

Effect of a Mediterranean Diet Supplemented With Nuts on Metabolic Syndrome Status

One-Year Results of the PREDIMED Randomized Trial

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Background: Epidemiological studies suggest that the Mediterranean diet (MedDiet) may reduce the risk of developing the metabolic syndrome (MetS). We compared the 1-year effect of 2 behavioral interventions to implement the MedDiet vs advice on a low-fat diet on MetS status.

Methods: A total of 1224 participants were recruited from the PREDIMED (Prevención con Dieta Mediterránea) Study, a multicenter, 3-arm, randomized clinical trial to determine the efficacy of the MedDiet on the primary prevention of cardiovascular disease. Participants were older subjects at high risk for cardiovascular disease. Interventions were quarterly education about the MedDiet plus provision of either 1 L/wk of virgin olive oil (MedDiet + VOO) or 30 g/d of mixed nuts (MedDiet + nuts), and advice on a low-fat diet (control diet). All diets were ad libitum, and there was no increase in physical activity for any of the interventions. Lifestyle variables and MetS features as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria were assessed.

Results: At baseline, 61.4% of participants met criteria for the MetS. One-year prevalence was reduced by 6.7%, 13.7%, and 2.0% in the MedDiet + VOO, MedDiet + nuts, and control diet groups, respectively (MedDiet + nuts vs control groups, $P = .01$; MedDiet + VOO vs control group, $P = .18$). Incident rates of the MetS were not significantly different among groups (22.9%, 17.9%, and 23.4%, respectively). After adjustment for sex, age, baseline obesity status, and weight changes, the odds ratios for reversion of MetS were 1.3 (95% confidence interval, 0.8-2.1) for the MedDiet + VOO group and 1.7 (1.1-2.6) for the MedDiet + nuts group compared with the control diet group.

Conclusion: A traditional MedDiet enriched with nuts could be a useful tool in the management of the MetS.

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THE METABOLIC SYNDROME (MetS) is a constellation of metabolic abnormalities that includes abdominal obesity, dyslipidemia, elevated blood pressure, and hyperglycemia, all of which are well-documented risk factors for cardiovascular disease (CVD). The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) recommends identification and treatment of this high-risk condition and provides a simple set of diagnostic criteria.^{1,2} The MetS components separately increase the risk of diabetes mellitus, CVD, and all-cause mortality, but the full syn-

drome is associated with risk increases that are greater than the sum of those incurred by each each feature.³ The prevalence of the MetS is increasing, affecting almost one-fourth of the global adult population, in direct relation to the global epidemic of obesity and diabetes mellitus.⁴ As such, the MetS is becoming a major public health problem worldwide.⁵

Development of the MetS depends on a complex interaction between still largely unknown genetic determinants and environmental factors, including dietary patterns.⁶

Epidemiological studies suggest that unhealthy diets (ie, Western-style di-

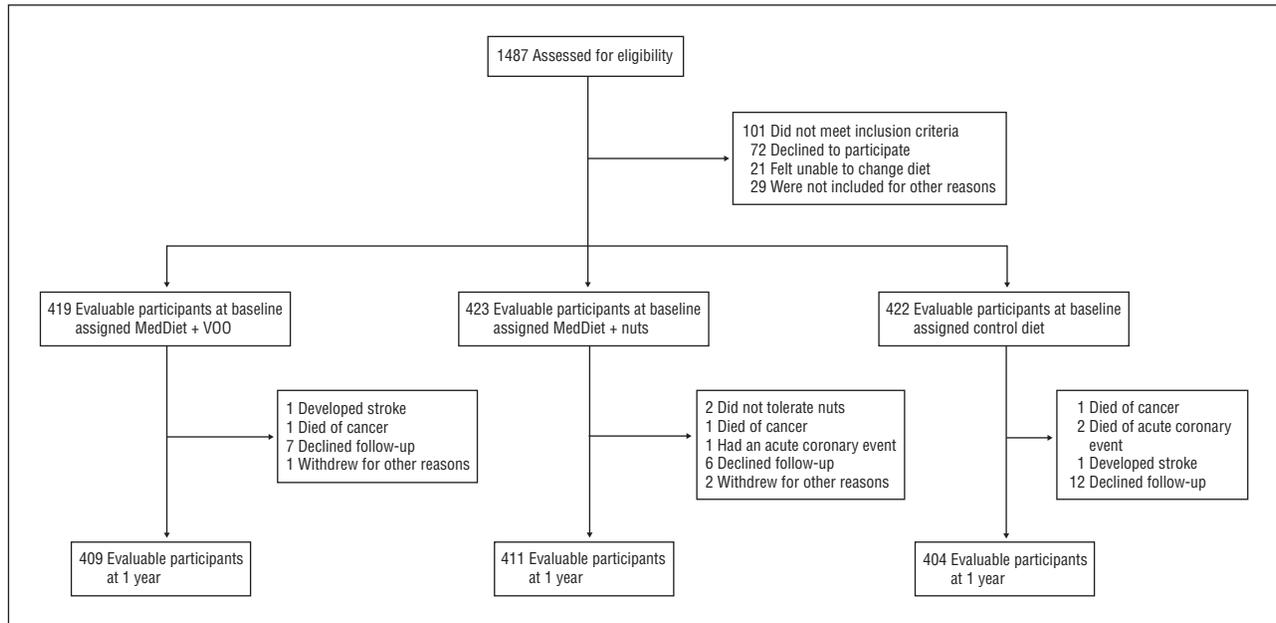


Figure 1. Flowchart of study participants. MedDiet indicates Mediterranean diet; VOO, virgin olive oil.

etary patterns) promote the MetS, whereas diets rich in fruits, vegetables, grains, fish, and low-fat dairy products have a protective role.⁶⁻⁹ Recently, 2 studies conducted in southern European populations showed that greater adherence to the Mediterranean diet (MedDiet), a reputedly healthy dietary pattern,¹⁰ was also associated with reduced prevalent¹¹ and incident¹² MetS. To our knowledge, only 3 feeding trials have assessed the effect of dietary patterns on MetS status to date.¹³⁻¹⁵ These studies used a behavioral program to implement a relatively low-fat MedDiet,¹³ intensive lifestyle intervention with inclusion of a vegetable-rich diet restricted in animal fat,¹⁴ and the Dietary Approaches to Stop Hypertension eating plan,¹⁵ in comparison with standard advice. In all of these studies, a decreased prevalence of MetS was shown among the intervention groups. Of note, energy intake was reduced in the intervention arms, and substantial weight loss was achieved.¹³⁻¹⁵

The traditional MedDiet is characterized by a high intake of cereals, vegetables, fruits, and olive oil; a moderate intake of fish and alcohol, mostly wine; and a low intake of dairy products, meats, and sweets.¹⁰ The MedDiet is a high-fat, high-unsaturated-fat food pattern because olive oil is used abundantly as culinary fat and for dressing dishes, which facilitates intake of substantial quantities of vegetables. Nuts are another high-fat, high-unsaturated-fat food commonly consumed in the MedDiet. Evidence from epidemiological and clinical studies suggests that regular nut intake might have a positive effect on adiposity, insulin resistance, and other metabolic disturbances linked to the MetS.^{16,17} An ad libitum (without energy restriction), high-fat MedDiet, as traditionally followed in Mediterranean countries, has not been tested for effects on the MetS. Therefore, we compared the 1-year effect on MetS status of behavioral intervention with 2 high-fat MedDiets, one supplemented with virgin olive oil (VOO) and another supplemented with mixed nuts, with that of advice

on a low-fat diet in volunteers at high risk for CVD; all diets were ad libitum.

METHODS

PATIENTS

The study included participants recruited into the PREDIMED (Prevención con Dieta Mediterránea) trial between October 1, 2003, and June 25, 2004. The PREDIMED study is a large, parallel-group, multicenter, controlled 4-year clinical trial that aims to assess the effects of the traditional MedDiet on the primary prevention of CVD. Full details of the protocol have been published elsewhere.¹⁸ The trial is currently ongoing with an estimated 9000 participants at high risk for CVD assigned to 3 intervention groups: MedDiet with VOO (MedDiet + VOO), MedDiet with mixed nuts (MedDiet + nuts), and advice about a low-fat diet (control). All participants gave informed consent to a protocol approved by the local institutional review boards.

Potential candidates (n=1487) were selected by physicians at primary care centers affiliated with 10 teaching hospitals in Spain on the basis of the following eligibility criteria: community-dwelling men, aged 55 to 80 years, and women, aged 60 to 80 years; absence of prior CVD; and presence of type 2 diabetes mellitus and/or 3 or more CVD risk factors: current smoker, hypertension (blood pressure $\geq 140/90$ mm Hg or treatment with antihypertensive drugs), low-density lipoprotein cholesterol level of 160 mg/dL or higher or treatment with hypolipidemic drugs, high-density lipoprotein (HDL) cholesterol level of 40 mg/dL or lower, body mass index (calculated as weight in kilograms divided by height in meters squared) of 25 or higher, or family history of premature CVD. In addition to a history of CVD, exclusion criteria were having a severe long-term illness, drug or alcohol addiction, body mass index of 35 or higher, and history of allergy or intolerance to olive oil or nuts, as previously described.¹⁸ Eligible candidates were invited to attend a screening visit that included a face-to-face interview with an investigator and administration of a 26-item questionnaire to inquire about medical conditions and risk factors related to eligibility.

INTERVENTIONS

After the screening visit, participants were randomly assigned to 1 of 3 study arms. At each recruiting center, the same dietician delivered the interventions to participants in all 3 groups. Based on the initial 14-item questionnaire addressing individual adherence to the MedDiet, dieticians gave personalized dietary advice to participants in both MedDiet groups during a 30-minute session. Instructions were given about how to increase the MedDiet score, including use of olive oil for cooking and dressing; increased consumption of fruit, vegetables, and fish; consumption of white meat instead of red or processed meat; preparation of homemade sauce with tomato, garlic, onion, aromatic herbs, and olive oil to dress vegetables, pasta, rice, and other dishes; and, for alcohol drinkers, moderate consumption of red wine.

At study inclusion and quarterly thereafter, dieticians delivered a separate 60-minute group session for each MedDiet group. Sessions consisted of informative talks and delivery of written material with elaborated descriptions of typical Mediterranean foods, seasonal shopping lists, meal plans, and recipes. Participants assigned to the MedDiet groups were given either free VOO (15 L for 3 months) or packets of mixed nuts (1350 g of walnuts [15 g/d], 675 g of hazelnuts [7.5 g/d], and 675 g of almonds [7.5 g/d] every 3 months). To improve compliance and account for family needs, participants in the respective MedDiet groups received 5 L of extra VOO or an additional packet of 1000 g of nuts for 3 months. Participants assigned to the control diet received general oral and written recommendations to reduce all types of fat (from both animal and vegetable sources), but were not given individualized intervention. Nevertheless, to increase both compliance and retention, participants in the control group periodically received small gifts, such as oil dispensers to reduce oil consumption, aprons, shopping bags, or low-fat recipe books. Energy restriction was not advised for any of the intervention groups. All participants had free and continuous access to their center dietician throughout the study.

MEASUREMENTS

At baseline we administered a questionnaire about lifestyle variables, medical conditions, and medication use; a 14-item questionnaire designed to assess the degree of adherence to the traditional MedDiet that is an extension of a previously validated questionnaire¹⁹; a 137-item validated food frequency questionnaire²⁰; and the validated Spanish version²¹ of the Minnesota Leisure-Time Physical Activity Questionnaire. We performed anthropometrical and blood pressure measurements and obtained fasting blood samples. All examinations were repeated at 1 year.

Trained personnel made the following measurements: weight and height with calibrated scales and a wall-mounted stadiometer, respectively; waist circumference midway between the lowest rib and the iliac crest using an anthropometric tape; and blood pressure in triplicate with a validated semiautomatic oscillometer (HEM-70CP; OMRON, Hoofddrop, the Netherlands). Energy and nutrient intake were derived from Spanish food composition tables. Samples of fasting serum and EDTA plasma were coded, shipped to a central laboratory, and stored at -80°C until assay. Laboratory technicians were blinded to the intervention. Analytes measured in frozen serum or plasma samples, as appropriate, were blood glucose level by the glucose-oxidase method, cholesterol and triglyceride levels by enzymatic procedures, and HDL cholesterol level by an accelerator selective detergent method (Horiba ABX Diagnostics, Montpellier, France). In a random sample of participants, we measured urinary tyrosol and hydroxytyrosol levels ($n=375$) by gas chromatography-mass spectrometry as markers of compliance with

VOO intake²² and plasma α -linolenic acid level ($n=300$) by gas chromatography as a measure of adherence to walnut intake.²³

The MetS was defined according to updated ATP III criteria,² which require that 3 or more of the following conditions be met: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (triglycerides level ≥ 150 mg/dL), low HDL cholesterol level (<40 mg/dL in men and <50 mg/dL in women), elevated fasting blood glucose level (≥ 100 mg/dL), and elevated blood pressure (systolic ≥ 130 mm Hg, diastolic ≥ 85 mm Hg, or taking antihypertensive medication). Participants who were being treated with antidiabetic, antihypertensive, or triglyceride-lowering medications were considered to be diabetic, hypertensive, or hypertriglyceridemic, respectively. At the 1-year assessment, we calculated the proportion of participants who developed each of the components of MetS or whose status reverted. We also calculated the proportion of participants who did not meet criteria at baseline but developed at least 3 MetS features at 1 year (ie, incident MetS) and those who met MetS criteria at baseline but had fewer than 3 MetS features at the 1-year assessment (ie, reverted MetS). The severity of MetS was calculated as the average number of MetS features present.

To convert HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113.

STATISTICAL METHODS

Analysis of variance and χ^2 tests were used to compare qualitative traits and means of quantitative variables, respectively, between intervention groups. We used repeated-measures analysis of variance to examine changes of numerical variables between baseline and 1 year. The MetS status was based on measurements at 1 year and was assessed in the entire sample and separately for those who met the criterion at baseline but not at the 1-year assessment (reverted MetS) and those who did not meet the criterion at baseline but met the criterion at the 1-year assessment (incident MetS). Differences in the incidence of MetS development and reversion among treatment groups were assessed by using logistic regression analysis with models adjusted for sex, age, obesity status at baseline, and body weight change. The 2-sided level of significance was set at $P < .05$. Analyses were performed using SPSS statistical software, version 14 (SPSS Inc, Chicago, Illinois).

RESULTS

Of 1487 subjects assessed for eligibility, 1264 (85.0%) were randomly assigned to 1 of 3 intervention groups (**Figure 1**). After discounting withdrawals, MetS status at 1 year was assessed in 1224 participants (96.8%).

Participants' baseline characteristics indicated that they belonged to a high-risk cohort (**Table 1**). The groups were well balanced with respect to demographic characteristics, CVD risk factors, MetS features, and medication use, with the exception of the proportion of men, which was higher in the group assigned MedDiet + nuts. A total of 751 subjects (61.4%) met ATP III criteria for the MetS, and the distribution among groups was similar (**Table 1** and **Figure 2**). The MetS severity, calculated as the number of positive criteria (mean, 2.8), did not differ by treatment group, sex, or age. The most frequent MetS features were elevated blood pressure (95.8%), hyperglycemia (66.9%), and abdominal obesity (66.5%).

Table 1. Baseline Characteristics of Participants Completing 1 Year of Follow-up

Variable	Study Group ^a			P Value ^b
	MedDiet + VOO (n=409)	MedDiet + Nuts (n=411)	Control Diet (n=404)	
Age, y, mean (SD)	67.2 (5.9)	67.2 (5.7)	67.9 (6.2)	.14
Men	185 (45.2)	209 (50.9)	172 (42.6)	.05
Current smokers	61 (14.9)	71 (17.3)	67 (16.6)	.64
Body weight, kg, mean (SD)	75.1 (10.8)	75.8 (11.0)	75.4 (11.3)	.60
BMI, mean (SD)	29.2 (3.1)	29.3 (3.2)	29.5 (3.5)	.45
Hypertension ^c	332 (81.2)	333 (81.0)	328 (81.2)	.99
Dyslipidemia ^d	260 (63.6)	256 (62.3)	272 (67.3)	.30
Type 2 diabetes mellitus	191 (46.7)	188 (45.7)	184 (45.5)	.94
Metabolic syndrome	252 (61.6)	249 (60.6)	250 (61.9)	.92
Metabolic syndrome components ^e				
Abdominal obesity	267 (65.3)	265 (64.5)	282 (69.8)	.22
Low HDL cholesterol level	108 (26.4)	87 (21.2)	97 (24.0)	.12
High triglycerides level	122 (29.8)	119 (29.0)	127 (31.4)	.74
High fasting serum glucose level	276 (67.5)	274 (66.7)	269 (66.6)	.96
Blood pressure \geq 130/85 mm Hg	397 (97.1)	391 (95.1)	384 (95.0)	.27
Medication				
Antihypertensive agents	301 (73.6)	306 (74.5)	300 (74.3)	.96
Statins	143 (35.0)	138 (33.6)	154 (38.1)	.38
Fibrates	11 (2.7)	12 (2.9)	8 (2.0)	.67
Insulin	25 (6.1)	26 (6.3)	26 (6.4)	.98
Oral hypoglycemic agents	122 (29.8)	108 (26.3)	123 (30.4)	.37
Aspirin or antiplatelet drugs	100 (24.5)	100 (24.3)	80 (19.8)	.19

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL—high-density lipoprotein; MedDiet, Mediterranean diet; VOO, virgin olive oil.

^aData are given as number (percentage) unless otherwise indicated.

^bP value for comparisons across groups calculated with a Pearson χ^2 test for categorical variables or 1-way analysis of variance for continuous variables.

^cBlood pressure 140/90 mm Hg or higher or treatment with antihypertensive drugs.

^dFor an explanation of the criteria, see the “Measurements” subsection of the “Methods” section.

^eThe metabolic syndrome components are defined according to the National Cholesterol Education Program’s Adult Treatment Panel III criteria. For an explanation of the criteria, see the “Measurements” subsection of the “Methods” section.

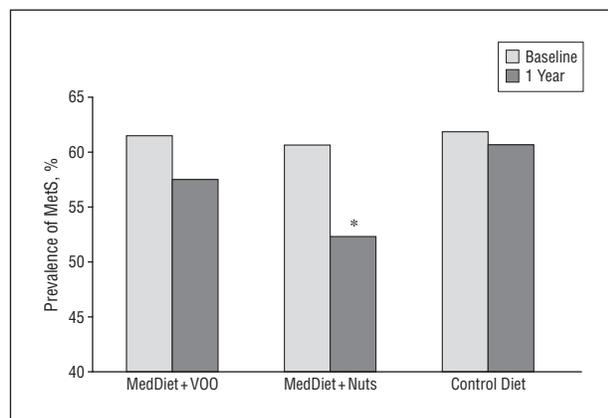


Figure 2. Baseline and 1-year prevalence of the metabolic syndrome (MetS) by diet assignment. MedDiet indicates Mediterranean diet; VOO, virgin olive oil. * $P < .05$ vs control diet.

FOOD INTAKE AND TOTAL BODY WEIGHT

Intake of supplemental foods was good, as was shown by objective measurements of intake markers in a random sample of participants. Urinary tyrosol and hydroxytyrosol levels increased from baseline among participants assigned to the MedDiet + VOO ($P = .01$) and participants assigned to the MedDiet + nuts group ($P = .03$); however, those assigned the MedDiet + nuts

showed increased plasma α -linolenic acid levels ($P = .02$). No changes occurred in the control group.

The main dietary changes recorded at 1 year were large increases in VOO and nut consumption in the corresponding MedDiet groups (**Table 2**). Olive oil and nut intake decreased in the low-fat control diet group. Compared with this group, the 2 MedDiet groups increased their intake of vegetables and legumes. Participants in all groups increased intake of fruits and decreased intake of meat and meat products while maintaining a low level of alcohol consumption. These food changes translated into the corresponding changes in energy and nutrient intake (**Table 3**). Participants assigned to the 2 MedDiet groups had increased energy and total fat intake as well as a reciprocal decrease in carbohydrate intake; these changes were more marked for the MedDiet + nuts group. Both MedDiet groups increased intake of fiber and unsaturated fatty acids. The control group had decreased intake of energy, total fat, and polyunsaturated fatty acids and increased intake of carbohydrates. All groups had decreased consumption of saturated fatty acids. The mean daily contribution of nutrients from supplemental foods is shown in **Table 4**. Estimated changes in energy expenditure from physical activity were similar among the 3 groups. The score of adherence to the MedDiet increased substantially in the 2 MedDiet groups and increased marginally in the control group. No significant mean (SD) 1-year changes in

Table 2. Daily Consumption of Key Foods and 14-Point MedDiet Score^a

Food, per Day	MedDiet + VOO	P Value ^b	MedDiet + Nuts	P Value ^b	Control Diet	P Value ^b	P Value ^c
VOO, g							
Baseline	24.0 (23.2)	<.001	24.6 (22.6)	.001	20.0 (22.9)	.07	<.001 ^{d,e}
1 Year	49.8 (17.1)		28.3 (25.1)		22.1 (22.5)		
Refined OO, g							
Baseline	18.5 (21.8)	<.001	16.8 (20.4)	.15	20.5 (20.1)	.001	<.001 ^{d,e,f}
1 Year	1.01 (6.0)		18.3 (23.0)		17.0 (19.8)		
Total nuts, g							
Baseline	9.4 (11.6)	<.001	12.2 (13.7)	<.001	9.9 (13.7)	.03	<.001 ^{d,e,f}
1 Year	15.2 (14.1)		39.0 (19.6)		7.8 (11.5)		
Vegetables, No. of 125-g servings							
Baseline	2.36 (0.96)	<.001	2.47 (1.01)	<.001	2.36 (1.10)	.21	.02 ^d
1 Year	2.65 (1.00)		2.70 (0.99)		2.43 (1.10)		
Legumes, No. of 40-g servings							
Baseline	0.44 (0.20)	<.001	0.45 (0.20)	<.001	0.44 (0.23)	.75	<.001 ^{d,f}
1 Year	0.53 (0.21)		0.53 (0.21)		0.44 (0.22)		
Fruits, No. of 125-g servings							
Baseline	2.57 (1.44)	<.001	2.80 (1.54)	<.001	2.75 (1.66)	<.001	.35
1 Year	3.04 (1.25)		3.11 (1.47)		3.10 (1.57)		
Fish or seafood, No. of 125-g servings							
Baseline	0.77 (0.32)	.07	0.81 (0.32)	.003	0.76 (0.32)	.09	.003 ^{d,f}
1 Year	0.81 (0.32)		0.86 (0.32)		0.73 (0.33)		
Meat or meat products, No. of 150-g servings							
Baseline	0.96 (0.38)	.02	0.97 (0.35)	<.001	0.92 (0.35)	.001	.27
1 Year	0.92 (0.33)		0.89 (0.32)		0.86 (0.30)		
Cereals, No. of 50-g servings							
Baseline	3.04 (1.73)	.62	3.05 (1.69)	.86	2.93 (1.65)	.38	.89
1 Year	2.96 (1.41)		3.00 (1.50)		2.84 (1.62)		
Dairy products, No. of 200-g servings							
Baseline	1.87 (1.04)	.02	1.82 (1.02)	.34	1.67 (1.18)	.63	.04
1 Year	1.99 (1.05)		1.78 (1.02)		1.85 (1.12)		
Alcohol, g							
Baseline	10.1 (14.9)	.73	12.1 (17.8)	.63	10.1 (15.4)	.42	.96
1 Year	9.9 (14.3)		11.8 (16.5)		9.7 (14.9)		
MedDiet score							
Baseline	8.0 (1.8)	<.001	8.1 (1.9)	<.001	8.4 (1.8)	.05	<.008 ^{d,f}
1 Year	9.8 (1.6)		9.9 (1.4)		8.7 (1.5)		

Abbreviations: MedDiet, Mediterranean diet; OO, olive oil; VOO, virgin olive oil.

^aData are given as mean (SD) unless otherwise indicated. $P < .05$ indicates statistical significance.

^bDifferences from baseline by paired t test.

^cDifferences among diets by repeated measures analysis of variance.

^d $P < .05$ for differences between MedDiet + VOO and control diet groups.

^e $P < .05$ for differences between MedDiet + VOO and MedDiet + nuts groups.

^f $P < .05$ for differences between MedDiet + nuts and control diet groups.

body weight occurred: 0.3 (3.0), -0.2 (3.7), and -0.1 (3.2) kg after the MedDiet + VOO, MedDiet + nuts, and control groups, respectively (analysis of variance, $P = .05$).

Dieticians reported that 49 participants in the MedDiet + nuts group had difficulty chewing nuts. Advice to consume nuts crushed and mixed with low-fat yogurt or salad solved this problem for all but 2 participants, who withdrew from the study (Figure 1). Subjects who were assigned to the MedDiet + VOO or to the low-fat diet reported no adverse effects.

CHANGES IN MetS STATUS

One-year prevalence of high waist circumference, elevated triglycerides level, and high blood pressure were significantly reduced in the MedDiet + nuts group compared with the control group ($P < .05$). The overall preva-

lence of MetS at the 1-year assessment was reduced by 6.7%, 13.7%, and 2.0% in the MedDiet + VOO, MedDiet + nuts, and control groups, respectively (MedDiet + nuts vs control diet, $P < .05$) (Figure 2). No significant differences in MetS severity were observed at the end of the study. The changes in MetS prevalence were the result of variations in incidence rates among participants who did not meet criteria at baseline and in reversion rates among those who had the MetS when the study began (Table 5). Incident MetS rates were not significantly different among groups (MedDiet + VOO, 22.9%; MedDiet + nuts, 17.9%; and control, 23.4%), whereas reversion rates were highest in the MedDiet + nuts group ($P < .05$ vs control group). This was in part owing to a lesser incidence of elevated triglyceride levels and high blood pressure, together with higher rates of reversion of abdominal obesity. Compared with participants in the control group, those in the MedDiet +

Table 3. Baseline Level and 1-Year Changes in Energy, Nutrient Intake, and Physical Activity^a

Variable	MedDiet + VOO	P Value ^b	MedDiet + Nuts	P Value ^b	Control Diet	P Value ^b	P Value ^c
Energy, kcal							
Baseline	2266 (563)	.07	2351 (611)	.001	2223 (546)	<.001	<.001 ^{d,e}
1 Year	2314 (508)		2442 (517)		2122 (523)		
Energy from total protein, %							
Baseline	16.5 (2.7)	.86	16.4 (2.5)	.06	16.5 (2.7)	.26	.11
1 Year	16.5 (2.5)		16.2 (2.4)		16.7 (2.9)		
Energy from total carbohydrates, %							
Baseline	40.4 (6.2)	.05	40.4 (6.6)	<.001	41.0 (7.7)	.01	<.001 ^{d,e}
1 Year	39.8 (5.6)		37.8 (5.8)		42.0 (6.2)		
Fiber, g/1000 kcal							
Baseline	10.3 (2.7)	<.001	10.6 (2.7)	<.001	10.8 (3.1)	.001	.08
1 Year	11.1 (2.6)		11.5 (2.9)		11.1 (3.1)		
Energy from total fat, %							
Baseline	40.0 (5.9)	.03	39.8 (5.9)	<.001	39.3 (6.4)	.002	.001 ^{d,e,f}
1 Year	40.8 (5.4)		42.7 (5.8)		38.2 (5.9)		
Saturated fatty acids, %							
Baseline	10.2 (2.0)	<.001	10.2 (2.0)	<.001	10.0 (2.0)	<.001	0.78
1 Year	9.6 (1.9)		9.7 (1.9)		9.5 (2.0)		
Monounsaturated fatty acids, %							
Baseline	20.4 (4.0)	<.001	20.5 (4.0)	<.001	19.8 (4.2)	.07	<.001 ^{d,e,f}
1 Year	21.5 (3.8)		21.4 (3.8)		19.4 (4.0)		
Polyunsaturated fatty acids, %							
Baseline	6.0 (1.8)	.006	6.2 (1.8)	<.001	6.0 (1.8)	.002	<.001 ^{d,e,f}
1 Year	6.3 (1.4)		8.2 (2.0)		5.7 (1.6)		
Energy expenditure in physical activity (MET-min per day)							
Baseline	266 (216)	.43	300 (240)	.05	243 (225)	.38	.07
1 Year	275 (238)		278 (214)		254 (219)		

Abbreviations: MedDiet, Mediterranean diet; MET-min, minutes at a given metabolic equivalent level (units of energy expenditure in physical activity; 1 MET-min is roughly equivalent to 1 kcal); VOO, virgin olive oil.

^aData are given as mean (SD) unless otherwise indicated. $P < .05$ indicates statistical significance.

^bDifferences from baseline by paired t test.

^cDifferences among diets by repeated measures analysis of variance.

^d $P < .05$ for differences between MedDiet + VOO and control diet group.

^e $P < .05$ for differences between MedDiet + nuts and control diet group.

^f $P < .05$ for differences between MedDiet + VOO and MedDiet + nuts groups.

Table 4. Average Daily Intake of Energy and Nutrients Provided by VOO and Mixed Nuts^a

Variable	VOO, 50 g/d	Nuts, 30 g/d
Energy, kcal	442	189
Total protein, g	0	5.0
Arginine, g	0	0.7
Total carbohydrates, g	0	4.8
Fiber, g	0	2.6
Total fat, g	50.0	17.2
Oleic acid, g	37.5	6.5
Linoleic acid, g	3.4	2.3
α -Linolenic acid, g	0.2	1.3
Total plant sterols, mg	77.9	59.7
α -Tocopherol, mg	7.3	7.2
β -Tocopherol, mg	0.2	1.4
δ -Tocopherol, mg	2.1	9.4
Calcium, mg	0.5	42.9
Magnesium, mg	0	57.3
Sodium, mg	1.0	0.4
Potassium, mg	0.5	172.0

Abbreviations: PREDIMED, Prevención con Dieta Mediterránea; VOO, virgin olive oil.

^aData on lipid components are from analyses of supplemental foods supplied in the PREDIMED study, as previously reported.¹⁸ The source of information about other nutrients was the US Department of Agriculture Nutrient Database (<http://www.nal.usda.gov/fnic/foodcomp/search>; accessed April 1, 2008).

VOO group had a lower incidence of elevated triglyceride levels and less reversion of abdominal obesity. There were no differences among groups in the incidence or reversion of high fasting glucose or low HDL cholesterol levels.

Logistic regression analysis confirmed that the MedDiet + nuts was associated with MetS reversion among individuals who had the syndrome at baseline. Compared with the control group, crude odds ratios (95% confidence intervals) for MetS reversion were 1.4 (0.9-2.1) and 1.7 (1.1-2.7) for the MedDiet + VOO and the MedDiet + nuts groups, respectively. The corresponding odds ratios for incident MetS among individuals without the syndrome at baseline were 1.0 (0.6-1.7) and 0.7 (0.4-1.3). The odds ratios changed little after adjusting for sex, age, baseline obesity status, and changes in body weight (**Figure 3**). In addition, the need for antidiabetic or antihypertensive medications was unchanged from baseline in all study groups.

COMMENT

In this clinical trial, older participants at high risk for developing CVD who consumed a non-energy-restricted, traditional Mediterranean-style diet supplemented with

Table 5. Metabolic Syndrome Components by Intervention Group

Metabolic Syndrome Component ^a	Intervention Group, No. (%) of Participants		
	MedDiet + VOO (n=409)	MedDiet + Nuts (n=411)	Control Diet (n=404)
Abdominal obesity			
Baseline prevalence	267 (65.3)	265 (64.5)	282 (69.8)
1-y Prevalence	278 (68.0) ^c	245 (59.6) ^{c,d}	271 (67.1)
Reversion rate ^b	17 (6.4) ^c	50 (18.9) ^{c,d}	33 (11.7)
Incidence rate ^b	28 (19.7)	30 (20.5)	22 (18.0)
Low HDL cholesterol level			
Baseline prevalence	108 (26.4)	87 (21.2)	97 (24.0)
1-y Prevalence	104 (25.4)	80 (19.5)	88 (21.8)
Reversion rate ^b	39 (36.1)	34 (39.1)	33 (34.3)
Incidence rate ^b	35 (11.6)	27 (8.3)	34 (11.1)
Hypertriglyceridemia			
Baseline prevalence	122 (29.8)	119 (29.0)	127 (31.4)
1-y Prevalence	127 (31.1)	116 (28.2) ^c	143 (35.4)
Reversion rate ^b	34 (27.9)	39 (32.8)	43 (33.9)
Incidence rate ^b	39 (13.6) ^c	36 (12.3) ^c	59 (21.3)
Elevated fasting glucose level			
Baseline prevalence	276 (67.5)	274 (66.7)	269 (66.6)
1-y Prevalence	248 (60.6)	266 (64.7)	250 (61.9)
Reversion rate ^b	30 (10.9)	21 (7.7)	28 (10.4)
Incidence rate ^b	15 (11.3)	23 (16.8)	15 (11.1)
High blood pressure			
Baseline prevalence	397 (97.1)	391 (95.1)	384 (95.0)
1-y Prevalence	397 (97.1)	387 (94.2) ^{c,d}	394 (97.5)
Reversion rate ^b	9 (2.3)	11 (2.8)	5 (1.3)
Incidence rate ^b	10 (83.3)	8 (40.0) ^d	11 (64.7)
Metabolic syndrome			
Reversion rate ^b	53 (21.0)	63 (25.3) ^c	41 (16.4)
Incidence rate ^b	36 (22.9)	29 (17.9)	36 (23.4)
Reversion/incidence ratio ^e	0.92	1.41	0.70

Abbreviations: HDL, high-density lipoprotein; MedDiet, Mediterranean diet; VOO, virgin olive oil.

^aThe metabolic syndrome components are defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria. For a complete explanation of the criteria, see the "Measurements" subsection of the "Methods" section.

^bReversion rate indicates the percentage of participants who met the criterion at baseline but not at the 1-year assessment; incidence rate, the percentage of participants who did not meet the criterion at baseline but met the criterion at the 1-year assessment.

^c*P* < .05 vs control diet.

^d*P* < .05 vs MedDiet + VOO.

^eReversion to incidence ratio indicates the rate of reverted cases divided by the rate of incident cases.

1 daily serving of mixed nuts for 1 year showed a reduction in the overall prevalence of MetS compared with participants given advice on following a low-fat diet. Subjects in the MedDiet + VOO group showed a nonsignificant reduction in MetS prevalence. The beneficial effect of the MedDiet + nuts was more a consequence of higher rates of reversion among participants who had the MetS at baseline than of a lesser incidence among those not meeting criteria for the syndrome at baseline, and was independent of sex, age, baseline obesity status, or changes in body weight. These results provide further evidence of the potential benefit of healthy dietary patterns on MetS status.¹³⁻¹⁵ The novelty of our findings is that a positive effect on MetS was achieved by diet alone, in the absence of weight loss or increased energy expenditure in physical activity.

The protective effect of the MedDiet + nuts on MetS prevalence appears to be owing to the sum of small effects in individual components of the MetS rather than to a great effect on any single component. Both MedDiet groups showed a lower incidence of hypertriglyceridemia compared with the control group. The observed re-

duction in the incidence of elevated blood pressure after the MedDiet + nuts may be a chance finding, given that more than 95% of participants met ATP III criteria for elevated blood pressure at baseline. The lack of beneficial effect of the MedDiets on hyperglycemia may also be spurious because nearly 45% of participants had diabetes mellitus, and in this context it is improbable to attain a fasting blood glucose level of less than 100 mg/dL with only lifestyle intervention. Our finding that individual components of the MetS were not always statistically significantly affected is consistent with other studies involving lifestyle changes.²⁴

The beneficial effect of the MedDiet + nuts on MetS status occurred despite relatively small macronutrient changes, as derived from self-reported food records (Table 3). Nevertheless, all nutrient changes were in the intended direction, with increases in the intake of fiber, monounsaturated fatty acids, and polyunsaturated fatty acids and reduced saturated fatty acid intake, mainly reflecting increased consumption of nuts. There are several reasons why the higher total fat and unsaturated fat content of the MedDiet + nuts might beneficially affect

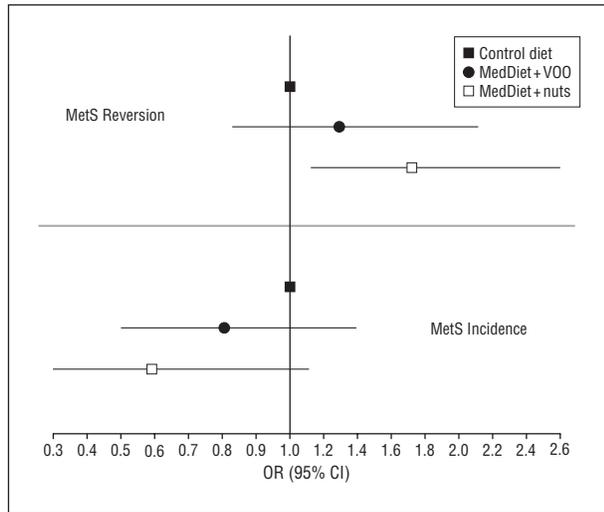


Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of 1-year reversion among participants who had the metabolic syndrome (MetS) at baseline (top) and incidence among participants who did not have MetS at baseline (bottom) in the 2 Mediterranean diet (MedDiet) groups compared with the control diet group. The logistic regression model was adjusted for sex, age, baseline obesity status, and weight changes. VOO indicates virgin olive oil.

MetS status compared with a control diet relatively higher in carbohydrates.

First, there is increasing evidence that dietary fat need not be drastically reduced, as advocated in the past, to provide protection from CVD. In the Women's Health Initiative study,²⁵ a low-fat dietary pattern was not associated with a reduced risk of CVD during an 8-year follow-up period. In the prospective Nurses' Health Study,²⁶ recent results from a 20-year follow-up period suggest that a low-carbohydrate diet (high fat and/or high protein) does not promote CVD and might reduce its incidence when the diet is high in unsaturated fat and vegetable protein, such as the MedDiet. Greater conformity with a Mediterranean-style diet was also associated with lower CVD prevalence and all-cause mortality rates in a large study in a US-based population sample.²⁷ There is also ample evidence that, as opposed to high-fat diets, high-carbohydrate diets may increase triglyceride levels and reduce HDL cholesterol levels.²⁸ Second, diets high in monounsaturated fatty acids, like the MedDiet, are beneficial for insulin resistance and associated metabolic abnormalities²⁹ and for blood pressure and the lipid profile.³⁰ Finally, increased intake of VOO and nuts was the main dietary change in the 2 MedDiet arms of our study. In a former 3-month evaluation of the PREDIMED study, both MedDiets were associated with improved blood pressure, fasting blood glucose levels, and lipid profiles.¹⁸ Recently, VOO has been shown to improve cardiovascular risk factors compared with refined olive oil.³¹ However, in our study, nuts outperformed VOO regarding MetS status at 1 year and likely had as much or more of a salutary effect than the MedDiet itself. Both the VOO and nuts used in this study are rich in unsaturated fatty acids, antioxidants, and phytosterols.¹⁸ However, VOO is a lipid extract from olives, whereas nuts are whole foods that provide additional nonlipid nutrients, including fiber; arginine, the precursor of the endogenous vasodilator ni-

trous oxide; and minerals, such as potassium, calcium, and magnesium (Table 4).³²⁻³⁴ In addition, walnuts (one-half of the daily serving of nuts in our study) are much richer than olive oil in α -linolenic acid, the vegetable omega-3 fatty acid.³⁵ Therefore, nuts, but not olive oil, contain various nutrients that have been shown to beneficially affect cardiometabolic risk factors, such as insulin resistance, blood pressure, and dyslipidemia, in addition to modulating inflammation and endothelial function.^{16,17,32-35} Nut consumption also has been associated with protection from CVD in several large prospective studies.³⁵

More important, in our study, MetS status improved among the MedDiet + nuts group despite the absence of weight loss, unlike what has been reported in previous studies of the effects of dietary patterns on MetS.¹³⁻¹⁵ Judging from the almost universal reversion of MetS observed after massive weight loss among morbidly obese subjects who underwent weight-reduction surgery,³⁶ weight loss appears to be the driving force for the reversion of MetS. That the MedDiet + nuts in itself, without energy restriction, is beneficial for reversing MetS status suggests that its components, principally nuts, have positive effects on insulin resistance and/or other factors central to the pathophysiological characteristics of MetS, such as systemic oxidation and related chronic inflammation.² Recently, persuasive evidence has been provided that oxidative stress is associated with insulin resistance.³⁷ Besides VOO and nuts, the high content of vegetables and fresh fruits of the PREDIMED diets, together with a moderate consumption of wine, guarantees a high intake of antioxidant vitamins and phenolic compounds. Indeed, previous reports from the PREDIMED study showed that MedDiets were associated with improved insulin sensitivity¹⁸ and decreased oxidative damage to low-density lipoprotein cholesterol.³⁸ The decreased oxidative stress promoted by the MedDiet concurs with the reduction in inflammatory markers, as previously shown in the PREDIMED study¹⁸ and another feeding trial in patients with MetS.¹³ Reversion of abdominal obesity in the MedDiet + nuts group is plausible, given that consumption of nuts has been associated with satiety, increased thermogenesis, fat malabsorption, and lower adiposity,¹⁷ and could further reduce inflammation. Therefore, a reduced inflammatory state might account for an important part of the beneficial effect of the MedDiet + nuts on MetS status.

Our study has limitations. The participants were older subjects at high risk for CVD, nearly 45% had diabetes mellitus, and 61.4% had MetS; therefore, the results cannot be extrapolated to the general population. An added limitation is that nutritional education for the low-fat diet group was less intense than the behavioral intervention in the MedDiet groups. In fact, fat intake was only marginally reduced in the group assigned the low-fat diet. This was partly because of the study design, but also because participants belonged to a Mediterranean culture, in which people have a long-standing preference for using olive oil in the kitchen and at the table. Therefore, the differences in outcomes observed between the MedDiet + nuts and control groups might be attributed mainly to the supplemental nuts provided.

Traditionally, dietary patterns recommended for health have been low-fat, high-carbohydrate diets, which generally are not palatable. The results of the present study show that a non-energy-restricted traditional MedDiet enriched with nuts, which is high in fat, high in unsaturated fat, and palatable, is a useful tool in managing the MetS. Dietary intervention may reduce cardiovascular risk among persons with the MetS. Our study duration was too short to address clinical outcomes. Longer follow-up of the entire PREDIMED cohort may eventually provide stronger evidence of the cardiovascular benefits of the MedDiet.

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REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
2. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735-2752.
3. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49(4):403-414.
4. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414(6865):782-787.
5. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am*. 2004;33(2):351-375.
6. Phillips C, Lopez-Miranda J, Perez-Jimenez F, McManus R, Roche HM. Genetic and nutrient determinants of the metabolic syndrome. *Curr Opin Cardiol*. 2006;21(3):185-193.
7. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care*. 2004;27(2):538-546.
8. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet*. 2005;365(9453):36-42.
9. Esmailzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary patterns, insulin resistance, and prevalence of the metabolic syndrome in women. *Am J Clin Nutr*. 2007;85(3):910-918.
10. Willett WC, Sacks F, Trichopoulos A, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr*. 1995;61(6 suppl):1402S-1406S.
11. Panagiotakos DB, Pitsavos CH, Chrysohou 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(1):106-112.
12. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, Basterra-Gortari FJ, Nuñez-Cordoba JM, Martínez-González MA. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. *Diabetes Care*. 2007;30(11):2957-2959.
13. 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(12):1440-1446.
14. Orchard TJ, Temprosa M, Goldberg R, et al; Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142(8):611-619.
15. Azadbakht L, Mirmiran P, Esmailzadeh A, Azizi T, Azizi F. Beneficial effects of a Dietary Approaches to Stop Hypertension eating plan on features of the metabolic syndrome. *Diabetes Care*. 2005;28(12):2823-2831.
16. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002;288(20):2554-2560.
17. Rajaram S, Sabaté J. Nuts, body weight and insulin resistance. *Br J Nutr*. 2006;96(suppl 2):S79-S86.
18. Estruch R, Martínez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med*. 2006;145(1):1-11.
19. Martínez-González MA, Fernández-Jarne E, Serrano-Martínez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. *Eur J Clin Nutr*. 2004;58(11):1550-1552.
20. Martín-Moreno JM, Boyle P, Gorgojo L, et al. Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol*. 1993;22(3):512-519.
21. Elosua R, Garcia M, Aguilar A, Molina L, Covas MI, Marrugat J; Investigators of the MARATDON Group. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish women. *Med Sci Sports Exerc*. 2000;32(8):1431-1437.
22. Miró-Casas E, Farré Albaladejo M, Covas MI, et al. Capillary gas chromatography-mass spectrometry quantitative determination of hydroxytyrosol and tyrosol in human urine after olive oil intake. *Anal Biochem*. 2001;294(1):63-72.
23. Bondia-Pons I, Castellote AI, Lopez-Sabater MC. Comparison of conventional and fast gas chromatography in human plasma fatty acid determination. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2004;809(2):339-344.
24. O'Malley PG, Kowalczyk C, Bindeman J, Taylor AJ. The impact of cardiovascular risk factor case management on the metabolic syndrome in a primary prevention population: results from a randomized controlled trial. *J Cardiometa Syndr*. 2006;1(1):6-12.
25. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):655-666.
26. Halton TL, Willett WC, Liu S, et al. Low carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006;355(19):1991-2002.
27. Mitrou PN, Kipnis V, Thiebaut ACM, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health study. *Arch Intern Med*. 2007;167(22):2461-2468.
28. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77(5):1146-1155.
29. Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity, and the metabolic syndrome. *Clin Nutr*. 2004;23(4):447-456.
30. Appel LJ, Sacks FM, Carey VJ, et al; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294(19):2455-2464.
31. Covas MI, Nyyssönen K, Poulsen HE, et al. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med*. 2006;145(5):333-341.
32. Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. *Br J Nutr*. 2006;96(suppl 2):S46-S51.
33. Brufau G, Boatella J, Rafecas M. Nuts: source of energy and macronutrients. *Br J Nutr*. 2006;96(suppl 2):S24-S28.
34. Segura R, Javierre C, Lizarraaga MA, Ros E. Other relevant components of nuts: phytosterols, folate and minerals. *Br J Nutr*. 2006;96(suppl 2):S36-S44.
35. Kelly JH Jr, Sabaté J. Nuts and coronary heart disease: an epidemiological perspective. *Br J Nutr*. 2006;96(suppl 2):S61-S67.
36. Lee WJ, Huang MT, Wang W, Lin CM, Chen TC, Lai IR. Effects of obesity surgery on the metabolic syndrome. *Arch Surg*. 2004;139(10):1088-1092.
37. Meigs JB, Larson MG, Fox CS, Keaney JF Jr, Vasan RS, Benjamin EJ. Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. *Diabetes Care*. 2007;30(10):2529-2535.
38. Fitó M, Guxens M, Corella D, et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med*. 2007;167(11):1195-1203.