Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials[1–3]

Ronald P Mensink, Peter L Zock, Arnold DM Kester, and Martijn B Katan

ABSTRACT

Background: The effects of dietary fats on the risk of coronary artery disease (CAD) have traditionally been estimated from their effects on LDL cholesterol. Fats, however, also affect HDL cholesterol, and the ratio of total to HDL cholesterol is a more specific marker of CAD than is LDL cholesterol.

Objective: The objective was to evaluate the effects of individual fatty acids on the ratis of total to HDL cholesterol and on serum lipoproteins.

Design: We performed a meta-analysis of 60 selected trials and calculated the effects of the amount and type of fat on total:HDL cholesterol and on other lipids.

Results: The ratio did not change if carbohydrates replaced saturated fatty acids, but it decreased if *cis* unsaturated fatty acids replaced saturated fatty acids. The effect on total:HDL cholesterol of replacing *trans* fatty acids with a mix of carbohydrates and *cis* unsaturated fatty acids was almost twice as large as that of replacing saturated fatty acids. Lauric acid greatly increased total cholesterol, but much of its effect was on HDL cholesterol. Consequently, oils rich in lauric acid decreased the ratio of total to HDL cholesterol. Myristic and palmitic acids had little effect on the ratio, and stearic acid reduced the ratio slightly. Replacing fats with carbohydrates increased fasting triacylglycerol concentrations.

Conclusions: The effects of dietary fats on total:HDL cholesterol may differ markedly from their effects on LDL. The effects of fats on these risk markers should not in themselves be considered to reflect changes in risk but should be confirmed by prospective observational studies or clinical trials. By that standard, risk is reduced most effectively when *trans* fatty acids and saturated fatty acids are replaced with *cis* unsaturated fatty acids. The effects of carbohydrates and of lauric acid–rich fats on CAD risk remain uncertain.   *Am J Clin Nutr* 2003;77:1146–55.

KEY WORDS   Diet, fatty acids, carbohydrates, serum lipoproteins, coronary artery disease risk

INTRODUCTION

The effects of dietary fats on the risk of coronary artery disease (CAD) have traditionally been estimated from their effects on serum total cholesterol (1, 2). As a result, fats high in lauric, myristic, and palmitic acids, such as dairy fat and tropical oils, were considered the most noxious of fats, and diets low in fat and high in carbohydrates were considered optimal. Such an approach, however, ignores the effects of diet on HDL cholesterol. There is a wealth of obser-vational, mechanistic, and genetic evidence that increasing the concentration of HDL cholesterol through diet will lower the risk of CAD (3–6). In addition, a study with gemfibrozil showed that increasing the concentration of HDL cholesterol lowers the risk of CAD (7). In fact, the ratio of total to HDL cholesterol is considered more important than the total or lipoprotein cholesterol concentrations in estimating the risk of CAD (8–10). There is thus a need for coefficients that estimate the effect of fats on total:HDL cholesterol. This report presents such coefficients, which are based on the outcomes of selected studies published by investigators in 11 countries from 1970 through 1998. The effects of dietary fatty acids on plasma apolipoprotein (apo) B and apo A-I were also evaluated.

METHODS

Selection of studies

Original-research studies that were published in English between January 1970 and December 1998 were selected through a computer-assisted literature search. We also scanned reference lists and performed hands-on searches of journals. Studies had to meet a number of criteria.

1) Food intake had to be thoroughly controlled and described, with dietary fatty acids as the sole variable. Cholesterol intake had to be constant; because animal fats high in saturated fatty acids (SFAs) are generally high in dietary cholesterol, and veg-etable oils high in unsaturated fatty acids are low in choles-terol, it would otherwise be difficult to reliably identify the independent effects of fatty acids or dietary cholesterol. If nec-essary, cholesterol intake was kept constant by using eggs or egg yolk or by adding crystalline cholesterol to the diets.

---

2) Studies had to have a parallel, crossover, or Latin-square design. Before-and-after (sequential) designs that lacked a control group were excluded.

3) Feeding periods had to be sufficiently long to allow the achievement of new steady-state concentrations of serum lipids and lipoproteins, ie, >13 d (1, 11).

4) Only adult subjects (aged >17 y) who did not have disturbances of lipid metabolism or diabetes were included.

We excluded studies that focused on very-long-chain (n−3) polyunsaturated fatty acids (PUFAs) such as fish oils. The effects of these oils have been reviewed elsewhere (12). Therefore, in this report, total PUFAs may be considered to equal the n−6 PUFAs with 18 carbon atoms (linoleic acid plus some α-linolenic acid). We also excluded studies on medium-chain fatty acids, because there were too few to allow proper statistical analysis.

To convert them to serum values, plasma concentrations of total and HDL cholesterol were multiplied by 1.030 and those for triacylglycerols were multiplied by 1.029 (13). LDL-cholesterol concentrations were calculated (14). For the sake of uniformity, we also recalculated the ratio of total to HDL cholesterol and the LDL-cholesterol concentrations, even if they were reported by the authors of the report. Plasma values for apo B and apo A-I were also multiplied by 1.030 to convert them to serum values.

On average, dietary fat contains 96% (by wt) fatty acids; the other 4% is made up of glycerol and other lipids (15). For publications in which the intakes of the various fatty acid classes had been normalized to add up to 100% of total fat, we converted intakes back to true fatty acid intakes by multiplying them by 0.96.

Statistical analysis

Each data point consisted of the fatty acid composition of a particular diet (the independent variable) and the mean ratio of serum total to HDL cholesterol or the mean serum lipid or apolipoprotein concentration (the dependent variable) of a group of subjects, as obtained at the end of a dietary period. In all trials, fatty acids were exchanged for either other fatty acids or carbohydrates. Possible effects of protein and alcohol thus could not be estimated. The regression coefficients estimated in this way are the predicted change in the ratio of serum total to cholesterol or in the serum lipid or apolipoprotein concentrations when carbohydrate intake decreases by 1% of energy and that of a particular fatty acid increases by the same amount (16).

Two different models were used for SFAs and *cis* unsaturated fatty acids, and a third approach was used for *trans* fatty acids. The models used as dependent variables the absolute lipid or apolipoprotein concentrations during particular diets rather than changes induced by diet. Therefore, all models were corrected for the intrinsic concentrations to ensure that only within-study diet-induced differences were analyzed. The intrinsic concentration is a constant for a particular study. It reflects the mean estimated serum lipid or apolipoprotein concentration or their ratios that would result if this particular group of subjects consumed a standardized fat-free, high-carbohydrate diet. The intrinsic concentration is determined by such factors as genetic makeup, age, and body mass index and by such factors as the fiber, protein, or alcohol content of the background diet, which was constant within studies but differed between studies.

In the first model, the effects on a particular outcome of all fatty acids within a certain category—SFAs, *cis* monounsaturated fatty acids (MUFAs), or n−6 *cis* PUFAs—were estimated. Diets in which the fatty acid composition of a particular class of fatty acids diverged markedly from that in normal mixed diets were excluded. For example, Grande et al (17) specifically examined the effects of stearic acid on serum lipids. Because stearic acid is hypocholesterolemic compared with other SFAs (2), including this data point would have resulted in a biased estimate of the effect of a normal mixture of SFAs.

The second model estimated the effects of individual SFAs. The proportions of energy from lauric, myristic, palmitic, and stearic acids were used as independent variables, together with the sum of all *cis* MUFAs and the sum of all *cis* PUFAs. Diets rich in *trans* fatty acids were not included.

The validity of the regression models was examined in several ways (18). First, the influence of each separate observation (ie, trial or trial arm) on the estimated regression coefficients was assessed with the use of Cook's distance to detect possible outliers. Our initial analysis showed that there were 1 or 2 observations with Cook's distance >0.3 that caused nonnormality of the residuals. Excluding these observations did not change our conclusions but resulted in normally distributed variables as indicated by the Shapiro-Wilk test (18) and narrower confidence intervals, a measure of the variability in dietary response between studies. Therefore, we decided to exclude from the final analysis observations with Cook's distances >0.3. Another source of errors in regression statistics can be collinearity—ie, correlations between supposedly independent variables (in this case, the various fatty acids). Collinearity can be quantitated as tolerance. For all models used, the tolerance for each fatty acid was ≥0.22, which indicated that relation between the independent variables did not lead to inappropriate estimates of the regression coefficients. Finally, visual inspection of plots did not suggest a relation between residuals and predicted values or between residuals and the independent variables. This suggests that the differences between observed and predicted values (ie, the residuals) did not depend on the absolute serum lipid or lipoprotein of a trial or on the absolute intake of a particular fatty acid or class of fatty acids. All statistical analyses were carried out with PROC REG software, version 6 (19). Each study was represented by a dummy variable (the intrinsic concentration). The use of a random-effects model, which is frequently used in meta-analyses to correct for error within a study, was not possible, because it requires standard errors of treatment differences within studies, which generally were not given. Therefore, we could not differentiate within-study and between-study variability. However, the estimates of the regression coefficients in the present analysis would have been comparable with those of a random-effects analysis.

The effects of *trans* MUFAs were examined in a different way because the number of studies was too small for multiple regression analysis. For each single study, the difference in outcome variables between the *trans* diet and the control diet was adjusted for differences in the intakes of other fatty acids with the use of results from the regression analysis described above. The effects of *trans* MUFAs relative to those of carbohydrates were calculated per 1% of energy, and the results from the various studies were then averaged.

RESULTS

The 60 trials that met our criteria yielded 159 diet data points and included 1672 volunteers, at a ratio of men to women of 70:30. Thirty-four studies were from the United States (17,

TABLE 1
Estimated regression coefficients for mean changes (Δ) in serum lipids and lipoproteins when carbohydrates constituting 1% of dietary energy are replaced isoenergetically with saturated fatty acids (SFAs) (Carbohydrates → SFAs), *cis* monounsaturated fatty acids (MUFAs) (Carbohydrates → MUFAs), or *cis* polyunsaturated fatty acids (PUFAs) (Carbohydrates → PUFAs)[1]

Lipid or lipoprotein	No. of diets; no. of studies	Carbohydrates → SFAs	Carbohydrates → MUFAs	Carbohydrates → PUFAs
ΔTotal:HDL cholesterol	99; 42	0.003 (−0.008, 0.013)	−0.026 (−0.035, −0.017)	−0.032 (−0.042, −0.022)
P		0.613	<0.001	<0.001
ΔTotal cholesterol (mmol/L)	114; 47	0.036 (0.029, 0.043)	−0.006 (−0.012, 0.000)	−0.021 (−0.027, −0.015)
P		<0.001	0.061	<0.001
ΔLDL cholesterol (mmol/L)	102; 43	0.032 (0.025, 0.039)	−0.009 (−0.014, −0.003)	−0.019 (−0.025, −0.013)
P		<0.001	0.004	<0.001
ΔHDL cholesterol (mmol/L)	102; 43	0.010 (0.007, 0.013)	0.008 (0.005, 0.011)	0.006 (0.003, 0.009)
P		<0.001	<0.001	<0.001
ΔTriacylglycerol (mmol/L)	110; 45	−0.021 (−0.027, −0.015)	−0.019 (−0.024, −0.014)	−0.026 (−0.031, −0.020)
P		<0.001	<0.001	<0.001
ΔApo B (mg/L)	57; 23	2.6 (−1.4, 6.5)	−4.8 (−8.1, −1.5)	−7.7 (−11.3, −4.2)
P		0.195	0.006	<0.001
ΔApo A-I (mg/L)	55; 22	5.7 (2.3, 9.1)	5.2 (2.3, 8.1)	2.2 (−0.9, 5.3)
P		0.002	0.001	0.165

[1] 95% CI in parentheses. Apo, apolipoprotein.

20–55); 8 from Netherlands (11, 56–63); 4 from Denmark (64–67); 3 from Canada (68–70); 2 each from Finland (71, 72), Israel (73, 74), Malaysia (75, 76), and Norway (77, 78); and 1 each from Germany (79), Italy (80), and the United Kingdom (81, 82). The test diets were fed for 13–91 d. For 40 studies, mean prestudy concentrations of total cholesterol were given; they ranged between 3.7 and 6.5 mmol/L. Eleven studies were carried out on an inpatient basis, whereas 6 studies used liquid formula diets. Fifty-one trials reported the mean age of their participants, which varied between 21 and 72 y. Analysis of residuals did not suggest that study characteristics (eg, length of the feeding periods, inpatient or outpatient studies, mixed solid diets or liquid formula diets) were important determinants of the observed changes in serum lipid or lipoproteins as responses to a change in diet. Moreover, excluding the inpatient studies or the studies that used liquid formula diets did not change the conclusions.

Classes of fatty acids

The number of diet data points included in the calculations varied from 102 for total:HDL cholesterol to 114 for total cholesterol concentration (**Table 1**). In these diets, the mean intakes of fat, SFAs, MUFAs, and PUFAs were 34.3% of total daily energy (range: 4.5–53.0%), 10.2% of energy (2.2–24.4%), 13.5% of energy (1.5–39.8%), and 8.8% of energy (0.6–28.8%), respectively.

The regression coefficients (Table 1 and **Figure 1**) showed that total:HDL cholesterol did not change if SFAs were replaced with carbohydrates, because total and HDL cholesterol decreased to a similar extent. The ratio decreased if SFAs or carbohydrates were replaced with *cis* unsaturated fatty acids. As shown in **Figure 2**, the observed and predicted values for total:HDL cholesterol were in excellent agreement.

The effects of the classes of fatty acids on serum total, LDL, and HDL cholesterol concentrations and on serum triacylglycerol concentrations agreed well with the results of our earlier meta-analysis (16). The *cis* MUFAs had a modest but significant LDL cholesterol–lowering effect relative to carbohydrates. All 3 classes of fatty acids increased HDL cholesterol relative to carbohydrates. Unsaturated fatty acids increased HDL cholesterol less than did

SFAs. As a result, the replacement of 1% of energy in the form of SFAs with an equal percentage in the form of *cis* MUFAs is predicted to lower HDL-cholesterol concentrations by 0.002 mmol/L. A similar decrease is expected when 1% of energy in the form of MUFAs is replaced with an equal percentage in the form of PUFAs. These effects, however, are small compared with those of replacement of carbohydrates with any of the 3 classes of fatty acids. Replacement of carbohydrates with any class of fatty acids decreased fasting serum triacylglycerol concentrations (Table 1). The effect was slightly but not significantly larger for PUFAs than for other fatty acids. This contrasts with the powerful triacylglycerol-lowering effect of n−3 PUFAs from fish (12), which is evidently not shared by linoleic acid, the major n−6 PUFA.

Replacement of carbohydrates with SFAs did not change apo B concentrations. The *cis* unsaturated fatty acids, however, decreased apo B, and this effect was slightly stronger for PUFAs.
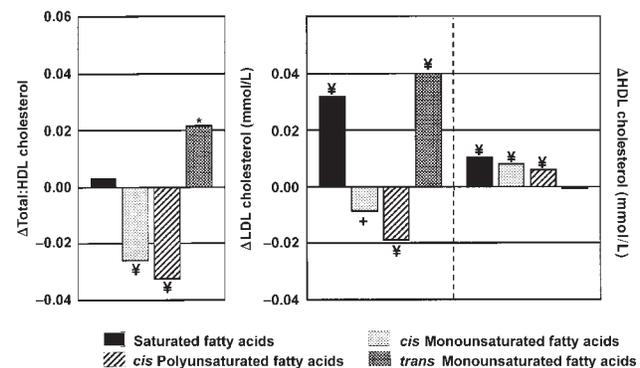

FIGURE 1. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with saturated, *cis* monounsaturated, *cis* polyunsaturated, or *trans* monounsaturated fatty acids. *P < 0.05; +P < 0.01; ¥P < 0.001.
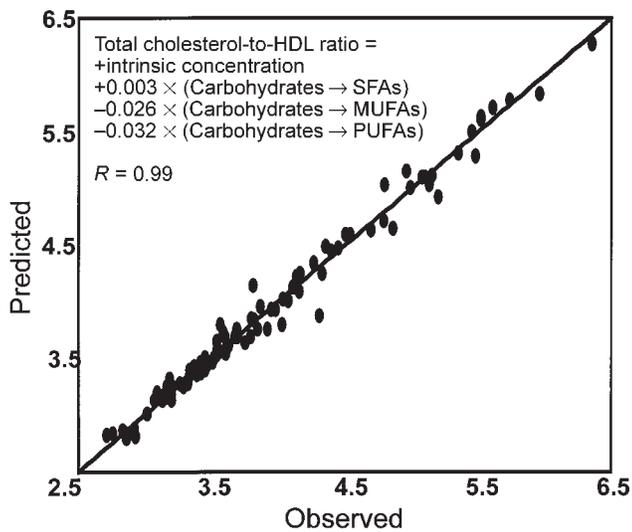
FIGURE 2. Scatterplot showing observed versus predicted ratios of serum total to HDL cholesterol. Each point refers to a specific test diet in one of the studies. "Predicted" values were calculated as the intrinsic concentration of the group under study plus the predicted change induced by their test diet (*see* Table 1). The intrinsic concentration reflects the total:HDL cholesterol that would result if this particular group of subjects consumed a standardized fat-free, high-carbohydrate diet. It is determined by factors such as genetic makeup, age, and body mass index and by factors such as the fiber, protein, or alcohol content of the background diet, which was constant within studies but differed between studies. (Carbohydrates → SFAs), (Carbohydrates → MUFAs), and (Carbohydrates → PUFAs), percentage of energy in the form of carbohydrates replaced with an equal percentage in the form of saturated fatty acids, *cis* monounsaturated fatty acids, or *cis* polyunsaturated acids, respectively.

SFAs and MUFAs increased apo A-I concentrations relative to carbohydrates. PUFAs did not significantly change apo A-I concentrations.

Individual saturated fatty acids

Intakes of individual SFAs were reported for 35 studies, yielding 91 data points. The mean intakes of lauric, myristic, palmitic, and stearic acids were 1.1% of total daily energy (0.0–16.9%), 1.3% of energy (0.0–14.3%), 6.2% of energy (1.0–19.9%), and 3.0% of energy (0.7–16.5%), respectively. The diet with the highest lauric acid intake, 16.9% of energy (42), was included in the model for total:HDL cholesterol but excluded from the models for total, LDL, and HDL cholesterol, because its Cook's distance exceeded 0.3 (*see* Methods). The next highest lauric acid intake was 10.7% of energy.

Although lauric acid was the most potent total and LDL cholesterol–raising SFA (**Table 2** and **Figure 3**), it actually decreased total:HDL cholesterol relative to carbohydrates. Thus, the cholesterol-raising effect of lauric acid is proportionally higher for HDL than for LDL. The ratio of total to HDL cholesterol was less affected by the other 3 SFAs, although it was somewhat more favorably affected by stearic acid than by myristic or palmitic acid.

The HDL cholesterol–raising effects of the various SFAs relative to carbohydrates decreased with increasing chain length, from 0.027 mmol/L per % of energy for lauric acid to ≈0 mmol/L per % of energy for stearic acid. Replacement of the different SFAs with carbohydrates increased serum triacylglycerol concentrations to the same extent.

trans MUFAs

In the 8 studies that specifically examined *trans* MUFAS, the intake of *trans* MUFAs ranged between 0.0 and 10.9% of energy; these values include the *trans* fatty acid–free control diets in these studies. As shown in **Table 3**, *trans* 18:1 has the largest effect of all the fatty acids on total:HDL cholesterol. Furthermore, *trans* 18:1 does not increase HDL cholesterol or apo A-I concentrations relative to carbohydrates. Isoenergetic replacement of *trans* 18:1 constituting 1% of energy with SFAs decreased total:HDL cholesterol by 0.019; replacement with *cis* MUFAs, by 0.048; and replacement with *cis* PUFAs, by 0.054.

Effects of actual food fats

Predicted changes in total:HDL cholesterol are shown in **Figure 4** when mixed fat constituting 10% of energy in the "average" US diet (55, 83) is replaced with one particular fat source or with carbohydrates. For animal fats, we adjusted for the slight effects of dietary cholesterol on this ratio (84). The largest reduction is seen with unhydrogenated oils, such as rapeseed, soybean, and olive oils. Replacement of the average fat with stick margarines or butter would cause a small increase in the ratio, but, surprisingly, so would replacement with carbohydrates.

DISCUSSION

Is total:HDL cholesterol a reliable predictor of risk?

The use of total:HDL cholesterol implies that diet-induced decreases in HDL cholesterol increase CAD risk. Such a causal role for diet-induced changes in HDL cholesterol has not been proven in controlled clinical trials. However, results of prospective observational studies, controlled clinical trials with drugs, mechanistic studies, and genetic "experiments of nature" all strongly suggest that high concentrations of HDL cholesterol in the circulation help to prevent CAD and other cardiovascular diseases (3–7). Given these observations, it appears imprudent to ignore the marked effects of diet on HDL cholesterol. An additional justification for using total:HDL cholesterol might be that it includes the amount of cholesterol in the triacylglycerol-rich VLDL fraction, which also positively correlates with CAD risk (85). However, our analysis also underlines the fact that effects of diet on biomarkers such as blood lipids can never replace studies that employ disease or death as outcomes. Total:HDL cholesterol is more sensitive and specific than is total cholesterol as a risk predictor (8–10), but the favorable effects on this ratio by such factors as coconut fat, which is rich in lauric acid, do not exclude the possibility that coconut fat may promote CAD through other pathways, known or as yet unknown. Similarly, the unfavorable effect of carbohydrates on the ratio does not rule out a favorable effect of high-carbohydrate diets on health outcomes.

Predicted effects on coronary artery disease risk

Epidemiologic studies suggest that a change of 1 U in total:HDL cholesterol is associated with a 53% change in the risk of myocardial infarction (9). We can use this figure and the coefficients in Table 1 to speculate about the effect of changes in fatty acid intake on the risk of CAD. The most clear-cut test of such speculations is provided by the clinical trials of dietary fat and heart disease. For the Finnish Mental Hospital Trial, our coefficients predict a decrease of 18% in the incidence of CAD in both sexes, compared with actual decreases of 44% in men (86) and

TABLE 2
Estimated regression coefficients for mean changes (Δ) in serum lipids and lipoproteins when carbohydrates constituting 1% of dietary energy are replaced isoenergetically with lauric acid (Carbohydrates → 12:0), myristic acid (Carbohydrates → 14:0), palmitic acid (Carbohydrates → 16:0), or stearic acid (Carbohydrates → 18:0)[1]

Lipid or lipoprotein	No. of diets; no. of studies	Carbohydrates → 12:0	Carbohydrates → 14:0	Carbohydrates → 16:0	Carbohydrates → 18:0
ΔTotal:HDL cholesterol	91; 35	−0.037 (−0.057, −0.017)	−0.003 (−0.026, 0.021)	0.005 (−0.008, 0.019)	−0.013 (−0.030, 0.003)
P		<0.001	0.832	0.431	0.119
ΔTotal cholesterol (mmol/L)	90; 35	0.069 (0.040, 0.097)	0.059 (0.036, 0.082)	0.041 (0.028, 0.054)	−0.010 (−0.026, 0.006)
P		<0.001	<0.001	<0.001	0.227
ΔLDL cholesterol (mmol/L)	90; 35	0.052 (0.026, 0.078)	0.048 (0.027, 0.069)	0.039 (0.027, 0.051)	−0.004 (−0.019, 0.011)
P		<0.001	<0.001	<0.001	0.464
ΔHDL cholesterol (mmol/L)	90; 35	0.027 (0.021, 0.033)	0.018 (0.013, 0.023)	0.010 (0.007, 0.013)	0.002 (−0.001, 0.006)
P		<0.001	0.841	0.418	0.390
ΔTriacylglycerol (mmolL)	91; 35	−0.019 (−0.028, −0.011)	−0.017 (−0.027, −0.006)	−0.017 (−0.023, −0.011)	−0.017 (−0.024, −0.010)
P		<0.001	0.002	<0.001	<0.001
ΔApo B (mg/L)	66; 25	5.6 (−2.6, 13.8)	1.9 (−4.6, 8.5)	4.2 (−0.5, 8.9)	−3.8 (−9.2, 1.5)
P		0.173	0.552	0.078	0.152
ΔApo A-I (mg/L)	65; 25	13.8 (1.8, 25.8)	10.4 (5.0, 15.7)	7.5 (3.7, 11.4)	−1.6 (−6.0, 2.8)
P		<0.001	<0.001	<0.001	0.371

[1] 95% CI in parentheses. Apo, apolipoprotein.

36% in women (87). For the Veterans Administration trial, the predicted and observed changes are 20% and 24%, respectively (88). Predicted effects are thus somewhat lower than observed effects, which suggests that dietary fatty acids also affect other risk factors for CAD. Epidemiologic observations, however, suggest a much larger effect of changes in the amount and quality of dietary fat and carbohydrates on CAD risk (89), and the possible reasons for this were discussed elsewhere (90, 91).

Effects of fatty acids and carbohydrates on serum lipids and lipoproteins

Our results suggest that isoenergetic replacement of SFAs with carbohydrates does not improve the serum total:HDL cholesterol. All natural fats contain both SFAs, which do not change this ratio, and unsaturated fatty acids, which lower it. As a result, even the replacement of dairy fat and tropical fats with carbohydrates will

FIGURE 3. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), or stearic acid (18:0). *P < 0.001.

increase the ratio of total to HDL cholesterol (Figure 4). The products with the most favorable effect on this ratio are oils that are rich in *cis* unsaturated fatty acids, such as rapeseed, soybean, sunflower, and olive oils. The effects of the PUFAs, which in our analyses consisted mainly of linoleic acid plus some α-linolenic acid, are more favorable than those of MUFAs such as oleic acid, but the difference is slight. Our study did not address the effects of n−3 PUFAs from fish. Their major effect on plasma lipids is to lower triacylglycerols (12), but their favorable effects on CAD mortality may also involve pathways other than plasma lipoproteins (92).

Apolipoprotein B and LDL particle size

There is evidence that not only the amount of cholesterol transported by LDL particles but also the size and density of these particles and their apo B content affect CAD risk (93). Effects of carbohydrates on apo B were less favorable than those of unsaturated fatty acids (Table 1), which may agree with the findings of studies in which high-carbohydrate diets not only increased triacylglycerol concentrations but also induced a shift toward smaller, denser LDL particles (93).

Individual saturated fatty acids

Lauric acid markedly increases cholesterol, whereas stearic acid lowers it somewhat when it is used to replace carbohydrates. However, the picture reverses if one looks at total:HDL cholesterol: both lauric and stearic acid are now more favorable than carbohydrates. Lauric acid—a major component of tropical oils such as coconut and palm kernel fat—has the largest cholesterol-raising effect of all fatty acids, but much of this is due to HDL cholesterol. As a result, lauric acid had a more favorable effect on total:HDL cholesterol than any other fatty acid, either saturated or unsaturated.

trans Fatty acids

The *trans* MUFAs were the most harmful macronutrient in terms of the ratio of total to HDL cholesterol. If *trans* MUFAs constituting 1% of energy are isoenergetically replaced with a 1:1:1 mix of carbohydrates, *cis* MUFAs, and *cis* PUFAs, then the
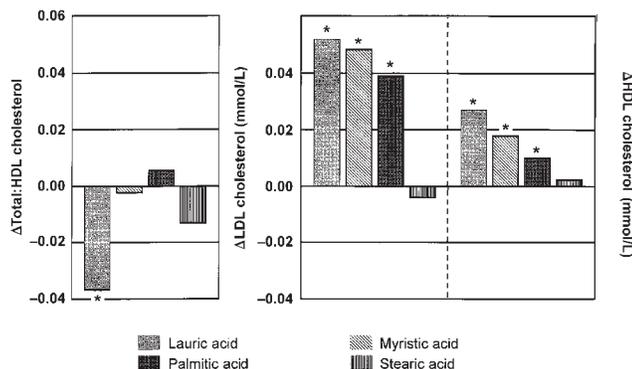
TABLE 3
Estimated regression coefficients for mean changes (Δ) in serum lipids and lipoproteins when carbohydrates constituting 1% of dietary energy are replaced isoenergetically with *trans* monounsaturated fatty acids (Carbohydrates → *trans*)[1]

Lipid or lipoprotein	No. of diets; no. of studies	Coefficient
ΔTotal:HDL cholesterol	18; 8	0.022 (0.005, 0.038)
P		0.015
ΔTotal cholesterol (mmol/L)	18; 8	0.031 (0.020, 0.042)
P		<0.001
ΔLDL cholesterol (mmol/L)	18; 8	0.040 (0.020, 0.060)
P		0.002
ΔHDL cholesterol (mmol/L)	18; 8	0.000 (−0.007, 0.006)
P		0.937
ΔTriacylglycerol (mmolL)	18; 8	0.000 (−0.012, 0.012)
P		0.970
ΔApo B (mg/L)	15; 7	5.4 (2.3, 8.5)
P		0.005
ΔApo A-I (mg/L)	15; 7	2.2 (−5.1, 9.4)
P		0.501

[1] 95% CI in parentheses. Apo, apolipoprotein.

FIGURE 4. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol when mixed fat constituting 10% of energy in the "average" US diet is replaced isoenergetically with a particular fat or with carbohydrates.

ratio decreases by 0.04. This is equivalent to replacing SFAs constituting 1.8% of energy with such a mixture. If fat is replaced exclusively with carbohydrates, then the difference becomes even larger: isoenergetically replacing *trans* MUFAs constituting 1% of energy with carbohydrates has the same effect on this ratio as isoenergetically replacing SFAs constituting 7.3% of energy with carbohydrates (Tables 1 and 3). The US diet provides, on average, 2.6% of energy from *trans* MUFAs and nearly 13% of energy from SFAs (3), so that the total replacement of *trans* fatty acids in the diet with carbohydrates would have a greater effect on total:HDL cholesterol than would total replacement of SFAs. Therefore, even low concentrations of *trans* MUFAs in the diet should deserve attention as a target for efforts to lower CAD risk.

Consumption of *trans* fatty acids from partially hydrogenated oils is associated with the risk of CAD in observational studies. Unfortunately, the price, mouth-feel, and stability of such hydrogenated oils make them a favorite of manufacturers of fast foods (94). Palm oil is an acceptable alternative for the industry, and, in terms of the effect on total:HDL cholesterol, palm oil is still better than the partially hydrogenated vegetable oils used in the food service industry. However, unhydrogenated vegetable oils produce a much more favorable lipid profile than do either palm oil or hydrogenated oils, and they should be preferred.

The intake of *trans* fatty acids from ruminant fats including milk and cheese shows a less consistent association with CAD than does the intake of industrially hydrogenated fats. However, Oomen et al (95) found that the intakes of both ruminant and industrially produced *trans* fatty acids predicted a higher risk of CAD in the Zutphen Elderly Study. The intake of ruminant *trans* fatty acids can be kept low by a choice of skimmed dairy products and lean meat, in accordance with current guidelines.

Low-fat, high-carbohydrate diets and body weight

The unfavorable effect of carbohydrates on total:HDL cholesterol might be opposed by a favorable effect of carbohydrates on body weight, because low-fat diets may promote weight reduction.
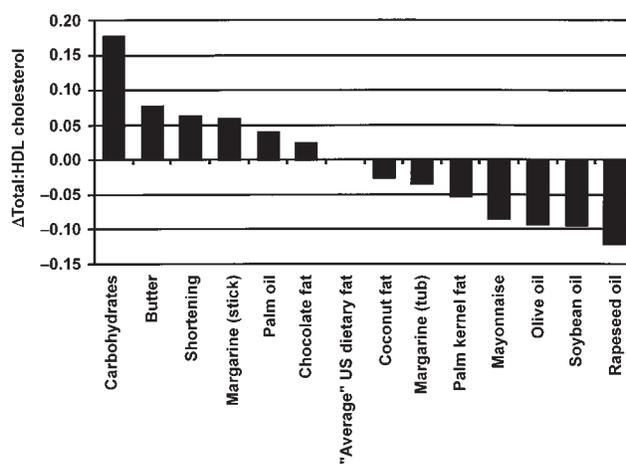
Isoenergetically replacing fat constituting 10% of energy with carbohydrates may reduce weight by 3 kg (96, 97). The data of Leenen et al (98) suggest that a weight loss of 3 kg may lead to a decrease of 0.24 in total:HDL cholesterol. If a high-carbohydrate diet reduces energy intake sufficiently to cause a 3-kg weight loss, then the effect on total:HDL cholesterol would be approximately equal that of isoenergetic replacement of SFAs constituting 10% of energy with *cis* unsaturated oils. This underlines the importance of weight management in the reduction of CAD risk. Unfortunately, the effects of low-fat diets on body weight over the long term are uncertain (99). The introduction of low-fat, high-carbohydrate foods in the United States does not appear to have reduced caloric intake; rather, carbohydrates seem to have been added to existing intakes. However, further studies on the long-term effect of high-carbohydrate diets on body weight are urgently needed.

Thus, it is not certain whether weight loss per se is a strong argument for replacing fat with carbohydrates. Without doubt, reducing the high prevalence of obesity should be a major public health target, but increased intakes of carbohydrates could be shown to be insufficient to counter the effects of low energy expenditure and high caloric intake that characterize modern societies.

Dietary fat and other risk factors

High-fat diets lower fasting triacylglycerol concentrations, which may reduce cardiovascular disease risk (85), but they also increase postprandial concentrations of triacylglycerol-rich lipoproteins, which are positively associated with CAD risk (100). In addition, the elevated factor VII coagulant activity that occurs during the postprandial phase of high-fat diets may predispose a person to coronary thrombosis (101, 102). Whether a high-fat diet or a high-carbohydrate diet changes insulin sensitivity or leads to the development of type 2 diabetes is still controversial (103). The final answer as to the overall effect of *cis* unsaturated fatty acids and carbohydrates on CAD risk can only be decided by long-term controlled clinical trials. Clinical trials have indeed shown that the replacement of SFAs and *trans* fatty acids with polyunsaturated oils reduces the incidence of CAD (104). The few trials that studied replacement of SFAs with carbohydrates

were inconclusive (105, 106). Present trial data thus favor *cis* unsaturated fatty acids over carbohydrates.

Extrapolation to specific population groups and long-term effects

The number of studies of hyperlipidemic subjects who met our selection criteria was too limited for useful statistical analyses. We cannot be sure, therefore, whether the predictive coefficients for the effects of fatty acids will also apply to groups of patients with hyperlipidemia. However, persons with high baseline cholesterol concentrations are probably more sensitive to dietary changes than are persons with normal cholesterol concentrations (107, 108). Therefore, we think that our coefficients are also applicable to hyperlipidemic patients. If anything, the coefficients would underestimate the effect in persons with higher cholesterol concentrations, rather than overestimate it.

In one of our studies, we reported that the responses of total and LDL cholesterol to SFAs were slightly larger in men than in women (109). A sex effect could not be examined in the present meta-analysis because too many studies did not report separate data for men and women. Therefore, we may have slightly overestimated the effects of SFAs in women and underestimated those in men, and this issue certainly deserves further attention.

The studies included in our meta-analysis lasted between 13 and 91 d. This raises the question of whether the effects observed are transitory. However, long-term epidemiologic findings support our findings. For example, a life-long high intake of carbohydrates is associated with increased triacylglycerol concentrations (110), whereas the effects on total cholesterol of fatty acids in observational studies also agree with the trials analyzed here (111). This gives us confidence that the effects seen in our present meta-analysis are not transient.

Conclusions

The replacement of *trans* fatty acids with unsaturated fatty acids from unhydrogenated oils is the single most effective measure for improving blood lipid profiles. Even small amounts of unsaturated fatty acids have a major effect on the ratio of total to HDL cholesterol. The efficacy of replacing SFAs with carbohydrates depends on the effects on body weight in the long term, and that effect is uncertain.

Our results emphasize the risk of relying on cholesterol alone as a marker of CAD risk. Replacement of carbohydrates with tropical oils markedly raises total cholesterol, which is unfavorable, but the picture changes if effects on HDL and apo B are taken into account. The picture may change again once we know how to interpret the effects of diet on postprandial lipemia, thrombogenic factors, and other, newer markers. However, as long as information directly linking the consumption of certain fats and oils with CAD is lacking, we can never be sure what such fats and oils do to CAD risk.

The situation is much clearer for replacement of SFAs with *cis* unsaturated fatty acids. In that case, the effects on surrogate lipid markers (Tables 1 and 2), the epidemiologic findings (89), and the results of controlled clinical trials (104) all suggest that replacement of SFAs with *cis* unsaturated fatty acids reduces CAD risk. For *trans* fatty acids, the effect on lipid markers is strongly supported by prospective epidemiologic findings (95, 112). Studies such as ours can predict the effects of fats on plasma lipids, but they cannot determine whether a fat will cause CAD. Finally, it should be emphasized that our results may apply only

to populationwide issues of lipid management and not to individual patients, whereas total:HDL cholesterol may not be useful for subjects with specific lipid abnormalities such as greatly decreased HDL- or increased LDL-cholesterol concentrations. In fact, this is true for any population-based study, and only a health care professional can ultimately determine the most appropriate (dietary) advice for any person. However, the effect of carbohydrates on total:HDL cholesterol justifies some caution in the application of high-carbohydrate diets to the prevention of heart disease. ✿

REFERENCES

1. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. Lancet 1957;2:959–66.
2. Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. Am J Clin Nutr 1965;17:281–95.
3. Kitamura A, Iso H, Naito Y, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. Circulation 1994;89:2533–9.
4. Stein O, Stein Y. Atheroprotective mechanisms of HDL. Atherosclerosis 1999;144:285–301.
5. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. Proc Natl Acad Sci U S A 1994;91:9607–11.
6. Vega GL, Grundy SM. Hypoalphalipoproteinemia (low high density lipoprotein) as a risk factor for coronary heart disease. Curr Opin Lipidol 1996;7:209–16.
7. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999;341:410–8.
8. Kinosian B, Glick H, Preiss L, Puder KL. Cholesterol and coronary heart disease: predicting risks in men by changes in levels and ratios. J Invest Med 1995;43:443–50.
9. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med 1991;325:373–81.
10. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis 1996;124(suppl):S11–20.
11. Brussaard JH, Katan MB, Groot PHE, Havekes LM, Hautvast JGAJ. Serum lipoproteins of healthy persons fed a low-fat diet or a polyunsaturated fat diet for three months. Atherosclerosis 1982;42:205–19.
12. Harris WS. n−3 Fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;65(suppl):1645S–54S.
13. Laboratory Methods Committee of the Lipid Research Clinics Program. Cholesterol and triglyceride concentrations in serum/plasma pairs. Clin Chem 1977;23:60–3.
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifugation. Clin Chem 1972;18:499–502.
15. US Department of Agriculture, Agricultural Research Service. USDA Nutrient Database for Standard Reference, Release 14. Nutrient Data Laboratory Home Page. Internet: http://www.nal.usda.gov/fnic/foodcomp (accessed 10 June 2000).
16. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipid and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb 1992;12:911–9.

17. Grande F, Anderson JT, Keys A. Comparison of effects of palmitic and stearic acids in the diet on serum cholesterol in man. Am J Clin Nutr 1970;23:1184–93.

18. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. Boston: PWS-KENT Publishing Company, 1988.

19. SAS Institute Inc. SAS/STAT user's guide: version 6. Cary, NC: SAS Institute Inc, 1989.

20. Grande F, Anderson JT, Keys A. Diets of different fatty acid composition producing identical serum cholesterol levels in man. Am J Clin Nutr 1972;25:53–60.

21. Anderson JT, Grande F, Keys A. Independence of the effects of cholesterol and degree of saturation of the fat diet on serum cholesterol in man. Am J Clin Nutr 1976;29:1184–9.

22. Laine DC, Snodgrass CM, Dawson EA, Ener MA, Kuba K, Frantz ID. Lightly hydrogenated soy oil versus other vegetable oils as a lipid-lowering dietary constituent. Am J Clin Nutr 1982;35:683–90.

23. Becker N, Illingworth DR, Alaupovic P, Connor WE, Sundberg EE. Effects of saturated, monounsaturated, and n−6 polyunsaturated fatty acids on plasma lipids, lipoproteins, and apoproteins in humans. Am J Clin Nutr 1983;37:355–60.

24. Harris WS, Connor WE, McMurry MP. The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oils. Metabolism 1983;32:179–84.

25. Wolf RN, Grundy SM. Influence of exchanging carbohydrate for saturated fatty acids on plasma lipids and lipoproteins in men. J Nutr 1983;113:1521–8.

26. 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.

27. Reiser R, Probstfield JL, Silvers A, et al. Plasma lipid and lipoprotein response of humans to beef fat, coconut oil and safflower oil. Am J Clin Nutr 1985;42:190–7.

28. Grundy SM. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. N Engl J Med 1986;314:745–8.

29. Grundy SM, Nix D, Whelan MF, Franklin L. Comparison of three cholesterol lowering diets in normolipidemic men. JAMA 1986;256:2351–5.

30. Marshall MW, Judd JT, Matusik E Jr, Church J, Canary JJ. Effects of low fat diets varying in P/S ratio on nutrient intakes, fecal excretion, blood chemistry profiles, and fatty acids of adult men. J Am Coll Nutr 1986;5:263–79.

31. Bonanome A, Grundy SM. Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. N Engl J Med 1988;318:1244–8.

32. Grundy SM, Florentin L, Nix D, Whelan MF. Comparison of monounsaturated fatty acids and carbohydrates for reducing raised levels of plasma cholesterol. Am J Clin Nutr 1988;47:965–9.

33. Judd JT, Oh SY, Hennig B, Dupont J, Marshall MW. Effects of low fat diets differing in degree of fat unsaturation on plasma lipids, lipoproteins, and apoproteins in adult men. J Am Coll Nutr 1988;7:223–34.

34. Ginsberg HN, Barr SL, Gilbert A, et al. Reduction of plasma cholesterol levels in normal men on an American Heart Association step 1 diet or a step 1 diet with added monounsaturated fat. N Engl J Med 1990;322:574–9.

35. Wardlaw GM, Snook JT. Effect of diets high in butter, corn oil, or high-oleic acid sunflower oil on serum lipids and apolipoproteins in men. Am J Clin Nutr 1990;51:815–21.

36. Iacono JM, Dougherty RM. Lack of effect of linoleic acid on the high-density lipoprotein cholesterol fraction of plasma lipoproteins. Am J Clin Nutr 1991;53:660–4.

37. Kwon JS, Snook JT, Wardlaw GM, Hwang DH. Effects of diets high in saturated fatty acids, canola oil, or safflower oil on platelet function, thromboxane B2 formation, and fatty acid composition of platelet phospholpids. Am J Clin Nutr 1991;54:351–8.

38. Wardlaw GM, Snook JT, Lin M-C, Puangco MA, Kwon JS. Serum lipid and apolipoprotein concentrations in healthy men on diets enriched in either canola oil or sunflower oil. Am J Clin Nutr 1991;54:104–10.

39. Barr SL, Ramakrishan R, Johnson C, Holleran S, Dell RB, Ginsberg HN. Reducing total dietary fat without reducing saturated fatty acids does not significantly lower total plasma cholesterol concentrations in normal males. Am J Clin Nutr 1992;55:675–81.

40. Denke MA, Grundy SM. Comparison of effects of lauric acid and palmitic acid on plasma lipids and lipoproteins. Am J Clin Nutr 1992;56:895–8.

41. 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.

42. Kris-Etherton PM, Derr J, Mitchell DC, et al. The role of fatty acid saturation on plasma lipids, lipoproteins, and apoproteins: 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.

43. Lichtenstein AH, Ausman LM, Carrasco W, et al. Effects of canola, corn, and olive oils on fasting and postprandial plasma lipoproteins in humans as part of a National Cholesterol Education Program Step 2 diet. Arterioscler Thromb 1993;13:1533–42.

44. Ginsberg HN, Karmally W, Barr SL, Johnson C, Holleran S, Ramakrishnan R. Effects of increasing dietary polyunsaturated fatty acids within the guidelines of the AHA Step 1 diet on plasma lipid and lipprotein levels in normal males. Arterioscler Thromb 1994;14:892–901.

45. 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.

46. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ. Hypercholesterolemic effect of dietary cholesterol in diets enriched in polyunsaturated and saturated fat. Arterioscler Thromb 1994;14:168–75.

47. Lichtenstein AH, Ausman LM, Carrasco W, et al. Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans. Arterioscler Thromb 1994;14:549–56.

48. Dougherty RM, Allman MA, Iacono JM. Effects of diets containing high or low amounts of stearic acid on plasma lipoprotein fractions and fecal fatty acid excretion in man. Am J Clin Nutr 1995;61:1120–8.

49. Howard BV, Hannah JS, Heiser CC, et al. Polyunsaturated fatty acids result in greater cholesterol lowering and less triacylglycerol elevation than do monounsaturated fatty acids in a dose response comparison in a multiracial study group. Am J Clin Nutr 1995;62:392–402.

50. Fielding CJ, Havel RJ, Todd KM, et al. Effects of dietary cholesterol and fat saturation on plasma lipoproteins in an ethnically diverse population of healthy young men. J Clin Invest 1995;95:611–8.

51. Nelson GJ, Schmidt PC, Kelly DS. Low-fat diets do not lower plasma cholesterol levels in healthy men compared to high-fat diets with similar fatty acid composition at constant caloric intake. Lipids 1995;30:969–76.

52. Park S, Snook JT, Bricker L, et al. Relative effects of high saturated fatty acid levels in meat, dairy products, and tropical oils on serum lipoproteins and low-density lipoproteins degradation by mononuclear cells in healthy males. Metabolism 1996;45:550–8.

53. Cater NB, Heller HJ, Denke MA. Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans. Am J Clin Nutr 1997;65:41–5.

54. Judd JT, Baer DJ, Clevidence BA, et al. Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipidemic adults fed controlled diets. Am J Clin Nutr 1998;68:768–77.

55. Ginsberg HN, Kris-Etherton P, Dennis B, et al. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. Arterioscler Thromb Vasc Biol 1998;18:441–9.

56. Brussaard JH, Dallinga-Thie G, Groot PHE, Katan MB. Effects of amount and type of dietary fat on serum lipids, lipoproteins and apolipoproteins in man. A controlled 8- week trial. Atherosclerosis 1980;36:515–27.

57. Mensink RP, Katan MB. Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women. Lancet 1987;1:122–5.

58. Mensink RP, de Groot MJM, van den Broeke LT, Severijnen-Nobels AP, Demacker PNM, Katan MB. Effects of monounsaturated fatty acids v complex carbohydrates on serum lipoproteins and apoproteins in healthy men and women. Metabolism 1989;38:172–8.

59. Katan MB, Berns MAM, Glatz JFC, Knuiman JT, Nobels A, de Vries JHM. Congruence of individual responsiveness to dietary cholesterol and to saturated fat in humans. J Lipid Res 1988;29:883–92.

60. Mensink RP, Katan MB. Effect of a diet enriched with monounsaturated or polyunsaturated fatty acids on levels of low-density and high-density lipoprotein cholesterol in healthy women and men. N Engl J Med 1989;321:436–41.

61. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N Engl J Med 1990;323:439–45.

62. Zock PL, Katan MB. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoprotein in humans. J Lipid Res 1992;33:399–410.

63. Zock PL, de Vries JHM, Katan MB. Impact of myristic acid versus palmitic acid on serum lipid and lipoprotein levels in healthy women and men. Arterioscler Thromb 1994;14:567–75.

64. Marckmann P, Sandström B, Jespersen J. Fasting blood coagulation and fibrinolysis of young adults unchanged by reduction in dietary fat content. Arterioscler Thromb 1992;12:201–5.

65. Tholstrup T, Marckmann P, Jesperen J, Vessby B, Jart A, Sandström B. Effect on blood lipids, coagulation, and fibrinolysis of a fat high in myristic acid and a fat high in palmitic acid. Am J Clin Nutr 1994; 60:919–25.

66. Tholstrup T, Marckmann P, Jespersen J, Sandström B. Fat high in stearic acid favorably affects blood lipids and factor VII coagulant activity in comparison with fats high in palmitic and lauric acids. Am J Clin Nutr 1994;59:371–7.

67. Tholstrup T, Sandström B, Hermansen JE, Hølmer. Effect of modified dairy fat on postprandial and fasting plasma lipids and lipoproteins in healthy young men. Lipids 1998;33:11–22.

68. McDonald BE, Gerrard JM, Bruce VM, Corner EJ. Comparison of the effect of canola oil and sunflower oil on plasma lipids and lipoproteins and on in vivo thromboxane A2 and prostacyclin production in healthy young men. Am J Clin Nutr 1989;50:1382–8.

69. Chan JK, Bruce VM, McDonald BE. Dietary α-linolenic acid is as effective as oleic acid and linoleic acid in lowering blood cholesterol in normolipidemic men. Am J Clin Nutr 1991;53:1230–4.

70. Mazier MJ, Jones PJH. Diet fat saturation and feeding state modulate rates of cholesterol synthesis in normolipidemic men. J Nutr 1997;127:332–40.

71. Valsta LM, Jauhiainen M, Aro A, Katan MB, Mutanen M. Effects of a monounsaturated rapeseed oil and a polyunsaturated sunflower oil diet on lipoprotein levels in humans. Arterioscler Thromb 1992; 12:50–7.

72. Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. Stearic acid, trans fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins of healthy subjects. Am J Clin Nutr 1997;65:1419–26.

73. Berry EM, Eisenberg S, Haratz D, et al. Effects of diets rich in monounsaturated fatty acids on plasma lipoproteins—the Jerusalem Nutrition Study: high MUFAs vs high PUFAs. Am J Clin Nutr 1991; 53:899–907.

74. Berry EM, Eisenberg S, Friedlander Y, et al. Effects of diets rich in monounsaturated fatty acids on plasma lipoproteins—the Jerusalem Nutrition Study. II. Monounsaturated fatty acids vs carbohydrates. Am J Clin Nutr 1992;56:394–403.

75. Sundram K, Hayes KC, Siru OH. Dietary palmitic acid results in lower serum cholesterol than does a lauric-myristic acid combination. Am J Clin Nutr 1994;59:841–6.

76. Sundram K, Hayes KC, Siru OH. Both dietary 18:2 and 16:0 may be required to improve the serum LDL/HDL cholesterol ratio in normocholesterolemic men. J Nutr Biochem 1995;6:179–87.

77. Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. J Lipid Res 1995; 36:1370–84.

78. Müller H, Jordal O, Kierulf P, Kirkhus B, Pederson JI. Replacement of partially hydrogenated soybean oil by palm oil in margarine without unfavorable effects on serum lipoproteins. Lipids 1998;33: 879–87.

79. Wahrburg U, Martin H, Sandkamp M, Schulte H, Assmann G. Comparative effects of a recommended lipid-lowering diet vs a diet rich in monounsaturated fatty acids on serum lipid profiles in healthy young adults. Am J Clin Nutr 1992;56:678–83.

80. Bonanome A, Pagnan A, Biffanti S, et al. Effect of dietary monounsaturated and polyunsaturated fatty acids on the susceptibility of low-density lipoproteins to oxidative modification. Arterioscler Thromb 1992;12:529–33.

81. Lewis B, Hammett F, Katan M, et al. Towards an improved lipid-lowering diet: additive effects of changes in nutrient intake. Lancet 1981;2:1310–3.

82. McPherson Kay R, Jacobs M, Katan MB, Lewis B. Relationship between changes in plasma lipoprotein concentrations and fecal steroid excretion in man during consumption of four experimental diets. Atherosclerosis 1985;55:15–23.

83. Allison, DB, Egan SK, Barraj LM, Caughman C, Infante M, Heimbach JT. Estimated intakes of trans fatty and other fatty acids in the US population. J Am Diet Assoc 1999;99:166–74.

84. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. Am J Clin Nutr 2001;73:885–91.

85. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–9.

86. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. Int J Epidemiol 1979;8:99–118.

87. Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish Mental Hospital Study. Int J Epidemiol 1983;12:17–25.

88. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat. Circulation 1969; 40(suppl):1–63.

89. Hu FB, Stampfer MJ, Manson J, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9.

90. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. N Engl J Med 1999;340:1994–8.

91. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569–78.

92. De Deckere EA, Korver O, Verschuren PM, Katan MB. Health aspects of fish and n−3 polyunsaturated fatty acids from plant and marine origin. Eur J Clin Nutr 1998;52:749–53.

93. Krauss RM. Atherogenic lipoprotein phenotype and diet-gene interactions. J Nutr 2001;131:340S–3S.

94. Katan MB. Trans fatty acids and plasma lipoproteins. Nutr Rev 2000; 58:188–91.

95. Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. Lancet 2001;357:746–51.

96. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. Am J Clin Nutr 1999;69:632–46.

97. Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. Int J Obes Relat Metab Disord 2000;24:1545–52.

98. Leenen R, van der Kooy K, Meyboom S, Seidell JC, Deurenberg P, Weststrate JA. Relative effects of weight loss and dietary fat modification on serum lipid levels in the dietary treatment of obesity. J Lipid Res 1993;34:2183–91.

99. Katan MB, Grundy SM, Willett WC. Beyond low-fat diets. N Engl J Med 1997;337:563–6.

100. Karpe F. Postprandial lipoprotein metabolism and atherosclerosis. J Intern Med 1999;246:341–55.

101. Larsen LF, Marckmann P, Bladbjerg EM, Ostergaard PB, Sidelmann J, Jespersen J. The link between high-fat meals and postprandial activation of blood coagulation factor VII possibly involves kallikrein. Scand J Clin Lab Invest 2000;60:45–54.

102. Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. Fibrinolytic activity, clotting factors, and long term incidence of ischaemic heart disease in the Northwick Park Heart Study. Lancet 1993;342:1076–9.

103. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis 2000;150:227–43.

104. Sacks FM. Dietary fats and coronary heart disease. Overview. J Cardiovasc Risk 1994;1:3–8.

105. Research Committee. Low-fat diet in myocardial infarction: a controlled trial. Lancet 1965;2:501–4.

106. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). Lancet 1989;2:757–61.

107. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. III. Differences among individuals. Metabolism 1965;14:766–75.

108. Katan MB, Beynen AC. Characteristics of human hypo- and hyper-responders to dietary cholesterol. Am J Epidemiol 1987;125:387–99.

109. Weggemans RM, Zock PL, Urgert R, Katan MB. Differences between men and women in the resonse of serum cholesterol to dietary changes. Eur J Clin Invest 1999;29:827–34.

110. 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.

111. Keys A, ed. Coronary heart disease in seven countries. Circulation 1970;41(suppl 1):I1–I211.

112. Willett WC, Stampfer MJ, Manson JE, et al. Intake of *trans* fatty acids and risk of coronary heart disease among women. Lancet 1993;341:581–5.