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The Effect of Mediterranean Diet on Metabolic Syndrome and its Components

A Meta-Analysis of 50 Studies and 534,906 Individuals

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Objectives The aim of this study was to meta-analyze epidemiological studies and clinical trials that have assessed the effect of a Mediterranean diet on metabolic syndrome (MS) as well as its components.

Background The Mediterranean diet has long been associated with low cardiovascular disease risk in adult population.

Methods The authors conducted a systematic review and random effects meta-analysis of epidemiological studies and randomized controlled trials, including English-language publications in PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials until April 30, 2010; 50 original research studies (35 clinical trials, 2 prospective and 13 cross-sectional), with 534,906 participants, were included in the analysis.

Results The combined effect of prospective studies and clinical trials showed that adherence to the Mediterranean diet was associated with reduced risk of MS (log hazard ratio: −0.69, 95% confidence interval [CI]: −1.24 to −1.16). Additionally, results from clinical studies (mean difference, 95% CI) revealed the protective role of the Mediterranean diet on components of MS, like waist circumference (−0.42 cm, 95% CI: −0.82 to −0.02), high-density lipoprotein cholesterol (1.17 mg/dl, 95% CI: 0.38 to 1.96), triglycerides (−6.14 mg/dl, 95% CI: −10.35 to −1.93), systolic (−2.35 mm Hg, 95% CI: −3.51 to −1.18) and diastolic blood pressure (−1.58 mm Hg, 95% CI: −2.02 to −1.13), and glucose (−3.89 mg/dl, 95% CI:−5.84 to −1.95), whereas results from epidemiological studies also confirmed those of clinical trials.

Conclusions These results are of considerable public health importance, because this dietary pattern can be easily adopted by all population groups and various cultures and cost-effectively serve for primary and secondary prevention of the MS and its individual components. (J Am Coll Cardiol 2011;57:1299–313) © 2011 by the American College of Cardiology Foundation

The prevalence of the metabolic syndrome (MS) is increasing rapidly throughout the world, in parallel with the increasing prevalence of diabetes and obesity; thus, it is now considered as a major public health problem (1). With the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition, prevalence of the MS in Europe, Asia, Australia, and North and South America ranges between 9.6% and 55.7%; with the World Health Organization (WHO) definition, prevalence ranges between 13.4% and 70.0%; and with the International Diabetes Federation definition, prevalence ranges between 7.4% and 50% (2–4).

Regardless of the true actual figures, there is undoubtedly a dramatic increase of this condition, and therefore, emerging action should be taken to prevent and control its development. Lifestyle interventions, including dietary changes and physical activity, play a crucial role in the prevention of this condition (5). In fact, the NCEP ATP III has already suggested dietary intervention to prevent this epidemic. Diets rich in whole grain cereals, fruits, and vegetables, with low animal-fat consumption, seem to confer the prevention of cardiovascular disease risk factors, like hypertension, hypercholesterolemia, and obesity (6). The Mediterranean diet (MD) is a dietary pattern that has already shown its cardioprotective effects. The MD was first presented by Ancel Keys in the 1960s (7), and it is characterized by high consumption of monounsaturated

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Abbreviations and Acronyms

CVD = cardiovascular disease

HDL = high-density lipoprotein

HOMA-IR = Homeostatic Model Assessment insulin resistance

MD = Mediterranean diet

MS = metabolic syndrome

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

fatty acids, primarily from olives and olive oil, and encourages daily consumption of fruits, vegetables, whole grain cereals, and low-fat dairy products; weekly consumption of fish, poultry, tree nuts, and legumes; a relatively low consumption of red meat, approximately twice/month; as well as a moderate daily consumption of alcohol, normally with meals. The beneficial role of the MD with regard to mortality from all causes, cardiovascular disease (CVD) and cancer (8), as well as obesity and type 2 diabetes (9,10) has already been reported from the results of many epidemiological studies and clinical trials. Major biopathophysiological mechanisms include antioxidant and anti-inflammatory effects of the foods included in the Mediterranean dietary pattern (9,11–17). However, the influence of the MD on the development of the MS has never been extensively studied. Thus, the aim of this work was to perform a systematic review and a meta-analysis of the findings of published original research articles in which the investigators have assessed the effect of a Mediterranean type of diet on the development of the MS as well as on its components.

Methods

Data sources. Original research studies that were published in English until April 30, 2010 were selected through a computer-assisted published data search (i.e., PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials databases). Computer searches used combinations of Medical Subject Headings or other key words relating to the aim of the study (i.e., MD, moderate fat diet, monounsaturated fat diet, MS, syndrome X). Also, specific searches were included: MD and high-density lipoprotein (HDL)-cholesterol, MD and triglycerides, MD and blood pressure, MD and glucose, MD and waist circumference. In addition, the reference list of the retrieved articles was in some cases used to find other articles relevant to the present articles that were not allocated through the searching procedure. The initial search resulted in 48 entries in PubMed on MD and MS, 31 entries on MD and syndrome X, 94 entries on MD and HDL cholesterol, 77 entries on MD and triglycerides, 106 entries on MD and blood pressure, 26 entries on MD and waist circumference, and 92 entries on MD and glucose. The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract, and the full manuscript. For the reports that were not fully available, a copy of the article was requested from the authors.

Study selection. In total, 474 studies that evaluated the effect of an MD on MS and its components were identified. Exclusion criteria with regard to clinical trials included studies that reported lack of randomization, lack of a control diet group, comparison of the MD against the MD plus an additional intervention or intervention without inclusion of all the components of an MD and especially olive oil. Observational studies and clinical trials not published in English and studies that performed a post hoc analysis of previously published studies—already selected for this review—were also excluded. Thus, of the initial 474 studies that were extracted from the search machines, 398 were excluded on the basis of the title or abstract (i.e., irrelevant research hypothesis studied). Of the remaining 76 studies, 24 were excluded for the following reasons: lacking a control group (n = 7), intervention of Mediterranean versus a Mediterranean plus diet (n = 5), not clear MD (n = 6), written in a language other than English (n = 5), and post-hoc analysis (n = 1). Therefore, 52 studies were eligible for inclusion in the meta-analysis. Studies included in the meta-analysis were those that had available results in a form that could be used for the present analysis. When it was necessary, data in the required form were requested from the authors. Overall, 50 studies with a total of 534,906 participants were finally included in this meta-analysis; of these, 2 were prospective, 13 were cross-sectional, and 35 were clinical trials. In addition, for the meta-analysis of the selected studies, the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and QUOROM (Quality of Reporting of Meta-analyses) guidelines have been followed (18,19) (Fig. 1).

Data extraction. The following characteristics were extracted from the original reports with a standardized data extraction form and included in the meta-analysis: design of the study (clinical-trial, cross-sectional, or prospective cohort), lead author, year of publication, country of origin, sample size, mean age and gender of participants, health status, follow-up duration, effect size measurements (i.e., relative risk, odds ratio), and variables that entered into the multivariable model as potential confounding factors.

Two investigators (C.M.K., D.B.P.) collected the relevant reports, whereas 2 other authors independently reviewed the published data (H.M., J.G.), and disagreements were solved by consensus and by the opinion of a fifth author, if necessary. Outcomes of interest were development or progression of the MS and changes in the levels of the main components of the MS: waist circumference (in cm), HDL cholesterol (in mg/dl), triglycerides (in mg/dl), systolic and diastolic blood pressure (in mm Hg), as well as glucose (in mg/dl). When the data were provided in other units (i.e., mmol/l), they were transformed into mg/dl for consistency of the results. Quality of studies was assessed according to the number of participants, the duration of follow-up, and adjustment for potential confounders. Studies with a high number of participants (i.e., >30/group for trials or >1,000 for observational), long dura-

tion of follow-up (>3 months for trials or >1 year for observational), and adjustment for confounding factors (including demographic, anthropometric, and traditional risk factors) were considered to be of high quality. The characteristics of the studies and the diet regimens are shown in Tables 1 and 2.

Statistical analysis. Random effects meta-analysis of the selected studies was applied on the basis of within-study comparisons, thereby avoiding any biases being caused by methodological differences between studies. Each study was represented by a dummy variable, and the use of a random-effects model was possible, because standard errors of the point estimates within studies were provided by the investigators. With regard to the analysis for the MS, each data point consisted of adherence to the MD and the odds ratio or the relative risk (hazard ratio) of having the MS. The estimated models used as dependent variables the (eventual) presence or absence of MS. With regard to the analysis for the components of the syndrome, each data point consisted of adherence to the MD and the difference in mean values and SD, of the group closer to the MD and the group away from the diet for epidemiological studies, while for clinical trials of the difference in mean values and SD after the intervention and at baseline, in the intervention and the control group. The validity of the models was examined with the influence of each separate data point (i.e., study) on the estimated regression coefficients. The latter was assessed with the use of Cook's distance to detect possible outliers. Heterogeneity was assessed with Cochran's Q and I^2 (I^2 ranges between 0% and 100%, with lower values representing less heterogeneity) and evaluated with the chi-square test. To examine the source of heterogeneity, sensitivity analyses were performed according to some characteristics of the studies, such as: country of origin (Mediterranean or not), follow-up time (below or above the median of the clinical trials [i.e., 3 months]), number of participants in clinical trials (below or above the median size [i.e., 66 participants]), recommendation regarding physical activity (yes or no), and quality of intervention (i.e., clinical trials with >30 participants and duration of follow-up >3 months or not). To assess the presence of publication bias, the "funnel plot" was tested. All statistical calculations were performed in NCSS 2004 software (Number Cruncher Statistical Systems, Kaysville, Utah).

Results

Sample sizes of the 15 observational studies that were included in the meta-analysis varied between 328 and 497,308 and, for the 35 clinical trials, varied between 8 and 1,224 participants; 35 of the selected studies were conducted in Mediterranean populations, 6 were performed in U.S. populations (20–25), 7 were performed in northern European populations (26–32), 1 was performed in a European population (Mediterranean and non-Mediterranean) (33), and 1 was performed in an Australian population (34).

MD and MS. Eight studies with 10,399 subjects evaluated the role of the MD on the development or progression of the MS. Five of these 8 studies (35–39) reported a beneficial effect of compliance with the MD, as compared with the control diet (i.e., low-fat diet or usual care) or with low adherence to the Mediterranean dietary pattern. Overall, adherence to the MD was associated with a beneficial effect with regard to the MS in 2 of 2 clinical trials, in 1 of 2 prospective studies, and in 2 of 4 cross-sectional studies, as compared with lower compliance with this pattern or with a control diet (i.e., low-fat diet or usual care) (Fig. 2). The combined effect of both clinical trials and prospective studies was highly protective (log-hazard ratio = −0.69, 95% CI: −1.24 to −1.16), whereas the combined effect of cross-sectional studies was not significant (log-odds ratio = −0.16, 95% CI: −0.49 to 0.17). No publication bias was observed as indicated by the funnel plot (not presented here).

MD and MS components. WAIST CIRCUMFERENCE LEVELS. Three cross-sectional studies (20,33,40) reported a beneficial effect of close adherence to the MD, as compared with low adherence (Table 3). Heterogeneity of the effect measures regarding waist circumference was observed [Cochran's Q = 628.32(4), $p < 0.001$, $I^2 = 99.4\%$]. Moreover, 11 clinical trials with 1,646 subjects (997 assigned to an MD, and 669 assigned to a control diet) evaluated the role of adherence to the MD on waist circumference. Overall, adherence to the MD was associated with a beneficial effect with regard to waist circumference as compared with the control diet (Table 4); but, it should be noted that the previous finding was mainly attributed to 1 study (21) that found a beneficial effect of the MD, as compared with the control diet. No significant heterogeneity of the effect measures regarding waist circumference [Cochran's Q = 8.23(13), $p = 0.83$, $I^2 = \sim 0\%$] was observed.

LIPIDS LEVELS. Three studies (14,20,40) reported a beneficial effect of close adherence to the MD on HDL cholesterol levels, as compared with low adherence. Overall, adherence to the MD was associated with higher HDL-cholesterol levels as compared with the control diet (Table 3). Heterogeneity of the effect measures was observed [Cochran's Q = 52.78(6), $p < 0.001$, $I^2 = 88.6\%$]. Moreover, 29 clinical trials with 3,822 subjects (2,202 assigned to an MD, and 1,903 assigned to a control diet) examined the effect of adherence to the MD on HDL-cholesterol. Seven studies (31,39,41–45) reported a beneficial effect of an MD, as compared with the control diet, whereas 2 studies reported a beneficial effect of a high saturated fat diet as compared with the MD (46,47). Overall, adherence to the MD was associated with higher HDL-cholesterol levels as compared with the control diet (Table 4). Heterogeneity of the effect measures was observed [Cochran's Q = 109.99(40), $p < 0.001$, $I^2 = 63.6\%$].

Concerning triglycerides, 3 observational studies (14,40,48) reported a beneficial effect of MD, as compared with low adherence to this traditional pattern. Overall, adherence to the

Table 1 Characteristics of Observational Studies That Evaluated Effect of MD on Development of MS and/or its Components

First Author (Ref. #)	Country, Year	n	Age (yrs), Sex	Health Status	MD Assessment Tool	MS	Adjustments
Prospective studies (n = 2)							
Tortosa et al. (35)	Spain, 2007	2,563	20–90, M/F	No CVD risk factors	MDS	IDF	Age, sex, PA, smoking, total energy intake
Rumawas et al. (25)	U.S., 2009	1,932	Mean 54, M/F	Without DM Free of MS	MSDPS	NCEP ATP III	Age, sex, BMI at baseline energy intake, smoking, BMI change
Cross-sectional studies (n = 14)							
Psaltopoulou et al. (17)	Greece, 2004	20,343	20–86, M/F	Without hypertension	MDS	—	Age, sex, place of residence, education, BMI, waste-to-hip ratio, energy, PA
Panagiotakos et al. (38)	Greece, 2004	2,282	>18, M/F	General population	MDS	NCEP ATP III	Age, sex, PA, education, smoking, apoA1, apoB, WBC, LDL, CRP, Lp-a, homocysteine, fibrinogen, amyloid A
Chrysohoou et al. (14)	Greece, 2004	3,042	>18, M/F	General population	MedDietScore	—	—
Mantzoros et al. (20)	U.S., 2006	987	30–55, F	Diabetic Women	MDS	—	—
Alvarez-Leon et al. (66)	Spain Canary Islands, 2006	578	>18, M/F	General population	Specific 10-item score	NCEP ATP III	Age, sex, PA, education, smoking, BMI, diet in the past 12 months, energy intake
Bach-Faig et al. (67)	Spain, 2006	328	18–75, M/F	General population	MDS or score by Sanchez-Villegas et al. (77)	—	—
Tzima et al. (40)	Greece, 2007	1,762	>18, M/F	Overweight and obese	MedDiet Score	—	—
Panagiotakos et al. (52)	Greece, 2007	3,042	>18, M/F	General population	MedDiet Score	—	—
di Giuseppe et al. (68)	Italy, 2008	522	18–96, M/F	General population	MAI	—	—
Nunez-Cordoba et al. (50)	Spain, 2008	9,408	20–90, M/F	University graduates	MDS		
Esposito et al. (69)	Italy, 2009	901	35–70, M/F	Type 2 Diabetes	MDS	—	—
Romaguera et al. (33)	Europe, 2009	497,308	25–70, M/F	General population	MDS	—	—
Babio et al. (36)	Spain, 2009	808 (prior CVD)	Mean 67, M/F	Prior CVD	14-point questionnaire	NCEP ATP III	Age, sex, PA, smoking, energy intake
Doupis et al. (70)	Greece, 2009	832	17–39, M	Healthy young, navy recruits	MedDiet Score	IDF, NCEP ATP III	Age, smoking, PA, marital status, coffee consumption, family history of DM and CHD, biochemical measurements

Observational studies (n = 16).

apo = apolipoprotein; BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; IDF = definition of the MS according to the International Diabetes Federation (76); LDL = low-density lipoprotein; MAI = Mediterranean adequacy index (74); MD = Mediterranean diet; MDS = Mediterranean diet scale (range 0 to 9) (71); MedDietScore = Mediterranean diet score (range 0 to 55) (72); MS = metabolic syndrome; MSDPS = Mediterranean style dietary pattern score (73); NCEP ATP III = definition of the metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (75); PA = physical activity.

Table 2 Characteristics of Clinical Trials That Evaluated Effect of MD on Development of MS and/or Its Components

First Author (Ref. #)	Country, Year	Sample Size Control Intervention	Age (yrs), Sex	Health Status	MD Intervention	Duration	MS, Adjustments
Barzi et al. (48) Use of cross-sectional, baseline data	Italy, 2003	11,246 2,811 2,811	19–90, M/F	Post-MI patients	—	—	—
De Lorgeril et al. (64)	France, 1994	605 303 302	<70, M/F	Post-MI	Bread, root and green vegetables, fish, less red meat, daily fruits intake, fats replaced with margarine supplied by the study	5 yrs	—
Castro et al. (62)	Spain, 2000	22 22 22	Mean 23, M	Healthy normolipidemic	15% Pro, 45% CHO, 40% fat (10% SF, 22% MUFA, 8% PUFA), chol 285–300 mg	4 weeks*3	—
Mc Manus et al. (21)	U.S., 2001	101 51 50	18–70, M/F	Overweight and obese, no chronic disease	35% energy from fat, SF 5%, MUFA 15%–20%, PUFA 10%, Pro 15–20%, CHO 45%–50%, chol <200 mg, fiber 25 g	18 months	—
Perez-Jimenez et al. (59)	Spain, 2001	59 59 59	<30 Mean 23, M/F	Healthy young	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA, 6% PUFA)	28 days*3	—
Fuentes et al. (57)	Spain, 2001	22 22 22	18–65, M	Hypercholesterolemic	5% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA, 75% of which from extra virgin olive oil, 6% PUFA)	28 days*3	—
Singh et al. (26)	UK, 2002	56 18 18	57–80, M/F	Healthy older subjects	Increase fruits and vegetables, red meat replaced by poultry and fish, butter and cream replaced by margarine and use of olive oil	6 weeks	—
Jula et al. (16)	Finland, 2002	120 60 60	38–64, M	Hypercholesterolemic	Energy intake from SF plus trans fat <10%, replace with MUFA and PUFA, chol <250 mg, increase intake of fruits, vegetables, soluble fiber	12 weeks	—
Esposito et al. (41)	Italy, 2003	120 60 60	20–46, F	Pre-menopausal and obese	CHO: 50%–60%, Pro: 15-20%, FAT: <30%, SF: <10%, MUFA: 10%–15%, PUFA: 5%–8%, Fiber: 18 g/1,000 kcal	2 yrs	—
Sondergaard et al. (27)	Denmark, 2003	131 63 68	18–80, M/F	IHD, hypercholesterolemic	>600 g of fruits and vegetables daily, reduce intake of fat, eat fatty fish at least once a week, eat bread and cereals, and to replace refined, hard, animal margarine products with canola oil	1 yr	—
Toobert et al. (22)	U.S., 2003	279 116 163	<75, F	Post-menopausal with DM	Increase: bread, root vegetables, green vegetables, legumes, fish, poultry, fruit, olive oil, canola oil, commercially available olive oil-canola oil–based margarine. Decrease: red meat, butter, cream	6 months	—
Rodriguez-Villar et al. (55)	Spain, 2003	22 22 22	Mean 61, M/F	Type 2 diabetes	15% Pro, 40% CHO, 40% fat, <10% SF, 25% MUFA, olive oil: 25% energy)—only whole grain products. Limitation of red meat, eggs, whole fat dairy products, emphasis on vegetables and fish	6 weeks 6 weeks	—
Piers et al. (34)	Australia, 2003	8 8 8	24–49, M	Overweight and obese	Olive oil, nuts, avocados 41.9% CHO, 40.1% fat (11% SF, 22.3% MUFA), fiber 3.4 g/MJ	4 weeks 4 weeks	—
Fernandez de la Puebla et al. (61)	Spain, 2003	34 34 34	18–63, M	Hypercholesterolemic	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA, 75% of which from olive oil, 6% PUFA)	28 days*3	—
Ambring et al. (28)	Sweden, 2004	22 22 22	31–51, M/F	Healthy subjects	2× dietary fiber, 3× more PUFA and ω-3, less than one-half of the SF, 3× less cholesterol and 35% decrease in glycemic index, 2 g/day sterol esters, 10 g of alcohol/day	4 weeks 4 weeks 4 weeks Wash out	—

(Continued on next page)

Table 2 Continued

First Author (Ref. #)	Country, Year	Sample Size Control Intervention	Age (yrs), Sex	Health Status	MD Intervention	Duration	MS, Adjustments
Gerhard et al. (23)	U.S., 2004	11 11 11	Mean 50.4, M/F	Type 2 diabetes	High-MUFA: 40% fat (26% MUFA), 45% CHO	6 weeks 6 weeks 6–12 weeks Wash out	—
Bravo-Herrera et al. (47)	Spain, 2004	41 41 41	Mean 23.4, M/F	Healthy young	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA—80% from virgin olive oil, 6% PUFA)	28 days*3	—
Esposito et al. (39)	Italy, 2004	180 90 90	Mean 44, M/F	MS	At least 250–300 g fruits, 125–150 g vegetables, 25–50 g walnuts, 400 g whole grains, increase consumption of olive oil CHO: 50%–60%, Pro: 15%–20%, FAT: <30%, SF: <10%, Chol: <300 g/day	2 yrs	NCEP ATP III age, sex, body weight change, drug use, associated diseases
Gomez et al. (46)	Spain, 2005	16 16 16	<30 Mean 21, M	Healthy normolipidemic	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA, 75% of which from extra virgin olive oil, 6% PUFA)	28 days*3	—
Vincent-Baudry et al. (56)	France, 2006	212 110 102	18–70, M/F	Moderate CVD risk	Nuts, whole meal bread, cereals, raw and cooked fruits and vegetables, legumes, olive oil as the main source of fat, fish 4×/week, red meat 1 time/week, sheep and poultry the main source of meat, cheeses mainly from sheep and goat, alcohol 1 glass for women, 2 glasses for men (FAT 35%–38%, MUFA: 50%, PUFA: 25%, SF: 25%, 25 g fiber)	3 months	—
Michalsen et al. (29)	Germany, 2006	101 53 48	Mean 59.4, M/F	Established and treated CAD	>5 fruits and vegetables/day, emphasis on root and green vegetables, >2 portions fatty fish/week, whole grains, flaxseed and nuts recommended, 3 servings/week meat replaced by poultry, fish or vegetarian dishes, olive oil, canola oil mainly, walnut and flaxseed oil for some dishes, margarine discouraged, modest red wine consumption with meals	1 yr	—
Bellido et al. (58)	Spain, 2006	20 20 20	Mean 23, M	Healthy young	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA—80% from virgin olive oil, 6% PUFA)	28 days*3	—
Estruch et al. (42)	Spain, 2006	772 257 257,258	55–80, M/F	High CVD risk	Instructions to increase the 14-item Mediterranean score MD-virgin olive oil: free provision of olive oil MD-mixed nuts: free provision of nuts	3 months	—
Paniagua et al. (53)	Spain, 2007	11 11 11	35–75, M/F	Obese and type 2 diabetes	15% Pro, 47% CHO, 38% fat 9% SFA, 23% MUFA—75% from extra virgin olive oil, 6% PUFA)	28 days*3	—
Lindeberg et al. (32)	Sweden, 2007	29 15 14	Pal 67 Med 57, M	IHD and Glu intolerance or DM	Whole-grain cereals, low-fat dairy products, potatoes, legumes, vegetables, fruits, fatty fish and refined fats rich in monounsaturated fatty acids and alpha-linolenic acid	3 months	—

(Continued on next page)

Table 2 Continued

First Author (Ref. #)	Country, Year	Sample Size Control Intervention	Age (yrs), Sex	Health Status	MD Intervention	Duration	MS, Adjustments
Perez-Martinez et al. (60)	Spain, 2007	16 16 16	M	Healthy	15% Pro, 47% CHO, 38% fat, <10% SF, 24% MUFA, 4% PUFA	4 weeks*3	—
Salas-Salvado et al. (37)	Spain, 2008	1,224 422 419/423	Older, M/F	High CVD risk	Instructions to increase the 14-item Mediterranean score MD-virgin olive oil: free provision of olive oil MD-mixed nuts: free provision of nuts	1 yr	NCEP ATP III age, sex, baseline obesity status, weight changes
Papadaki and Scott (31)	Scotland, 2008	72 19 53	25–55, F	Healthy	The intervention aimed depending on participants current dietary intake to encourage by e-mail to attempt increasing the consumption of vegetables, fruits-nuts-seeds, legumes, and MUFA/SFA ratio	6 months	—
Tuttle et al. (24)	U.S., 2008	101 50 51	Mean 58, M/F	Post-MI	Omega-3 (>0.75% kcal), MUFA (20%–25% kcal); emphasis on the increased consumption of cold water fish (3–5×/week), oils from olives, canola, and soybeans	2 yrs	—
Shai et al. (49)	Israel, 2008	322 104,109 109	40–65, M/F	Moderately obese	1,500 kcal for women, 1,800 kcal for men, <35% fat, 30–45 g of olive oil and <20 g nuts daily Rich in vegetables, low in red meat with poultry and fish replacing beef and lamb	2 yrs	—
Rallidis et al. (51)	Greece, 2009	90 44 46	<70, M/F	Abdominal obesity no CVD or DM	Daily consumption of whole wheat grains and products, 2–3 portions of low-fat dairy, 2 salads (1 of which should contain >2 tomatoes), >3 fruits, concentrated fruit juice without preservatives, 5 ml olive oil-based margarine, extra virgin olive oil as the main source of fat, 45 ml, 6 whole raw almonds, 150 ml red wine, >1 portion of fish/week, <1 portion red meat/week	2 months	—
Buscemi et al. (63)	Italy, 2009	20 10 10	30–50, F	Overweight and obese	MD: fatty fish 3 servings/week, unrefined grain, nuts (15 g/day), legumes (40 g/day), red wine (1 glass/day)—80 g Pro	2 months	—
Bos et al. (30)	the Netherlands, 2009	60 20 20	40–65, M/F	No DM, with mild abdominal obesity	Rich in extra virgin olive oil higher intake of vegetables (250 g MD, 200 g high-MUFA diet) fruits (3 MD, 1 high-MUFA diet), lower intake of dairy products (224 g MD, 360 g high-MUFA diet, red meat (64 g MD, 84 g high-MUFA diet)	2 months	—
Esposito et al. (43)	Italy, 2009	215 107 108	30–75, M/F	Overweight New DM	50% from complex CHO, >30% fat, 30–50 g from olive oil. Diet rich in vegetables and whole grains, low in red meat, which was replaced with poultry and fish	4 yrs	—
Athyros et al. (44)	Greece, 2009	150 50 50	Mean 55, M/F	Mildly hypercholesterolemic	7-day menus that incorporated the salient characteristics of the MD	4 months	—
Elhayany et al. (45)	Israel, 2009	179 55 63,61	30–65, M/F	Overweight with DM	TM: 20% Pro, 50% CHO, 30% fat, 7% SF, 10% MUFA, 12% PUFA, fiber 30 g LCM: 20% Pro, 35% CHO, 45% fat, 7% SF, 23% MUFA, 15% PUFA, fiber 30 g	1 yr	—

Clinical trials (n = 36).

chol = cholesterol; CHO = carbohydrates; IHD = ischemic heart disease; LCM = low-carbohydrate Mediterranean diet; MI = myocardial infarction; MUFA = monounsaturated fatty acids; Pro = protein; PUFA = polyunsaturated fatty acids; SF = saturated fat; SFA = saturated fatty acids; TM = traditional Mediterranean diet; other abbreviations as in Table 1.

Table 3 Results From Observational Studies That Evaluated the Effect of MD on Components of MS

First Author (Ref. #)	Waist Circumference (cm)	HDL Cholesterol (mg/dl)	Triglycerides (mg/dl)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Glucose (mg/dl)	HOMA-IR
Cross-sectional studies							
Chrysohoou et al. (14), men		3.00 (1.46 to 4.54)	−7.00 (−15.76 to 1.76)	−4.00 (−6.09 to −1.91)	−3.00 (−4.35 to −1.65)	−3.00 (−6.40 to 0.40)	
Chrysohoou et al. (14), women		5.00 (3.58 to 6.42)	−8.00 (−15.53 to −0.47)	−9.00 (−11.28 to −6.72)	−5.00 (−6.30 to −3.70)	−3.00 (−6.40 to 0.40)	
Mantzoros et al. (20)	−5.30 (−8.15 to −2.45)	2.70 (0.01. to 5.39)	−26.30 (−56.75 to 4.15)				
Bach-Faig et al. (67)		3.44 (−0.91 to 7.79)	−7.03 (−23.17 to 9.11)				
Tzima et al. (40)	−24.2 (−26.15 to −22.25)	2.30 (2.22 to 2.38)	−17.0 (−18.85 to −15.15)	−3.00 (−3.18 to −2.82)	−7.00 (−7.18 to −6.82)	−6.00 (−6.34 to −5.66)	−0.40 (−0.42 to −0.38)
Panagiotakos et al. (52), diabetes mellitus or IFG						−23.00 (−30.59 to −15.41)	−2.20 (−2.50 to −1.90)
Panagiotakos et al. (52)						−6.00 (−7.24 to −4.76)	−0.40 (−0.45 to −0.35)
di Giuseppe et al. (68), men				0.00 (−6.45 to 6.45)	0.00 (−3.48 to 3.48)	2.00 (−1.37 to 5.37)	
di Giuseppe et al. (68), women				9.00 (1.98 to 16.01)	1.00 (−2.34 to 4.34)	0.00 (−3.05. to 3.05)	
Nunez-Cordoba et al. (50)				1.80 (0.96 to 2.64)	0.50 (−0.11 to 1.10)		
Esposito et al. (69)	−0.70 (−2.85 to 1.45)	0.00 (−1.61 to 1.61)	−8.86 (−19.64 to 1.92)			1.80 (−5.97 to 9.57)	
Barzi et al. (48)		0.60 (−0.01 to 3.07)	−5.00 (−9.39 to −0.61)				
Romaguera et al. (33), men	−0.80 (−0.93 to −0.67)						
Romaguera et al. (33), women	−1.60 (−1.70 to −1.50)						
Combined effect	−5.78 (−7.26 to −4.31)	2.25 (1.15 to 3.34)*	−9.88 (−16.05 to −3.71)*	−1.81 (−4.83 to 1.21)	−2.36 (−6.12 to 1.39)	−3.93 (−6.25 to −1.61)*	−0.87 (−1.15 to −0.59)*
Prospective studies							
Tortosa et al. (35)	−0.50 (−1.96 to 0.96)	0.30 (−1.77 to 2.37)	−2.00 (−6.74 to 2.74)	0.80 (−0.84 to 2.44)	0.90 (−0.38 to 2.18)	1.20 (−0.53 to 2.93)	

Data are presented as mean difference between highest versus lowest category of diet score (95% confidence interval). *Significant associations.

BP = blood pressure; HDL = high-density lipoprotein; HOMA-IR = Homeostatic Model Assessment insulin resistance; other abbreviations as in Table 1.

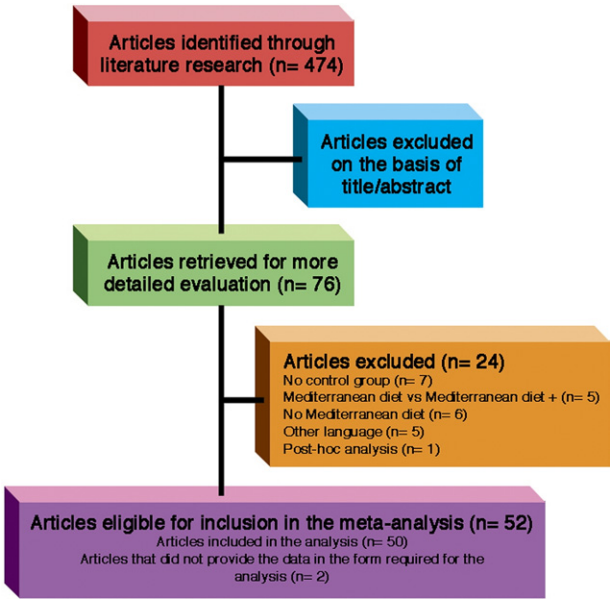

Figure 1 **Process of Study Selection**

Studies (n = 474) that evaluated the effect of a Mediterranean diet on metabolic syndrome and its components were identified. After exclusions, 50 studies were finally included in the meta-analysis.

MD was associated with lower triglycerides levels (Table 3). Heterogeneity of the effect measures regarding triglycerides levels was observed [Cochran's Q = 33.18(6), $p < 0.001$, $I^2 = 81.9\%$]. In addition, 29 clinical trials with 3,822 subjects (2,202 assigned to an MD, and 1,903 assigned to a control diet) examined the relationship between compliance with the Mediterranean dietary pattern and triglycerides levels. Five studies (39,42,43,45,49) reported a beneficial effect of an MD, as compared with the control diet, whereas the rest of the studies observed no significant differences. Overall, adherence to the MD was associated with lower triglyceride levels as compared with the control diet (Table 4). Heterogeneity of the effect measures regarding triglyceride levels [Cochran's Q = 89.50(40), $p < 0.001$, $I^2 = 55.3\%$] was also evident.

BLOOD PRESSURE LEVELS. Five observational studies with 15,535 participants were included in the analysis. Two studies (14,40) reported a beneficial effect of close adherence to the MD on systolic blood pressure, as compared with low adherence, whereas 1 study showed higher systolic blood pressure levels for the group more closely following the MD (50). Overall, adherence to the MD was not associated with systolic blood pressure levels, as compared with the control diet (Table 3). Heterogeneity of the effect measures regarding systolic blood pressure levels was also observed [Cochran's Q = 161.28(5), $p < 0.001$, $I^2 = 96.8\%$]. Moreover, 14 clinical trials with 3,060 subjects (1,632 assigned to an MD, and 1,436 assigned to a control diet) evaluated the effect of the MD on systolic blood pressure levels. Three

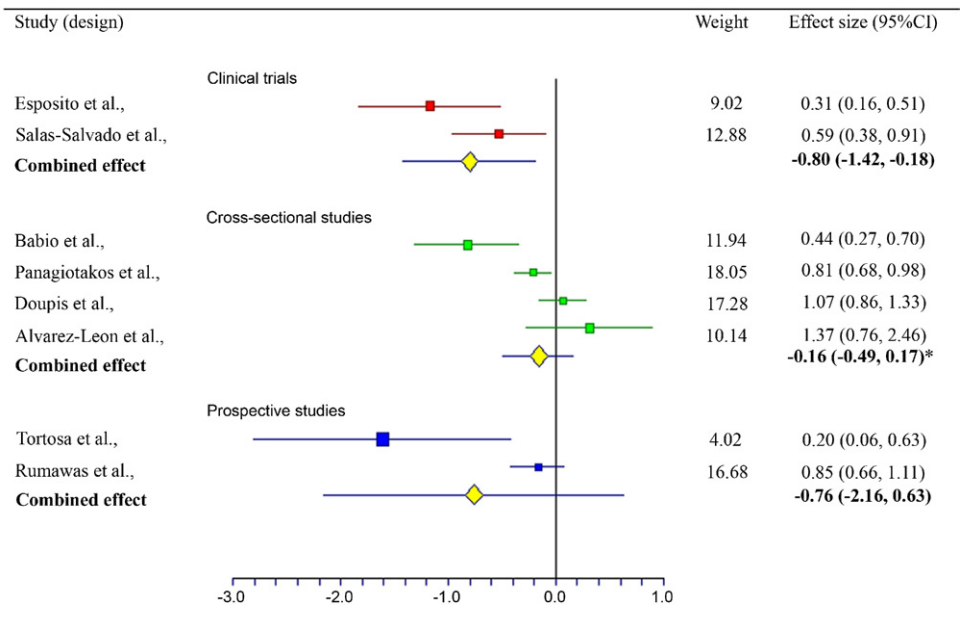

Figure 2 **Mediterranean Diet and Metabolic Syndrome**

Forest plot of studies that evaluated the effect of Mediterranean diet on the presence of the metabolic syndrome (**squares** and **diamonds** represent effect size; **extended lines** show 95% confidence intervals [CIs]). Adherence to the Mediterranean diet was associated with a protective effect in 2 of 2 clinical trials, 2 of 4 cross-sectional studies, and 1 of 2 prospective studies, as compared with lower compliance with this pattern or with a control diet. The combined effect of both clinical trials and prospective studies was highly protective (log-hazard ratio: −0.69, 95% CI: −1.24 to −1.16). *Log(odds ratio) or log(relative risk).

Table 4 Results From Clinical Trials That Evaluated Effect of MD on Components of MS

First Author (Ref. #)	WC (cm)	HDL Cholesterol (mg/dl)	Triglycerides (mg/dl)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Glucose (mg/dl)	HOMA-IR
De Lorgeril et al. (64)		−1.16 (−3.58 to 1.26)	−19.49 (−44.62 to 5.65)	−2.00 (−4.77 to 0.77)	−1.00 (−3.77 to 1.77)		
Castro et al. (NCEP) (62)		3.87 (2.03 to 5.71)	0.00 (−16.44 to 16.44)				
Castro et al. (sunflower) (62)		1.55 (0.46 to 2.63)	2.66 (−12.02 to 17.33)				
Mc Manus et al. (21)	−4.20 (−7.99 to −0.41)						
Perez-Jimenez et al. (SF) (59)		−3.48 (−7.38 to 0.41)	1.77 (−7.92 to 11.46)			−1.80 (−3.94 to 0.34)	
Perez-Jimenez et al. (CHO) (59)		1.55 (−1.98 to 5.08)	0.89 (−8.03 to 9.80)			−1.44 (−3.74 to 0.86)	
Fuentes et al. (SF) (57)		−1.00 (−6.15 to 4.15)	9.00 (−17.33 to 35.33)				
Fuentes et al. (NCEP) (57)		1.00 (−4.09 to 6.09)	−9.00 (−29.58 to 11.58)				
Singh et al. (26)				8.00 (−4.99 to 20.99)	1.00 (−5.50 to 7.50)		
Esposito et al. (41)		8.00 (3.66 to 12.34)	−11.00 (−27.00 to 4.99)	−1.00 (−3.95 to 1.95)	−1.70 (−3.39 to −0.01)	−7.00 (−11.62 to −2.38)	−0.90 (−1.05 to −0.75)
Sondergaard et al. (27)		0.77 (−4.31 to 5.86)	−5.31 (−34.11 to 23.49)				
Toobert et al. (22)		0.96 (−1.74 to 3.66)	−11.9 (−40.31 to 16.51)	0.33 (−3.06 to 3.72)	−1.70 (−3.84 to 0.44)		
Rodriguez-Villar et al. (55)	0.00 (−4.56 to 4.56)	−1.55 (−9.14 to 6.05)	2.66 (−54.24 to 59.55)			18.00 (−12.20 to 48.20)	
Piers et al. (34)	−3.10 (−11.49 to 5.29)	−3.87 (−11.21 to 3.47)	0.00 (−96.16 to 96.16)	−8.80 (−20.89 to 3.29)	−5.90 (−14.65 to 2.85)	−1.80 (−11.95 to 8.35)	
de la Puebla et al. (SF) (61)		−1.00 (−5.16 to 3.16)	9.00 (−34.85 to 52.85)				
de la Puebla et al. (CHO) (61)		1.00 (−3.11 to 5.11)	−9.00 (−48.38 to 30.38)				
Ambring et al. (28)		0.00 (−11.07 to 11.07)	−17.71 (−43.04 to 7.62)			1.80 (−3.35 to 6.95)	
Gerhard et al. (23)		1.00 (−6.34 to 8.34)	−18.0 (−123.8 to 87.85)			6.00 (−22.83 to 34.83)	
Bravo-Herera et al. (ctr) (47)		2.32 (−1.08 to 5.72)	0.89 (−9.86 to 11.64)				
Bravo-Herera et al. (SF) (47)		−3.87 (−7.62 to −0.11)	5.31 (−5.44 to 16.06)				
Esposito et al. (39)	−2.00 (−4.73 to 0.73)	3.00 (0.28 to 5,72)	−19.00 (−34.67 to −3.34)	−3.00 (−5.73 to −0.27)	−2.00 (−3.77 to −0.23)	−6.00 (−8.79 to −3.21)	−1.10 (−1.30 to −0.90)
Gomez et al. (ctr) (46)		3.10 (to 5.29 to 11.48)	−4.43 (−28.46 to 19.61)				
Gomez et al. (SF) (46)		−13.93 (−21.65 to −6.22)	−9.74 (−32.13 to 12.64)				
Vincent-Baudry et al. (56)		0.00 (−5.58 to 5.58)	0.00 (−23.73 to 23.73)	1.00 (−3.34 to 5.34)	2.00 (−1.69 to 5.69)	0.00 (−3.42 to 3.42)	0.00 (−0.49 to 0.49)
Michalsen et al. (29)		1.94 (−2.88 to 6,75)	−3.54 (−35.23 to 28.15)				
Bellido et al. (SF) (58)		−3.87 (−8.64 to 0.89)	5.31 (−14.39 to 25.02)				
Bellido et al. (CHO) (58)		2.71 (−1.76 to 7.18)	4.43 (−15.56 to 24.42)				
Estruch et al. (nuts) (42)	0.08 (−0.97 to 1.13)	1.31 (0.14 to 2.48)	−10.00 (−19.37 to −0.63)	−7.14 (−9.98 to −4.30)	−2.75 (−4.20 to −1.30)	−6.00 (−11.40 to −0.60)	−0.86 (−1.41 to −0.31)
Estruch et al. (olive) (42)	−0.45 (−1.72 to 0.82)	2.77 (1.67 to 3.87)	−5.40 (−16.57 to 5,77)	−5.44 (−8.13 to −2.75)	−1.65 (−3.02 to −0.28)	−7.30 (−13.06 to −1.54)	−0.85 (−1.41 to −0.29)
Paniagua et al. (ctr) (53)						−0.18 (−5.26 to 4.90)	
Paniagua et al. (SF) (53)						−8.64 (−13.97 to −3.31)	
Lindeberg et al. (32)	2.60 (−3.48 to 8.68)						0.03 (−0.03 to 0.36)
Perez-Martinez et al. (wst) (60)		0.39 (−5.20 to 5.98)	−4.43 (−22.34 to 13.48)				
Perez-Martinez et al. (CHO) (60)		2.32 (−3.27 to 7.91)	−0.89 (−18.47 to 16.70)				
Papadaki and Scott (31)		7.74 (0.93 to 14.55)	7.09 (−16.12 to 30.29)				
Tuttle et al. (24)		−2.00 (−5.60 to 1.60)	41 (−1.33 to 83.33)	−1.00 (−7.07 to 5.07)	0.00 (−3.58 to 3.58)		

(Continued on next page)

Table 4 Continued

First Author (Ref. #)	WC (cm)	HDL Cholesterol (mg/dl)	Triglycerides (mg/dl)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Glucose (mg/dl)	HOMA-IR
Shai et al. (49)		0.59 (−2.26 to 3.44)	−22.44 (−42.04 to −2.84)	−1.25 (−4.70 to 2.20)	−1.35 (−3.73 to 1.03)	−4.98 (−12.10 to 2.14)	
Shai et al. (49)		−2.24 (−4.88 to 0.39)	14.24 (−8.22 to 36,70)	−1.52 (−5.19 to 2.15)	−0.97 (−3.49 to 1.55)	−0.25 (−7.56 to 7.06)	
Rallidis et al. (51)	−1.20 (−5.19 to 2.79)	0.00 (−4.78 to 4.78)	−6.20 (−28.81 to 16.41)	−3.90 (−9.85 to 2.05)	−5.50 (−8.83 to −2.17)	−1.44 (−6.95 to 4.07)	−1.20 (−1.95 to −0.45)
Buscemi et al. (63)	2.00 (−12.62 to 16.62)	4.00 (−9.45 to 17.45)	6.00 (−29.56 to 41.56)	−1.00 (−12.95 to 10.95)	−4.00 (−12.21 to 4.21)	5.00 (−9.09 to 19.09)	0.67 (−1.06 to 2.40)
Bos et al. (SF) (30)	−0.50 (−8.33 to 7.33)	3.87 (−6.10 to 13.84)	−21.26 (−53.50 to 10.99)			−1.26 (−6.04 to 3.52)	0.01 (−0.22 to 0.24)
Bos et al. (h−MUFA) (30)	−1.70 (−10.29 to 6.99)	3.87 (0.73 to 2.61)	−12.40 (−45.21 to 20.41)			−0.72 (−4.96 to 3.52)	−0.12 (−0.74 to −0.16)
Esposito et al. (43)	−0.40 (−0.90 to 0.10)	2.71 (2.10 to 3.31)	−18.60 (−23.59 to −13.61)	−1.50 (−2.03 to −0.97)	−1.40 (−1.85 to −0.95)	−16.20 (−20.83 to −11.57)	
Athyros et al. (44)		3.00 (0.62 to 5.38)	−6.00 (−15.36 to 3.36)	−3.00 (−6.18 to 0.18)	−1.00 (−3.09 to 1.09)	−3.00 (−6.70 to 0.70)	−0.60 (−0.82 to −0.38)
Elhayany et al. (TM) (45)	−0.2 (−3.55 to 3.15)	1.94 (−0.85 to 4.72)	−51.37 (−75.81 to −26.93)			−7.74 (−18.70 to 3.22)	0.26 (−0.67 to 1.19)
Elhayany et al. (LCM) (45)	−1.3 (−4.96 to 2.36)	6.97 (3.93 to 10.00)	−56.68 (−82.21 to −31.19)			−21.96 (−32.54 to −11.38)	−0.21 (−1.24 to 0.82)
Combined effect	−0.42 (−0.82 to −0.02)*	1.17 (0.38 to 1.96)*	−6.14 (−10.35 to −1.93)*	−2.35 (−3.51 to −1.18)*	−1.58 (−2.02 to −1.13)*	−3.89 (−5.84 to −1.95)*	−0.45 (−0.74 to −0.16)*

Data are presented as mean difference between intervention groups (95% confidence interval). *Significant associations.
ctr = control diet; NCEP = National Cholesterol Education Program; WC = waist circumference; wst = western diet; other abbreviations as in Tables 2 and 3.

studies (39,42,43) reported a beneficial effect of an MD, as compared with the control diet, and the overall adherence to the MD was associated with lower systolic blood pressure levels as compared with the control diet (Table 4). Heterogeneity of the effect measures regarding systolic blood pressure levels was observed [Cochran's Q = 31.18(15), p = 0.01, I^2 = 51.8%].

With regard to diastolic blood pressure levels, no significant associations were observed in observational studies (Table 3). However, in clinical trials (3,060 subjects, 1,632 assigned to an MD, and 1,436 assigned to a control diet) 5 studies (39,41–43,51) reported a beneficial effect of an MD, and the overall effect suggested that adherence to the MD was associated with lower diastolic blood pressure levels as compared with the control diet (Table 4). No heterogeneity of the effect measures regarding blood pressure levels [Cochran's Q = 16.09(15), p = 0.38, I^2 = 6.7%] was observed.

GLUCOSE AND HOMEOSTATIC MODEL ASSESSMENT INSULIN RESISTANCE LEVELS. Two observational studies (40,52) reported a beneficial effect of close adherence to the MD as compared with the control diet, and overall adherence to the MD was associated with lower fasting glucose levels (Table 3). Heterogeneity of the effect measures regarding glucose levels was observed [Cochran's Q = 65.05(7), p < 0.001, I^2 = 89.2%]. Moreover, among the 17 clinical trials with 2,373 subjects (1,357 assigned to an MD, and 1,139 assigned to a control diet), 6 studies (39,41–43,45,53) reported a beneficial effect of an MD, as compared with the control diet. Overall, adherence to the MD was associated with lower fasting glucose levels as compared with the control diet (Table 4). Heterogeneity of the effect measures regarding glucose levels was observed [Cochran's Q = 77.49(22), p < 0.001, I^2 = 71.6%].

Two observational studies with 3,042 subjects evaluated the role of the MD on Homeostatic Model Assessment insulin resistance (HOMA-IR) levels (40,52). Both studies reported a beneficial effect of close adherence to the MD on HOMA-IR levels, as compared with low adherence (Table 3). Heterogeneity of the effect measures regarding HOMA-IR levels [Cochran's Q = 135.69(2), p < 0.001, I^2 = 98.5%] was observed. In addition, 10 clinical trials with 1,742 subjects (1,031 assigned to a MD and 711 to a control diet), examined the relationship between adherence to the MD and HOMA-IR. Six studies (30,39,41,42,44,51) reported a beneficial effect of a MD, as compared with the control diet. Overall, adherence to the MD was associated with lower HOMA-IR levels as compared with the control diet (Table 4). Heterogeneity of the effect measures regarding HOMA-IR levels [Cochran's Q = 118.06(12), p < 0.001, I^2 = 89.8%] was observed.

Sensitivity analysis. Heterogeneity of the effect sizes of MD on MS as well as its components has already been reported in the preceding text. Studies included in the present meta-analysis varied in some characteristics with regard to their design. The meta-analysis of clinical trials

revealed the beneficial role of the MD on MS, whereas results from observational studies (cross-sectional and prospective) showed a protective but not significant trend (Fig. 2). Moreover, the heterogeneity found regarding the overall effect of diet on MS was not attributed to the weight of each study.

However, heterogeneity was also observed with regard to the effect of diet on MS components. Specifically, differences were revealed with regard to: location of the studied population (i.e., Mediterranean or non-Mediterranean countries), sample size, duration of the intervention, encouraging of lifestyle changes, as well as trial quality. In particular, in studies conducted in Mediterranean countries, the effect of diet was significant with regard to all MS components except for weight circumference, whereas in studies not located in the Mediterranean region the effect of diet was not associated with any of the MS components; similarly, studies with intervention duration more than 3 months showed significant results for all the components studied except for waist circumference, whereas clinical trials with a <3-month intervention showed significant results only with regard to diastolic blood pressure and glucose levels. Moreover, all studies with sample size above the median (i.e., n >66) presented significant associations between diet and all the MS components, whereas studies with <66 participants did not show any significant associations. Studies also encouraging physical activity showed significant associations with regard to all the components studied, except waist circumference; however, studies focusing only on dietary intervention showed significant associations only with regard to blood pressure and glucose levels. Clinical trials of high quality showed significant results between diet and all the components studied, except for waist circumference, whereas clinical trials with low quality showed significant results only with regard to diastolic blood pressure and glucose levels (Table 5). Furthermore, when the control diets were categorized (where this was possible) into "low-fat diet" (i.e., <30% fat),"usual treatment" type (i.e., no further dietary advice apart from that of hospital dietitians or written advice), "high saturated fat diet" (i.e., saturated fat >20%), the subgroup meta-analysis showed that MD was associated with beneficial effects, as compared with the "low-fat diet" (with regard to HDL cholesterol, triglycerides, systolic and diastolic blood pressure, glucose levels) as well as with the "usual dietary recommendations" (with regard to HDL cholesterol and triglyceride levels).

Table 5 Sensitivity Analysis of Selected Studies in Present Meta-Analysis

	Waist (cm)	HDL Cholesterol (mg/dl)	Triglycerides (mg/dl)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Glucose (mg/dl)	HOMA-IR
Country, n	9/5†	31/10	31/10	12/4	12/4	19/5	10/3
Mediterranean	−0.38 (−0.79 to 0.03)	1.21 (0.34 to 2.08)*	−6.30 (−10.94 to −1.66)*	−2.62 (−3.87 to −1.37)*	−1.64 (−2.19 to −1.09)*	−4.79 (−7.05 to −2.53)*	−0.67 (−0.92 to −0.43)*
Not Mediterranean	−2.05 (−4.63 to 0.53)	0.71 (−0.94 to 2.37)	−5.36 (−15.42 to 4.70)	−0.37 (−4.27 to 3.53)	−1.29 (−3.01 to 0.42)	−0.26 (−2.77 to 2.24)	−0.04 (−0.18 to 0.11)
Duration of study, n	8/6	17/24	17/24	12/4	12/4	11/13	9/4
>3 months	−0.42 (−0.89 to 0.05)	1.91 (0.91 to 2.91)*	−12.02 (−18.96 to −5.08)*	−2.33 (−3.54 to −1.12)*	−1.47 (−1.83 to −1.11)*	−6.69 (−9.93 to −3.46)*	−0.55 (−0.84 to −0.25)*
<3 months	−0.90 (−3.32 to 1.53)	0.14 (−1.17 to 1.45)	−0.04 (−3.59 to 3.51)	−2.36 (−8.01 to 3.30)	−4.09 (−7.01 to −1.16)*	−1.50 (−2.93 to −0.07)*	−0.21 (−0.59 to 0.17)
Participants, n	8/6	18/23	18/23	13/3	13/3	12/12	9/4
n ≥ 66	−0.43 (−0.84 to −0.02)*	1.85 (0.87 to 2.83)*	−11.74 (−18.41, −5.07)*	−2.38 (−3.55 to −1.21)*	−1.59 (−2.08 to −1.09)*	−6.22 (−9.26 to −3.18)*	−0.71 (−0.95 to −0.46)*
n < 66	0.02 (−2.70 to 2.74)	0.13 (−1.23 to 1.49)	0.12 (−3.48 to 3.72)	−0.97 (−10.27 to 8.34)	−2.33 (−6.52 to 1.85)	−1.48 (−3.08 to 0.12)	−0.03 (−0.17 to 0.11)
Physical activity, n	6/8	8/33	8/33	5/11	5/11	5/19	5/8
Recommended	−0.85 (−1.95 to 0.25)	2.83 (1.20 to 4.47)*	−19.82 (−32.45 to −7.19)*	−1.49 (−1.99 to −0.99)*	−1.44 (−1.85 to −1.03)*	−11.0 (−16.53 to 5.58)*	−0.62 (−0.92 to −0.32)*
No recommendation	−0.21 (−0.98 to 0.56)	0.58 (−0.34 to 1.51)	−2.34 (−5.21 to 0.52)	−2.96 (−4.78 to −1.13)*	−1.71 (−2.66 to −0.75)*	−1.98 (−3.23 to −0.73)*	−0.16 (−0.46 to 0.15)
Study quality, n	8/6	17/24	17/24	12/4	12/4	11/13	9/4
High	−0.42 (−0.89 to 0.05)	1.91 (0.91 to 2.91)*	−12.02 (−18.96 to −5.08)*	−2.33 (−3.54 to −1.12)*	−1.47 (−1.83 to −1.11)*	−6.69 (−9.93 to −3.46)*	−0.55 (−0.84 to −0.25)*
Low	−0.90 (−3.32 to 1.53)	0.14 (−1.17 to 1.45)	−0.04 (−3.59 to 3.51)	−2.36 (−8.01 to 3.30)	−4.09 (−7.01 to −1.16)*	−1.50 (−2.93 to −0.07)*	−0.21 (−0.59 to 0.17)

Data are presented as mean difference between intervention groups (95% confidence interval). *Significant associations; †n = number of studies.
Abbreviations as in Table 3.

Discussion

The present meta-analysis, performed in 50 studies, with an overall incorporated population of approximately one-half million subjects, revealed the beneficial effect of the MD, with regard to not only the MS but also its individual components, namely waist circumference, HDL cholesterol levels, triglyceride levels, blood pressure levels, and glucose metabolism. The significant heterogeneity observed mainly

on the effect of the MD on MS components was partially attributed to the location of studies (i.e., Mediterranean or not), the intervention duration, the number of the participants, and the quality of the studies. To the best of our knowledge, this is the first work that has systematically assessed, through meta-analysis, the role of the MD on MS and its components.

The MD is one of the most known and well-studied dietary patterns, which has been shown to be associated with human health, especially decreased mortality from all causes, lower risk for cardiovascular disease, and cancer (8); it is also exerting a beneficial role with regard to type 2 diabetes and obesity (9,10). The results of the present meta-analysis add to the existing knowledge, because they indicate that adherence to the MD has a positive effect on human health through different ways. The MD has a beneficial effect on abdominal obesity, lipids levels, glucose metabolism, and blood pressure levels, all the components of the MS, which are also risk factors for the development of cardiovascular disease, insulin resistance, and diabetes. The antioxidant and anti-inflammatory effects of the MD as a whole as well as the effects of the individual components of the MD and specifically olive oil, fruits and vegetables, whole grains, and fish could offer a possible explanation for the aforementioned findings (9,11–15).

At this point it should be mentioned that abdominal obesity is one of the main causes for the appearance of all the components of the MS, because adipose tissue plays an important role in lipid and glucose metabolism and is responsible for the production of various cytokines influencing the development of the syndrome (54). The present meta-analysis based on results from both observational studies and clinical trials revealed the beneficial effect of the MD with regard to central obesity.

Furthermore, results from studies conducted in Mediterranean countries showed more prominent effects of the Mediterranean-type dietary pattern, possibly due to the easy access of consumers to the Mediterranean products. Nevertheless, these results could be attributed to other potential confounders such as genetics or environmental factors (i.e., physical activity; food sources, enrichment, contamination). In addition results of the present meta-analysis suggested that adherence to the MD coupled with physical activity has even more beneficial effects, showing the significant role of an active lifestyle for the prevention of the MS components. Finally, studies of high quality, longer intervention duration, and higher number of participants showed more prominent results—a fact that can be attributed to the crucial role of the design of a study.

Practical implications. The prevalence of the MS has drastically increased during recent years and is very unlikely to decrease, unless drastic measures are applied. For the delay and prevention of its development, emphasis should be placed on modifiable lifestyle factors. However, in spite of efforts to promote a healthy lifestyle and encourage a healthier diet and increase physical activity, dietary habits in the developed world and in some developing countries are changing toward the opposite direction. Even around the Mediterranean basin, consumption of fat, meat, eggs, dairy products, and sugar has increased, and consumption of cereals, legumes, vegetables, and seafood has decreased. Therefore, encouraging adherence to the MD might be a solution to the problem, because the foods comprising this dietary pattern—apart from its various health benefits—are tasty and it is easy to follow in the long-term.

Study limitations. Certain limitations of this study warrant consideration. The Mediterranean dietary pattern is not homogeneous; however, the basic characteristics of this diet were present in all of the included epidemiological studies. In addition, the MD intervention varied between the clinical trials in terms of hours of intervention, detail of the recommendations given, and macronutrient composition of the diet. In most trials, the control diet was a low-fat, high-carbohydrate diet (21,23,24,42,43,46,47,49,53,55–62), a low-carbohydrate diet (49,63), a prudent diet (30,32), usual patient treatment (22,64), American Diabetes Association diet (45), receiving general healthy dietary information (27,29,31,39,41), high-saturated-fat diet (30,34,46,47,53,58–61), or less counselling on an MD prescription (51). In 9 trials, MD was part of a lifestyle intervention comprising exercise (24,32,43) or a structured plan (smoking cessation, exercise, stress management) (21,22,29,39,41,45). Moreover, significant heterogeneity is present in our analysis, which introduces a warning about the generalization of the present results. More cohort studies evaluating the role of the MD on MS are needed.

Conclusions

The results of the present meta-analysis suggest that adherence to the Mediterranean dietary pattern was associated with lower MS prevalence and progression. Moreover, greater adherence to this traditional dietary pattern was associated with favorable effects on the MS components. These results are of considerable public health importance, because this dietary pattern can be easily adopted by all population groups and various cultures (65) and cost-effectively serve for the primary and secondary prevention of the MS and its individual components.

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