

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 trials¹⁻³

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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 ratio 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-

vatational, 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 vegetable oils high in unsaturated fatty acids are low in cholesterol, it would otherwise be difficult to reliably identify the independent effects of fatty acids or dietary cholesterol. If necessary, cholesterol intake was kept constant by using eggs or egg yolk or by adding crystalline cholesterol to the diets.

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- 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 the 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 \rightarrow SFAs), *cis* monounsaturated fatty acids (MUFAs) (Carbohydrates \rightarrow MUFAs), or *cis* polyunsaturated fatty acids (PUFAs) (Carbohydrates \rightarrow PUFAs)¹

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

¹95% 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.

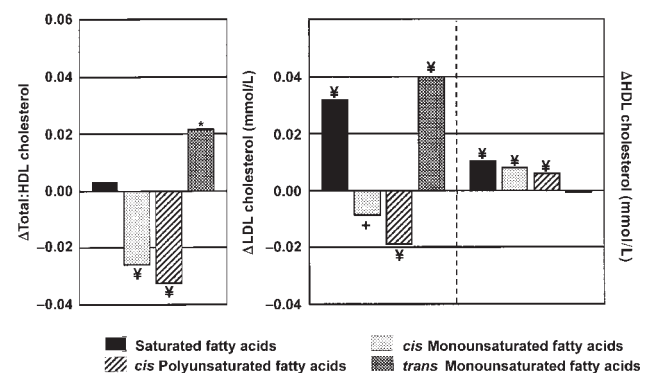


FIGURE 1. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with saturated, *cis* monounsaturated, *cis* polyunsaturated, or *trans* monounsaturated fatty acids. **P* < 0.05; +*P* < 0.01; †*P* < 0.001.

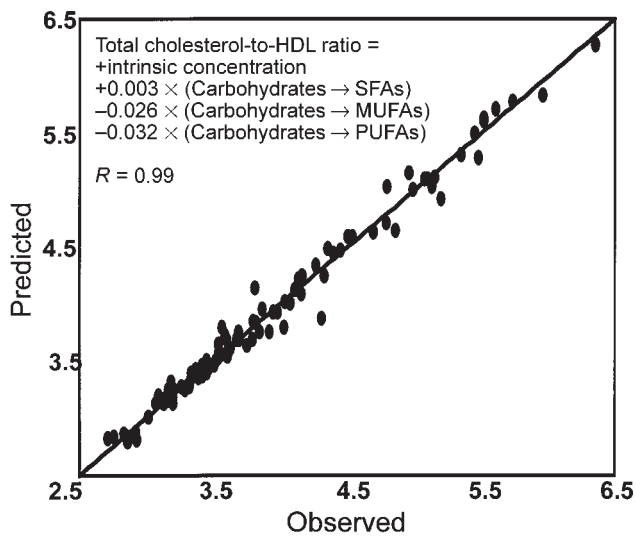


FIGURE 2. Scatterplot showing observed versus predicted ratios of serum total to HDL cholesterol. Each point refers to a specific test diet in one of the studies. “Predicted” values were calculated as the intrinsic concentration of the group under study plus the predicted change induced by their test 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 \rightarrow 12:0), myristic acid (Carbohydrates \rightarrow 14:0), palmitic acid (Carbohydrates \rightarrow 16:0), or stearic acid (Carbohydrates \rightarrow 18:0)¹

Lipid or lipoprotein	No. of diets; no. of studies	Carbohydrates \rightarrow 12:0	Carbohydrates \rightarrow 14:0	Carbohydrates \rightarrow 16:0	Carbohydrates \rightarrow 18:0
Δ Total: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)
<i>P</i>		<0.001	0.832	0.431	0.119
Δ Total 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)
<i>P</i>		<0.001	<0.001	<0.001	0.227
Δ LDL 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)
<i>P</i>		<0.001	<0.001	<0.001	0.464
Δ HDL 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)
<i>P</i>		<0.001	0.841	0.418	0.390
Δ Triacylglycerol (mmol/L)	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)
<i>P</i>		<0.001	0.002	<0.001	<0.001
Δ Apo 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)
<i>P</i>		0.173	0.552	0.078	0.152
Δ Apo 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)
<i>P</i>		<0.001	<0.001	<0.001	0.371

¹95% 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

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

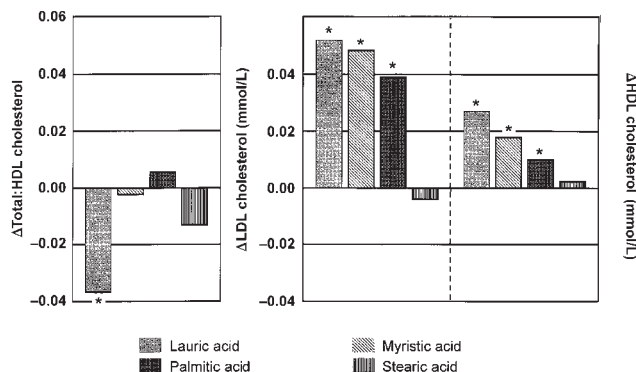


FIGURE 3. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), or stearic acid (18:0). **P* <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

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 \rightarrow *trans*)¹

Lipid or lipoprotein	No. of diets; no. of studies	Coefficient
Δ Total:HDL cholesterol	18; 8	0.022 (0.005, 0.038)
<i>P</i>		0.015
Δ Total cholesterol (mmol/L)	18; 8	0.031 (0.020, 0.042)
<i>P</i>		<0.001
Δ LDL cholesterol (mmol/L)	18; 8	0.040 (0.020, 0.060)
<i>P</i>		0.002
Δ HDL cholesterol (mmol/L)	18; 8	0.000 (-0.007, 0.006)
<i>P</i>		0.937
Δ Triacylglycerol (mmol/L)	18; 8	0.000 (-0.012, 0.012)
<i>P</i>		0.970
Δ Apo B (mg/L)	15; 7	5.4 (2.3, 8.5)
<i>P</i>		0.005
Δ Apo A-I (mg/L)	15; 7	2.2 (-5.1, 9.4)
<i>P</i>		0.501

¹95% CI in parentheses. Apo, apolipoprotein.

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.

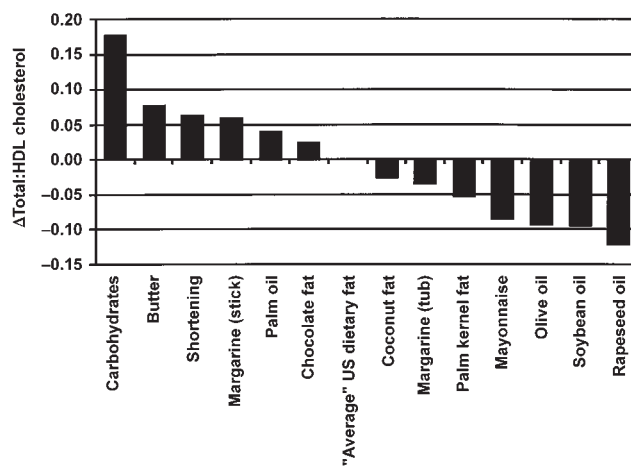


FIGURE 4. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol when mixed fat constituting 10% of energy in the "average" US diet is replaced isoenergetically with a particular fat or with carbohydrates.

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. 

This study was planned, executed, and reported by RPM, PLZ, and MBK. ADMK assisted with the statistical analysis and data interpretation. None of the authors had any financial or personal conflict of interest.

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