CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Meta-Analysis Comparing Mediterranean to Low-Fat Diets for Modification of Cardiovascular Risk Factors

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ABSTRACT

BACKGROUND: Evidence from individual trials comparing Mediterranean to low-fat diets to modify cardiovascular risk factors remains preliminary.

METHODS: We systematically searched MEDLINE, EMBASE, Biosis, Web of Science, and the Cochrane Central Register of Controlled Trials from their inception until January 2011, as well as contacted experts in the field, to identify randomized controlled trials comparing Mediterranean to low-fat diets in overweight/obese individuals, with a minimum follow-up of 6 months, reporting intention-to-treat data on cardiovascular risk factors. Two authors independently assessed trial eligibility and quality.

RESULTS: We identified 6 trials, including 2650 individuals (50% women) fulfilling our inclusion criteria. Mean age of enrolled patients ranged from 35 to 68 years, mean body mass index from 29 to 35 kg/m^2. After 2 years of follow-up, individuals assigned to a Mediterranean diet had more favorable changes in weighted mean differences of body weight (−2.2 kg; 95% confidence interval [CI], −3.9 to −0.6), body mass index (−0.6 kg/m^2; 95% CI, −1 to −0.1), systolic blood pressure (−1.7 mm Hg; 95% CI, −3.3 to −0.05), diastolic blood pressure (−1.5 mm Hg; 95% CI, −2.1 to −0.8), fasting plasma glucose (−3.8 mg/dL, 95% CI, −7 to −0.6), total cholesterol (−7.4 mg/dL; 95% CI, −10.3 to −4.4), and high-sensitivity C-reactive protein (−1.0 mg/L; 95% CI, −1.5 to −0.5). The observed heterogeneity across individual trials could, by and large, be eliminated by restricting analyses to trials with balanced co-interventions or trials with restriction of daily calorie intake in both diet groups.

CONCLUSION: Mediterranean diets appear to be more effective than low-fat diets in inducing clinically relevant long-term changes in cardiovascular risk factors and inflammatory markers.

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KEYWORDS: Low-fat diet; Mediterranean diet; Meta-analysis

Funding: A. Nordmann, M. Briel, K. Suter-Zimmermann, and H. Bucher, as collaborators of the Basel Institute for Clinical Epidemiology and Biostatistics, are supported by an unrestricted grant from santésuisse and the Gottfried and Julia Bangerter-Rhyner Foundation. The Heart Institute of Spokane Diet Intervention and Evaluation Trial was supported by a grant from the Washington State Attorney General Vitamins Settlement Fund. The Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial was supported by the Nuclear Research Center Negev, the Dr. Robert C. and Veronica Atkins Research Foundation, and the Daniel S. Abraham International Center for Health and Nutrition, Ben Gurion University, Israel. The Predimed study was supported by unrestricted grants from the Spanish Ministry of Health and the Generalitat Valenciana. This meta-analysis was supported by an unrestricted grant from the Forlen Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest: None of the authors have a relationship with industry or financial associations that might pose a conflict of interest in connection with the submitted article.

Authorship: A. Nordmann and M. Briel had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the data and fulfill criteria for authorship.

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0002-9343/$ -see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2011.04.024

Unhealthy diet and physical inactivity are major risk factors for cardiovascular disease in the US, leading to 400,000 excess deaths in the year 2000.[1] Different dietary approaches for cardiovascular risk factor management have been investigated. Low-fat, high-carbohydrate diets may have benefits such as continuing weight loss for 3 years, prevention of type 2 diabetes, and improved control of hypertension as shown in clinical trials.[2] However, there is a lack of evidence in terms of a benefit on cardiovascular mortality.[3]

The traditional Mediterranean, moderate-fat diet is becoming increasingly promoted as a model of healthy eating,[4-6] despite the lack of evidence that this diet leads to sustained weight loss.[7] It is characterized by a high intake of monounsaturated fat, plant proteins, whole grains, and fish; moderate intake of alcohol, and low consumption of red meat, refined grains, and sweets.[4] In several cohort studies, Mediterranean diet was associated with a reduced incidence of coronary heart disease and stroke as well as cardiovascular, cancer, and overall mortality.[8-11]

The goal of this meta-analysis was to summarize the evidence of all randomized controlled trials with a minimum follow-up of 6 months comparing the effects of Mediterranean to low-fat diets on cardiovascular risk factors. We restricted the analysis to overweight/obese individuals with at least one additional cardiovascular risk factor because we did not identify any trial comparing the effects of the 2 diets in normal-weight individuals.

CLINICAL SIGNIFICANCE

- In overweight/obese individuals at increased cardiovascular risk, Mediterranean diets modify most cardiovascular risk factors more efficiently than low-fat diets.
- Current evidence demonstrates a lasting benefit of Mediterranean diets for 2 years after the beginning of the diet.
- Mediterranean, and not low-fat diets, should be recommended to modify cardiovascular risk factors in overweight/obese individuals.

METHODS

Literature Search

We searched the electronic databases MEDLINE, EMBASE, Biosis, Web of Science (all from their inception to January 2011), and the Cochrane Central Register of Controlled Trials using the terms "diets, fat restricted [Mesh]" and "Mediterranean diets." We restricted the search to articles indexed as clinical trial (publication type) and those that included the root *random* in their titles or abstracts. We also searched reference lists of identified articles, clinical trial registries of ongoing or planned trials, recently published editorials and reviews on the topic, and we contacted experts in the field for further eligible trials. No language restrictions were imposed.

Study Selection and Quality Assessment

Two authors (KS, AN) independently assessed trial eligibility and quality. Eligible trials had to compare Mediterranean with low-fat diets in either overweight/obese patients with at least one additional cardiovascular risk factor (primary prevention) or patients with established coronary artery disease (secondary prevention); to have a randomized controlled design and a minimum follow-up of 6 months; and to report intention-to-treat data on changes of body weight, blood pressure, and lipid values. We included trials where Mediterranean diets were defined as diets with moderate fat intake (where the main sources of added fat were olive oil and nuts), rich in vegetables, and low in red meat (with poultry and fish replacing beef and lamb).[12] Low-fat diets were defined as diets aiming at an energy intake with ≤30% of calories from fat.[13] We evaluated the quality of trials according to concealment of treatment allocation; blinding of patients, caregivers, and clinical outcome assessors; full description of losses to follow-up and withdrawals; the proportion of patients with complete clinical follow-up; and trials not stopping early for benefit.[14,15]

Outcomes and Data Extraction

Two authors (KS, AN) independently extracted published trial data and additional data provided by the original investigators. We considered the following cardiovascular risk factors baseline and 2 years of follow-up as outcomes of interest: mean differences in body weight, body mass index, waist circumference, systolic and diastolic blood pressure, total high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose, and serum insulin between. In addition, we extracted any clinical outcome data when available.

Statistical Analysis

We pooled treatment effects and calculated weighted mean differences for all risk factors between patients randomized to Mediterranean and low-fat diets by using a random-effects model.[16] Because we could not obtain standard deviations for the differences of the means of risk factors from one trial,[17] we first calculated the standard errors by dividing the differences of the means by the percentage points of the *t*-distributions corresponding to the *P*-values given, and then calculated the standard deviations by multiplying the standard errors by the square roots of the number of observations.

We investigated the presence of publication bias by means of funnel plots.[18] We tested for heterogeneity with

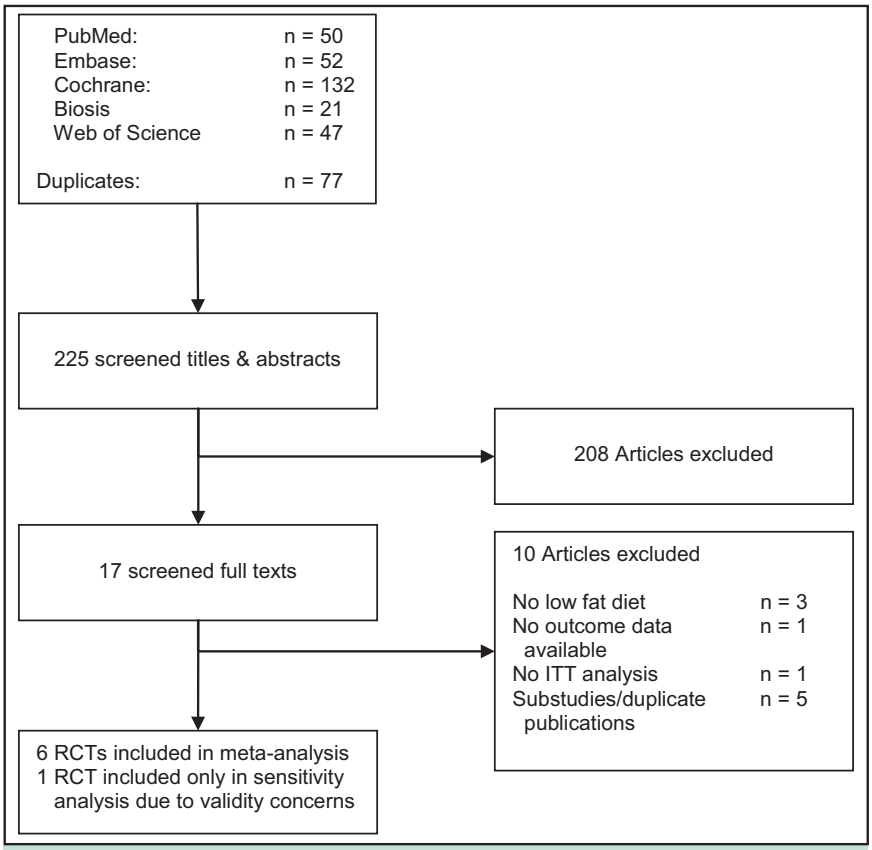

Figure 1 Trial flow. ITT = intention to treat; RCT = randomized controlled trial.

the Cochran Q test and measured inconsistency (I^2; the percentage of total variance across studies that is due to heterogeneity rather than chance) of treatment effects across all cardiovascular risk factors of interest.[19,20] We conducted sensitivity analyses to examine treatment effects according to quality components of included trials; primary versus secondary prevention trials, trials with balanced versus trials with unbalanced co-interventions, and trials with restriction of daily calorie intake versus trials without restriction of daily calorie intake. We used Stata 10.1 (StataCorp LP, College Station, Tex) for data analysis.

RESULTS

Seven trials including a total of 3650 patients fulfilled our inclusion criteria (Figure 1). One of the identified trials was the Indo-Mediterranean Diet Heart Study.[21] Because the validity of this trial, which includes 1000 patients, has been seriously questioned,[22] we did not include the results of this trial in our primary analysis. However, because the paper has never been officially retracted, we conducted a sensitivity analysis including this trial to evaluate whether the results of our meta-analysis would change after its inclusion. We did not include the Lyon Diet Heart Study[23] in our analyses because changes in cardiovascular risk factors were only assessed on a per-protocol, but not on an intention-to-treat, basis.

The relatively small number of included trials precluded a sensitive exploration of publication bias, although the plots of standardized effect against precision for all outcomes did not indicate evidence for such a bias ($P > .1$).[18]

Characteristics and methodological quality of included trials are summarized in Table 1.[6,13,17,21,24-29] Follow-up of included trials was 2 years in 4 trials[17,24-26] and 4 years in one trial.[27] The Predimed trial[6] is still ongoing and is planned to have a mean follow-up of 6 years; we included 2-year follow-up data of this trial in our meta-analysis except for laboratory analyses, which were measured after only 1 year of follow-up and pooled with the 2-year lipid values of the other trials (for further details of included trials see Appendix 1, online).

Baseline characteristics of included individuals are summarized in Table 2. Mean age of enrolled patients ranged from 35 to 68 years. Mean body mass index of included subjects ranged from 29 to 35 kg/m^2. There was only one pure secondary prevention trial,[26] and only one more trial included individuals with established cardiovascular disease

Table 1 Characteristics of Included Trials

Study (First Author, Year)	Primary/Secondary Prevention and Inclusion Criteria	Recruitment Period and Place	Follow-up (Years)	Caloric Restriction	Recommendations for Mediterranean Diet	Recommendations for Low-fat Diet	Co-interventions	Reported Concealed Allocation/ Blinded Assessors/Loss to Follow-up <10%, % Follow-up
Esposito, 2003[17]	Primary prevention: Obese premenopausal women (20-46 years), <1 hour of physical activity per week.	2/1999 to 2/2002; Outpatient Department of the Division of Metabolic Diseases, Second University of Naples, Italy	2	MD group only (mean caloric intake ≤1300 kcal/day first year, ≤1500 kcal/day year)	50%-60% carbohydrates; 15%-20% proteins; <30% total fat, <10% saturated fat; 10%-15% monounsaturated fat, 5%-8% polyunsaturated fat; 18 g of fiber per 1000 kcal[28]	<30% of daily caloric intake from fat	MD group: Individualized program to reduce dietary calories, to set personal goals and optimize self-monitoring, monthly sessions with nutritionist and exercise trainer in the first year and offer of behavioral and psychological counseling LF group: None	Yes/Yes (for laboratory values)/Yes, 93%
Esposito, 2004[24]	Primary prevention: Sedentary individuals (<1 hour of physical activity per week) with metabolic syndrome as defined by the Adult Treatment Panel III criteria *	6/2001 to 1/2004; Outpatient Department of the Division of Metabolic Diseases, Second University of Naples, Italy	2	No	50%-60% carbohydrates;15%-20% proteins; <30% total fat, <10% saturated fat; <300 mg of cholesterol per day; ≥250-300 g fruits, ≥125-150 g of vegetables, ≥25-50 g walnuts, encouraged to eat 400 g of whole grain/day, increase of intake of olive oil	50%-60% of calorie intake from carbohydrates, 15%-20% from proteins, <30% from total fat	MD group: Individualized program to reduce dietary calories, to set personal goals and optimize self-monitoring, monthly sessions with nutritionist in the first year LF group: None	No/No/Yes, 91%
Shai, 2008[25]	Primary and secondary (40% of included individuals) prevention: Obese (BMI >27 kg/m^2) patients (40-65 years), or type 2 diabetes or coronary heart disease (independent of age and BMI)	7/2005 to 6/2007; Workplace at research center in Dimona, Israel	2	Yes, both groups (mean caloric intake ≤1500 kcal/day for women, ≤1800 kcal/day for men)	≤35% of calories from fat (main source of fat 30-45 g of olive oil and <20 g of nuts/day); diet rich in vegetables, low in red meat (poultry and fish replacing beef and lamb)	30% of calories from fat, 10% from saturated fat, <300 mg of cholesterol/day; low-fat grains, vegetables, fruits and legumes; limit additional fats, sweets and high-fat snacks.	None	Yes/Yes/No, 88%

Table 1 Continued

Study (First Author, Year)	Primary/Secondary Prevention and Inclusion Criteria	Recruitment Period and Place	Follow-up (Years)	Caloric Restriction	Recommendations for Mediterranean Diet	Recommendations for Low-fat Diet	Co-interventions	Reported Concealed Allocation/ Blinded Assessors/Loss to Follow-up <10%, % Follow-up
Tuttle, 2008[26]	Secondary prevention: Confirmed diagnosis of first MI (<6 weeks)	7/2000 to 6/2005; Heart Institute of Spokane, WA, USA	2	No	I ≤200 mg of cholesterol/day; ≤7% from saturated fat calories; increased intake of omega-3 fatty acids (>0.75% of calories) and mono-unsaturated fat (20%-25% of calories); cold-water fish 3-5 times/week and oils from olives, canola, and soybeans	American Heart Association Step II diet: ≤200 mg of cholesterol/day, ≤7% from saturated fat calories	None	Yes/Yes/Yes, 62%
Estruch, 2008 (Predimed study)[6]	Primary prevention: Type 2 diabetes or ≥3 cardiovascular risk factors, 55-80 years	From 10/2003 to 10/2004; Primary care centers of 10 teaching hospitals in 8 Spanish cities	Ongoing, 6 years planned (1-year data used for lab. values, 2-year for other risk factors)	No	Virgin olive oil for cooking and dressings; ≥2 servings/day of vegetables; ≥3 servings/week of fish or seafood; ≥3 servings/week of nuts or seeds; white meat (poultry or rabbit) instead of red or processed meat; ≥7 glasses of wine/week; ≥2 dishes with salsa/week	American Heart Association Dietary Guidelines 2000[13]	MD group: Quarterly dietary group sessions and free provision of virgin olive oil or mixed nuts LF group: None	Yes/No/Yes, 95%
Esposito, 2009[27]	Primary prevention: Newly diagnosed type 2 diabetes, BMI >25 kg/m^2, 30-75 years, <1 hour of physical activity per week	1/2004 to 9/2008; Research Center Diabetes Clinic of the Azienda Ospedalaria Universitaria, Naples, Italy	4 (2-year data used for this meta-analysis)	Yes, both groups (mean caloric intake ≤1500 kcal/day for women, ≤1800 kcal/day for men)	<50% of calorie intake from carbohydrates, rich in vegetables and whole grains, low in red meat (replaced by poultry and fish), ≤30% from fat (main source 30-50 g olive oil)	<30% of total calorie intake from fat, <10% from saturated fat, rich in whole grains; American Heart Association Dietary Guidelines 2000[13]	None	Yes/Yes (for laboratory values)/Yes, 91%
Singh, 2002[21]	Primary and secondary prevention: ≥1 cardiovascular risk factor or type 2 diabetes or angina pectoris or previous MI	NA	2	No	<30% of total calorie intake from fat, <10% from saturated fat, <300 mg of cholesterol/day; ≥400-500 g of fruits, vegetables and nuts/d; 400-500 g of whole grains, legumes, rice, maize and wheat/d; 3-4 servings of mustard seed or soy bean oil /day	<30% of total calorie intake from fat, <10% from saturated fat, <300 mg of cholesterol/day; (NCEP step I diet)[29]	None	No/No/Yes, 98%

BMI = body mass index; LF = low-fat diet; MD = Mediterranean diet; MI = myocardial infarction; NA = not available; NCEP = National Cholesterol Education program.

*Three or more of the following criteria: abdominal adiposity (waist circumference >102 cm for men or >88 cm for women); high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women; hypertriglyceridemia (≥150 mg/dL); blood pressure ≥130/85 mm Hg; impaired glucose homeostasis (fasting plasma glucose ≥110 mg/dL).

Table 2 Characteristics of Included Individuals at Baseline

Study (First Author, Year)	No. Randomized		Mean Age, Years		Male No (%)		Mean Body Weight, kg		Mean BMI, kg/m^2		Hypertension No. (%)		Diabetes No. (%)		Dyslipidemia No. (%)		Current Smokers No. (%)		Coronary Artery Disease No. (%)	
	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF
Esposito, 2003[17]	60	60	34	35	0	0	94	95	35	35	0	0	0	0	NA	NA	0	0	0	0
Esposito, 2004[24]	90	90	44	44	49 (54)	50 (56)	78	77	28	28	NA	NA	NA	NA	NA	NA	0	0	0	0
Shai, 2008[25]	109	104	53	51	89 (82)	89 (86)	91	91	31	31	37 (34)	23 (22)	15 (14)	12 (12)	29 (27)	28 (27)	16 (15)	19 (18)	46 (42)	38 (37)
Tuttle, 2008[26]	51	50	58	58	41 (80)	34 (68)	90	91	29	30	22 (43)	25 (50)	10 (20)	10 (20)	NA	NA	13 (25)	15 (30)	51 (100)	50 (100)
Estruch, 2008 (Predimed study)[6]	1223	598	68	68	563 (46)	305 (51)	75	76	29	30	978 (80)	484 (81)	599 (49)	281 (47)	807 (66)	395 (66)	171 (14)	84 (14)	0	0
Esposito, 2009[27]	108	107	52 (10)	52 (11)	54 (50)	52 (49)	86 (10)	86 (10)	30 (3)	30 (4)	26 (24)	25 (23)	108 (100)	107 (100)	16 (15)	17 (16)	23 (21)	22 (21)	NA	NA
Singh, 2002[21]*	499	501	49 (10)	48 (9)	454 (91)	441 (88)	66 (8)	66 (7)	24 (3)	24 (2)	195 (39)	175 (35)	95 (19)	115 (23)	359 (72)	371 (74)	254 (51)	220 (44)	289 (58)	296 (59)

LF = low-fat diet; MD = Mediterranean diet; NA = not available; SD = standard deviation.
*The results of this trial were only used in sensitivity analyses.

(40% of included individuals).[25] All but one trial directed their interventions to individuals consenting to actively adopt diet changes in free-living individuals.[25] In the Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial,[25] meals were provided during lunch in the self-service cafeteria of a workplace at a research centre in Israel. Two trials restricted calorie intake in both groups,[25,27] one trial restricted calories only in subjects randomized to a Mediterranean diet;[17] in all other trials, calorie intake was not restricted in either of the 2 groups.

Persistence on diet varied between 85% and 95% in subjects assigned to Mediterranean diets and from 78% to 93% in subjects assigned to low-fat diets. Baseline and mean changes in dietary intake between baseline and 2-year follow-up are summarized in Table 3. Baseline values and mean changes in cardiovascular risk factors from baseline to 2-year follow-up are presented in Appendix 2, online.

Unbalanced Co-interventions among Included Trials

In 2 trials,[17,24] only participants randomized to the Mediterranean, but not the low-fat, group were offered specific individualized programs. In one of these trials,[17] the level of physical activity increased more in the Mediterranean (from 64 to 175 minutes per week) than in the low-fat diet group (from 71 to 102 minutes per week) ($P = .009$). In the Predimed study,[6] only participants randomized to the Mediterranean groups received individual motivational interviews and group educational sessions on a quarterly basis, and either 30 g per day of mixed nuts or 1 L of olive oil per week for free. In 3 trials,[25-27] there was no difference in trial design between participants assigned to Mediterranean or low-fat diets.

Body Weight, Body Mass Index, and Waist Circumference

Body weight, body mass index, and waist circumference decreased more in subjects randomized to Mediterranean diets than in subjects randomized to low-fat diets. After 2 years, the weighted mean difference (WMD) in body weight between subjects randomized to Mediterranean and low-fat diets was −2.2 kg (95% confidence interval [CI], −3.9 to −0.6, P for heterogeneity <.001, I^2 = 97%), the WMD in body mass index −0.6 kg/m^2 (95% CI, −1 to −0.1, P for heterogeneity <.001, $I^2 = 94\%$), and the WMD in waist circumference −0.9 cm (95% CI, −2-0.2, P for heterogeneity <.001, $I^2 = 92\%$) (Figure 2).

Blood Pressure

Both systolic and diastolic blood pressure values decreased more favorably in subjects randomized to Mediterranean diets than in subjects randomized to low-fat diets (Figure 2). The WMD for systolic blood pressure was −1.7 mm Hg (95% CI, −3.4 to −0.1, P for heterogeneity <.001, $I^2 = 89\%$), and for diastolic blood pressure −1.5 mm Hg (95% CI, −2.1 to −0.8, P for heterogeneity = .03, $I^2 = 60\%$) (Figure 2).

Table 3 Baseline and Mean Changes in Dietary Intake between Baseline and 2-Year Follow-up

Study (First Author, Year)	Baseline Energy Intake (kcal/day)		Δ-Energy (kcal/day)		Baseline Protein Intake (in % of Total Calories)		Δ-Protein (% of Total Calories)		Baseline Carbohydrate Intake (in % of Total Calories)		Δ-Carbo-hydrates (% of Total Calories)		Baseline Fat Intake (in % of Total Calories)		Δ-Fat (% of Total Calories)		Baseline Saturated Fat Intake (in % of Total Calories)		Δ-Saturated Fat (% of Total Calories)	
	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF	MD	LF
Esposito, 2003[17]	2070	2100	−420	−110	14	17	3	0.5	58	55	−3	−1	28	28	0	1	12	8	−4	−0.5
Esposito, 2004[24]	2235	2065	−170	−70	14	14	0.3	0.1	57	58	0.7	0.1	29	28	−1	0.4	13	8	−5	0.3
Shai, 2008[25]	NA	NA	−372	−573	18	18	0.4	0.8	52	52	−1.3	−1.1	32	31	1.4	−1.4	10	10	−0.1	−0.1
Tuttle, 2008[26]	1759	1811	62	3	18	18	0	−1	52	53	2	1	30	27	−0.5	2.4	9	8	−0.6	0.1
Estruch, 2008 (Predimed study)[6]	2378	2264	−1	−164	17	17	−0.1*	0.2*	40	42	−1.1*	1*	40	39	1.8*	−1.1*	10	10	−0.6*	−0.5*
Esposito, 2009[27]	2345	2304	−505	−470	17	16	1.4	1.7	52	52	−8.9	0.4	31	32	NA	NA	10	10	−0.3	−1
Singh, 2002[21]†	2159	2170	−144	−81	15	15	−0.6	0.3	57	57	2.5	−0.9	28	28	−1.5	1.1	13	13	−4.8	−0.4

LF = low-fat diet; MD = Mediterranean diet; NA = not available.
*Mean changes in dietary intake from baseline to 1-year follow-up.
†The results of this trial were only used in sensitivity analyses.

Lipid Values

Total cholesterol and triglyceride values changed more favorably in subjects randomized to Mediterranean diets than in subjects randomized to low-fat diets (WMD for total cholesterol −7.4 mg/dL (95% CI, −10.3 to −4.4, *P* for heterogeneity = .002, $I^2 = 73\%$) (Figure 3). There were no statistically significant differences in low-density lipoprotein cholesterol (WMD −3.3 m g/dL; 95% CI, −7.3-0.6; *P* for heterogeneity = .3, $I^2 = 23\%$) or HDL cholesterol (WMD 0.9 mg/dL; 95% CI, −1.9-3.8, *P* for heterogeneity < 0.001, $I^2 = 99\%$).

High-sensitivity C-reactive Protein

High-sensitivity C-reactive protein (Hs-CRP) decreased more favorably in subjects randomized to Mediterranean diets than in subjects randomized to low-fat diets. The WMD for hs-CRP was −1.0 mg/L (95% CI, −1.5 to −0.5, *P* for heterogeneity <.001, $I^2 = 82\%$) (Figure 3).

Fasting Plasma Glucose and Serum Insulin

Plasma glucose decreased more favorably in subjects randomized to Mediterranean diets than in subjects randomized to low-fat diets (WMD −3.8 mg/dL, 95% CI, −7.0 to −0.6, *P* for heterogeneity = .18, $I^2 = 97\%$) (Figure 3). There was no significant difference in serum insulin between the 2 groups (WMD −1.1 μU/mL, 95% CI, −2.9 to 0.8, *P* for heterogeneity <.001, $I^2 = 98\%$).

Clinical Outcomes

Only one trial reported clinical outcomes.[26] There were 3 nonfatal myocardial infarctions and 1 stroke in the low-fat diet group, and 1 nonfatal myocardial infarction and 3 strokes in the Mediterranean diet group. No deaths were reported.

Sensitivity Analyses

There were no qualitative changes in the point estimates of all analyses when we restricted the analyses to the trials with reported concealed treatment allocation or blinded outcome assessment, or when we included the results of the trial by Singh et al[21] in the meta-analysis.

Point estimates for most outcomes consistently favored subjects randomized to Mediterranean diets both in primary and secondary prevention trials. Point estimates for differences in HDL cholesterol favored Mediterranean diets only in primary, but not in secondary prevention subjects, but neither of these changes reached statistical significance.

When we compared trials with balanced[25-27] versus unbalanced[6,17,24] co-interventions, and trials with restriction[25,27] versus no restriction of daily calorie intake in both groups,[6,17,26] we found no qualitative differences in the point estimates of the mean changes of any of the cardiovascular risk factors. There was no longer evidence of heterogeneity when restricting analyses to trials with balanced co-interventions or to trials with restriction of daily

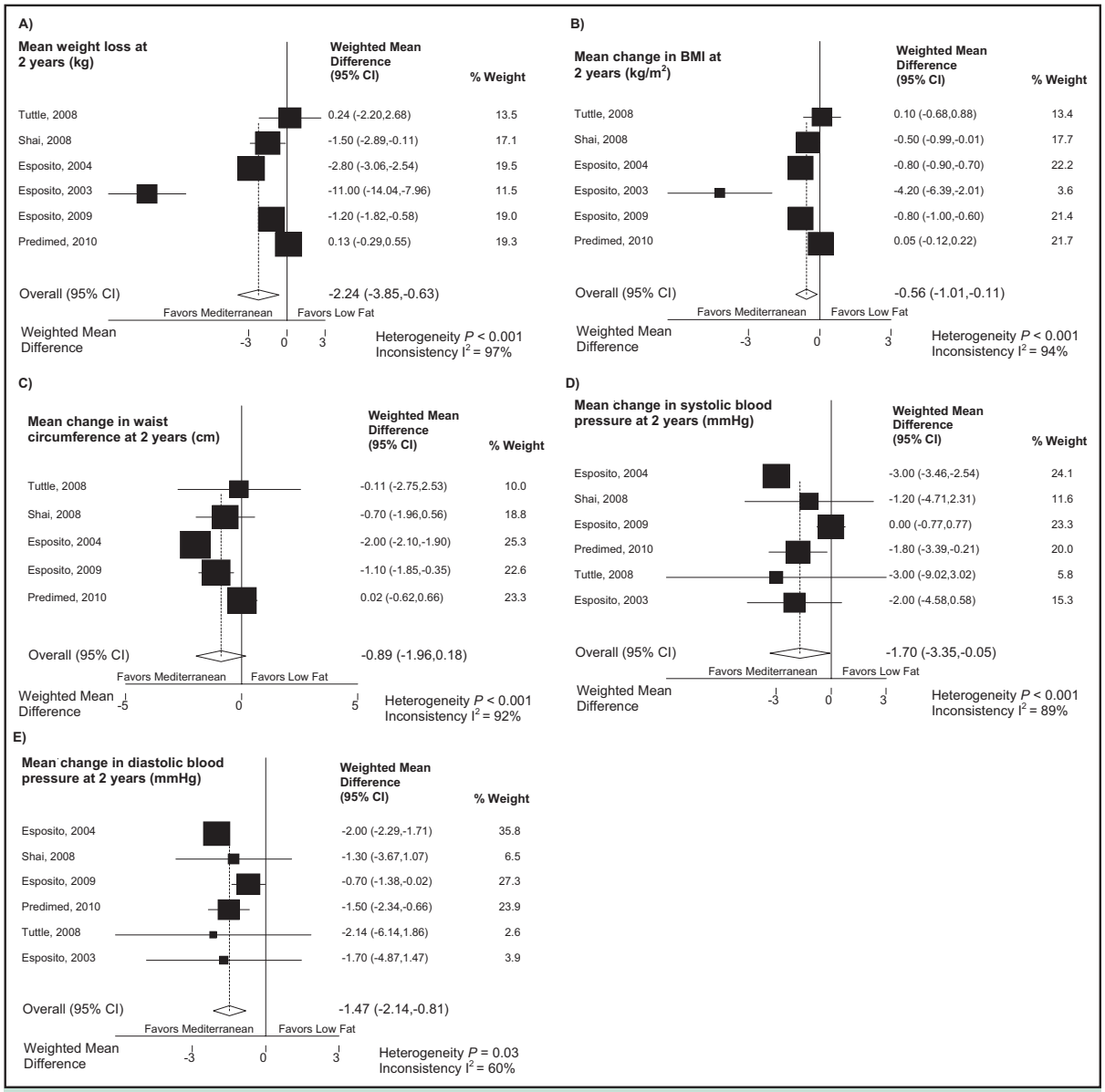

Figure 2 Mean changes in body weight, body mass index, waist circumference, systolic and diastolic blood pressure after 2 years of follow-up in randomized controlled trials comparing Mediterranean to low-fat diets. BMI = body mass index; CI = confidence interval.

calorie intake in both groups, except for body mass index, waist circumference, and HDL cholesterol.

DISCUSSION

In this meta-analysis of all available randomized controlled trials comparing Mediterranean with low-fat diets in overweight/obese individuals, most cardiovascular risk factors and vascular inflammatory markers improved more favorably in individuals allocated to a Mediterranean diet. The observed differences for the individual risk factors were modest, but the direction of the changes consistently favored Mediterranean over low-fat diets across outcomes. The observed heterogeneity across individual trials could be eliminated by restricting analyses to trials with balanced trial design or trials with restriction of daily calorie intake in both diet groups. Evidence on clinical outcomes remains inconclusive because only one trial reported clinical events.

The present study has strengths and limitations. We carried out a comprehensive literature search for randomized

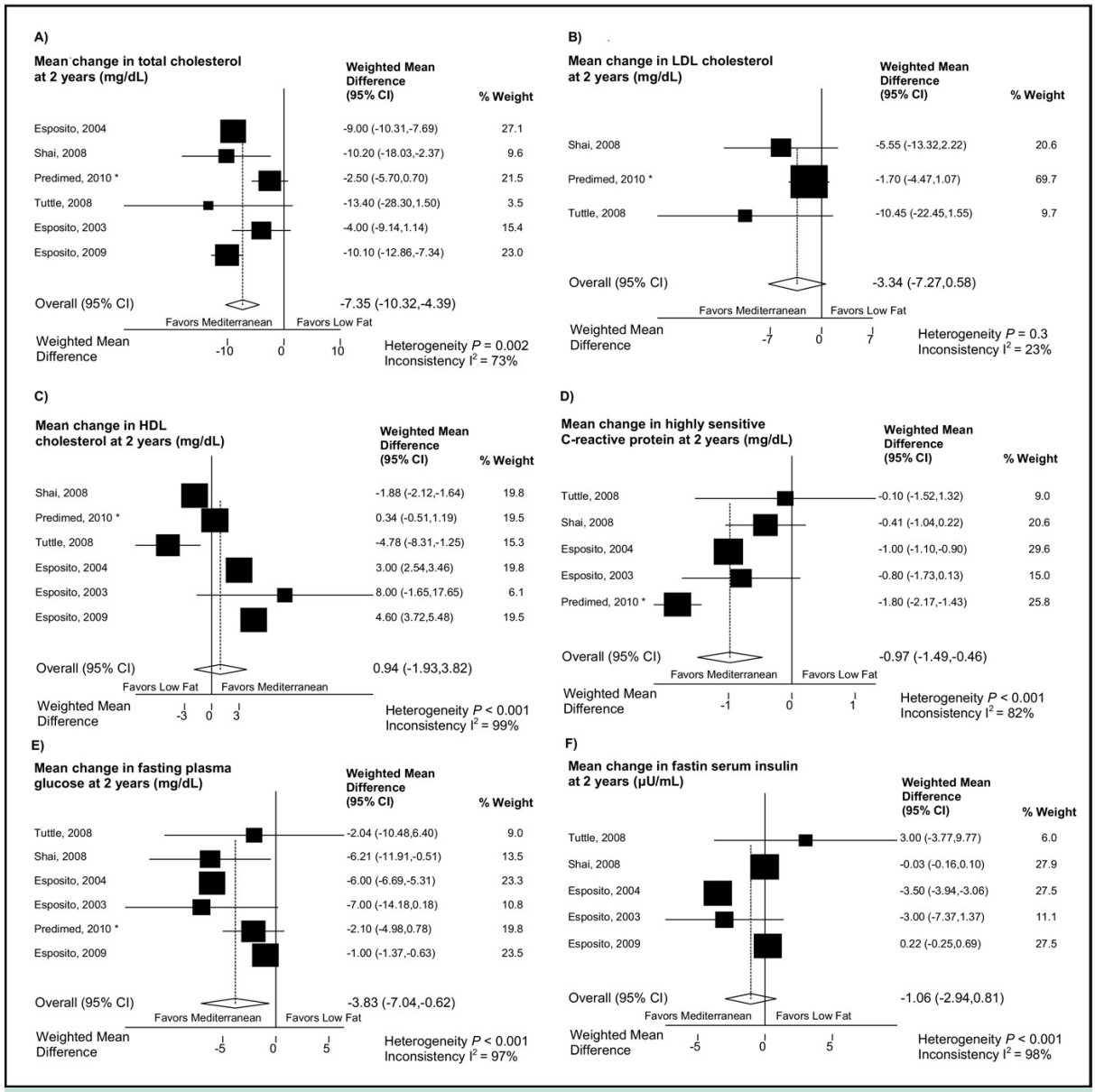

Figure 3 Mean changes in cholesterol values, high-sensitivity C-reactive protein, fasting plasma glucose, and serum insulin after 2 years of follow-up in randomized controlled trials comparing Mediterranean to low-fat diets. *1-year follow-up data. CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

controlled trials reporting intention-to-treat data in individuals at increased cardiovascular risk, allowing us to assess the impact of the 2 diets on a broad spectrum of cardiovascular risk factors. Although formal testing did not indicate any publication bias, such bias cannot be definitely ruled out due to the relatively small number of trials included and the low power of any test to detect publication bias. Although only 2 of the included trials reported blinded outcome assessment for all outcomes, the quality of the included trials was reasonably good, with all but one trial each reporting concealed treatment allocation and almost complete follow-up of >90%. In addition, the results of our analyses proved to be robust across various sensitivity analyses accounting for differences in trial quality, population studied, and co-interventions.

Our analysis has some limitations. It is based on only 6 trials, with 3 trials published by the same group of authors.[17,24,27] We observed significant heterogeneity for most

outcomes analyzed. However, when we restricted analyses to trials with balanced co-interventions, most cardiovascular risk factors were modified more favorably in individuals on Mediterranean diets and there was no longer evidence of heterogeneity for cardiovascular risk factors, with the exception of body mass index, waist circumference, and HDL cholesterol. The same was true when restricting analyses to trials with restricted daily calorie intake in both groups.

Only one of the identified trials was a pure secondary prevention trial,[26] so our results may be limited to the modification of cardiovascular risk factors in primary prevention. Because sensitivity analysis did not reveal any major differences in changes of cardiovascular risk factors between primary and secondary prevention trials, there is a suggestion that Mediterranean diets are superior to low-fat diets not only in primary, but also in secondary prevention.

None of the included trials addressed participants' quality of life while adhering to the prescribed diet. Thus, we lack information about potential differences in quality of life among participants randomized to Mediterranean or low-fat diets. However, rates of persistence on Mediterranean and low-fat diets were similar, making large differences in quality of life unlikely.

The methodology of our meta-analysis did not allow us to identify any individual component of Mediterranean diets that may be particularly beneficial in modifying cardiovascular risk factors. The results of our meta-analysis imply that heterogeneous patterns of Mediterranean diets are effective in lowering cardiovascular risk focusing on a specific type of a diet as a whole rather than on individual diet components.

All but one trial included in our meta-analysis were conducted in Mediterranean countries.[26] This may add to the strengths of our results because individuals randomized to low-fat diets may have followed a Mediterranean-style diet to some extent. On the other hand, it raises the question about the generalizability of our results to non-Mediterranean countries.

None of the included trials was powered to detect any differences in clinical outcomes between the 2 diets. However, the findings of our meta-analysis are supported by many prospective cohort studies demonstrating a beneficial effect of Mediterranean diets on cardiovascular outcomes.[30] Evidence from cohort studies studying self-elected eating patterns may, however, be biased by confounding.[31] In order to rule out potential confounding, there is a need for unbiased evidence from randomized controlled trials demonstrating the benefit of a particular diet on patient-important outcomes. So far, only 2 secondary and no primary prevention trials comparing the effects of Mediterranean with low-fat diets on clinical outcomes have been published. Unfortunately, serious concern has been raised about the integrity of the principal investigator of one of these trials.[22] In the other trial, the Lyon Diet Heart Study from 1994,[32] the combined primary endpoint of cardiac death and nonfatal myocardial infarction was reduced by an impressive 73% (95% CI, 41%-88%) after a mean follow-up of 27 months. The Lyon Diet Heart Study was stopped early for apparent benefit after only 41 primary outcome events. Early stopping for benefit may result in an overestimate of the net health benefit.[15] In addition, hardly any of the patients in the Lyon Diet Heart Study were on statin therapy at the time. It thus remains unclear whether the benefit of Mediterranean diets persists with statin therapy in patients at high risk of cardiovascular events.

Given the limitations of our meta-analysis and of the 2 secondary prevention trials, more evidence is needed before calling for the implementation of Mediterranean diet in individuals at increased vascular risk from a public health perspective. The observed beneficial results of Mediterranean diets on cardiovascular risk factors and cardiovascular morbidity and mortality should be reproduced in at least one adequately powered cardiovascular disease prevention trial.

In summary, our meta-analysis suggests a favorable effect of Mediterranean, as compared with low-fat, diets on most cardiovascular risk factors and inflammatory markers. Although the observed effects on individual risk factors were modest, the consistent benefit over a broad range of cardiovascular risk factors may eventually lead to a reduction in cardiovascular outcomes.

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APPENDIX 1

Characteristics of Included Trials

Characteristics of included trials are summarized in Table 1. One trial included patients with established cardiovascular disease only.[26] One trial enrolled subjects who were either obese, or had type 2 diabetes or established cardiovascular disease.[25] Four trials were primary prevention trials including either obese, sedentary, postmenopausal women,[17] sedentary subjects with the metabolic syndrome,[24] overweight subjects with newly diagnosed type 2 diabetes[27] or individuals at high cardiovascular risk (either type 2 diabetes or 3 or more cardiovascular risk factors).[6] In the latter trial, subjects randomized to a Mediterranean diet were randomized to provision of either a free liter of virgin olive oil per week or provision of free nuts (30g/day). For the purpose of this analysis, we collapsed the 2 groups into one without differentiating between subjects assigned free virgin olive oil or free nuts.

Follow-up of included trials was 2 years in 4 trials,[17,24-26] and 4 years in one trial.[27] The Predimed trial[6] is still ongoing and is planned to have a mean follow-up of 6 years; we included 2-year follow-up data of this trial in our meta-analysis, except for laboratory analyses, which were measured after only 1 year of follow-up and pooled with the 2-year lipid values of the other trials.

Quality of the Trials

Assignment of study participants was concealed in 5 trials,[6,17,25-27] and possibly concealed in one trial.[24] All trials used an open design. Blinded outcome assessment for all outcomes was reported in 2 trials,[25,26] and only for laboratory analyses in 2 trials.[17,27] There was no blinded outcome assessment in one trial,[24] and one trial[6] did not mention whether blinded outcome assessment was performed for any of the outcomes. Full description of losses to follow-up and withdrawals was reported in one trial,[25] partially reported in 3 trials,[17,26,27] and not reported in 2 trials.[6,24] Four of the 6 included trials[6,17,24,27] had a loss to follow-up <10%. No trial was stopped early for benefit. The 2 reviewers were in full agreement when rating the methodological quality of included trials. In 3 trials[6,17,24] the method used to account for missing data remained unclear, 2 trials[25,27] used the last value carried forward method, and one trial a multilevel random effects model.[26]

APPENDIX 2

Baseline and Mean Changes (Standard Deviations) in Outcomes between Baseline and 2-year Follow-up

	Mediterranean Diet		Low-fat Diet	
Study	Baseline (SD)	Mean change (SD)	Baseline (SD)	Mean change (SD)
Weight (kg)				
Esposito, 2003[17]	95 (9.4)	−14 (8.5)	94 (9.2)	−3 (8.5)
Esposito, 2004[24]	78 (8.0)	−4.0 (1.1)	77 (8.0)	−1.2 (0.6)
Shai, 2008[25]	91 (14)	−4.4 (6.0)	91 (12)	−2.9 (4.2)
Tuttle, 2008[26]	90 (17)	−0.75 (6.5)	91 (18)	−0.99 (6.0)
Predimed, 2008[6]	75 (11)	−0.07 (4.2)	76 (11)	−0.2 (4.4)
Esposito, 2009[27]	86 (10)	−4.9 (2.5)	86 (10)	−3.7 (2.1)
Singh, 2002[21]*	66 (7.5)	−3.5 (5.2)	66 (7.3)	−0.9 (2.7)
Body Mass Index (kg/m²)				
Esposito, 2003[17]	35 (2.3)	−5.2 (8.1)	34.7 (2.4)	−1 (3.1)
Esposito, 2004[24]	28 (3.4)	−1.2 (0.3)	28 (3.2)	−0.4 (0.4)
Shai, 2008[25]	31 (4.1)	−1.5 (2.2)	31 (3.2)	−1 (1.4)
Tuttle, 2008[26]	29 (5.0)	−0.2 (2.1)	30 (5.0)	−0.3 (1.9)
Predimed, 2008[6]	29 (3.3)	−0.03 (1.6)	30 (3.6)	−0.08 (1.8)
Esposito, 2009[27]	30 (3.4)	−1.9 (0.9)	30 (3.6)	−1.1 (0.6)
Singh, 2002[21]*	24 (3.0)	−1.3 (2)	24 (2.3)	−0.3 (1)
Waist circumference (cm)				
Esposito, 2003[17]	NA	NA	NA	NA
Esposito, 2004[24]	92 (9.0)	−2.0 (0.5)	93 (10)	0 (0.01)
Shai, 2008[25]	106 (9.1)	−3.5 (5.1)	105 (9.2)	−2.8 (4.3)
Tuttle, 2008[26]	101 (15)	−0.18 (6.4)	103 (14)	−0.72 (7.1)
Predimed, 2008[6]	100 (9.5)	−0.83 (6.4)	100 (10)	−0.85 (6.7)
Esposito, 2009[27]	98 (10)	−4.4 (2.8)	98 (10)	−3.3 (2.8)
Singh, 2002[21]*	NA	NA	NA	NA
Systolic blood pressure (mm Hg)				
Esposito, 2003[17]	124 (8.5)	−3.0 (8.7)	123 (7.9)	−1.0 (5.3)
Esposito, 2004[24]	134 (9.0)	−4.0 (2.0)	136 (10)	−1.0 (1.0)
Shai, 2008[25]	133 (14)	−5.5 (14.3)	130 (13)	−4.3 (11.8)
Tuttle, 2008[26]	120 (18)	1.6 (14.7)	119 (15)	4.6 (16.1)
Predimed, 2008[6]	152 (18)	−3.4 (15.9)	151 (19)	−1.6 (16.4)
Esposito, 2009[27]	139 (12)	−4.5 (3.7)	140 (12)	−4.5 (1.7)
Singh, 2002[21]*	132 (17)	−5.3 (10.4)	131 (17)	−2.2 (5.2)
Diastolic blood pressure (mm Hg)				
Esposito, 2003[17]	85 (4.7)	−3 (8.7)	85 (4.9)	−1.3 (9)
Esposito, 2004[24]	85 (6.0)	−3 (1)	86 (7.0)	−1 (1)
Shai, 2008[25]	81 (9.2)	−2.2 (9.5)	79 (9.1)	−0.9 (8.1)
Tuttle, 2008[26]	73 (11)	−0.74 (11.3)	71 (8.0)	1.4 (9.1)
Predimed, 2008[6]	85 (9.6)	−3.4 (8.0)	84 (9.8)	−1.9(8.8)
Esposito, 2009[27]	87 (8.0)	−3.2 (2.8)	86 (8.0)	−2.5 (2.3)
Singh, 2002[21]*	86 (10)	−2.7 (6.8)	86 (9.0)	−1.1 (3.5)
Total cholesterol (mg/dL)				
Esposito, 2003[17]	197 (23)	−4.0 (15)	193 (23)	0 (14)
Esposito, 2004[24]	199 (34)	−11 (6)	193 (32)	−2.0 (2.0)
Shai, 2008[25]	213 (NA)	−7.9 (27)	201 (NA)	2.3 (31)
Tuttle, 2008[26]	161 (36)	−3.7 (35)	161 (38)	9.7 (42)
Predimed, 2008[6]	213 (39)	−3.6 (34)	212 (38)	−1.1 (32)
Esposito, 2009[27]	220 (35)	−18 (12)	217 (35)	−7.7 (7.7)
Singh, 2002[21]*	222 (38)	−26 (32.8)	223 (38)	−7.4 (9.3)
Low-density lipoprotein cholesterol (mg/dL)				
Esposito, 2003[17]	NA	NA	NA	NA
Esposito, 2004[24]	NA	NA	NA	NA
Shai, 2008[25]	123 (34)	−5.6 (27)	117 (36)	−0.05 (31)
Tuttle, 2008[26]	93 (28)	−0.45 (30)	93 (32)	10 (32)
Predimed, 2008[6]	131 (32)	-3 (28)	130 (32)	−1.3 (29)
Esposito, 2009[27]	NA	NA	NA	NA
Singh, 2002[21]*	141 (30)	−−24.2 (18)	137 (26)	−6.1 (9.4)
High-density lipoprotein cholesterol (mg/dL)				
Esposito, 2003[17]	46 (10)	8 (27.9)	46 (10)	0 (26)
Esposito, 2004[24]	41 (9.0)	4 (2.0)	42 (9.0)	1.0 (1.0)
Shai, 2008[25]	39 (9.4)	7.26 (0.79)	39 (9.6)	9.14 (0.97)
Tuttle, 2008[26]	38 (7.0)	0.82 (8.2)	36 (9.0)	5.6 (9.8)
Predimed, 20086	56 (13)	0.44 (8.9)	55 (12)	0.1 (8.6)
Esposito, 2009[27]	43 (7.7)	4.6 (4.6)	43 (7.7)	0 (0.8)
Singh, 2002[21]*	45 (10)	1.4 (7.0)	44 (5.8)	−1.5 (1.5)

	Mediterranean Diet		Low-fat Diet	
Study	Baseline (SD)	Mean change (SD)	Baseline (SD)	Mean change (SD)
Triglycerides (mg/dL)				
Esposito, 2003[17]	142 (44)	−19 (70)	142 (53)	−8.0 (59)
Esposito, 2004[24]	168 (57)	−18 (8.0)	172 (54)	1.0 (3.0)
Shai, 2008[25]	174 (68)	−21.8 (62)	157 (62)	−2.7 (91)
Tuttle, 2008[26]	143 (71)	−19 (48)	183 (196)	−50 (189)
Predimed, 2008[6]	133 (66)	−2.0 (59)	143 (81)	−2.0 (62)
Esposito, 2009[27]	168 (71)	−42 (46)	168 (71)	−25 (37)
Singh, 2002[21]*	163 (34)	−44.4 (49)	164 (25)	−9.7 (13)
Highly sensitive C-reactive protein (mg/dL)				
Esposito, 2003[17]	3.2 (1.5-8.4)†	−1.1 (3.2)	3.4 (1.4-8.3)†	−0.3 (1.8)
Esposito, 2004[24]	2.8 (0.7-5.4)†	−1.1 (0.4)	2.9 (0.5-5.7)†	−0.1 (0.3)
Shai, 2008[25]	4.6 (3.4)	−0.9 (2.4)	3.6 (2.9)	−0.5 (2.3)
Tuttle, 2008[26]	3.8 (3.9)	−1.5 (3.8)	4.4 (4.6)	−1.4 (3.5)
Predimed, 2008[6]	5.2 (5.1)	−0.1 (3.6)	5.1 (3.6)	1.7 (3.9)
Esposito, 2009[27]	NA	NA	NA	NA
Singh, 2002[21]*	NA	NA	NA	NA
Plasma glucose (mg/dL)				
Esposito, 2003[17]	106 (14)	−9.0 (26)	105 (13)	−2.0 (11)
Esposito, 2004[24]	113 (10)	−8.0 (3.0)	114 (10)	−2.0 (1.5)
Shai, 2008[25]	94 (38)	−2.0 (26)	87 (26)	4.2 (15)
Tuttle, 2008[26]	92 (43)	−2.7 (25)	94 (34)	−0.7 (18)
Predimed, 2008[6]	119 (41)	−3.3 (24)	120 (38)	−1.2 (32)
Esposito, 2009[27]	162 (34)	−2.1 (1.6)	159 (33)	−1.1 (1.1)
Singh, 2002[21]*	108 (25)	−7.7 (13)	107 (28)	−3.8 (10)
Serum insulin (μU/mL)				
Esposito, 2003[17]	14 (4.0)	−5.0 (16)	14 (4.0)	−2.0 (6.5)
Esposito, 2004[24]	15 (6.0)	−4.0 (1.9)	16 (7.0)	−0.5 (1.0)
Shai, 2008[25]	15 (8.0)	−0.18 (0.5)	13 (6.8)	−0.15 (0.5)
Tuttle, 2008[26]	10 (5.0)	2.2 (9.6)	13 (8.0)	−0.8 (23)
Predimed, 2008[6]	NA	NA	NA	NA
Esposito, 2009[27]	18 (7.2)	−1.8 (1.8)	19 (8.3)	−2.0 (1.8)
Singh, 2002[21]*	NA	NA	NA	NA

SD = standard deviation. SI conversion factors. To convert plasma glucose values to millimoles per liter, multiply by 0.0555. To convert cholesterol values to millimoles per liter, multiply by 0.0259. To convert triglyceride values to millimoles per liter, multiply by 0.0113. To convert serum insulin values to picomoles per liter, multiply by 6.

*The results of this trial were only used in sensitivity analyses.

†Median (25th and 75th percentile).