Metabolic Effects of Monounsaturated Fatty Acid–Enriched Diets Compared With Carbohydrate or Polyunsaturated Fatty Acid–Enriched Diets in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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META-ANALYSIS

OBJECTIVE

Dietary interventions in patients with type 2 diabetes (T2D) are important for preventing long-term complications. Although a healthy diet is crucial, there is still uncertainty about the optimal macronutrient composition. We performed a meta-analysis comparing diets high in *cis*-monounsaturated fatty acids (MUFA) to diets high in carbohydrates (CHO) or in polyunsaturated fatty acids (PUFA) on metabolic risk factors in patients with T2D.

RESEARCH DESIGN AND METHODS

We systematically reviewed PubMed, MEDLINE, and Cochrane databases and prior systematic reviews and meta-analyses to identify interventions assessing HbA_{1c}, fasting plasma glucose and insulin, LDL and HDL cholesterol, triglycerides, body weight, or systolic/diastolic blood pressure. Meta-analyses were conducted using both fixed- and random-effects models to calculate the weighted mean difference (WMD) and 95% CI.

RESULTS

We identified 24 studies totaling 1,460 participants comparing high-MUFA to high-CHO diets and 4 studies totaling 44 participants comparing high-MUFA to high-PUFA diets. When comparing high-MUFA to high-CHO diets, there were significant reductions in fasting plasma glucose (WMD −0.57 mmol/L [95% CI −0.76, −0.39]), triglycerides (−0.31 mmol/L [−0.44, −0.18]), body weight (−1.56 kg [−2.89, −0.23]), and systolic blood pressure (−2.31 mmHg [−4.13, −0.49]) along with significant increases in HDL cholesterol (0.06 mmol/L [0.02, 0.10]). When high-MUFA diets were compared with high-PUFA diets, there was a significant reduction in fasting plasma glucose (−0.87 mmol/L [−1.67, −0.07]). All of the outcomes had low to medium levels of heterogeneity, ranging from 0.0 to 69.5% for diastolic blood pressure (P_{het} = 0.011).

CONCLUSIONS

Our meta-analysis provides evidence that consuming diets high in MUFA can improve metabolic risk factors among patients with T2D.

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Dietary interventions in patients with type 2 diabetes (T2D) are an important adjunct to physical activity, medication, and insulin therapy in the prevention of diabetes-associated complications, particularly cardiovascular disease (CVD) (1). Current recommendations by the American Diabetes Association emphasize the inclusion of *cis*-monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) in the diet of individuals with T2D over intake of saturated fats and *trans* fatty acids (2). Although the evidence for quantity of total fat intake is inconclusive, there is a growing body of evidence supporting the importance of the quality of fat (1,3) for the prevention of CVD in this group. Results from the PREvención con DIeta MEDiterránea (PREDIMED) trial, which recruited individuals with prevalent T2D, also showed that diets high in olive oil and nuts, foods that are rich in MUFA, prevented CVD events in a high-risk population (4). Foods rich in MUFA and PUFA have been shown to favorably impact blood lipid concentrations thus decreasing the risk of CVD (5,6). High-MUFA diets have gained significant attention as an alternative dietary pattern to the commonly recommended low-fat and high-carbohydrate (CHO) pattern. Several prior meta-analyses of randomized controlled trials (RCTs) suggested potential benefits of a high-MUFA diet compared with a high-CHO diet in improving metabolic factors, such as glycemic control, serum lipids, and blood pressure, among both healthy individuals and T2D patients (3,5,7) but were usually based on a relatively small number of studies/subjects or short duration of follow-up. Hence, there is still uncertainty regarding whether longer-term interventions that substitute MUFA for CHO will yield the same metabolic effects as short-term trials. Furthermore, many of the RCTs also implemented caloric restriction as part of the dietary intervention, which may impede long-term compliance. Thus we conducted an updated meta-analysis comparing high-MUFA to high-CHO diets on metabolic risk factors among patients with T2D. We also included a comparison between high-MUFA and high-PUFA diets, which has not been previously assessed in a systematic manner to our knowledge.

RESEARCH DESIGN AND METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) (8).

Data Sources and Searches

We searched PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, and prior meta-analyses for articles up through 31 March 2015. The key words used to identify studies included "type 2 diabetes" or "type II diabetes" or "non-insulin diabetes"; "monounsaturated fatty acid" or "MUFA"; "polyunsaturated fatty acid" or "PUFA"; "glycemic" or "glucose" or "HbA_{1c}"; "lipid" or "cholesterol"; and "randomized" or "trial." The search was limited to RCTs that were published in English and had an intervention and follow-up duration of at least 2 weeks. Full details on our search terms and strategy for PubMed are shown in Supplementary Fig. 1.

Study Selection

RCTs (either parallel or crossover designs) comparing the effects of high-CHO or high-PUFA diets (from plant sources or n-6) with those of high-MUFA diets on metabolic parameters among adults with T2D were included in the meta-analysis. Studies that included the additional use of medications or supplements, changes in physical activity, patients with type 1 diabetes or unconfirmed T2D/glucose intolerance, or interventions using n-3 fatty acids or other unspecified dietary changes were excluded. Detailed inclusion/exclusion criteria are shown in Supplementary Table 1. From the initial search results, one author (F.Q.) screened titles and abstracts and identified the full-text articles for inclusion in the meta-analysis. A second author (A.A.K.) confirmed that all articles

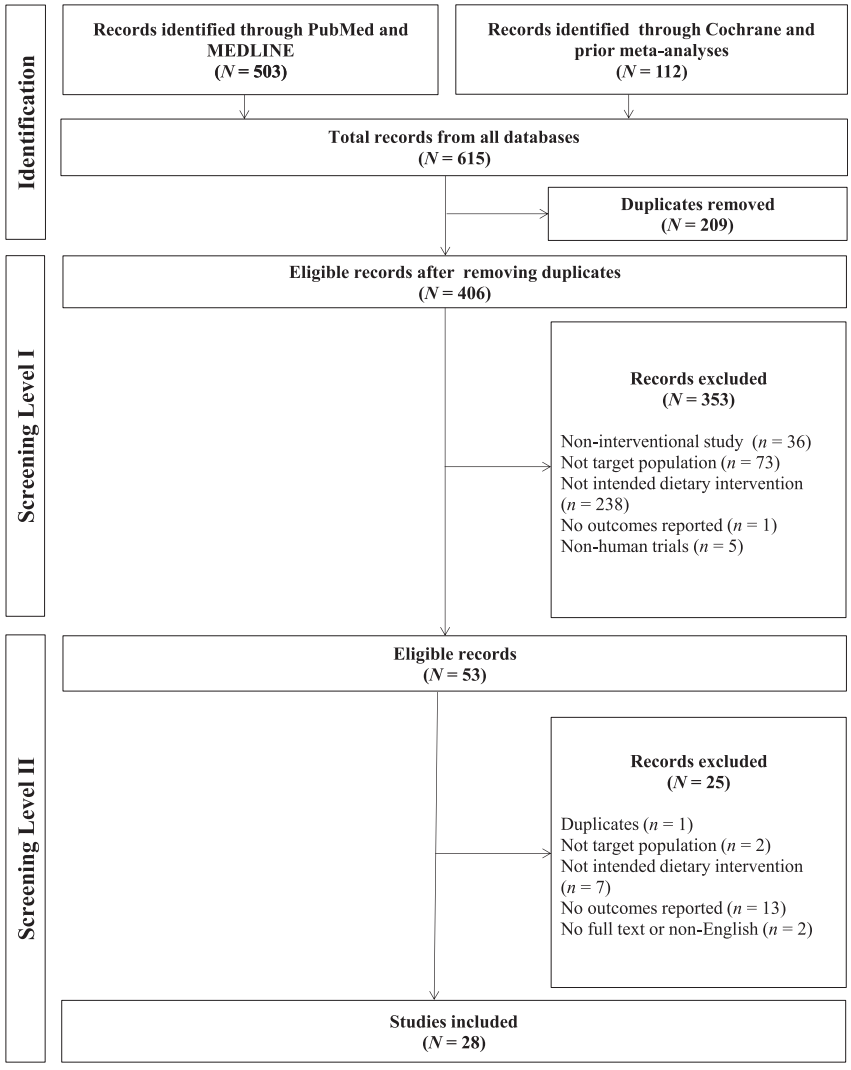

Figure 1—PRISMA diagram on trials of MUFA or PUFA dietary interventions in patients with T2D.

that were included in the meta-analysis met the inclusion and exclusion criteria.

Data Extraction and Quality Assessment

Data were extracted independently by two authors (F.Q. and A.A.K.) and any discrepancies that arose were adjudicated by a third author (F.B.H.). The following information was extracted: study design (randomized parallel, randomized crossover, inpatient/outpatient), trial arms/sample size, study duration, mean dietary composition (percent of total energy), age of participants, baseline BMI, duration of diabetes, and means and SDs of changes in HbA_{1c} (%), fasting plasma glucose (mmol/L), fasting insulin (pmol/L), LDL cholesterol (mmol/L), HDL cholesterol (mmol/L), triglycerides (mmol/L), body weight (kg), and 24-h measurements of systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) from baseline to the end of follow-up. Data were extracted from the primary publications with proper transformations done to harmonize the units used. Authors of original publications were contacted when necessary to obtain additional data.

Study Quality and Risk of Bias

RCTs meeting the inclusion criteria above were evaluated for risk of bias using the Cochrane Collaboration's tool for assessing risk of bias and were categorized as having a "high risk of bias," "low risk of bias," or "unclear risk of bias" (9). Specifically, RCTs were reviewed for allocation concealment, blinding approaches, approaches for incomplete outcome data, selective reporting, and bias due to problems arising from other issues.

Data Synthesis and Analysis

Our outcome of interest was the weighted mean difference (WMD) from baseline to the end of follow-up in the metabolic parameters listed above between the high-MUFA diet and the high-CHO or high-PUFA diets. WMD was calculated using both the random-effects and fixed-effects models. We considered random-effects analysis the main focus of our meta-analysis. Subgroup analyses were conducted based on the age of participants, baseline BMI, duration of diabetes, MUFA replacement (difference in percent energy from MUFA in the intervention and control arms), duration of follow-up (weeks), and study design (parallel vs. crossover). Heterogeneity between trial results was tested with a standard χ^2 test. The I^2 parameter was used to quantify any inconsistency: $I^2 = [(Q - d.f.)] \times 100\%$, where Q is the χ^2 statistic and d.f. is its degrees of freedom (10). Meta-regressions involving the above baseline characteristics as both continuous and categorical variables were also performed to identify potential sources of heterogeneity. Publication bias was assessed visually with funnel plots and with Egger and Begg-Mazudumar regression tests (11,12). Sensitivity analyses in which each study was removed in turn to assess the influence of that study on the overall effect size were also conducted. Statistical analyses were conducted with Stata 13.0, including the metan module (StataCorp, College Station, TX).

RESULTS

Literature

A total of 615 records were identified in the initial search and 406 abstracts were selected for review after removing duplicates. After stage 1 screening, 53 records underwent full-text screening. Overall, 28 studies were included in the meta-analysis with 24 for MUFA vs. CHO diets (13–37), totaling 1,460 participants, and 4 for MUFA vs. PUFA diets (38–41), totaling 44 participants. The number of available comparisons for MUFA vs. CHO diets was 28 as some trials had more than two arms. The baseline characteristics of the included studies are shown in Table 1. Outcome results at the end of follow-up for each study were included in Supplementary Table 4. Because of a limited number of studies comparing high-MUFA and high-PUFA diets, only certain metabolic outcomes were analyzed in the meta-analysis for this comparison.

Of the 24 studies identified for the MUFA vs. CHO diet comparisons, 12 had a parallel design and 12 had a crossover design. The mean dietary composition for the high-MUFA arm was 17.0% protein, 39.4% CHO, 43.1% fat, and 24.5% MUFA; the mean dietary composition for the high-CHO arm was 17.3% protein, 54.1% CHO, 27.6% fat, and 11.0% MUFA. The mean and median duration of the interventions were 19.3 and 6 weeks, respectively.

All of the MUFA vs. PUFA diet comparisons used a crossover design. The mean dietary composition for the high-MUFA arm was 13.7% protein, 39.5% CHO, 46.1% fat, 26.2% MUFA, and 6.0% PUFA; the mean dietary composition for the high-PUFA arm was 14.5% protein, 38.9% CHO, 45.5% fat, 12.3% MUFA, and 19.0% PUFA. The mean and median duration of the interventions were 3.5 and 3 weeks, respectively.

Glycemic Control

The meta-analysis showed that a high-MUFA diet compared with a high-CHO diet resulted in a significant reduction in fasting plasma glucose (WMD −0.57 mmol/L [95% CI −0.76, −0.39]) and a nonsignificant reduction in HbA_{1c} (%) and fasting insulin (pmol/L) (Table 2). There was a moderate level of heterogeneity for HbA_{1c} (%) (I^2 = 40.2%, P_{het} = 0.044). A high-MUFA diet compared with a high-PUFA diet resulted in significant reductions in fasting plasma glucose (−0.87 mmol/L [−1.67, −0.07]) and a nonsignificant reduction in fasting insulin (Table 3). Forest plots for all of these outcomes can be found in Supplementary Fig. 2.

Serum Lipids

On the basis of our meta-analysis, a high-MUFA diet compared with a high-CHO diet resulted in a nonsignificant increase in LDL cholesterol, a significant increase in HDL cholesterol (WMD 0.06 mmol/L [95% CI 0.02, 0.10]), and a significant reduction in triglycerides (−0.31 mmol/L [−0.44, −0.18]) (Table 2), although there was considerable heterogeneity (HDL cholesterol I^2 = 45.4%, P = 0.010; triglycerides I^2 = 54.0%, P = 0.001) (Table 2). Comparing a high-MUFA diet to a high-PUFA diet, there was a nonsignificant reduction in of LDL cholesterol and nonsignificant increases in HDL cholesterol and triglycerides (Table 3).

Other Metabolic Effects

Body Weight

A high-MUFA diet compared with a high-CHO diet resulted in a significant mean decrease in body weight (WMD −1.56 kg [95% CI −2.89, −0.23]), with low heterogeneity (I^2 = 0.0%, P = 1.000) (Table 2).

Blood Pressure

In examining 24-h blood pressure monitoring, a high-MUFA diet compared with a high-CHO diet resulted in a significant reduction in systolic blood pressure

Table 1—Baseline characteristics of published studies

					Intervention								Control								
								Mean dietary composition (% of energy)								Mean dietary composition (% of energy)					
	Study design	Duration of intervention and follow-up (weeks)	Trial arms	Sample size*	Age (years)	BMI (kg/m^2)	Duration of diabetes (years)	Protein	CHO	Fat	MUFA	PUFA	Age (years)	BMI (kg/m^2)	Duration of diabetes (years)	Protein	Carbohydrate	Fat	MUFA	PUFA	Difference in % of energy from MUFA
High-MUFA vs. high-CHO diet																					
Lasa 2014 (13)	Parallel, outpatient	52	MUFA (olive oil) vs. LF	141	67.4	29.4	—	16.5	38.6	42.0	22.1	—	67.2	29.8	—	17.0	41.2	39.3	19.6	—	2.5
Lasa 2014 (13)	Parallel, outpatient	52	MUFA (nuts) vs. LF	117	67.1	30.1	—	16.5	36.6	44.5	21.3	—	67.2	29.8	—	17.0	41.2	39.3	19.6	—	1.7
Itsiopoulos 2011 (14)	Crossover, outpatient	12	MED vs. control	54	—	—	6.0	13.5	43.5	39.0	21.3	—	—	—	6.0	18.2	46.4	31.5	11.1	—	10.2
Elhayany 2010 (15)	Parallel, outpatient	48	MED (low-CHO) vs. LF	116	55.5	31.4	5.3	32.0	35.0	45.0	23.0	—	56.0	31.8	5.3	20.0	50.0	30.0	10.0	—	13.0
Elhayany 2010 (15)	Parallel, outpatient	48	MED (traditional) vs. LF	118	57.4	31.1	5.7	60.0	50.0	30.0	10.0	—	56.0	31.8	5.7	20.0	50.0	30.0	10.0	—	0.0
Brehm 2009 (16)	Parallel, outpatient	48	MUFA vs. CHO	95	56.5	35.9	—	15.0	45.0	40.0	20.0	—	56.5	35.9	—	15.0	60.0	25.0	—	—	—
Esposito 2009 (17)	Parallel, outpatient	52	MED vs. LF	215	52.4	29.7	0.0	18.3	42.7	39.0	18.0	—	51.9	29.5	0.0	18.3	53.2	28.3	12.0	—	6.0
Wolever 2008 (18,19)	Parallel, outpatient	48	MUFA vs. HGI	101	58.6	31.1	—	19.1	39.3	40.1	18.3	—	60.4	30.1	—	20.4	46.5	30.8	12.3	—	6.0
Wolever 2008 (18,19)	Parallel, outpatient	48	MUFA vs. LGI	108	58.6	31.1	—	19.1	39.3	40.1	18.3	—	60.6	31.6	—	20.6	51.9	26.5	10.7	—	7.6
Brunerova 2007 (20)	Parallel, outpatient	12	MUFA vs. CHO	27	54.7	33.4	—	10.0	45.0	45.0	22.5	—	51.2	34.7	—	10.0	60.0	30.0	10.0	—	12.5
Leon-Sanz 2005 (21)	Parallel, inpatient	2	MUFA vs. CHO	63	73.9	25.5	—	16.7	37.5	50.1	34.2	—	70.6	26.5	—	13.6	50.0	28.8	8.7	—	25.5
Shah 2005 (22)	Parallel, outpatient	14	MUFA vs. CHO	21	58.0	28.1	—	15.0	40.0	45.0	25.0	—	58.0	28.1	—	15.0	55.0	30.0	10.0	—	15.0
Gerhard 2004 (23)	Crossover, outpatient	6	MUFA vs. LF	22	50.4	37.2	—	35.3	45.1	39.6	25.1	—	50.4	37.2	—	14.5	64.7	20.8	8.3	—	16.8
Rodriguez-Villar 2004 (24)	Crossover, outpatient	6	MUFA vs. CHO	44	61.0	28.3	5.3	17.5	41.4	40.2	24.9	—	61.0	28.3	5.3	18.9	52.3	27.9	13.6	—	11.3
Lovejoy 2002 (25)	Crossover, outpatient	4	HF vs. LF	60	53.8	33.0	—	14.9	45.8	39.0	22.5	—	53.8	33.0	—	14.7	58.1	27.2	15.5	—	7.0
Rodriguez-Villar 2000 (26)	Crossover, outpatient	6	MUFA vs. CHO	24	—	27.9	6.0	16.3	43.3	40.1	24.8	—	—	27.9	6.0	17.3	53.5	28.6	11.6	—	13.2
Tsihlias 2000 (27)	Parallel, outpatient	24	MUFA vs. HGI	61	63.0	27.8	—	17.8	43.2	37.2	17.5	—	62.9	28.0	—	17.0	53.5	28.9	11.3	—	6.2
Tsihlias 2000 (27)	Parallel, outpatient	24	MUFA vs. LGI	62	63.0	27.8	—	17.8	43.2	37.2	17.5	—	61.8	27.7	—	19.7	50.1	28.3	10.7	—	6.8
Gumbiner 1998 (28)	Parallel, outpatient	6	MUFA vs. CHO	17	55.0	36.3	7.4	20.6	9.5	69.9	49.0	—	51.0	37.2	7.4	19.5	70.1	10.3	1.0	—	48.0
McCargar 1998 (29)	Parallel, inpatient	4	MUFA vs. CHO	32	55.0	28.4	4.5	17.6	33.0	50.0	32.4	—	59.0	28.7	4.5	14.5	55.0	30.5	—	—	—
Campbell 1994 (30)	Crossover, outpatient	2	MUFA vs. CHO	20	55.0	26.5	4.6	41.0	40.0	37.0	22.0	—	55.0	26.5	4.6	23.0	55.0	22.0	8.0	—	14.0
Garg 1994 (31)	Parallel, outpatient	6	MUFA vs. CHO	42	58.0	28.1	—	15.0	40.0	45.0	25.0	—	58.0	28.1	—	15.0	55.0	30.0	10.0	—	15.0
Lerman-Garber 1994 (32)	Crossover, outpatient	4	MUFA vs. CHO	24	56.0	28.0	—	20.0	40.0	40.0	24.0	—	56.0	28.0	—	20.0	60.0	20.0	6.6	—	17.4
Rasmussen 1993 (33)	Crossover, outpatient	3	MUFA vs. CHO	30	57.0	27.0	6.0	14.0	36.0	50.0	30.0	—	57.0	27.0	6.0	17.0	49.0	32.0	11.0	—	19.0
Garg 1992 (34)	Crossover, outpatient	3	MUFA vs. CHO	16	63.0	30.0	—	15.0	35.0	50.0	32.0	—	63.0	30.0	—	15.0	60.0	25.0	12.0	—	20.0
Parillo 1992 (35)	Crossover, outpatient	2	MUFA vs. CHO	20	52.7	26.7	8.4	20.0	40.0	40.0	29.0	—	52.7	26.7	8.4	20.0	60.0	20.0	13.0	—	16.0
Rivellese 1990 (36)	Crossover, outpatient	2	MUFA vs. CHO	16	45.0	22.0	5.0	—	—	—	—	—	45.0	22.0	5.0	—	—	—	—	—	—
Garg 1988 (37)	Crossover, outpatient	4	MUFA vs. CHO	20	56.0	29.0	—	15.0	35.0	50.0	33.0	—	56.0	29.0	—	15.0	60.0	25.0	9.0	—	24.0
High-MUFA vs. high-PUFA																					
Madigan 2005 (38)	Crossover, outpatient	2	MUFA vs. PUFA	12	56.0	28.0	—	—	—	—	—	—	56.0	28.0	—	—	—	—	—	—	—
Brynes 2000 (39)	Crossover, outpatient	3	MUFA vs. PUFA	18	56.0	29.8	3.0	13.5	47.2	39.1	20.3	4.2	56.0	29.8	3.0	12.4	46.5	41.1	11.7	13.4	8.6
Thomsen 1995 (40)	Crossover, outpatient	3	MUFA vs. PUFA	32	59.0	28.0	6.0	13.0	37.0	49.0	30.0	7.0	59.0	28.0	6.0	13.0	36.0	49.0	10.0	27.0	20.0
Parfitt 1994 (41)	Crossover, outpatient	6	MUFA vs. PUFA	26	58.0	28.4	4.2	14.6	34.4	50.2	28.2	6.8	59.0	28.4	4.2	18.0	34.3	46.5	15.1	16.7	13.1

HF, high fat; HGI, high glycemic index; LF, low fat; LGI, low glycemic index; MED, Mediterranean diet. *For crossover trials, the sample size is double the number of actual participants because each participant received both interventions.

Table 2—Metabolic effects in T2D patients consuming a high-MUFA diet compared with a high-CHO diet

Metabolic parameter	Number of studies	Number of participants	WMD (95% CI)*	WMD (95% CI)†	I^2 (%)	P_{het}
HbA_{1c} (%)	14	925	−0.08 (−0.15, 0.00)	−0.11 (−0.24, 0.02)	40.2	0.044
Fasting plasma glucose (mmol/L)	22	1,283	**−0.57 (−0.76, −0.39)**	**−0.57 (−0.76, −0.39)**	0.0	0.521
Fasting insulin (pmol/L)	11	679	−3.98 (−9.83, 1.87)	−3.98 (−9.83, 1.87)	0.0	0.768
LDL cholesterol (mmol/L)	17	791	0.00 (−0.08, 0.08)	0.05 (−0.07, 0.16)	40.2	0.033
HDL cholesterol (mmol/L)	20	1,067	**0.07 (0.05, 0.10)**	**0.06 (0.02, 0.10)**	45.4	0.010
Triglycerides (mmol/L)	21	1,075	**−0.29 (−0.36, −0.22)**	**−0.31 (−0.44, −0.18)**	54.0	0.001
Body weight (kg)	16	1,081	**−1.56 (−2.89, −0.23)**	**−1.56 (−2.89, −0.23)**	0.0	1.000
Systolic blood pressure (mmHg)	6	529	**−2.25 (−3.79, −0.70)**	**−2.31 (−4.13, −0.49)**	16.5	0.304
Diastolic blood pressure (mmHg)	5	373	−1.33 (−2.91, 0.25)	−2.64 (−5.91, 0.63)	69.5	0.011

Values in boldface type indicate statistical significance at $P < 0.05$. *Calculated using a fixed-effects model. †Calculated using a random-effects model.

(WMD −2.31 mmHg [95% CI −4.13, −0.49]) and a nonsignificant reduction in diastolic blood pressure, with significant heterogeneity (I^2 = 69.5%, P = 0.011) (Table 2).

Subgroup Analysis and Meta-regression

For comparisons between high-MUFA and high-CHO diets, we conducted stratified analysis for HbA_{1c}, fasting plasma glucose, LDL and HDL cholesterol, triglycerides, and body weight by age (<60, ≥60 years), baseline BMI (<30, ≥30 kg/m^2), duration of diabetes (<5, ≥5 years), MUFA replacement (<15, ≥15% of energy), duration of study (≤6, >6 weeks), and trial design (parallel, crossover) to identify possible sources of heterogeneity (Table 4). For HbA_{1c}, no considerable differences were observed within each of the subgroups assessed. For fasting plasma glucose, there was greater reduction among studies in which the mean age of participants was <60 years (WMD −0.63 mmol/L [95% CI −0.85, −0.41]) than studies in which mean age was ≥60 years (−0.32 mmol/L [−0.76, 0.12]). For HDL cholesterol, greater increases were observed in the subgroups in which trial duration was greater than 6 weeks or had a parallel design. There was a greater reduction in triglycerides for participants with a duration of diabetes of ≥5 years (−0.37 mmol/L [−0.57, −0.17]) compared with <5 years (−0.16 mmol/L [−0.44, 0.12]). The reduction in triglycerides also tended to be greater in subgroups that had trial duration greater than 6 weeks or had a parallel design. Among subgroups of patients who had mean age ≥60 years (0.38 mmol/L [−0.08, 0.85]) compared with patients <60 years (−0.05 mmol/L [−0.14, 0.03]), there tended to be greater increase in LDL cholesterol, though this difference was not statistically significant. Similarly, among subgroups of patients who had mean BMI <30 kg/m^2 (0.23 mmol/L [−0.02, 0.48]) compared with patients with BMI ≥30 kg/m^2 (−0.06 mmol/L [−0.15, 0.03]), there tended to be greater increase in LDL cholesterol, though this difference was also not significant. For body weight, we observed a statistically significant weight reduction in the subgroups with BMI <30 kg/m^2 compared with BMI ≥30 kg/m^2, MUFA replacement <15% compared with ≥15% of energy, trial time >6 weeks compared with ≤6 weeks, and parallel design compared with crossover design.

Meta-regressions were also performed for these outcomes using the baseline characteristics described above and we identified age (β = 0.50, P = 0.002) and BMI (β = −0.32, P = 0.011) as significant predictors for the effect on LDL cholesterol. This suggests that these factors may be potential sources of heterogeneity in these analyses.

Publication Bias and Risk of Bias

Statistically significant publication bias was not found for any of the main outcomes using both the Egger and the Begg-Mazudumar tests (Supplementary Table 2). This was also confirmed based on visual inspection of the corresponding funnel plot (Supplementary Fig. 3). No study exerted overt influence on the pooled effect size for any of the primary outcomes (data not shown). Furthermore, most studies were assessed to be of low risk for bias (Supplementary Table 3).

CONCLUSIONS

In our meta-analysis of RCTs, we observed beneficial effects of a high-MUFA diet compared with a high-CHO

Table 3—Metabolic effects in T2D patients consuming a high-MUFA diet compared with a high-PUFA diet

Metabolic parameter	Number of studies	Number of participants	WMD (95% CI)*	WMD (95% CI)†	I^2 (%)	P_{het}
Fasting plasma glucose (mmol/L)	3	31	**−0.87 (−1.67, −0.07)**	**−0.87 (−1.67, −0.07)**	26.3	0.257
Fasting insulin (pmol/L)	2	15	−7.56 (−26.15, 11.03)	−7.56 (−26.15, 11.03)	0.0	0.516
LDL cholesterol (mmol/L)	4	44	−0.15 (−0.43, 0.13)	−0.15 (−0.44, 0.14)	5.9	0.363
HDL cholesterol (mmol/L)	4	44	0.04 (−0.07, 0.15)	0.04 (−0.07, 0.15)	0.0	0.848
Triglycerides (mmol/L)	3	31	0.01 (−0.46, 0.47)	0.01 (−0.46, 0.47)	0.0	0.941

HbA_{1c}, weight, systolic blood pressure, and diastolic blood pressure were not included in this analysis due to the limited number of studies reporting these outcomes. Values in boldface type indicate statistical significance at $P < 0.05$. *Calculated using a fixed-effects model. †Calculated using a random-effects model.

Table 4—Subgroup analysis of metabolic effects on T2D patients consuming a high-MUFA diet compared with a high-CHO diet

Metabolic parameter	Number of studies	Number of participants	WMD (95% CI)*	WMD (95% CI)†	I^2 (%)	P_{het}
HbA_{1c} (%)						
Age (years)						
<60	9	765	−0.08 (−0.16, 0.01)	−0.12 (−0.28, 0.05)	59.2	0.006
≥60	3	121	−0.08 (−0.38, 0.23)	−0.08 (−0.38, 0.23)	0.0	0.671
BMI (kg/m^2)						
<30	6	382	**−0.34 (−0.52, −0.16)**	−0.21 (−0.50, 0.07)	36.1	0.153
≥30	7	506	−0.01 (−0.10, 0.07)	−0.01 (−0.10, 0.07)	0.0	0.545
Duration of diabetes (years)						
<5†	—	—	—	—	—	—
≥5	4	240	−0.18 (−0.39, 0.02)	−0.18 (−0.39, 0.02)	0.0	0.561
MUFA replacement (%)‡						
<15	8	580	−0.06 (−0.14, 0.02)	−0.10 (−0.27, 0.07)	58.2	0.010
≥15	4	71	−0.01 (−0.60, 0.59)	−0.01 (−0.60, 0.59)	0.0	0.787
Trial time (weeks)						
≤6	7	135	0.03 (−0.29, 0.36)	0.03 (−0.29, 0.36)	63.6	0.003
>6	7	790	**−0.08 (−0.16, 0.00)**	−0.14 (−0.30, 0.02)	0.0	0.955
Study design						
Parallel	7	805	**−0.08 (−0.16, 0.00)**	−0.13 (−0.30, 0.03)	63.3	0.004
Crossover	7	120	0.00 (−0.31, 0.31)	0.00 (−0.31, 0.31)	0.0	0.924
Fasting plasma glucose (mmol/L)						
Age (years)						
<60	15	713	**−0.64 (−0.85, −0.43)**	**−0.63 (−0.85, −0.41)**	5.9	0.387
≥60	5	375	−0.32 (−0.76, 0.12)	−0.32 (−0.76, 0.12)	0.0	0.627
BMI (kg/m^2)						
<30	14	733	**−0.64 (−0.89, −0.40)**	**−0.64 (−0.89, −0.40)**	0.0	0.760
≥30	7	367	**−0.49 (−0.77, −0.21)**	−0.40 (−0.82, 0.02)	38.6	0.122
Duration of diabetes (years)						
<5	3	257	**−0.90 (−1.36, −0.45)**	**−0.90 (−1.36, −0.45)**	0.0	0.620
≥5	8	290	**−0.69 (−1.01, −0.37)**	**−0.69 (−1.01, −0.37)**	0.0	0.553
MUFA replacement (%)						
<15	9	625	**−0.51 (−0.77, −0.24)**	**−0.51 (−0.77, −0.24)**	1.2	0.430
≥15	9	188	**−0.63 (−1.01, −0.25)**	**−0.63 (−1.01, −0.25)**	0.0	0.931
Trial time (weeks)						
≤6	15	302	**−0.54 (−0.87, −0.21)**	**−0.54 (−0.87, −0.21)**	0.0	0.901
>6	7	825	**−0.59 (−0.81, −0.37)**	**−0.53 (−0.84, −0.23)**	40.6	0.087
Study design						
Parallel	10	952	**−0.58 (−0.79, −0.36)**	**−0.54 (−0.81, −0.27)**	23.9	0.202
Crossover	12	175	**−0.56 (−0.91, −0.21)**	**−0.56 (−0.91, −0.21)**	0.0	0.783
LDL cholesterol (mmol/L)						
Age (years)						
<60	11	558	−0.05 (−0.14, 0.03)	−0.05 (−0.14, 0.03)	0.0	0.969
≥60	4	174	**0.45 (0.21, 0.69)**	0.38 (−0.08, 0.85)	67.4	0.015
BMI (kg/m^2)						
<30	10	182	**0.26 (0.09, 0.43)**	0.23 (−0.02, 0.48)	46.4	0.045
≥30	6	479	−0.06 (−0.15, 0.02)	−0.06 (−0.15, 0.02)	0.0	0.935
Duration of diabetes (years)						
<5†	—	—	—	—	—	—
≥5	6	263	−0.07 (−0.23, 0.09)	−0.07 (−0.23, 0.09)	0.0	0.747
MUFA replacement (%)						
<15	7	348	0.01 (−0.08, 0.11)	0.11 (−0.10, 0.32)	70.5	0.001
≥15	7	161	0.05 (−0.19, 0.29)	0.05 (−0.19, 0.29)	0.0	0.984
Trial time (weeks)						
≤6	12	243	−0.01 (−0.17, 0.15)	−0.01 (−0.17, 0.15)	0.0	0.993
>6	5	548	0.01 (−0.08, 0.09)	0.10 (−0.10, 0.30)	75.8	<0.001
Study design						
Parallel	6	626	0.01 (−0.08, 0.10)	0.11 (−0.09, 0.30)	72.7	<0.001
Crossover	11	165	−0.02 (−0.18, 0.14)	−0.02 (−0.18, 0.14)	0.0	0.992
HDL cholesterol (mmol/L)						
Age (years)						
<60	14	844	**0.07 (0.04, 0.09)**	**0.06 (0.02, 0.10)**	41.3	0.043
≥60	4	184	0.08 (−0.05, 0.22)	0.08 (−0.05, 0.22)	71.3	0.007

Continued on p. 1454

Table 4—Continued

Metabolic parameter	Number of studies	Number of participants	WMD (95% CI)*	WMD (95% CI)†	I^2 (%)	P_{het}
BMI (kg/m^2)						
<30	12	534	**0.07 (0.03, 0.11)**	**0.07 (0.02, 0.12)**	24.4	0.197
≥30	7	506	**0.07 (0.04, 0.10)**	0.06 (0.00, 0.11)	66.8	0.002
Duration of diabetes (years)						
<5	3	257	**0.08 (0.02, 0.13)**	**0.08 (0.02, 0.13)**	0.0	0.812
≥5	6	265	**0.11 (0.07, 0.15)**	0.08 (0.00, 0.15)	57.0	0.030
MUFA replacement (%)						
<15	9	590	**0.05 (0.02, 0.09)**	**0.05 (0.00, 0.10)**	40.4	0.079
≥15	8	171	0.04 (−0.02, 0.10)	0.04 (−0.02, 0.10)	0.0	0.815
Trial time (weeks)						
≤6	13	277	0.02 (−0.03, 0.07)	0.04 (−0.15, 0.24)	0.0	0.884
>6	7	790	**0.09 (0.06, 0.11)**	**0.09 (0.03, 0.14)**	68.5	0.001
Study design						
Parallel	9	900	**0.08 (0.06, 0.11)**	**0.08 (0.03, 0.13)**	65.9	0.001
Crossover	11	167	0.03 (−0.02, 0.08)	0.03 (−0.02, 0.08)	0.0	0.941
Triglycerides (mmol/L)						
Age (years)						
<60	15	852	**−0.28 (−0.36, −0.21)**	**−0.29 (−0.43, −0.15)**	61.2	0.001
≥60	4	184	**−0.49 (−0.82, −0.16)**	**−0.52 (−0.97, −0.07)**	44.0	0.129
BMI (kg/m^2)						
<30	13	542	**−0.21 (−0.34, −0.09)**	**−0.26 (−0.41, −0.10)**	18.1	0.257
≥30	7	506	**−0.33 (−0.42, −0.24)**	**−0.33 (−0.55, −0.12)**	74.8	<0.001
Duration of diabetes (years)						
<5	3	257	−0.10 (−0.28, 0.08)	−0.16 (−0.44, 0.12)	37.3	0.203
≥5	7	273	**−0.42 (−0.58, −0.26)**	**−0.37 (−0.57, −0.17)**	26.5	0.217
MUFA replacement (%)						
<15	9	590	**−0.24 (−0.33, −0.15)**	**−0.26 (−0.44, −0.07)**	68.0	0.001
≥15	8	171	**−0.31 (−0.52, −0.10)**	**−0.31 (−0.52, −0.10)**	0.0	0.854
Trial time (weeks)						
≤6	14	285	**−0.26 (−0.41, −0.11)**	**−0.26 (−0.41, −0.11)**	0.0	0.919
>6	7	790	**−0.30 (−0.39, −0.22)**	**−0.36 (−0.57, −0.15)**	79.9	<0.001
Study design						
Parallel	9	900	**−0.31 (−0.39, −0.22)**	**−0.37 (−0.56, −0.18)**	75.0	<0.001
Crossover	12	175	**−0.23 (−0.39, −0.06)**	**−0.23 (−0.39, −0.06)**	0.0	0.918
Body weight (kg)						
Age (years)						
<60	11	741	−1.40 (−3.07, 0.27)	−1.40 (−3.07, 0.27)	0.0	1.000
≥60	4	312	−1.95 (−4.25, 0.35)	−1.95 (−4.25, 0.35)	0.0	0.987
BMI (kg/m^2)						
<30	10	589	**−1.64 (−3.26, −0.03)**	**−1.64 (−3.26, −0.03)**	0.0	1.000
≥30	6	476	−1.39 (−3.75, 0.98)	−1.39 (−3.75, 0.98)	0.0	0.892
Duration of diabetes (years)						
<5	3	241	−1.53 (−4.09, 1.04)	−1.53 (−4.09, 1.04)	0.0	0.931
≥5	4	223	−1.69 (−4.38, 1.00)	−1.69 (−4.38, 1.00)	0.0	0.983
MUFA replacement (%)						
<15	8	724	**−1.73 (−3.33, −0.12)**	**−1.73 (−3.33, −0.12)**	0.0	0.989
≥15	5	51	−0.26 (−4.94, 4.42)	−0.26 (−4.94, 4.42)	0.0	0.999
Trial time (weeks)						
≤6	8	111	−0.28 (−3.57, 3.01)	−0.28 (−3.57, 3.01)	0.0	1.000
>6	7	954	**−1.81 (−3.27, −0.35)**	**−1.81 (−3.27, −0.35)**	0.0	0.976
Study design						
Parallel	8	970	**−1.78 (−3.23, −0.34)**	**−1.78 (−3.23, −0.34)**	0.0	0.986
Crossover	8	95	−0.29 (−3.75, 3.17)	−0.29 (−3.75, 3.17)	0.0	1.000

Values in boldface type indicate statistical significance at $P < 0.05$. *Calculated using a fixed-effects model. †Calculated using a random-effects model. ‡Indicates % energy difference from MUFA in the intervention and control arms.

diet on glycemic control, serum lipids, and systolic blood pressure among individuals with T2D, whereas a beneficial effect on fasting plasma glucose was observed for high-MUFA compared with high-PUFA diets. These improvements are important in the prevention of long-term complications in this population.

In observational studies, substituting dietary MUFA for CHO or saturated fatty acids (SFA) has generally not been associated with a decreased risk of CVD (42–46). However, this may be due to the fact that the main source of MUFA in the Western diet is from animal-based foods, including dairy and meat, which contain comparably higher levels of SFA compared with plant sources of

MUFA. In the current study, all of the trials evaluated plant sources of MUFA, such as olive oil, nuts, or avocado, which reduces the confounding by SFA intake observed in cohort studies. In several observational studies and meta-analyses, higher consumption of PUFA in place of SFA or CHO has been associated with lower rates of coronary events, though it is unclear whether substitution for MUFA would yield a similar benefit (43–46).

Better glycemic control and improved insulin sensitivity have often been observed in subjects consuming a high-MUFA diet, particularly when MUFA was used to replace CHO (47–49). The favorable increase in HDL cholesterol and reduction in triglycerides that we observed is also consistent with prior meta-analyses (5,50). These improvements are particularly important for the prevention of CVD among individuals with T2D given that the majority of this population has dyslipidemia. We observed a small reduction in systolic blood pressure, which is also consistent with the results from a prior meta-analysis (7). Our summary measures are consistent with a previous meta-analysis by Schwingshackl et al. (3) that reported significant reductions in HbA_{1c} when comparing high-MUFA to high-CHO diets and nonsignificant reductions in plasma insulin, plasma glucose, and HOMA-insulin resistance. The nonsignificant results of this previous analysis could be due to the fact that fewer studies were included for these measures. Garg et al. (5) also reported significant reductions in fasting glucose and a nonsignificant reduction in plasma insulin, also possibly due to the inclusion of fewer trials. Overall, the results for glycemic control favor high-MUFA compared with high-CHO diets, especially in the reduction of fasting plasma glucose. Moreover, we observed a modest but statistically significant difference in body weight on high-MUFA compared with high-CHO diets, both overall and in several subgroups. This finding suggests that the effects of the high-MUFA diets on the metabolic risk factors could be partially mediated by changes in body weight, which has been shown in prior studies evaluating blood lipids, blood pressure, and glycemic control (51,52).

Out of the outcomes we evaluated comparing high-MUFA to high-PUFA diets, we only observed a reduction in fasting plasma glucose. The overall lack of difference observed between these two diets on the metabolic risk factors we evaluated could be due to small sample sizes or similar metabolic effects between these two diets. In addition, the length of follow-up in these trials may have been too short to observe meaningful changes in the biomarkers. The intervention foods in the high-PUFA regimens varied from study to study (sunflower oil, nuts, corn oil) each containing other components (macro- and micronutrients, antioxidants) that may have influenced the results of a given trial due to their association with glycemic control or serum lipid levels (53–56).

Potential physiological mechanisms for the metabolic benefits observed when replacing CHO with MUFA are diminished glycemic load, leading to reduced demand for insulin, greater insulin sensitivity (57), and increased hepatic LDL receptors, resulting in accelerated LDL cholesterol turnover while having no appreciable effect on total cholesterol synthesis (e.g., does not lower HDL cholesterol) (58). There is also growing evidence that MUFA-rich foods, including olive oil and avocados, contain numerous other beneficial compounds such as phenolic compounds, plant phytochemicals, and fat-soluble vitamins (59–61). Oleic acid, a MUFA, which is the primary component in olive oil, has been directly implicated in blood pressure reduction by increasing cell membrane fluidity and exerting hypotensive effects via the α_2-adrenergic receptor system (62).

Our results are consistent with recent findings from the PREDIMED trial, which observed a decrease in CVD incidence among individuals with T2D who followed a Mediterranean diet compared with a low-fat diet. This suggests that changes in metabolic indices may be predictive of clinical end points (4). On the basis of our findings, body weight differed between the high-MUFA diet compared with the high-CHO diet. To account for the weight differences among these two diets, we performed a sensitivity analyses (Supplementary Table 5) in which we excluded trials that had a more than 1.5-kg difference in weight at the end of the trial, which included seven comparisons. Most of the outcomes were attenuated, although fasting plasma glucose (WMD −0.44 mmol/L [95% CI −0.74, −0.14]) and triglycerides (−0.19 mmol/L [−0.29, −0.10]) remained statistically significant. This is indicative of dietary composition having a favorable metabolic effect independent of weight reduction and is consistent with the results from the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT) that observed that a Mediterranean-type diet resulted in greater weight loss and improved metabolic profile compared with a low-fat diet among obese individuals (63). However, whether such an effect would be observed among obese individuals with T2D is not clear. Additional longer-term trials are needed to assess whether greater weight loss can be achieved with a high-MUFA diet among individuals with diabetes.

Our stratified analysis found modestly greater changes in several metabolic factors including HbA_{1c}, HDL cholesterol, and triglycerides in trials that were of longer duration ($>$6 vs. $\leq$6 weeks), suggesting that longer-term adherence to a high-MUFA diet may produce a more favorable metabolic profile. When we performed a sensitivity analysis and restricted the analysis to studies that were at least 3 months in duration, we observed a consistent or stronger effect on many of the metabolic parameters as in our overall analysis (Supplementary Table 6). Furthermore, this result is consistent with the nonsignificant reduction in HbA_{1c} (%), which is likely due to the relatively short duration of most studies in the meta-analysis; HbA_{1c} is more indicative of long-term glycemic control, over the span of 3–4 months. We tended to observe greater effects among studies using parallel rather than crossover designs, particularly for HDL cholesterol and triglycerides. This may be partially attributed to larger sample sizes in the parallel studies in our analysis. It is also possible that the duration of the washout period in the crossover trials was not sufficient to diminish a potential carryover effect. These subgroup findings may partially explain some of the heterogeneity observed in our effect estimates.

Our study has several strengths. We included both long-term and short-term studies in our overall and stratified analysis. In general, for studies evaluating MUFA compared with CHO diets, we selected studies that kept the percent of calories from protein and SFA consistent across the intervention and control arms. Similarly, for MUFA compared with PUFA diets, we selected studies that had minimal

differences in the percent of calories from protein, CHO, and SFA. Furthermore, we sought to identify potential sources of heterogeneity in our study through both subgroup analysis and meta-regression, particularly for HbA_{1c}, HDL cholesterol, and triglycerides. In addition, no outcome was observed to have potential publication bias based on our assessment (Supplementary Table 2), as we attempted to minimize bias by contacting authors to obtain unpublished results when necessary. There are several limitations to our study. Our study only included studies that examined individuals with T2D or noninsulin-dependent diabetes; hence, it is unclear whether these metabolic benefits can be extended to individuals with impaired glucose tolerance or type 1 diabetes, although some studies suggest a similar benefit (3,64). Furthermore, we examined only metabolic risk factors that were consistently measured and reported in each study, but the benefits of a high-MUFA diet may also be mediated through effects on inflammation (65), endothelial function (66), and body fat distribution (67), which all warrant further research. Most of the trials in our analysis were conducted among Western populations, which may limit the generalizability of our findings to other populations. In addition, comparisons of the foods consumed for the different diets in each study were generally not available. Hence, we cannot completely rule out the possibility that the metabolic differences we observed were attributable to some unmeasured dietary component. Finally, our analysis included a relatively small number of trials comparing high-MUFA to high-PUFA diets, which limits our conclusion regarding the metabolic effects of replacing MUFA with PUFA. Further studies are needed to examine whether replacement of CHO with PUFA exhibits similar metabolic benefits as MUFA among individuals with T2D.

In conclusion, our meta-analysis provides consistent evidence that replacing CHO with MUFA in the diet has beneficial effects on metabolic risk factors among individuals with T2D. Our findings have broad implications for dietary recommendations for this population.

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