

# 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 Diabetic

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 diabe-

tes (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
<b>Prospective studies (n = 2)</b>							
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
<b>Cross-sectional studies (n = 14)</b>							
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
Panagiōtakos 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	—	—
Panagiōtakos 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		Age (yrs), Sex	Health Status	MD Intervention	Duration	MS, Adjustments
		Control	Intervention					
Barzi et al. (48) Use of cross-sectional, baseline data	Italy, 2003	11,246	19-90, M/F	Post-MI patients	—	—	—	—
		2,811						
		2,811						
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	<30	Healthy young	15% Pro, 47% CHO, 38% fat (<10% SFA, 22% MUFA, 6% PUFA)	28 days*3	—	
		59	Mean 23, M/F					
		59						
Fuentes et al. (57)	Spain, 2001	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	—	
		22						
		22						
Singh et al. (26)	UK, 2002	56	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	—	
		18						
		18						
Jula et al. (16)	Finland, 2002	120	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	—	
		60						
		60						
Esposito et al. (41)	Italy, 2003	120	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	—	
		60						
		60						
Sondergaard et al. (27)	Denmark, 2003	131	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	—	
		63						
		68						
Toobert et al. (22)	U.S., 2003	279	<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	—	
		116						
		163						
Rodriguez-Villar et al. (55)	Spain, 2003	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	—	
		22				6 weeks		
		22						
Piers et al. (34)	Australia, 2003	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	—	
		8				4 weeks		
		8						
Fernandez de la Puebla et al. (61)	Spain, 2003	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	—	
		34						
		34						
Ambring et al. (28)	Sweden, 2004	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	—	
		22				4 weeks		
		22				4 weeks Wash out		

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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	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 28 days*3	—
		11					
		11					
Bravo-Herrera et al. (47)	Spain, 2004	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	—
		41					
		41					
Esposito et al. (39)	Italy, 2004	180	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
		90					
		90					
Gomez et al. (46)	Spain, 2005	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	—
		16					
		16					
Vincent-Baudry et al. (56)	France, 2006	212	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	—
		110					
		102					
Michalsen et al. (29)	Germany, 2006	101	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	—
		53					
		48					
Bellido et al. (58)	Spain, 2006	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	—
		20					
		20					
Estruch et al. (42)	Spain, 2006	772	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	—
		257					
		257,258					
Paniagua et al. (53)	Spain, 2007	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	—
		11					
		11					
Lindeberg et al. (32)	Sweden, 2007	29	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	—
		15					
		14					

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**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).

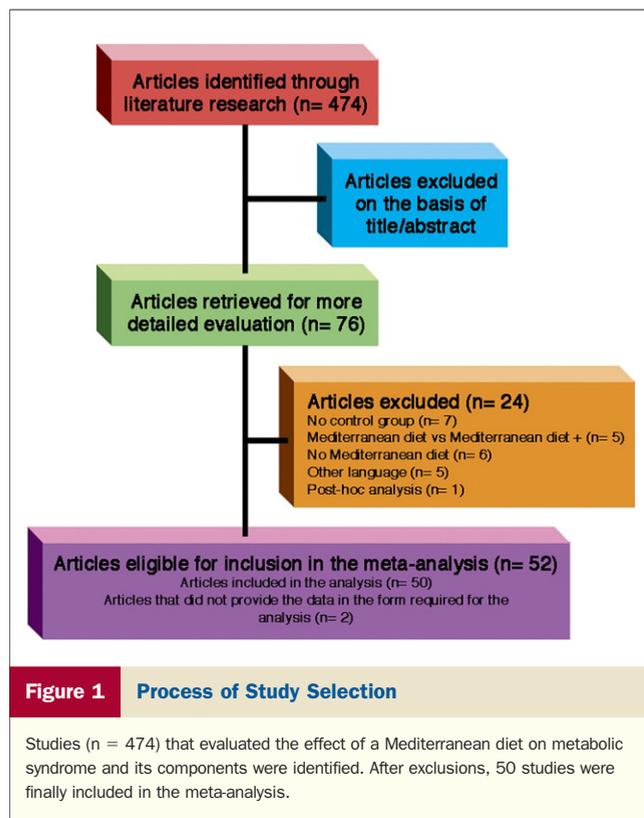
chol = cholesterol; CHO = carbohydrates; IHD = ischemic heart disease; LCM = low-carbohydrate Mediterranean diet; MI = myocardial infarction; MUFA = monounsaturated fatty acids; Pro = protein; PUFA = polyunsaturated fatty acids; SF = saturated fat; SFA = saturated fatty acids; TM = traditional Mediterranean 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
<b>Cross-sectional studies</b>							
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)*
<b>Prospective studies</b>							
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)	

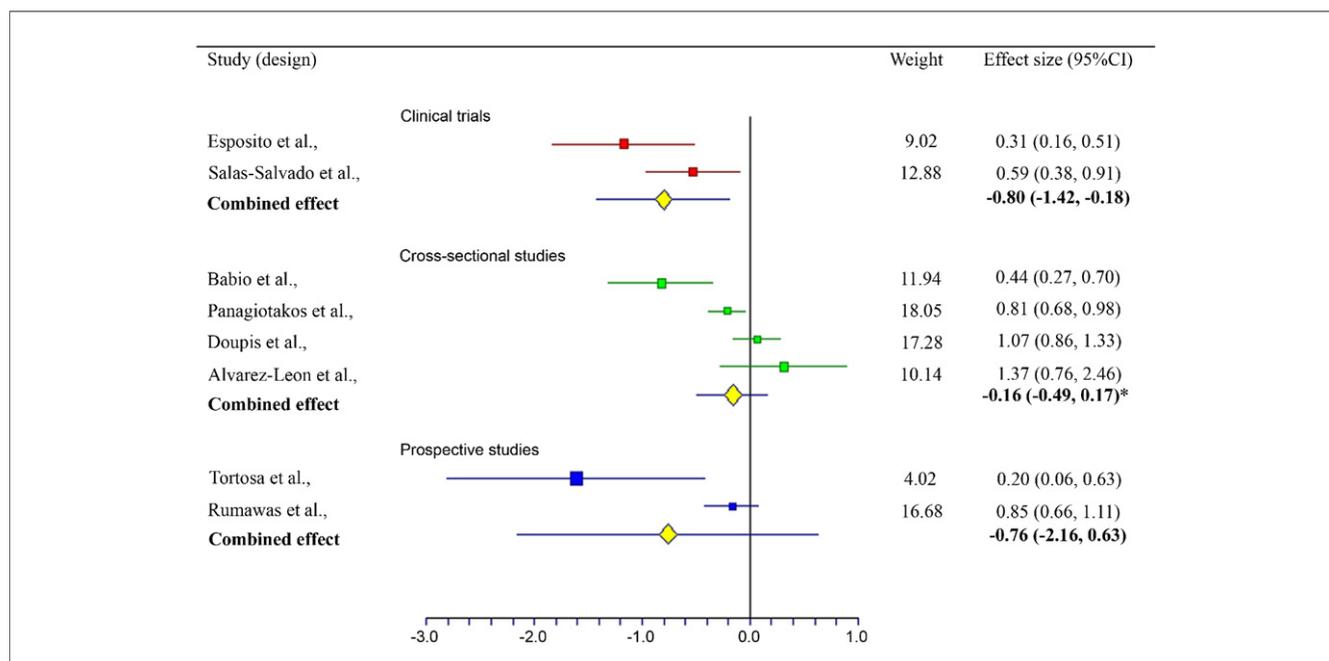
Data are presented as mean difference between highest versus lowest category of diet score (95% confidence interval). \*Significant associations.

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



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)
Busemi 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 -43.61)	-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).

### 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

**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.

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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## REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414–31.
2. Day C. Metabolic syndrome, or What you will: definitions and epidemiology. *Diab Vasc Dis Res* 2007;4:32–8.
3. Panagiotakos DB, Polychronopoulos E. The role of Mediterranean diet in the epidemiology of metabolic syndrome; converting epidemiology to clinical practice. *Lipids Health Dis* 2005;4:7.

4. Athyros VG, Ganotakis ES, Bathianaki M, et al. Awareness, treatment and control of the metabolic syndrome and its components: a multicentre Greek study. *Hellenic J Cardiol* 2005;46:380-6.
5. Pitsavos C, Panagiotakos D, Weinem M, Stefanadis C. Diet, exercise and the metabolic syndrome. *Rev Diabet Stud* 2006;3:118-26.
6. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002;288:2569-78.
7. Keys A, Menotti A, Karvonen MJ, et al. The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* 1986;124:903-15.
8. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
9. Giugliano D, Esposito K. Mediterranean diet and metabolic diseases. *Curr Opin Lipidol* 2008;19:63-8.
10. Buckland G, Bach A, Serra-Majem L. Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. *Obes Rev* 2008;9:582-93.
11. Pitsavos C, Panagiotakos DB, Tzima N, et al. Adherence to the Mediterranean diet is associated with total antioxidant capacity in healthy adults: the ATTICA study. *Am J Clin Nutr* 2005;82:694-9.
12. Ryan M, McInerney D, Owens D, Collins P, Johnson A, Tomkin GH. Diabetes and the Mediterranean diet: a beneficial effect of oleic acid on insulin sensitivity, adipocyte glucose transport and endothelium-dependent vasoreactivity. *QJM* 2000;93:85-91.
13. Dai J, Jones DP, Goldberg J, et al. Association between adherence to the Mediterranean diet and oxidative stress. *Am J Clin Nutr* 2008;88:1364-70.
14. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA study. *J Am Coll Cardiol* 2004;44:152-8.
15. Esposito K, Ciotola M, Giugliano D. Mediterranean diet and the metabolic syndrome. *Mol Nutr Food Res* 2007;51:1268-74.
16. Jula A, Marniemi J, Huupponen R, Virtanen A, Rastas M, Ronnema T. Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomized controlled trial. *JAMA* 2002;287:598-605.
17. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2004;80:1012-8.
18. Stroup DF, Berlin JA, Morton SC, et al., for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;283:2008-12.
19. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses. Lancet* 1999;354:1896-900.
20. Mantzoros CS, Williams CJ, Manson JE, Meigs JB, Hu FB. Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women. *Am J Clin Nutr* 2006;84:328-35.
21. McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. *Int J Obes Relat Metab Disord* 2001;25:1503-11.
22. Toobert DJ, Glasgow RE, Strycker LA, et al. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: a randomized clinical trial. *Diabetes Care* 2003;26:2288-93.
23. Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB, Connor WE. Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. *Am J Clin Nutr* 2004;80:668-73.
24. Tuttle KR, Shuler LA, Packard DP, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial). *Am J Cardiol* 2008;101:1523-30.
25. Rumawas ME, Meigs JB, Dwyer JT, McKeown NM, Jacques PF. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. *Am J Clin Nutr* 2009;90:1608-14.
26. Singh N, Graves J, Taylor PD, MacAllister RJ, Singer DR. Effects of a 'healthy' diet and of acute and long-term vitamin C on vascular function in healthy older subjects. *Cardiovasc Res* 2002;56:118-25.
27. Sondergaard E, Moller JE, Egstrup K. Effect of dietary intervention and lipid-lowering treatment on brachial vasoreactivity in patients with ischemic heart disease and hypercholesterolemia. *Am Heart J* 2003;145:E19.
28. Ambring A, Friberg P, Axelsen M, et al. Effects of a Mediterranean-inspired diet on blood lipids, vascular function and oxidative stress in healthy subjects. *Clin Sci (Lond)* 2004;106:519-25.
29. Michalsen A, Lehmann N, Pithan C, et al. Mediterranean diet has no effect on markers of inflammation and metabolic risk factors in patients with coronary artery disease. *Eur J Clin Nutr* 2006;60:478-85.
30. Bos MB, de Vries JH, Feskens EJ, et al. Effect of a high monounsaturated fatty acids diet and a Mediterranean diet on serum lipids and insulin sensitivity in adults with mild abdominal obesity. *Nutr Metab Cardiovasc Dis* 2010;20:591-8.
31. Papadaki A, Scott JA. Follow-up of a web-based tailored intervention promoting the Mediterranean diet in Scotland. *Patient Educ Couns* 2008;73:256-63.
32. Lindeberg S, Jonsson T, Granfeldt Y, et al. A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. *Diabetologia* 2007;50:1795-807.
33. Romaguera D, Norat T, Mouw T, et al. Adherence to the Mediterranean diet is associated with lower abdominal adiposity in European men and women. *J Nutr* 2009;139:1728-37.
34. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *Br J Nutr* 2003;90:717-27.
35. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, Basterra-Gortari FJ, Nunez-Cordoba JM, Martinez-Gonzalez MA. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. *Diabetes Care* 2007;30:2957-9.
36. Babio N, Bullo M, Basora J, et al. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. *Nutr Metab Cardiovasc Dis* 2009;19:563-70.
37. Salas-Salvado J, Fernandez-Ballart J, Ros E, et al. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med* 2008;168:2449-58.
38. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al. Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. *Am Heart J* 2004;147:106-12.
39. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004;292:1440-6.
40. Tzima N, Pitsavos C, Panagiotakos DB, et al. Mediterranean diet and insulin sensitivity, lipid profile and blood pressure levels, in overweight and obese people; the Attica study. *Lipids Health Dis* 2007;6:22.
41. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;289:1799-804.
42. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006;145:1-11.
43. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009;151:306-14.
44. Athyros VG, Kakafika AI, Papageorgiou AA, et al. Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. *Nutr Metab Cardiovasc Dis* 2010;21:213-21.
45. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab* 2011;12:204-9.
46. Gomez P, Fernandez de la Puebla RA, Castro P, et al. [Effect of the Mediterranean diet on fasting concentrations of activated factor VII in healthy persons]. *Rev Esp Cardiol* 2005;58:285-9.

47. Bravo-Herrera MD, Lopez-Miranda J, Marin C, et al. Tissue factor expression is decreased in monocytes obtained from blood during Mediterranean or high carbohydrate diets. *Nutr Metab Cardiovasc Dis* 2004;14:128–32.
48. Barzi F, Woodward M, Marfisi RM, Tavazzi L, Valagussa F, Marchioli R. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. *Eur J Clin Nutr* 2003;57:604–11.
49. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–41.
50. Nunez-Cordoba JM, Valencia-Serrano F, Toledo E, Alonso A, Martinez-Gonzalez MA. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) study. *Am J Epidemiol* 2009;169:339–46.
51. Rallidis LS, Lekakis J, Kolomvotsou A, et al. Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity. *Am J Clin Nutr* 2009;90:263–8.
52. Panagiotakos DB, Tzima N, Pitsavos C, et al. The association between adherence to the Mediterranean diet and fasting indices of glucose homeostasis: the ATTICA study. *J Am Coll Nutr* 2007;26:32–8.
53. Paniagua JA, de la Sacristana AG, Sanchez E, et al. A MUFA-rich diet improves postprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. *J Am Coll Nutr* 2007;26:434–44.
54. Hajer GR, van Haften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008;29:2959–71.
55. Rodriguez-Villar C, Perez-Heras A, Mercade I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. *Diabet Med* 2004;21:142–9.
56. Vincent-Baudry S, Defoort C, Gerber M, et al. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-months intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr* 2005;82:964–71.
57. Fuentes F, Lopez-Miranda J, Sanchez E, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. *Ann Intern Med* 2001;134:1115–9.
58. Bellido C, Lopez-Miranda J, Perez-Martinez P, et al. The Mediterranean and CHO diets decrease VCAM-1 and E-selectin expression induced by modified low-density lipoprotein in HUVECs. *Nutr Metab Cardiovasc Dis* 2006;16:524–30.
59. Perez-Jimenez F, Lopez-Miranda J, Pinillos MD, et al. A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. *Diabetologia* 2001;44:2038–43.
60. Perez-Martinez P, Lopez-Miranda J, Blanco-Colio L, et al. The chronic intake of a Mediterranean diet enriched in virgin olive oil, decreases nuclear transcription factor kappaB activation in peripheral blood mononuclear cells from healthy men. *Atherosclerosis* 2007;194:e141–6.
61. Fernandez de la Puebla RA, Fuentes F, Perez-Martinez P, et al. A reduction in dietary saturated fat decreases body fat content in overweight, hypercholesterolemic males. *Nutr Metab Cardiovasc Dis* 2003;13:273–7.
62. Castro P, Miranda JL, Gomez P, et al. Comparison of an oleic acid enriched-diet vs NCEP-I diet on LDL susceptibility to oxidative modifications. *Eur J Clin Nutr* 2000;54:61–7.
63. Buscemi S, Verga S, Tranchina MR, Cottone S, Cerasola G. Effects of hypocaloric very-low-carbohydrate diet vs. Mediterranean diet on endothelial function in obese women. *Eur J Clin Invest* 2009;39:339–47.
64. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454–9.
65. Trichopoulos A, Bamia C, Norat T, et al. Modified Mediterranean diet and survival after myocardial infarction: the EPIC-Elderly study. *Eur J Epidemiol* 2007;22:871–81.
66. Alvarez-Leon EE, Henriquez P, Serra-Majem L. Mediterranean diet and metabolic syndrome: a cross-sectional study in the Canary Islands. *Public Health Nutr* 2006;9:1089–98.
67. Bach-Faig A, Geleva D, Carrasco JL, Ribas-Barba L, Serra-Majem L. Evaluating associations between Mediterranean diet adherence indexes and biomarkers of diet and disease. *Public Health Nutr* 2006;9:1110–7.
68. di Giuseppe R, Bonanni A, Olivieri M, et al. Adherence to Mediterranean diet and anthropometric and metabolic parameters in an observational study in the ‘Alto Molise’ region: the MOLI-SAL project. *Nutr Metab Cardiovasc Dis* 2008;18:415–21.
69. Esposito K, Maiorino MI, Di Palo C, Giugliano D. Adherence to a Mediterranean diet and glycaemic control in Type 2 diabetes mellitus. *Diabet Med* 2009;26:900–7.
70. Doupis J, Dimosthenopoulos C, Diamanti K, Perrea D, Katsilambros N, Makrilakis K. Metabolic syndrome and Mediterranean dietary pattern in a sample of young, male, Greek navy recruits. *Nutr Metab Cardiovasc Dis* 2009;19:e7–8.
71. Trichopoulos A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599–608.
72. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis* 2006;16:559–68.
73. Rumawas ME, Dwyer JT, McKeown NM, Meigs JB, Rogers G, Jacques PF. The development of the Mediterranean-style dietary pattern score and its application to the American diet in the Framingham Offspring Cohort. *J Nutr* 2009;139:1150–6.
74. Alberti-Fidanza A, Fidanza F. Mediterranean Adequacy Index of Italian diets. *Public Health Nutr* 2004;7:937–41.
75. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–421.
76. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet* 2005;366:1059–62.
77. Sanchez-Villegas A, Martinez JA, De Irala J, Martinez-Gonzalez MA. Determinants of the adherence to an “a priori” defined Mediterranean dietary pattern. *Eur J Nutr* 2002;41:249–57.

**Key Words:** blood pressure ■ lipids ■ Mediterranean diet ■ meta-analysis ■ metabolic syndrome (MS) ■ waist circumference.