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Original Articles

Effects of moderate (MF) versus lower fat (LF) diets on lipids and lipoproteins: a meta-analysis of clinical trials in subjects with and without diabetes

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Lower-fat diets;
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Moderate-fat diets

BACKGROUND: Dyslipidemia increases coronary heart disease (CHD) risk and often presents in diabetes, which amplifies risk of CHD. Lower fat (LF) diets increase triglyceride (TG) and decrease high-density lipoprotein cholesterol (HDL-C); moderate fat (MF) diets decrease TG and lower HDL-C less.

OBJECTIVE: To quantify the magnitude of lipid and lipoprotein responses to MF versus LF cholesterol-lowering weight maintenance diets in subjects with and without diabetes.

METHODS: A meta-analysis of 30 controlled-feeding studies (n = 1213 subjects) was conducted to evaluate LF versus MF diets on lipids and lipoproteins in subjects with and without diabetes.

RESULTS: In all subjects, MF and LF diets decreased low-density lipoprotein cholesterol (LDL-C) similarly. MF diets decreased HDL-C less versus LF diets. The estimated increase in HDL-C after MF diets versus LF diets was 2.28 mg/dL (95% confidence interval 1.66 to 2.90 mg/dL, $P < .0001$). MF diets decreased TG, whereas LF diets increased TG. The decrease in TG was −9.36 mg/dL (−12.16 to −6.08 mg/dL, $P < .00001$) for MF versus LF diets. In subjects with diabetes, there was a similar increase in HDL-C (2.28 mg/dL) versus subjects without diabetes; however, there was a greater reduction in TG (−24.79 mg/dL, $P < .05$) on the MF diet. Subjects with diabetes had greater reductions in the total cholesterol (TC) to HDL-C ratio (TC:HDL-C) (—0.62, $P < .0001$) and non–HDL-C (−5.39 %, $P < .06$) after MF versus LF diets.

CONCLUSIONS: Both men and women had greater estimated reductions (6.37% and 9.34%, respectively) in predicted CHD risk after MF diets compared to LF diets. Moreover, based on greater reductions in TG, the TC:HDL-C ratio and non–HDL-C in subjects with diabetes, the CHD risk reduction would be greater for a MF versus a LF weight maintenance, cholesterol-lowering diet.

Diet is the cornerstone of intervention strategies for the prevention and treatment of coronary heart disease (CHD). The National Cholesterol Education Program (NCEP) recommends the Therapeutic Lifestyle Changes (TLC) diet (low in saturated fatty acids [SFA], <7% of energy;

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transfatty acids [TFA], as low as possible, and dietary cholesterol, <200 mg/day) to reduce low-density lipoprotein cholesterol (LDL-C) and risk of CHD. The total fat (TF) recommendation of 25% to 35% of energy (to be provided primarily by monounsaturated fat [MUFA], ≤20% and polyunsaturated fat [PUFA], ≤10 %)[1] is individualized. In addition to lowering LDL-C levels, the goal of medical nutrition therapy for the treatment of dyslipidemia is to increase or prevent decreases in high-density lipoprotein cholesterol (HDL-C), and decrease or prevent increases in triglyceride (TG).[2,3] Improving calorie balance to achieve desirable weight is the major change for the management of dyslipidemia, characterized by elevated TG levels (≥150 mg/dL) and low levels of high-density lipoprotein cholesterol (HDL-C) (men <40 mg/dL and women <50 mg/dL).[1] These nutrition goals are consistent with those made by the American Diabetes Association (ADA)[4] and the American Heart Association (AHA).[5]

Typically, energy from SFA is decreased by replacement with carbohydrate (resulting in a reduced fat diet) or unsaturated fatty acids (resulting in a moderate fat [MF] diet). Alternatively, SFA can be reduced without energy replacement, resulting in a lower fat (LF) diet. Although a MF diet that is low in SFA typically lowers LDL-C to the same extent as a LF diet, it decreases HDL-C less than a LF diet, and decreases TG, whereas a LF diet frequently increases TG.[6] Numerous studies have compared the effects of MF versus LF diets on lipids and lipoproteins.[7–38]

The objective of our meta-analysis is to quantify the magnitude of the changes in lipids and lipoproteins in response to a MF blood cholesterol-lowering diet rich in unsaturated fat versus a LF diet in subjects with and without diabetes. We conducted this analysis to ascertain whether substitution of SFA with carbohydrate versus unsaturated fat resulted in differential effects on the lipid and lipoprotein profile in subjects with and without diabetes. We also conducted a regression analysis to examine the relationship between the TF, SFA, MUFA, and PUFA content of the diets and the magnitude of change observed in the lipid and lipoprotein parameters. This is important because identifying a more optimal quantity of TF and fatty acid composition will be useful in clinical practice to achieve beneficial changes in the lipid and lipoprotein profile and the greatest reduction in CHD risk. For subjects with diabetes this is particularly germane because of their increased risk for CHD due, in part, to a high prevalence of dyslipidemia. We believe the present study is important because it is the first meta-analysis to compare responses to MF and LF diets in blood cholesterol-lowering weight maintenance diets in subjects with and without diabetes.

Methods

Selection of studies

Studies evaluating the effects of MF versus LF diets were identified by a literature search (MEDLINE, National Library of Medicine, Bethesda, MD) of articles published between 1987 and 2007. Keywords in the search included: moderate-fat diet, low-fat diet, controlled trial, cardiovascular disease, type 2 diabetes mellitus, lipoproteins, and lipids. Studies also were chosen by examining bibliographies of review articles. Thirty-two published studies[7–38] were included that met the following criteria: (1) controlled feeding with a crossover or parallel design comparing MF and LF diets; (2) designed to lower plasma total cholesterol (TC) and LDL-C with the primary purpose of reducing the risk of cardiovascular disease; (3) comparison diets were isoenergetic; (4) participants maintained a constant weight during the study; (5) dietary protein and cholesterol were kept constant between diets; (6) diet periods lasted ≥2 weeks to stabilize plasma cholesterol concentrations; and (7) studies were published in English.

Two articles[12,13] provided similar data because they were conducted with the same subjects. Therefore, only one was included. Seven studies[30–34,36,37] were conducted on subjects with diabetes and were included in the analysis. However, one article[37] did not report data for lipid and lipoprotein concentrations for the initial and after diet periods and therefore was excluded. Six studies[7–12] utilized a crossover design without randomization. Data were analyzed with and without these studies. Because the results did not differ, these studies were included.

Data abstraction

Study characteristics and data from each paper were extracted and input into the database. The following information was extracted: (1) subjects' characteristics, including sample size, number of male and female participants, age, and body mass index (BMI); (2) study design, including type of study (crossover or parallel), presence or absence of run-in period, duration of diet intervention, and wash-out period; (3) macronutrient composition of MF and LF diets, including cholesterol content and percentage of energy derived from TF, SFA, MUFA, and PUFA; (4) measurement of lipids and lipoproteins (TG, TC, LDL-C, and HDL-C) at baseline and after diet intervention, and standard deviations of means; and (5) non–HDL-C was calculated by subtracting HDL-C values from TC values and the ratio of TC:HDL-C was determined using the mean values for TC and HDL-C presented in each group.

Statistical analyses

To allow for direct comparisons between outcome variables and between studies, the results from each study were quantified as effect size (δ), defined as $\delta = (\mu_{MF} - \mu_{LF})/\sigma$, where μ_{MF} represents the average effect of the MF diet, μ_{LF} represents the average effect of the LF diets, and σ represents the pooled standard deviation.[39] Some variables (eg, TG and apolipoprotein A-I [Apo A-1]) are not directly comparable because they are measured on different scales. Effect sizes are unitless and thus permit direct

comparisons between variables. An effect size of 1.0 approximates one standard deviation between diets for each end point variable. In the present meta-analysis, one standard deviation for TC, LDL-C, HDL-C, and TG can be converted to 27.3, 24.1, 10.4, and 46.8 mg/dL, respectively.

Effect sizes were estimated differently for trials with parallel versus crossover designs. For parallel design studies, the average diet effects, μ_{MF} and $\mu_{LF,}$ were estimated separately as the difference between the reported post-diet and baseline means, and the effect difference, $\mu_{MF} - \mu_{LF,}$ was then calculated. The standard deviation was estimated from the reported between-subject standard deviation and the effect size was estimated as the effect difference divided by the standard deviation. For crossover design studies, the effect difference, $\mu_{MF} - \mu_{LF,}$ was estimated directly as the difference between the reported MF period and LF period means. The standard deviation was estimated from the reported within-subject standard deviation and the effect size was estimated as the effect difference divided by the standard deviation. An effect size (mean changes in end points) greater than zero indicates that end points were greater after the MF diet intervention, whereas an effect size less that zero indicates the end points were greater after the LF diet intervention. Not all studies reported all end points and therefore, the number of studies included in the analyses varied (Table 1).

Meta-analysis entails estimation of a pooled effect size across studies. In this analysis, the random effects model described by Hedges and Olkin[39] was used to estimate the pooled effect size for each variable. The results were weighted by taking the reciprocal of the estimated effect size variance for that study.[39] This method gives more weight to larger studies, because they have less variation, and less weight to smaller studies. Ninety-five percent confidence intervals (CI) for the pooled effect size estimates were also calculated based on the random effects model.

Not all of the studies implemented the same experimental diets, resulting in variation in the levels of TF, SFA, MUFA, and PUFA across studies. Meta-regression analysis was performed to assess the possibility of dose-dependent diet effects. This approach is analogous to a simple linear regression analysis in which the studies are the cases, the effect size is the dependent variable, and the dietary content is the independent variable.

Forest plots were used to present the meta-analysis results (Fig 1a–c and Fig 2). Each line in the plot represents one study. The midpoint of the line indicates the calculated estimated effect size and the size of the square denotes the relative weight that study received in the analysis. The ends of the line indicate the calculated 95% CI for the effect size. In general, studies with wider confidence intervals have smaller weights because those estimates are more variable. The diamond at the bottom of the plot represents the pooled effect size estimate and the width of the diamond indicates the 95% CI for the pooled estimates. The vertical stripe denotes an effect size of zero so that study lines that cross the stripe denote non-significant results. Even if all of the individual studies are not significantly different from zero, the pooled effect size estimate can be significantly different from zero.

Analyses were conducted with or without studies involving subjects with diabetes, and results were reported separately. Student's *t* tests were used for comparisons of the lipid and lipoprotein results between subjects with and without diabetes. Analyses were performed using the SAS statistical software package version 9 (SAS Institute, Cary, NC). $P < .05$ was used to denote statistical significance. *P* values $< .10$ and $> .05$ were considered statistical trends.

A standard measure of publication bias has not yet been set (although several tests exist) and funnel plots have been used widely.[40] Therefore, funnel plots were used to detect publication bias in the present meta-analysis (data not shown). The variables evaluated were continuous; therefore, sample size was plotted against effect size. The plot was relatively symmetric for HDL-C. The plots showed some asymmetry for TC, LDL-C, and TG. As noted previously, not all studies reported all four end points (TC, LDL-C, HDL-C, and TG), which may contribute to the asymmetry of the plots.

Table 1 Number of studies, sample sizes, and end points selected for inclusion in analyses

End points	Number of studies	Subjects without diabetes	Subjects with diabetes
TC	30	25	6
LDL-C	26	22	5
HDL-C	29	24	5
TG	28	24	6
Apo-A-I	13	13	0
Apo-B	13	13	0

Apo-A-I, apolipoprotein A-I; Apo-B apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Results

Characteristics of the studies

Thirty studies that met the inclusion criteria were included in the analysis. The study participants (n = 1213) ranged in age from 20 to 64 years and had a BMI of 21.1 to 30.2 kg/m^2. Sample size ranged from 8 to 161 subjects and the length of diet intervention ranged from 2 to 12 weeks. Selected characteristics of the studies and participants are presented in Tables 2 and 3. Macronutrient composition of the diets is shown in Table 4. Ninety individuals had diabetes (average age 58.8, range 52.7 to 63). The mean BMI for subjects with diabetes was 28.4 kg/m^2 (range 26.7 to 30.0). A parallel design was used in six trials and the remaining 24 were crossover studies.

The MF diets provided 30.2% to 50% of energy, whereas the LF diets provided 18.3% to 30.2%. Mean

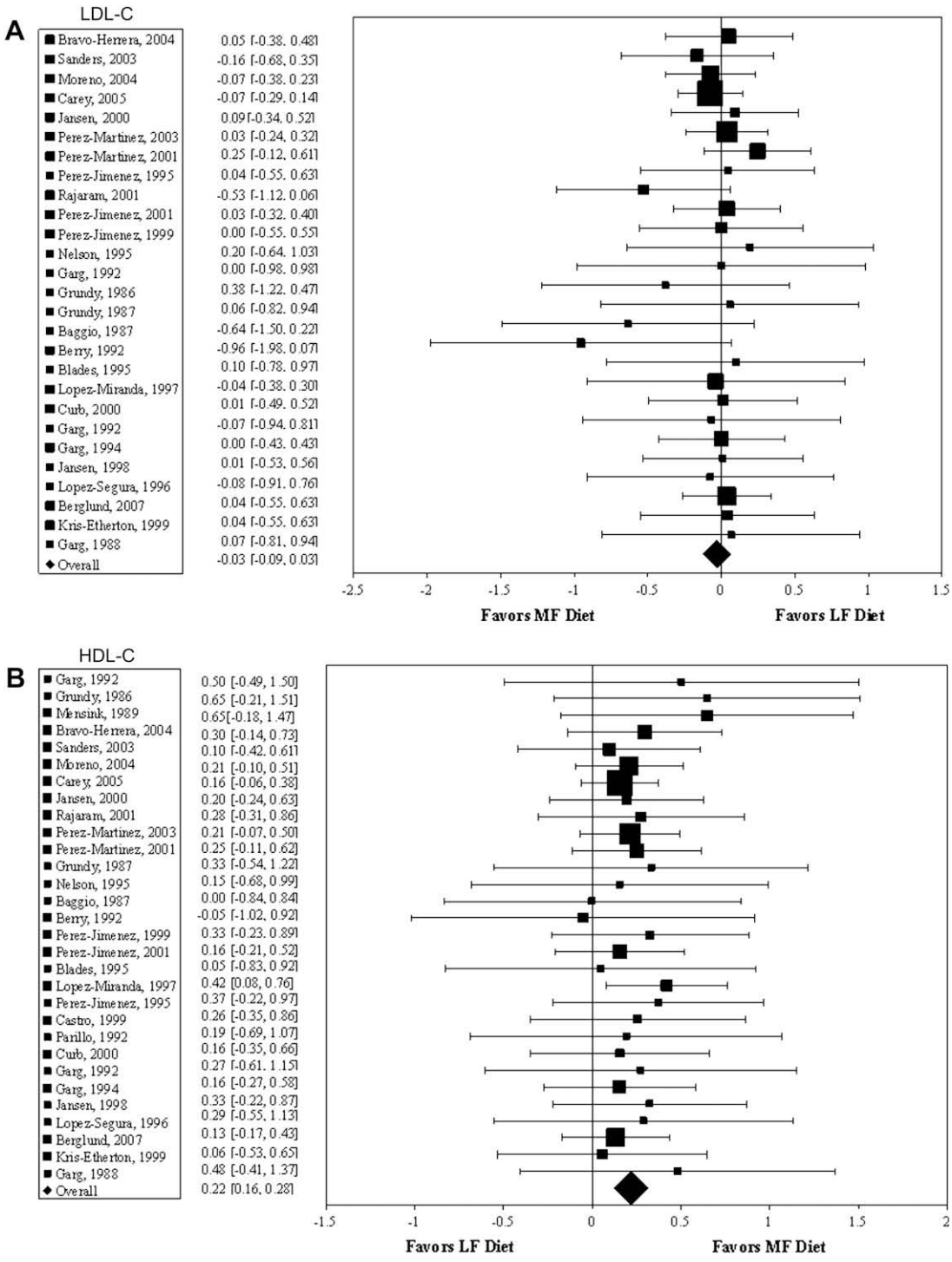

Figure 1 (A) Effect sizes for low-density lipoprotein cholesterol (LDL-C) comparing moderate fat (MF) and lower fat (LF) diets. There were no differences between these two diets for LDL-C. (B) Effect sizes for high-density lipoprotein cholesterol (HDL-C) comparing MF and LF diets. HDL-C concentrations were higher on the MF diets ($d = 0.22 \pm 0.03$, $P < .00001$; 2.28 mg/dL) compared to LF diets. (C) Effect sizes for triglyceride (TG) comparing MF and LF diets TG concentrations were reduced by the MF diets ($d = -0.20 \pm 0.03$, $P < .00001$; −9.36 mg/dL) compared to LF diets.

intakes of SFA, MUFA, and PUFA were 8.8% of energy (4 to 11), 23.6% (10.9 to 33), and 7.1% (3.5 to 20.8), respectively, for the MF diets. For the LF diets, the mean intakes of SFA, MUFA, and PUFA were 8.2% (3 to 12.9), 11.4% (range, 6 to 15.5), and 6.5% (range, 2 to 12), respectively.

Diet composition and lipid, lipoproteins, and apolipoproteins

Study effect sizes, pooled effect sizes, and the 95% CI for LDL-C, HDL-C, and TG are shown in Figure 1a–c. One

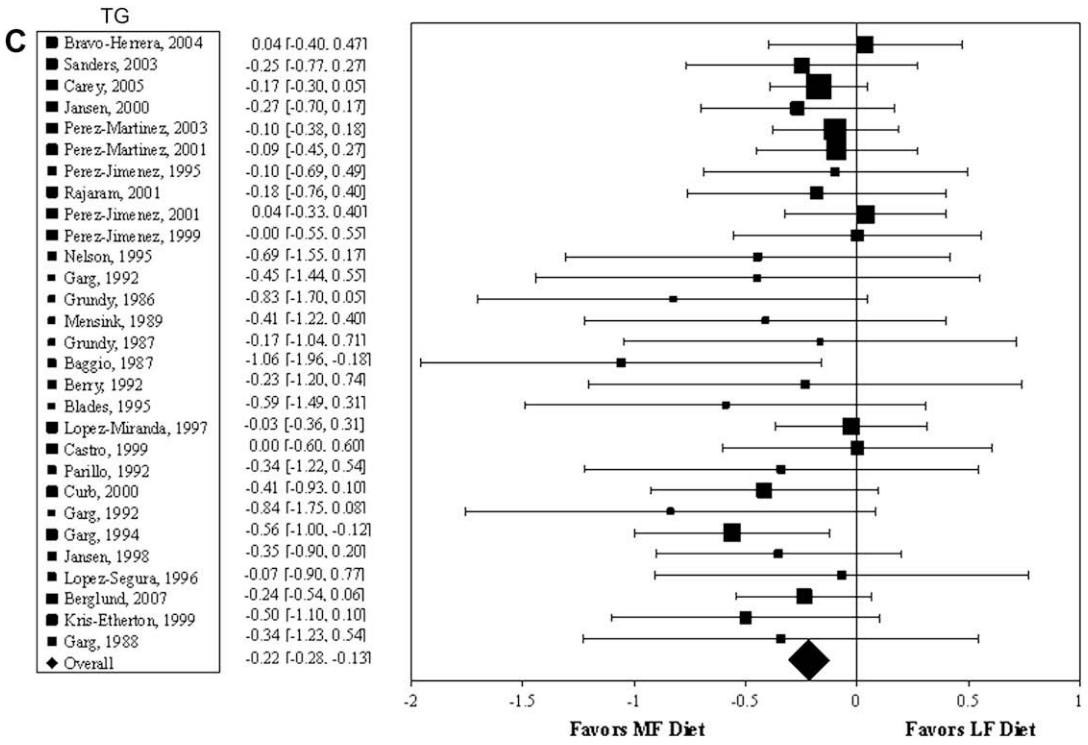

Figure 1 (*continued*).

study effect size was significantly different from zero for HDL-C; however, most of the studies showed a similar pattern (favoring MF diets). Two studies had significant negative effect sizes for TG, whereas the majority of studies showed a consistent pattern (favoring MF diets). HDL-C concentrations were significantly higher on MF diets ($\delta = 0.22 \pm 0.03$, $P < .00001$ vs. the LF diets). TG was significantly lower on MF diets ($\delta = -0.20 \pm 0.03$, $P < .00001$ vs. the LF diets). There were no significant differences in TC and LDL-C between diets.

The forest plot for ApoA-1 is shown in Figure 2. The majority of the studies favored the MF diet compared to the LF diet. The pooled effect size was 0.19 ± 0.07 (0.04 ± 0.01 g/L, $P = .006$), which suggests that Apo-A-1 increased

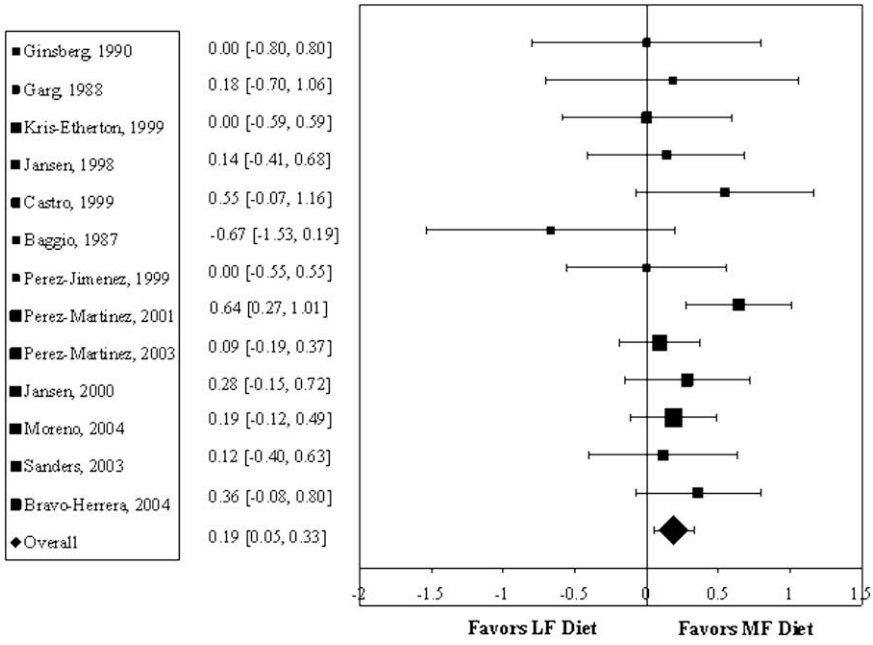

Figure 2 Effect sizes for apolipoprotein (Apo-A-I) comparing moderate fat (MF) and lower fat (LF) diets. Apo-A-I concentration was increased by the MF diets ($d = 0.19 \pm 0.07$, $P = .006$) compared to LF diets.

Table 2 Characteristics of studies and study participants

References	Sample size	Year	Age (y)	BMI (kg/m^2)	Study design	Duration (d)
Ginsberg et al[15]	36	1990	23	23.9	P	70
Berry et al[16]	17	1992	21	21.8	P	84
Baggio et al[7]	11	1988	20.9	24.0	C	21
Grundy et al[8]	10	1988	64	25.9	C	42
Mensink et al[14]	48	1989	27	22.6	P	36
Grundy et al[9]	11	1986	58	28	C	28
Garg et al[33]	10	1992	63	30	C	21
Garg et al[30]	10	1988	56	29	C	28
Kris-Etherton et al[21]	22	1999	34	24	C	24
Berglund et al[38]	85	N/A	35.5	27.6	C	49
Lopez-Segura et al[19]	21	1996	24.4	24.7	C	24
Jensen et al[12]	41	1998	20.6	23	P	28
Garg et al[34]	42	1994	58	28.1	C	42
Garg et al[32]	10	1992	61.5	27.7	C	28
Curb et al[22]	30	2000	35.3	23	C	30
Parillo et al[31]	10	1992	52.7	26.7	C	15
Castro et al[20]	21	2000	23	24.7	C	28
Perez-Jimenez et al[18]	22	1995	23	24.7	P	81
Lopez-Miranda et al[11]	90	1997	22.8	24.8	C	28
Perez-Jimenez et al[24]	59	2001	23.1	22.9	C	28
Perez-Jimenez et al[10]	25	1999	20.6	23.8	C	28
Nelson et al[17]	11	1995	32.9	23.1	C	50
Perez-Martinez et al[24]	59	2001	21	21.1	C	28
Perez-Martinez et al[26]	97	2003	20.1	23.6	C	28
Rajaram et al[25]	23	2001	38	N/A	C	28
Jansen et al[13]	41	2000	20.9	24.5	P	28
Appel et al[35]	161	2005	53.6	30.2	C	42
Moreno et al[27]	84	2004	23.8	22.2	C	28
Sanders et al[28]	29	2003	24.2	24.2	C	14
Bravo-Herrera et al[29]	41	2004	23.4	23	C	28

BMI, body mass index; C, crossover; N/A, not available; P, parallel.

Table 3 Baseline subject characteristics and fat content of diets by group

	All subjects(n = 1213)		Subjects without diabetes(n = 1123)		Subjects with diabetes(n = 90)	
Diet groups	MF diet	LF diet	MF Diet	LF diet	MF diet	LF diet
Age (y)	34.3 ± 15.9	34.3 ± 15.9	29.3 ± 11.9†	29.3 ± 11.9‡	60.5 ± 2.7	60.5 ± 2.7
BMI (kg/m^2)	24.8 ± 2.4	24.8 ± 2.4	23.9 ± 1.7†	23.9 ± 1.7‡	28.8 ± 0.9	28.8 ± 0.9
TF (%)	39.2 ± 4.5*	26.3 ± 3.7	37.7 ± 2.7†	26.5 ± 3.7	47.5 ± 2.9	25.0 ± 4.1
SFA (%)	8.8 ± 1.7*	8.0 ± 1.7	8.8 ± 1.5	8.1 ± 1.5	9.0 ± 2.7	7.5 ± 3.1
MUFA (%)	24.1 ± 4.2*	11.8 ± 2.5	22.9 ± 3.2†	12.0 ± 2.7‡	30.3 ± 3.6	10.5 ± 1.3
PUFA (%)	6.5 ± 2.2	6.2 ± 1.3	6.1 ± 2.1†	6.1 ± 1.7	8.5 ± 1.7	6.8 ± 2.2
Cholesterol (mg/dL)	253.1 ± 71.3	253.5 ± 72.5	267.5 ± 63.7[3]	267.9 ± 65.1‡	166.7 ± 57.7	166.7 ± 57.7
TC (mg/dL)	190.3 ± 29.3	189.9 ± 30.0	184.5 ± 26.9†	184.1 ± 27.7‡	224.6 ± 16.8	224.6 ± 16.8
LDL-C (mg/dL)	121.7 ± 23.4	120.5 ± 23.8	117.4 ± 22.2	116.2 ± 23.4	140.8 ± 17.9	140.8 ± 18.0
HDL-C (mg/dL)	45.2 ± 7.0	45.2 ± 7.0	48.0 ± 11.7†	48.0 ± 11.7‡	32.0 ± 2.0	32.0 ± 2.0
TG (mg/dL)	121.9 ± 75.7	121.9 ± 75.7	93.5 ± 11.7†	95.6 ± 11.7‡	273.2 ± 71.2	273.2 ± 71.2

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LF, lower fat; MF, moderate fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SFA, saturated fatty acid; TC, total cholesterol; TF, total fat; TG, triglyceride.

Data presented as mean ± standard deviation.

*$P < .05$ compared to LF diet in all subjects.

†$P < .05$ compared to MF diet in subjects with diabetes.

‡$P < .05$ compared to LF diet in subjects with diabetes.

Table 4 Macronutrient compositions (energy percentage) of moderate fat (MF) and lower fat (LF) diets in studies selected for inclusion

	% kcal CHO		% kcal protein		% kcal TF		% kcal from fatty acid classes (MF)			% kcal from fatty acid classes (LF)		
Reference	MF	LF	MF	LF	MF	LF	SFA	MUFA	PUFA	SFA	MUFA	PUFA
Ginsberg et al[15]	46.4	52.5	16.1	16.7	37.8	30.1	9.1	18.0	10.7	8.9	10.7	10.5
Berry et al[16]	50.5	64.9	17.0	16.9	32.5	18.3	6.6	16.6	7.5	4.7	6.8	5.7
Baggio et al[7]	46	56	16	16	38	28	9.7	24.6	3.5	11.7	12.6	4.1
Grundy et al[8]	45	65	15	15	40	20	7	27	6	7	7	6
Mensink et al[14]	46.0	62.2	12.2	14.1	40.6	22.1	9.8	24	5.1	6.7	9.3	5.2
Grundy et al[9]	43	63	17	17	40	20	4	28	7.5	6.7	6.7	6.7
Garg et al[33]	35	50	15	15	50	25	11	32	7	8	12	5
Garg et al[30]	35	60	15	15	50	25	10	33	7	9	9	6
Kris-Etherton et al[21]	50	59	16	16	34	25	7	21	6	7	12	6
Berglund et al[38]	48.8	54.9	15.5	16.1	35.7	29	8.7	20.8	6.2	8	15.5	5.5
Lopez-Segura et al[19]	44.1	54.5	17.2	17.6	38.7	27.9	9.2	24.7	4.8	9.2	13.5	5.2
Jensen et al[12]	44.1	54.5	15	15	38.4	27.9	9.2	24.4	4.8	9.2	13.5	5.2
Garg et al[34]	40	55	15	15	45	30	10	25	10	10	10	10
Garg et al[32]	38	65	17	15	45	20	5	31	10	3	11	6
Curb et al[22]	48	54	17	16	35	30	9	20	6	9	15	7
Parillo et al[31]	40	60	20	20	40	20	7	29	4	5	13	2
Castro et al[20]	45.7	56	14.7	14.3	39.6	29.7	9.8	25.3	4.5	6.8	13.8	9.1
Perez-Jimenez et al[23]	45.7	56	14.7	14.3	39.6	29.7	9.8	25.3	4.5	6.8	13.8	9.1
Lopez-Miranda et al[11]	44.1	54.5	17.2	17.6	38.7	27.9	9.2	24.7	4.8	9.2	13.5	5.2
Perez-Jimenez et al[24]	44.1	54.5	15	15	38	28	10	22	6	10	12	6
Perez-Jimenez et al[10]	44.1	54.5	17.5	17.6	38.4	27.9	9.2	24.4	4.8	9.2	13.5	5.2
Nelson et al[17]	45.7	61.9	15.7	15.9	38.7	22.2	10.6	15.5	12.6	6.4	9.2	6.6
Perez-Martinez et al[24]	44.1	54.5	17.5	17.6	38.4	27.9	9.2	24.4	4.8	9.2	13.5	5.2
Perez-Martinez et al[26]	44.1	54.5	17.7	17.5	38.1	27.5	9.1	24.1	4.9	9.1	13.2	5.2
Rajaram et al[25]	47.2	56.8	13.1	14.5	39.6	28.3	8.1	18.9	10.7	8.2	11	6.3
Jansen et al[13]	44.1	54.5	17.5	17.6	38.4	27.9	9.2	24.4	4.8	9.2	13.5	5.2
Appel et al[35]	48	58	15	15	37	27	6	21	10	6	13	8
Moreno et al[27]	44.1	54.5	17.7	17.5	38.1	27.5	9.1	24.1	4.9	9.1	13.2	5.2
Sanders et al[28]	47	53	13	14	37.5	30.2	10.2	10.9	20.8	12.9	6.5	6.4
Bravo-Herrera et al[29]	47	55	15	15	38	30	10	22	6	10	6	12

CHO, carbohydrate; LF, lower fat diets; MF, moderate-fat diets; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TF, total fat.

on the MF diet compared to the LF diet. The effect size for Apo-B was 0.05 ± 0.05 (0.007 ± 0.007 g/L, $P = .26$), which indicates there was no difference between the MF and LF diets.

Studies in subjects with or without diabetes

In studies of subjects without diabetes, HDL-C increased significantly ($\delta = 0.22 \pm 0.10$, $P < .000001$, approximately 2.28 mg/dL), whereas TG decreased significantly ($\delta = -0.17 \pm 0.04$, $P < .000001$, approximately 7.95 mg/dL) after MF diets compared to LF diets. TC and LDL-C were reduced similarly for the MF and LF diets. Studies of subjects with diabetes showed a similar increase in HDL-C ($\delta = 0.22 \pm 0.11$, $P = .04$, approximately 2.28 mg/dL), a nonsignificant reduction in TC ($\delta = -0.15 \pm 0.03$, $P = .16$, approximately −4.09 mg/dL), and a significant reduction in TG ($\delta = -0.53 \pm 0.11$, $P < .000001$, approximately −24.79 mg/dL) after the MF diets compared to LF diets. Subjects with diabetes had a greater reduction in TG (−0.26, approximately 12.16 mg/dL, $P < .05$) compared to subjects without diabetes on the MF diets (Fig. 3). The number of studies examining subjects with diabetes was relatively small (five for LDL-C and HDL-C[30–34] [n = 90] and six for TC and TG[30–34,36] [n = 108]). Therefore, only the increase in HDL-C and the decrease in TG reached significance, and the effect sizes had relatively larger standard errors.

Non–HDL-C decreased by 12.0% from baseline for subjects on MF diets and by 9.4% on LF diets. The decrease on the MF diets was 2.6% greater than on the LF diets ($P = .05$) (Fig. 4). A trend ($P < .06$) was found for a greater reduction (5.4%) in subjects with diabetes compared to subjects without diabetes in the non–HDL-C differences between MF and LF diets (Fig. 4). The TC:HDL-C ratio was reduced by −0.36 compared to baseline in subjects on the MF diet and −0.06 on the LF diet.

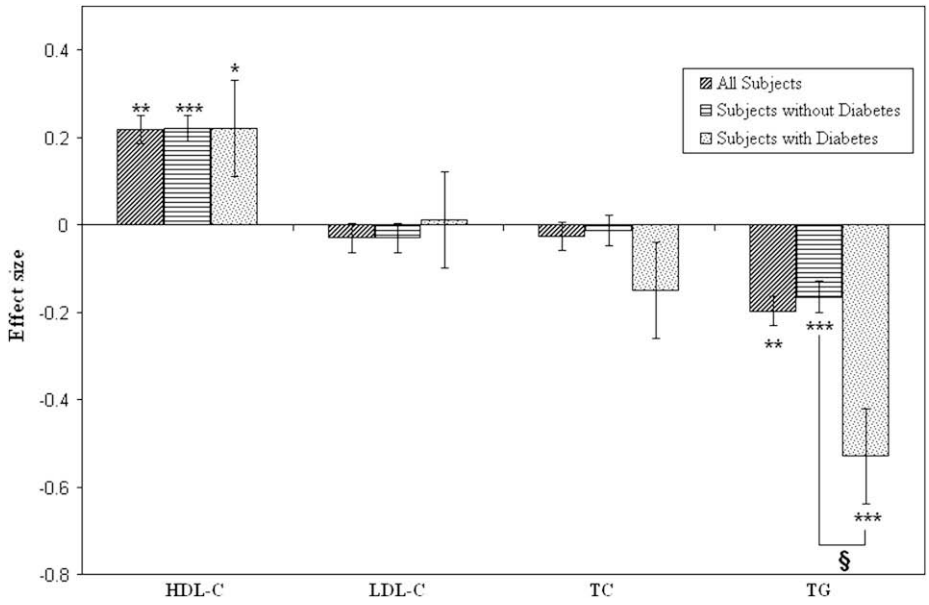

Figure 3 Effect sizes for changes in lipid and lipoproteins in subjects with and without diabetes Subjects with diabetes had a greater reduction in triglycerides (TG) (d = −0.51 ± 0.17, ≈ −23.86 mg/dL) compared to subjects without diabetes (d = −0.17 ± 0.04, ≈ −7.95 mg/dL) (P < 0.05). ***$P < .000001$; **$P < .00001$; *$P < .05$: significant difference between MF and LF diets; §$P < .05$: significant difference between subjects without and with diabetes.

The difference for this ratio between these two diets was significant (−0.30 ± 0.09, $P = .001$) (Fig. 5). A greater reduction (0.6, $P < .0001$) was seen in subjects with diabetes compared to subjects without diabetes in the TC:HDL-C ratio between MF and LF diets (Fig. 5).

Weighted averages of the changes in lipid and lipoproteins

The weighted averages show that subjects with diabetes had greater decreases in TC and TG after MF diets compared to LF diets (Table 5). In addition, in subjects with diabetes, HDL-C increased by 1.01 mg/dL in response to MF diets, whereas subjects without diabetes had decreases on both diets.

Regression analyses

TG changes from baseline were greater with increases in TF ($R^2 = 0.31$, $P < .0001$), SFA ($R^2 = 0.20$, $P = .0012$), and MUFA ($R^2 = 0.21$, $P = .0007$). However, stepwise regression analysis indicated that only increments in TF

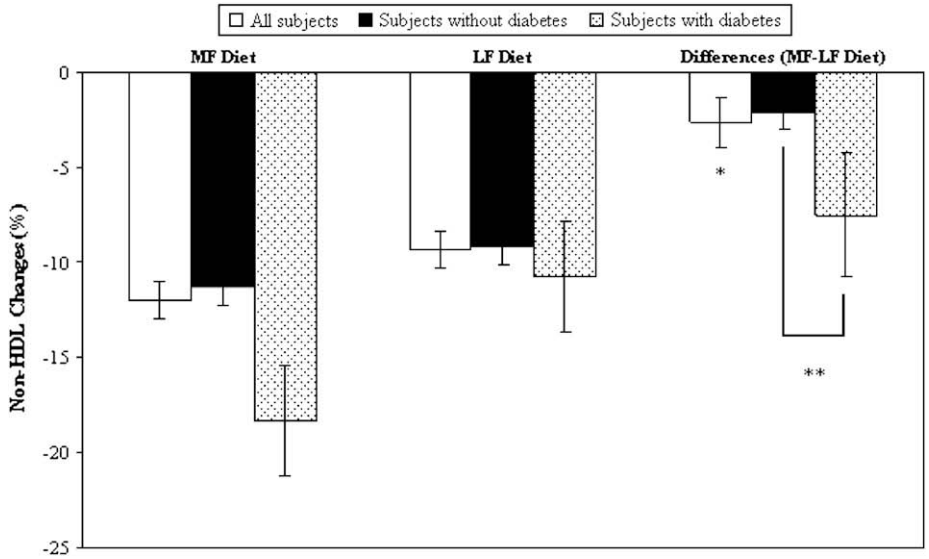

Figure 4 Non–high-density lipoprotein cholesterol (non–HDL-C) changes from baseline for moderate fat (MF) and lower fat (LF) diets. Non–HDL-C was decreased by 12.01% from baseline in the MF diets and by 9.37% in the LF diets. MF diets had a 2.64% greater decrease. Subjects with diabetes had a 5.39% greater reduction compared to subjects without diabetes ($P < .06$) in the differences between MF and LF diets. *$P < .05$; **$P < .06$.

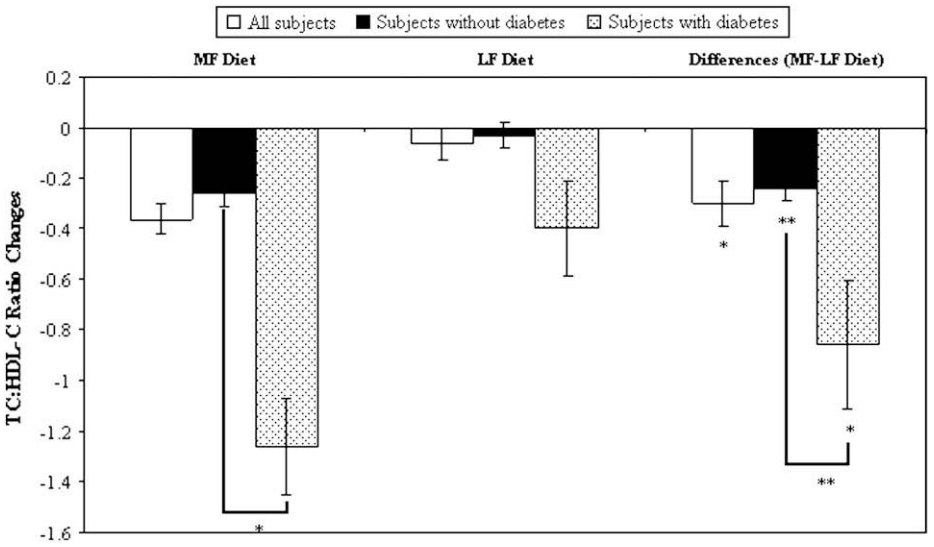

Figure 5 The total cholesterol:high-density lipoprotein cholesterol (TC:HDL-C) ratio changes from baseline. The TC:HDL-C ratio was reduced by −0.36 compared to baseline in MF diets and −0.06 in the LF diets. The difference between MF and LF diets was −0.30 ± 0.09 ($P < .001$). Subjects with diabetes had a greater reduction (0.62, $P < .0001$) compared to subjects without diabetes in the differences between MF and LF diets. *$P < .0001$; **$P < .001$.

($P < .0001$) and SFA ($P < 0.05$) were associated with decrements in TG. The changes in TG in subjects without and with diabetes were in the same direction but not of the same magnitude (eg, at the lower limit of recommended TF [25%], TG increased by 6.2% and 2.4% from baseline for subjects with and without diabetes, respectively; at the higher limit of recommended TF [35%], TG decreased from baseline by 3.1% and 12.2% for subjects without and with diabetes, respectively) (Fig. 6).

Increasing TF ($R^2 = 0.11$, $P = .008$) and MUFA ($R^2 = 0.13$, $P = .007$) resulted in greater decreases in TC from baseline. These dietary factors were not significant when entered into a multiple regression model. Percent HDL-C change from baseline was reduced with increases in TF ($R^2 = 0.26$, $P < .0001$) and MUFA ($R^2 = 0.23$, $P = .0003$). The changes in HDL-C in subjects without and with diabetes were similar at the higher limit of recommended TF (decreased by 1.42% and 1.32%) but not the same at the lower limit of recommended TF (decreased by 7.83% and 4.81% for subjects without and with diabetes, respectively) (Fig. 7). TF was the only dietary factor positively associated with HDL-C percent change from baseline in the stepwise regression analysis. We also included unsaturated fat (UNSAT) (MUFA + PUFA) in the model to explore the relationship between UNSAT and lipid and lipoprotein percent changes from baseline. HDL-C percent changes from baseline were positively correlated with UNSAT ($R^2 = 0.24$, $P = .003$), whereas changes of TG were negatively correlated with UNSAT ($R^2 = 0.24$, $P = .002$).

Predicted Changes in CHD incidence in men and women

On the basis of the changes in LDL-C, HDL-C, and TG, we calculated the predicted changes for CHD risk (Table 6) using a model presented by Sacks and Katan, Using data from other investigators.[6,41–43] Men had 13.73% reduction in predicted CHD incidence after MF diets and 7.36%

Table 5 Weighted averages of the lipid and lipoproteins in selected studies

	All subjects		Subjects without diabetes		Subjects with diabetes	
	MF diets	LF diets	MF diets	LF diets	MF Diets	LF diets
TC (mg/dL)	−16.75	−15.99	−15.99	−15.71	−33.66	−22.44
LDL-C (mg/dL)	−15.29	−14.10	−15.52	−13.98	−15.56	−16.48
HDL-C (mg/dL)	−0.78	−3.21	−0.81	−3.29	1.01	−1.50
TG (mg/dL)	−9.06	2.04	−5.43	2.25	−79.21	−2.06
Apo-A-I (g/L)	−0.03	−0.05	−0.03	−0.05	N/A	N/A
Apo-B (g/L)	−0.06	−0.06	−0.06	−0.06	N/A	N/A

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LF, lower fat; MF, moderate fat; TC, total cholesterol; TG, triglyceride.

The averages of the end points were weighted by the sample sizes. The values are presented as the difference between the after diet treatment and baseline.

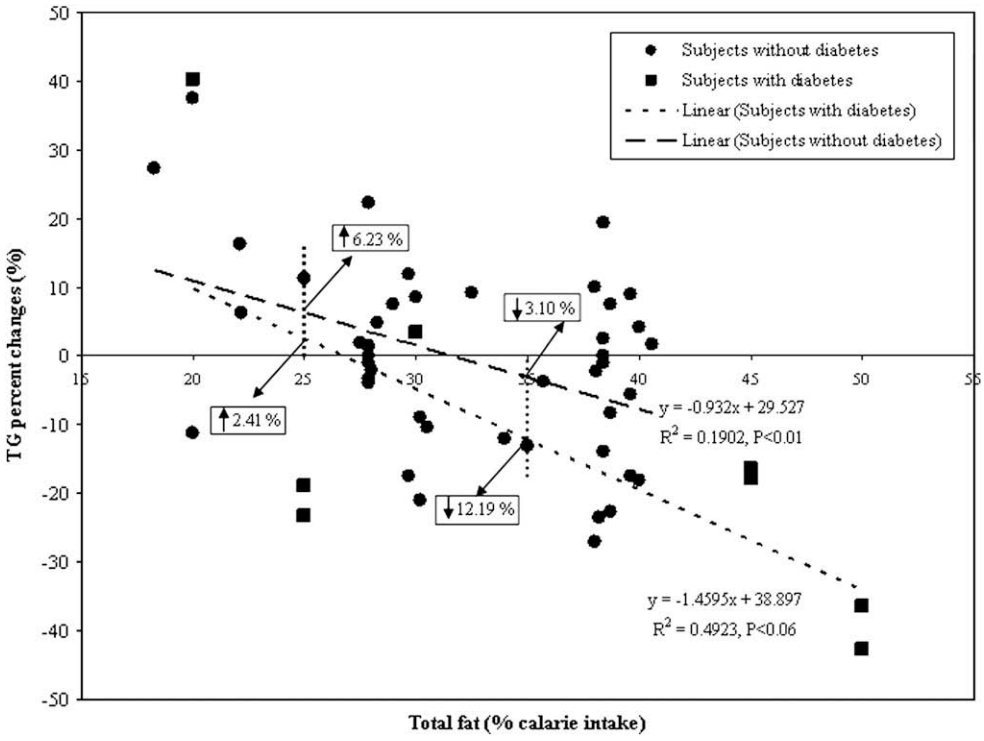

Figure 6 The correlation between triglyceride (TG) percent changes from baseline and total fat.

reduction after LF diets (Fig. 8). Similarly, women had 12.95% and 3.61% reduction in predicted CHD risk after MF diets and LF diets (Fig. 8), respectively.

Discussion

Our meta-analysis demonstrated similar TC and LDL-C lowering effects of both diets in subjects with and without diabetes and different effects on TG and HDL-C. However, there was a marked TG-lowering in subjects with diabetes versus subjects without diabetes on the MF diet versus the LF diet. Despite this, subjects with diabetes still had elevated TG levels on the MF diet, indicating the necessity for further treatment. In contrast, subjects without diabetes with normal TG levels still had a modest decrease in TG on the MF diet. HDL-C decreased similarly in subjects with and without diabetes on both diets (which likely was due to the decreased SFA intake), but the decrease from

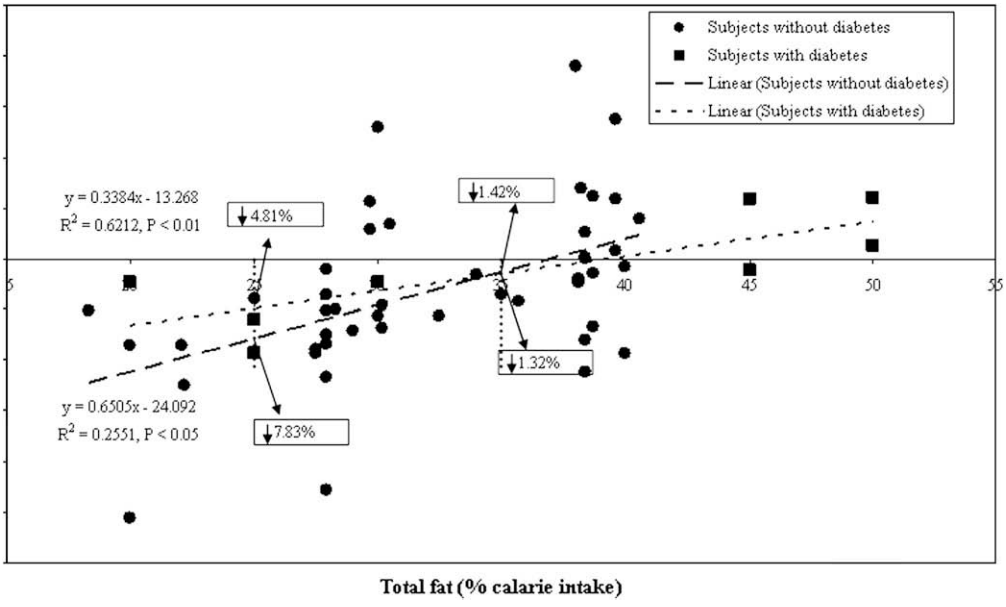

Figure 7 The correlation between HDL-C percent changes from baseline and total fat.

Table 6 Predicted changes in coronary heart disease (CHD) incidence

Serum lipid and lipoproteins	MF diet	LF diet
LDL-C* concentration (mg/dL)	−15.3	−14.1
CHD incidence	−15.3 %	−14.1 %
HDL-C† concentration (mg/dL)	−0.8	−3.2
CHD incidence		
Men	1.6 %	6.4 %
Women	2.3 %	9.6 %
TG‡ concentration (mg/dL)	−9.1	2.0
CHD incidence		
Men	ND	0.3 %
Women	ND	0.9 %

CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL, cholesterol, low-density lipoprotein cholesterol; LF, lower fat; MF, moderate fat; ND, not defined; TG, triglyceride.

*Δ LDL: −1 mg/dL leads to Δ CAD: −1%.[41]

†Δ HDL: −1 mg/dL leads to Δ CAD: + 2 % in men; + 3 % in women.[42]

‡Δ TG: + 88 mg/dL leads to Δ CAD: + 14 % in men; + 37 % in women.[43]

baseline was less on the MF versus LF diet. Based on predicted changes in CHD incidence, using the prediction model developed by Sacks and Katan,[6] both diets would lower CHD incidence; however, the MF diet would reduce risk more. A MF diet would have 5% and 6.5% greater reduction compared to the LF diet in predicted CHD incidence in men and women, respectively. The predicted reduction in CHD risk for persons with diabetes would be 12.6% for men and 12.0% for women on a LF diet and 17.6% (men) and 18.5% (women) for the MF diet.

Non–HDL-C and Apo-B are more potent predictors versus other risk factors for CHD incidence among men with diabetes, and the TC: HDL-C ratio is considered to be the best predictor of CHD.[44] In our study, the TC:HDL-C ratio and non–HDL-C were decreased significantly in subjects with diabetes after MF diets versus LF diets. Furthermore, the decreases were greater in subjects with diabetes than those without diabetes. Considering these other lipid risk factors, our results, in conjunction with other reports[6,45] indicate that an MF diet evokes a greater CHD risk reduction than the LF diet than would be predicted by changes in only LDL-C, HDL-C, and TG.

Our findings agree with those reported previously[30–34,36,37] and have extended those of others who have compared MF versus LF diets in either subjects with diabetes or healthy subjects. Garg[45] conducted a meta-analysis of high MUFA diets for subjects with diabetes mellitus and reported a reduction in plasma TG (−32.04 mg/dL; 95% CI minus;38.27 to −25.81 mg/dL), TC (−5.85 mg/dL; 95% CI −9.36 to −2.34 mg/dL), very low-density lipoprotein cholesterol (VLDL-C) (−7.8 mg/dL; 95% CI −9.36 to −5.85 mg/dL,) and a modest increase in HDL-C (1.95 mg/dL; 95% CI 1.17 to 2.73 mg/dL) compared with high carbohydrate (low fat) diets. LDL-C reduction (−0.39 mg/dL; 95% CI −3.9 to 3.12 mg/dL] was similar on both blood cholesterol-lowering diets.[45] Collectively, our results, which are a summary of many studies with both healthy individuals and subjects with diabetes, and those of other investigators, demonstrate that an MF diet elicits more favorable effects on TG and HDL-C in both healthy subjects and subjects with diabetes. This TG-lowering response has been reported to be due to a decrease in hepatic secretion of VLDL TG.[46]

It seems clear that less carbohydrate and additional unsaturated fat has a positive influence on the lipoprotein levels but this does not address the optimal ratio of MUFA to PUFA. Mediterranean diets are characterized by a low intake of SFA and a relatively high MUFA intake.[47] The

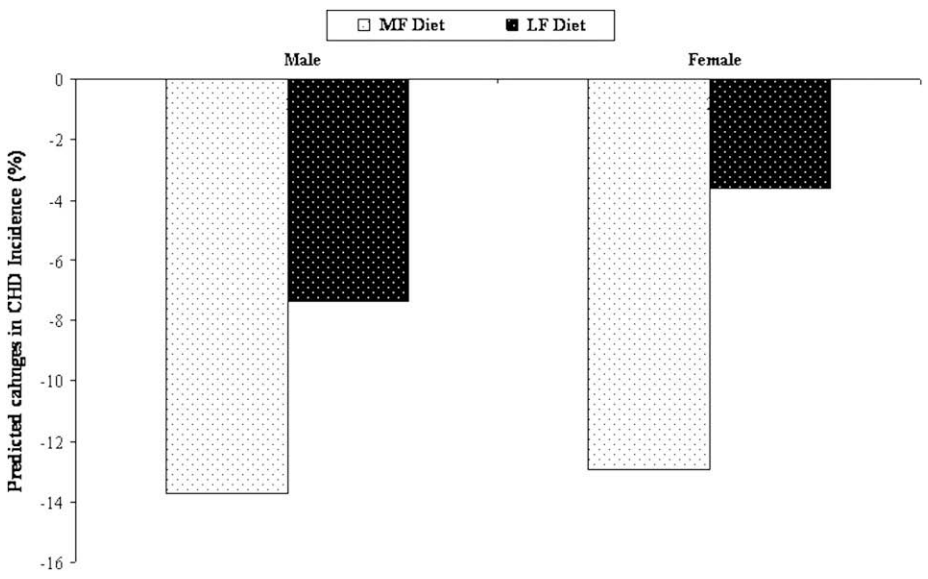

Figure 8 Predicted changes in coronary heart disease (CHD) incidence in males and females in response to moderate fat (MF) and lower fat (LF) diets. The predicted changes in CHD incidence was calculated based on data presented in Table 6.

Seven Countries Study[48] reported that all-cause death rate was negatively associated with MUFA intake and all-cause and CHD death rates were lower in cohorts that consumed olive oil as the primary source of dietary fat.[48] Despite evidence from observational studies showing that MUFA may be beneficial, results from experiments with African Green Monkeys seem to be disparate.[49–51] Monkeys were fed a diet that was similar in calories (35%) from fat but differed in SFA, MUFA, and PUFA. After 5 years, the monkeys fed the high MUFA and PUFA diets had significantly lower LDL-C than the monkeys fed a high SFA diet. HDL-C was higher in the monkeys fed MUFA and SFA versus PUFA. However, the monkeys fed MUFA had the greatest LDL particle enrichment with cholesteryl oleate, as well as the largest LDL particle size.[49,51] Coronary artery atherosclerosis was similar in monkeys fed MUFA and those fed SFA.[51] It has been suggested that increased amounts of cholesterol oleate proportional to an increase in LDL-C particle size in nonhuman primates is associated with an increase in coronary artery atherosclerosis.[52–55] Although these findings have been reported in other animal models,[56] there are no supportive data from human studies.

There are several strengths and limitations of our meta-analysis. An extensive literature search was conducted to identify eligible studies. Well-controlled feeding studies were selected in which body weight was maintained. We included 30 clinical trials with 1213 subjects (both healthy subjects and subjects with diabetes), which is a relatively large meta-analysis. However, only seven studies were conducted with subjects with diabetes (only six were used in our analyses). Some studies did not report all lipid and lipoprotein data at baseline or after diet intervention, which is probably a bias of publication. Furthermore, the studies analyzed were of relatively short duration (2 to 12 weeks). The analysis, therefore, does not address effects that may take longer to occur. HDL-C, for example, may change relatively slowly after weight loss or pharmacotherapy requiring many months to achieve a new stable level.

A key question that arises from our analysis is: what is the clinical application of these findings? Of note is that the average fat content of the MF diets evaluated exceeded the upper range recommended for TF (eg, 35% of calories). Because a major emphasis of nutrition recommendations for overweight persons, including individuals with insulin resistant syndrome and diabetes, is to decrease calories and lose weight, adding fat to the diet could be problematic if implemented incorrectly, resulting in a hypercaloric diet. Thus, a strategy for achieving a diet higher in TF is to decrease dietary carbohydrate calories (especially refined carbohydrates). Less dietary carbohydrate requires less insulin secretion for glucose homeostasis, thereby benefiting persons with insulin resistant syndrome.[57] Moreover, decreasing carbohydrate (without adding fat to the diet) would result in a higher fat (on the basis of percent calories), hypocaloric diet that would favor weight loss. Additional diet composition changes can be made in the type of fat included in the diet. Decreasing dietary carbohydrate, and hence calories, and not adding fat calories should be evaluated in clinical practice for ease of application and health outcomes in different population groups, including healthy persons,and persons with diabetes and insulin resistant syndrome.

In conclusion, a MF blood cholesterol-lowering diet is preferred for healthy individuals and persons with diabetes for improving the lipid profile. Importantly, the predicted CHD risks are 6.37% lower in men and 9.34% in women after the MF diet compared to the LF diet as measured by lipid risk factors. It will be important that MF diets are implemented in a way where fat is not added, but rather, dietary carbohydrate (especially refined) is reduced (as are calories), resulting in an accompanying increase in as a percent of calories. In addition, cholesterol-raising fatty acids need to be replaced with healthy, unsaturated fatty acids. The resulting reduction in energy intake will promote weight loss, and together with modifications in the type and amount of fat in the diet, great strides can be made in decreasing CHD risk by favorably modulating lipid and lipoprotein risk factors.

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