	0.0 [−2]	−0.1 [−3]	0.2 [21]
Chicken fat	0.0 [−1]	−0.2 [−6]	−0.2 [−7]	0.0 [−2]
Cottonseed oil	0.0 [−2]	−0.3 [−12]	−0.4 [−15]	−0.1 [−13]
Olive oil	0.0 [−2]	−0.5 [−17]	−0.5 [−19]	0.0 [3]
Carbohydrates	−0.4 [−16]	−0.4 [−17]	−0.6 [−24]	0.9 [82]
Corn oil	−0.1 [−3]	−0.6 [−24]	−0.7 [−28]	−0.1 [−8]
Soybean oil	−0.1 [−4]	−0.6 [−24]	−0.7 [−29]	−0.1 [−6]
Rapeseed, no 22:1	−0.1 [−3]	−0.7 [−26]	−0.8 [−29]	0.0 [1]
Sunflower, >60% 18:2	−0.1 [−5]	−0.7 [−28]	−0.9 [−34]	−0.1 [−5]
Safflower, >70% 18:2	−0.1 [−5]	−0.8 [−29]	−0.9 [−36]	−0.1 [−8]

[1] Only lauric, myristic, and palmitic acids were counted as cholesterol raising (*see* legend to Fig 5). TC, total cholesterol; TG, triglyceride.
[2] Fish oils cause a marked lowering of triglycerides, but in the absence of meta-analytical data no figure is given.

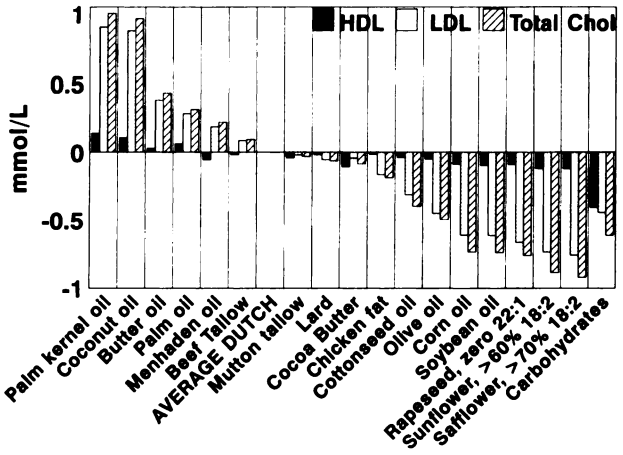

FIG 5. Predicted changes in serum cholesterol concentration when all the fat in an average Dutch diet is replaced by a particular fat or oil. The reference diet is similar to the average diet reported by 5898 Dutch men and women aged 1–74 y in the Dutch National Nutrition Surveillance 1987/1988 (47). The average diet provides 100 g fat/d, 300 mg cholesterol/d, and 9600 kJ/d (2300 kcal/d). It was postulated that 150 mg cholesterol was provided by fats and is thus removed when fat is replaced, and 140 mg is provided by eggs, lean meats, etc, and is not removable. The effects of fatty acids were calculated from the equations of Mensink and Katan (2), modified to take into account that only lauric, myristic, and palmitic acids raise cholesterol whereas other saturated fatty acids do not. Therefore, saturated fatty acids were replaced by 1.5 × (c-12 + c-14 + c-16 fatty acids). The effect of dietary cholesterol on serum cholesterol was calculated by using the Keys equation (51). To calculate the effect of dietary cholesterol on separate lipoproteins, 75% of the total effect was assigned to LDL and 25% to HDL. Compositions of fats were derived from USDA handbook 8-4 (50).

of individual fats and oils on lipoprotein concentrations we therefore replaced total saturates in the Mensink and Katan equations by 1.5 × (lauric + myristic + palmitic acids), and we set the effects of other saturates, including stearic acid, equal to those of carbohydrates.

There are no equations for the separate effects of dietary cholesterol on HDL-, LDL-, and VLDL-cholesterol concentrations. However, most authors agree that dietary cholesterol raises both HDL and LDL cholesterol, with the bulk of the change being due to LDL. We therefore assigned 75% of the effect of dietary cholesterol on serum cholesterol to LDL and the remaining 25% to HDL. This division is somewhat arbitrary, but the ranking of fats and oils by their effects on LDL was not very sensitive to the partitioning of the effect of dietary cholesterol over HDL and LDL.

Table 2 and **Figure 5** depict the predicted changes in plasma total cholesterol when all the fat plus its associated 150 mg cholesterol in the average Dutch diet is replaced by a particular fat or oil. The lauric oils, coconut and palm-kernel oil, top the list, followed by butter fat and palm oil. The lowest cholesterol values are obtained with rapeseed oil and the seed oils rich in linoleic acid. Effects on LDL parallel those on total cholesterol. The cholesterol-lowering oils also cause a decrease in HDL, but the overall effect on the ratio of HDL to LDL is still favorable (2). Differences in the predicted effects of the various fats on triglyceride concentrations are modest except for unhydrogenated fish oils, which have powerful triglyceride-lowering effects. In the absence of quantitative formulas to calculate these effects of fish oils, these data have not been incorporated into the tables and figures; the situation is the same for fats high in *trans* fatty acids.

Conclusion

As far as the effects of fatty acids on total cholesterol are concerned, the equations of Keys et al (33) and Hegsted et al (24) have stood the test of time. Recent studies find a somewhat smaller effect of polyunsaturates, but overall the consistency of the results obtained in the 1950s and 1960s with those obtained more recently is gratifying and reassuring (2). The major new development is the effect of fatty acids vs carbohydrates on HDL. It is now clear that low-fat, high-carbohydrate diets cause not only lower LDL but also lower HDL concentrations. In clinical practice this effect may be compensated for by a loss of body fat in patients on low-fat diets, but this remains to be established. Also remaining to be established is whether lowering HDL concentrations will increase the risk of cardiovascular disease; a causal link is plausible but not yet proven.

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References

1. 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.
2. 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.
3. Spady DK, Dietschy JM. Dietary saturated triacylglycerols suppress hepatic low density lipoprotein receptor activity in the hamster. Proc Natl Acad Sci USA 1985;82:4526–30.
4. 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.
5. 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.
6. Kesteloot H, Geboers J, Joossens JV. On the within-population relationship between nutrition and serum lipids: the B.I.R.N.H. study. Eur Heart J 1989;10:196–202.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. Katan MB. Diet and HDL. In: Miller NE, Miller G, eds. Clinical aspects of high density lipoproteins. Amsterdam: Elsevier, 1985: 103–31.

13. 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.
14. Keys A. Coronary heart disease in seven countries. Circulation 1970;41(suppl 1):162–83.
15. West CE, Sullivan DR, Katan MB, Halferkamps 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.
16. Rubinstein A, Landau E, Goldbourt U, Reisin L. Lipids and lipoproteins in new immigrant Ethiopian Jews in Israel. Am J Epidemiol 1988;128:153–64.
17. National Diet-Heart Study Research Group. The National Diet-Heart Study final report. XI. Body weight changes. Circulation 1968;37 and 38(suppl 1):170–80.
18. 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.
19. 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.
20. 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.
21. Bonanome A, Grundy SM. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. N Engl J Med 1988;318:1244–8.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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).
27. 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.
28. 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.
29. 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.
30. 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.
31. Temme EHM, Mensink RP, Hornstra G. Effects of lauric and palmitic acid on serum lipids. (Effecten van laurinezuur en palmitinezuur op serumlipiden.) Voeding 1994;55:32 (in Dutch).
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. Lawn RM. Lipoprotein(a) in heart disease. Sci Am 1992;266:26–32.
39. 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.
40. 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).
41. 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.
42. 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.
43. 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.
44. 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 normotriglyderidemic subjects. Am J Clin Nutr 1991;54:334–9.
45. 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.
46. Beil FU, Terres W, Orgass M, Greten H. Dietary fish oil lowers lipoprotein(a) in primary hypertriglyceridemia. Atherosclerosis 1991;90:95–7.
47. Hospers JJ, Katan MB, Van Oosten-van der Goes GJC, Van Staveren WA. Intake of fat, fatty acids and cholesterol by food group and social class in the Dutch National 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.
48. US Department of Health and Human Services. The Lipid Research Clinics population studies data book. Vol II. The prevalence study-nutrient intake. Bethesda, MD: National Institutes of Health, 1982. (DHHS publication NIH 82-2014.)
49. Sasaki S, Kesteloot H. Value of Food and Agriculture Organization data on food-balance shets as a data source for dietary fat intake in epidemiologic studies. Am J Clin Nutr 1992;56:716–23.
50. US Department of Agriculture. Composition of foods: fats and oils. Agriculture handbook no. 8-4. Washington, DC: Government Printing Office, 1990.
51. Keys A, Anderson JT, Grande F. Serum cholesterol responses to changes in the diet. II: The effect of cholesterol in the diet. Metabolism 1965;14:759–65.