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Original Contribution

Adherence to the Mediterranean Diet and Risk of Coronary Heart Disease in the Spanish EPIC Cohort Study

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No known cohort study has investigated whether the Mediterranean diet can reduce incident coronary heart disease (CHD) events in a Mediterranean population. This study examined the relation between Mediterranean diet adherence and risk of incident CHD events in the 5 Spanish centers of the European Prospective Investigation into Cancer and Nutrition. Analysis included 41,078 participants aged 29–69 years, recruited in 1992–1996 and followed up until December 2004 (mean follow-up:10.4 years). Confirmed incident fatal and nonfatal CHD events were analyzed according to Mediterranean diet adherence, measured by using an 18-unit relative Mediterranean diet score. A total of 609 participants (79% male) had a fatal or nonfatal confirmed acute myocardial infarction ($n = 468$) or unstable angina requiring revascularization ($n = 141$). After stratification by center and age and adjustment for recognized CHD risk factors, high compared with low relative Mediterranean diet score was associated with a significant reduction in CHD risk (hazard ratio = 0.60, 95% confidence interval: 0.47, 0.77). A 1-unit increase in relative Mediterranean diet score was associated with a 6% reduced risk of CHD (95% confidence interval: 0.91, 0.97), with similar risk reductions by sex. Mediterranean diet adherence was associated with a significantly reduced CHD risk in this Mediterranean country, supporting its role in primary prevention of CHD in healthy populations.

cohort studies; coronary disease; diet, Mediterranean; incidence; Mediterranean region; primary prevention

Abbreviations: CHD, coronary heart disease; EPIC, European Prospective Investigation into Cancer and Nutrition; rMED, relative Mediterranean diet.

Cardiovascular disease is the main cause of death worldwide, accounting for approximately 30% of global mortality, equivalent to approximately 17 million deaths annually (1). Nearly half of these deaths are attributable to coronary heart disease (CHD). Countries that have historically had some of the lowest CHD rates are China, Switzerland, Spain, and France. In Spain in 1997–1998, the estimated age-standardized incidence rates of acute myocardial infarction for men and women aged 35–64 years were 207 and 45 per 100,000, respectively (2). Although there are genetic predispositions to cardiovascular disease, a large proportion (approximately 80%) of premature CHD events are believed to be preventable by modifiable lifestyle behaviors, including a healthy diet (3).

Increased longevity and lower CHD incidence and mortality found in southern compared with northern Europe in the Seven Countries Study (4) and the MONICA survey (5) were attributed to the cardioprotective effect of the Mediterranean diet. To facilitate research into the health benefits of this diet pattern, a Mediterranean diet score was developed

Table 1. Distribution of Participants and Cases With Incident Coronary Heart Disease in the 5 Regions Participating in the EPIC-Spain Cohort

Center in Spain	No. in the Cohort Sample	No. of Person-years	Incident Coronary Heart Disease Event[a]						rMED Score, Mean (SD)
			Total		Male		Female		
			No.	% [b]	No.	% [c]	No.	% [c]	
Asturias	8,515	88,657.93	126	20.7	98	77.8	28	22.2	7.79 (2.6)
Gipuzkoa	8,355	87,835.43	170	27.9	150	88.2	20	11.8	8.70 (2.7)
Granada	7,716	78,476.16	45	7.4	24	53.3	21	46.7	9.10 (2.7)
Murcia	8,443	86,446.14	114	18.7	71	62.3	43	37.7	9.20 (2.8)
Navarra	8,049	84,015.59	154	25.3	138	89.6	16	10.4	8.11 (2.7)
Total	41,078	425,431.25	609	100	481	79.0	128	21.0	8.57 (2.7)

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; rMED, relative Mediterranean diet; SD, standard deviation.

[a] Incident coronary heart disease was defined as definite fatal and nonfatal acute myocardial infarction or unstable angina requiring a revascularization procedure.

[b] Column percentage.

[c] Row percentage.

(6), followed by several variations of this score and other scoring systems (7). Mediterranean diet scores take into account key components (food groups and nutrients) of the traditional Mediterranean diet. Although there are ambiguities in the definition of Mediterranean diet, the key features (8) include high consumption of olive oil and plant-based foods such as fruit, vegetables, legumes, whole-grain cereals, and nuts and seeds; moderate-to-high consumption of fish, depending on the region; moderate consumption of alcohol (red wine in particular) and dairy products; and relatively low consumption of meat (especially red meat).

In observational and intervention studies (9–13), evidence for the protective effect of the Mediterranean diet on CHD is accumulating. Intervention studies have shown that the Mediterranean diet reduces mortality risk for patients with a previous myocardial infarction and reduces cardiovascular disease risk factors (14, 15). Several studies have been conducted in Spain, including the PREDIMED trial, the largest randomized trial to assess the effect of a Mediterranean diet on cardiovascular disease outcomes (15, 16); a cohort study of elderly subjects (17); the SUN cohort study (18); and a case-control study (19). A meta-analysis of cohort studies (20), which included findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) Greece cohort study (21), estimated that a 2-point increase in Mediterranean diet score was significantly associated with a 9% reduced risk of mortality from cardiovascular disease. In addition, the prospective Nurses' Health Study has shown that a Mediterranean diet is associated with reduced risk of incidence of and mortality from CHD and stroke in women living in the United States (22). A Mediterranean diet is also associated with increased survival among individuals with CHD (23, 24). A systematic review of mostly case-control studies, which selected patients with a first acute myocardial infarction as cases, reported that the Mediterranean diet reduced the risk of CHD by 8%–45%, depending on the increment in score measured (11).

Although these studies provide evidence of the cardioprotective effect of the Mediterranean diet, case-control studies have inherent limitations, and cohort studies of this topic have focused mainly on mortality, the exception being the Nurses' Health Study (22). Studying diet in individuals with CHD is also problematic because they may have altered their diet following diagnosis. Finally, the nutritional factors related to secondary prevention of CHD may not be the same as those related to primary prevention. Thus, the purpose of this study was to prospectively investigate the relation between adherence to a relative Mediterranean diet (rMED) and incident CHD events (focusing on primary prevention) within the EPIC-Spain cohort.

MATERIALS AND METHODS

Recruitment

EPIC is a large, prospective study conducted in 10 European countries, whose methodological details have been published previously (25–27). The present study makes use of data from the Spanish cohort of EPIC-Heart (28), the cardiovascular branch of EPIC (29). The EPIC-Spain cohort was recruited between 1992 and 1996 from 3 regions in the north (Asturias, Gipuzkoa, and Navarra) and 2 regions in the south (Granada and Murcia) of Spain. Participants were followed up for this analysis until December 2004. They included 41,438 healthy volunteers (15,632 men), aged 29–69 years, of different social and educational levels and were recruited mostly from among blood donors, with a participation rate varying from 55% to 60% between centers. The study population covered a diverse range of socioeconomic levels and different geographic areas. At recruitment, all participants gave their informed consent, and the study was approved by the Medical Ethical Committee of Bellvitge Hospital (Barcelona).

Table 2. Baseline Characteristics of the 41,078 Participants in the EPIC-Spain Cohort According to Level of Adherence to a Relative Mediterranean Diet

Characteristic[a]	Whole Cohort (N = 41,078)	rMED Score[b]		
		Low (n = 9,505)	Medium (n = 21,541)	High (n = 10,032)
Sociodemographic				
Gender: male, no. (%)	15,442 (37.6)	3,001 (31.6)	7,928 (36.8)	4,513 (45.0)
Age at enrollment, mean years (SD)	49.3 (8.0)	48.2 (8.0)	49.3 (8.0)	50.2 (7.9)
Educational level, %				
No formal education	30.4	29.0	30.7	31.2
Primary school	38.7	42.0	38.7	35.7
Secondary school	6.5	6.9	6.4	6.3
Technical or professional training	8.2	7.9	8.1	8.8
University degree	11.5	10.5	11.7	12.2
Not specified	4.7	3.7	4.5	5.9
Anthropometric, mean (SD)				
Body mass index, kg/m^2	28.3 (4.3)	28.1 (4.4)	28.3 (4.3)	28.4 (4.2)
Height, cm	161.4 (8.5)	160.8 (8.2)	161.3 (8.5)	162.1 (8.6)
Weight, kg	73.7 (12.7)	72.7 (12.9)	73.6 (12.6)	74.7 (12.4)
Hip circumference, cm	105.5 (8.6)	105.4 (8.8)	105.5 (8.6)	105.7 (8.4)
Waist circumference, cm	91.9 (12.0)	90.9 (12.3)	91.8 (12.0)	93.1 (11.7)
Lifestyle, %				
Physical activity				
Active	9.6	8.9	9.5	10.4
Moderately active	57.8	59.1	58	56.2
Moderately inactive	20.9	20.6	21	21.2
Inactive	11.7	11.4	11.6	12.2
Smoking status				
Never	55.5	54.7	56.4	54.5
Former	17.5	14.5	17.3	20.7
Current (NS no. of cigarettes)	3.7	3.6	3.6	4.0
Current (1–10 cigarettes/day)	9.8	9.9	9.9	9.6
Current (11–20 cigarettes/day)	9.7	11.9	9.3	8.6
Current (>20 cigarettes/day)	3.7	5.4	3.5	2.6
Missing	0.1	0.1	0.1	0.1

Table continues

Dietary and lifestyle questionnaires

Participants were interviewed in person to collect information on usual food intake over the previous 12 months by means of a computerized version of a dietary history questionnaire, used at all centers (30). The validated dietary questionnaire was open but was structured by meals and included a list of approximately 600 common foods and recipes from each region (31, 32). The frequency and amount of food consumed at least twice a month was recorded, taking seasonal variability into account. The portion of each food (grams/day) consumed was quantified by using household measures, standard units, and a collection of 35 sets of photographs of simple foods, mixed foods, and drinks. Each diet history interview lasted about 40–50 minutes. Total energy (kilocalories/day) and ethanol (grams/day) intakes were estimated by using a food composition table (33).

An interviewer-administered lifestyle questionnaire was used to collect information on sociodemographic characteristics, lifestyle factors including history of tobacco use as well as work and leisure-time physical activity, medical history, and reproductive indicators (women). Anthropometric measurements (waist and hip circumferences, weight, and height) were also taken at recruitment by using standardized procedures. Participants were asked whether

Table 2. Continued

Characteristic[a]	Whole Cohort (*N* = 41,078)	rMED Score[b]		
		Low (*n* = 9,505)	Medium (*n* = 21,541)	High (*n* = 10,032)
Medical/health indicator, %				
Diabetic	4.9	4	4.9	5.8
Missing	0.2	0.2	0.2	0.2
Hypertensive	20.0	19	19.9	21.7
Missing	0.1	0.2	0.2	0.1
Hyperlipidemic	20.0	16.9	19.3	24.6
Missing	0.5	0.4	0.5	0.6
Oral contraceptive use	26.3	30.4	26.4	22.5
Not applicable (males)	37.6	31.6	36.8	45.0
Dietary composition (daily intake), median (SD)				
Energy intake, kcal	2,127 (725)	2,224 (793)	2,114 (723)	2,072 (640)
Protein, g/1,000 kcal	44.5 (7.2)	44.9 (8.0)	44.8 (7.4)	43.8 (6.0)
Carbohydrate, g/1,000 kcal	103.1 (18.5)	99.5 (19.6)	102.9 (18.5)	106.7 (16.7)
Dietary fiber, g/1,000 kcal	8.8 (3.0)	8.8 (3.0)	11.0 (3.4)	13.2 (3.6)
Fat total, g/1,000 kcal	41.2 (6.7)	42.6 (7.1)	41.2 (6.8)	39.8 (6.2)
Saturated fatty acids	12.3 (3.3)	13.9 (3.6)	12.4 (3.2)	10.9 (2.7)
Monounsaturated fatty acids	17.4 (4.0)	16.6 (3.9)	17.4 (4.1)	18.1 (3.8)
Polyunsaturated fatty acids	6.0 (2.6)	6.5 (2.9)	6.0 (2.7)	5.7 (2.1)
Vitamin C, mg	137.3 (82.9)	100.8 (69.3)	137.1 (79.5)	172.7 (85.9)

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; NS, not specified (for cigarette smokers or exclusive smokers of pipes or cigars); rMED, relative Mediterranean diet; SD, standard deviation.

[a] All comparisons between groups and tests for trend were statistically significant at $P < 0.001$ (chi-squared test for categorical variables or Kruskal-Wallis rank sum test for continuous variables). The Benjamini-Hochberg method was used to correct for multitest effects.

[b] Low score, 0–6; medium score, 7–10; high score, 11–18.

a physician had ever said they had an acute myocardial infarction, angina, a thrombosis, or other cerebrovascular problems; high blood pressure; hyperlipidemia; or diabetes mellitus and whether they used hormone replacement therapy. A follow-up telephone interview carried out 3 years after recruitment was administered to 98% of participants and included questions related to coronary events during this period.

Measuring adherence to an rMED

Each participant's degree of adherence to a Mediterranean diet was evaluated by using an rMED score, a variation of the original Mediterranean diet score (6, 21), based on intake of 9 key components of this diet. Each rMED component (apart from alcohol) was measured as grams per 1,000 kcal/day (to express intake as energy density) and was divided into tertiles of dietary intake. A value of 0, 1, and 2 was assigned to the first, second, and third tertiles of intake, respectively, positively scoring higher intakes for the 6 components presumed to fit the Mediterranean diet: fruit (including nuts and seeds but excluding fruit juices), vegetables (excluding potatoes), legumes, cereals (including whole-grain and refined flour, pasta, rice, other grains, and bread (69.5% of total cereals)), fresh fish (including seafood), and olive oil. The scoring was reversed for 2 components presumed not to fit the Mediterranean diet: total meat (including processed meat) and dairy products (including low-fat and high-fat milk, yogurt, cheese, cream desserts, and dairy and nondairy creams), positively scoring lower intakes. Alcohol, considered beneficial in moderation, was scored as a dichotomous variable by using the same ranges defined in previous EPIC studies (21). Two points were assigned for moderate consumers (5–25 g/day for women and 10–50 g/day for men) and 0 points for above and below the sex-specific range.

For each participant, the points received from each of the 9 components were summed to give an individual rMED score. The possible scores ranged from 0 units (minimal adherence) to 18 units (maximum adherence). An rMED score of 0–6 was labeled ''low,'' 7–10 as ''medium,'' and 11–18 as ''high'' Mediterranean diet adherence.

Ascertainment and validation of CHD endpoints

Nonfatal coronary events were identified through the self-reported questionnaires at recruitment and at 3-year follow-up (at all centers) as well as by record linkage for nonfatal and fatal coronary events (covering the period 1992–2004) with 3 sources of information that varied by center: 1) hospital discharge databases (Granada had limited access), 2) population-based myocardial infarction registries (available in Murcia, Navarra, and Gipuzkoa), and 3) Spanish national and regional mortality registry (National Statistical Institute) that has information on both date and cause of death for the entire Spanish population. Mortality and hospital discharges for CHD were classified according to *International Classification of Diseases*, Ninth Revision, codes 410–414 and *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, codes I20–I25.

A team of trained nurses and physicians carried out a validation process by reviewing patient hospital medical records and medico-legal necropsy reports to confirm and classify the coronary events. The events were classified on the basis of symptoms, enzymes, and electrocardiograms and laboratory findings as well as possible autopsy results according to the American Heart Association's scientific statement of 2003 (34).

The coronary events were classified as either definite or possible, as follows: 1) definite fatal or nonfatal acute myocardial infarction or unstable angina requiring revascularization procedures (coronary artery bypass graft or percutaneous transluminal coronary angioplasty), or 2) possible fatal or nonfatal myocardial infarction, because they did not meet all diagnostic criteria, and fatal CHD with insufficient information. The coronary event was considered incident if there was no indication in the patient's records of a recognized myocardial infarction or unstable angina requiring revascularization procedures occurring before recruitment. Participants with a definite coronary event (originally identified by record linkage and/or self-reported information) recorded before recruitment were considered prevalent cases. Only those participants with an incident and definite CHD event were classified as cases, whereas possible fatal and nonfatal CHD events were censored at diagnosis.

Statistical analysis

Analyses were performed by using the R statistical programming language (http://www.r-project.org/) and STATA statistical software, version 10 (Stata Corporation, College Station, Texas). Frequency distributions were used to describe the categorical variables. Medians, means, and standard deviations were used to describe continuous variables. The Mann-Whitney test examined gender differences in intakes of components of the rMED score. Participants reporting more than 3 standard deviations from the mean of total log-transformed energy intake per day (equivalent to $<$789.4 kcal/day or $>$5,707.7 kcal/day) were considered to have implausible dietary data and were therefore excluded from the analysis.

We examined associations between possible confounders and the rMED score and between possible confounders and cases and at-risk participants. Chi-squared tests were applied for categorical variables and Kruskal-Wallis tests for continuous variables. The Benjamini-Hochberg method was used to correct for multitest effects.

Cox proportional hazards regression was applied to assess the association of an incident CHD event with the rMED score as well as each of the individual rMED components. The models were stratified by age at recruitment (in 5-year intervals), sex, and center to control for potential confounding due to differences in follow-up procedures. Age was the primary time variable, with entry time defined as age at recruitment and exit time defined as age at diagnosis of first coronary event for cases or age at censoring or at death (whichever occurred first) for at-risk participants.

Linear trend tests were used to calculate the hazard ratio for the rMED score as a continuous variable (each 1-unit or 2-unit increase) and as a categorical variable (low-referent, medium, and high; coded as 1–3). All models were adjusted for a priori potential confounders: body mass index ($<$25, 25–30, and $>$30 kg/m^2); educational level (no formal education, primary school, secondary school, technical or professional training, university degree, and not specified); smoking status (never, former, current smoker, stratified according to smoking intensity of 1–10, 11–20, and $>$20 cigarettes/day) physical activity, which combines occupational with recreational and household activity (35) (inactive, moderately inactive, moderately active, and active); energy intake (kilocalories/day); and the presence of diabetes, hyperlipidemia, and hypertension. Confounding by oral contraceptive use and waist circumference was also tested; however, because we found no evidence of confounding by these variables, they were not included in the adjusted models. We tested whether the association between the rMED score and risk of CHD was modified by sex, smoking, body mass index, and physical activity level, and we found no evidence of interaction by these variables.

Different sensitivity analyses were carried out by separately 1) censoring the participants and 76 incident cases of CHD occurring during the first 2 years of follow-up, 2) censoring the 141 subjects with unstable anginas requiring revascularization procedures, 3) excluding participants diagnosed with diabetes at baseline, and 4) excluding participants in Granada (because of possible subestimation of cases at this center). We also assessed the association between CHD and the Mediterranean diet using the same original Mediterranean diet score developed by Trichopoulou et al. (21), the most frequently used operative score, to aid comparison of results between studies.

RESULTS

Prevalent cases (n = 193) and subjects with implausible dietary data (n = 167) were excluded from the 41,438 potentially eligible participants. Participants with possible acute myocardial infarctions or fatal coronary events with insufficient information (n = 119) were not considered as cases but were censored at the time of their coronary event. The risk analysis excluded 321 participants (including 3

Table 3. Daily Intake of Each Component of the Relative Mediterranean Diet Score in the EPIC-Spain Cohort

rMED Component (grams per day/ 1,000 kcal/day)[a]	Male				Female				Total			
	Mean (SD)	Percentile			Mean (SD)	Percentile			Mean (SD)	Percentile		
		33.3	50.0	66.6		33.3	50.0	66.6		33.3	50.0	66.6
Vegetables[b]	104.4 (68.1)	67.8	90.7	117.7	130.7 (84.0)	85.8	113.0	146.9	120.8 (79.4)	78.1	103.7	135.8
Fruit[c]	127.2 (99.1)	76.1	109.9	148.0	177.4 (125.8)	113.8	155.8	204.5	158.5 (119.0)	97.4	136.6	183.4
Legumes	26.3 (16.5)	17.8	23.7	30.3	21.6 (14.5)	14.2	19.4	25.2	23.4 (15.5)	15.5	20.9	27.1
Fish (fresh)[d]	27.7 (19.6)	17.2	23.3	31.4	27.3 (20.1)	16.7	23.1	30.7	27.4 (19.9)	16.9	23.2	31.0
Cereals[e]	92.8 (33.5)	77.6	91.2	105.3	86.5 (37.0)	69.1	84.4	100.6	88.9 (35.8)	72.5	87.2	102.6
Olive oil	8.7 (6.6)	5.5	8.8	11.6	9.6 (6.4)	7.0	9.5	12.0	9.3 (6.5)	6.5	9.3	11.9
Alcohol[f]	31.3 (32.5)	9.9	22.7	38.0	4.6 (9.2)	0.0	0.2	2.1	14.7 (24.8)	0.1	2.4	11.5
Meat[g]	59.9 (22.0)	49.9	58.7	67.7	56.0 (23.9)	44.8	54.0	63.7	57.4 (23.3)	46.7	55.8	65.4
Dairy products[h]	102.1 (73.3)	64.7	91.4	120.2	171.2 (100.6)	120.9	155.9	197.3	145.2 (97.2)	94.8	129.5	169.8

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; rMED, relative Mediterranean diet; SD, standard deviation.
[a] Mean calorie intake: males—2,691 kcal/day (SD, 710); females—1,950 kcal/day (SD, 577); total—2,229 kcal/day (SD, 725).
[b] Excludes potatoes.
[c] Includes nuts and seeds and excludes fruit juices.
[d] Excludes preserved and processed fish.
[e] Includes whole-grain and refined flour, pasta, rice, other grains, and bread.
[f] Alcohol expressed as grams of ethanol/day (not as a function of energy density).
[g] Includes all meat, including processed meat.
[h] Includes low-fat and high-fat milk, yogurt, cheese (including fresh cheese), cream desserts, and dairy and nondairy creams.

cases) because of missing information on smoking, diabetes, hypertension, or hyperlipidemia status.

Table 1 shows the distribution of the 41,078 participants (37.6% male), free of coronary events at baseline, who were included in the study sample. After a mean follow-up of 10.4 years (range, 0.01–12.24 years), 609 participants (79% male) were identified with a definite incident CHD event. This number included participants with a nonfatal ($n = 459$) or a fatal ($n = 9$) acute myocardial infarction and angina pectoris requiring a revascularization procedure ($n = 141$). The mean age at diagnosis was 60.2 years (standard deviation, 7.6). The majority of the participants with an incident CHD event were identified in Gipuzkoa and Navarra in the north of Spain. Adherence to an rMED varied across the Spanish regions, with participants in the south (Murcia and Granada) adhering more closely.

Table 2 presents the baseline characteristics for variables considered potential confounders for the whole cohort and for participants with low, medium, and high rMED scores. Mean age at recruitment was 49.3 years, and mean energy intake was 2,228.5 kcal/day. About a quarter (26.9%) of the cohort were current smokers, and average body mass index was 28.3 kg/m^2. Participants with the highest adherence to the rMED had a higher baseline prevalence of diabetes, hypertension, and hyperlipidemia. Higher rMED scores were observed for males and older participants.

Table 3 presents intakes (grams per 1,000 kcal/day) of the 9 rMED components. The cutoff points used to construct the rMED score were overall tertiles (the exception being alcohol). Compared with males, females consumed significantly more vegetables, fruit, olive oil, and dairy products, whereas men consumed significantly more legumes, fish, cereals, alcohol, and meat than females did. A large proportion of females did not consume or consumed very little alcohol.

Table 4 shows the results of the adjusted analysis of each rMED component (high and medium relative to lower intakes) and risk of CHD. In the overall results, intakes of vegetables, olive oil, and alcohol were associated with a statistically significant reduced risk of CHD, whereas intake of dairy products was associated with a statistically significant increased risk of CHD. Among men, there was a significant negative association with vegetables and fish intakes and a positive association with dairy products intake. Among women, there was a significant negative association with olive oil intake and a positive association with meat intake.

Table 5 presents the results of the adjusted analysis of adherence to an rMED and risk of CHD. In the overall results, rMED adherence was associated with a statistically significant reduction in risk of CHD. High compared with low rMED adherence corresponded to a 40% (95% confidence interval: 0.47, 0.77) reduced risk of CHD, and a significant inverse trend ($P < 0.001$) was observed from low to high adherence. A 1-unit increase in the 18-unit rMED score was associated with a 6% (95% confidence interval: 0.91, 0.97) reduced risk. Similar results were obtained for men and women; however, for women, the reduced risk of CHD was statistically significant with the score as a continuous variable only.

Table 6 shows the results of the sensitivity analyses. The association between rMED and CHD was almost identical after censoring the first 2 years of follow-up (76 incident cases) and the 140 subjects with unstable anginas requiring

Table 4. Multivariable Hazard Ratios of Coronary Heart Disease According to Tertile of Intake of Each Component of the Relative Mediterranean Diet in the EPIC-Spain Cohort

rMED Component (grams per 1,000 kcal/day)	Male (n = 15,335)				Female (n = 25,422)				Total (N = 40,757)[a]			
	Cases (n = 480)	HR[b]	95% CI	P-Trend	Cases (n = 126)	HR[b]	95% CI	P-Trend	Cases (n = 606)	HR[b,c]	95% CI	P-Trend
Vegetables												
0–78.1	224	1.00	Referent		31	1.00	Referent		255	1.00	Referent	
>78.1–135.8	150	0.78	0.63, 0.97		42	1.13	0.70, 1.82		192	0.83	0.69, 1.01	
>135.8–1,079.1	106	0.70	0.54, 0.90	0.01	53	1.08	0.67, 1.75	0.80	159	0.76	0.61, 0.94	0.01
Fruit												
0–97.4	224	1.00	Referent		26	1.00	Referent		250	1.00	Referent	
>97.4–183.4	148	0.91	0.73, 1.12		40	1.05	0.63, 1.73		188	0.90	0.74, 1.10	
>183.4–1,531.4	108	0.92	0.72, 1.18	0.46	60	0.94	0.58, 1.54	0.74	168	0.91	0.73, 1.12	0.34
Legumes												
0–15.5	121	1.00	Referent		46	1.00	Referent		167	1.00	Referent	
>15.5–27.1	157	1.07	0.84, 1.36		44	1.16	0.76, 1.76		201	1.10	0.89, 1.35	
>27.1–192.6	202	1.01	0.80, 1.27	0.97	36	0.94	0.60, 1.46	0.81	238	1.01	0.82, 1.24	0.99
Fish (fresh)												
0–16.9	156	1.00	Referent		39	1.00	Referent		195	1.00	Referent	
>16.9–31.0	154	0.89	0.71, 1.12		37	0.92	0.58, 1.45		191	0.90	0.73, 1.10	
>31.0–266.7	170	0.78	0.62, 0.98	0.04	50	0.98	0.63, 1.52	0.93	220	0.83	0.68, 1.02	0.82
Cereals												
0–72.5	136	1.00	Referent		45	1.00	Referent		181	1.00	Referent	
>72.5–102.6	162	0.97	0.77, 1.23		42	1.09	0.72, 1.67		204	1.01	0.83, 1.24	
>102.6–501.3	182	1.15	0.92, 1.45	0.21	39	0.88	0.56, 1.38	0.59	221	1.12	0.92, 1.38	0.26
Olive oil												
0–6.5	201	1.00	Referent		55	1.00	Referent		256	1.00	Referent	
>6.5–11.9	137	1.00	0.80, 1.25		33	0.58	0.37, 0.89		170	0.88	0.72, 1.07	
>11.9–48.0	142	0.87	0.70, 1.09	0.26	38	0.66	0.43, 1.02	0.05	180	0.82	0.68, 1.00	0.05
Alcohol[d]												
Outside range	292	1.00	Referent		107	1.00	Referent		399	1.00	Referent	
Inside range	188	0.85	0.71, 1.03	0.09	19	0.79	0.48, 1.31	0.37	207	0.84	0.71, 0.99	0.05
Meat												
0–46.7	134	1.00	Referent		36	1.00	Referent		170	1.00	Referent	
>46.7–65.4	144	0.83	0.66, 1.06		41	1.51	0.96, 2.37		185	0.95	0.77, 1.18	
>65.4–347.1	202	1.03	0.82, 1.29	0.65	49	1.76	1.12, 2.75	0.01	251	1.18	0.96, 1.44	0.09
Dairy products												
0–94.8	211	1.00	Referent		21	1.00	Referent		232	1.00	Referent	
>94.8–169.8	174	1.47	1.20, 1.80		40	1.29	0.76, 2.20		214	1.42	1.18, 1.72	
>169.8–1,141.3	95	1.62	1.26, 2.08	<0.001	65	1.19	0.72, 1.99	0.62	160	1.51	1.21, 1.89	<0.001

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; rMED, relative Mediterranean diet.

[a] Excluded were 321 participants (including 3 cases) because of missing information on smoking, diabetes, hypertension, and/or hyperlipidemia status.

[b] Cox proportional hazards regression models were stratified by center and age and were adjusted for education; physical activity; body mass index; smoking status; diabetes, hypertension, and hyperlipidemia status; and total calorie intake.

[c] This model was also stratified by sex.

[d] Alcohol was measured in grams of ethanol/day; inside range for males: ≥10 g to <50 g, inside range for females: ≥5 g to <25 g.

revascularization procedures and after excluding 2,009 participants who were diabetic at baseline (including 70 cases) and 33,103 participants from Granada. Finally, we compared the same original Mediterranean diet score developed by Trichopoulou et al. (21) with the rMED score used in this study and found exactly the same trends. There was also an

Table 5. Multivariable Hazard Ratios of Coronary Heart Disease According to Level of Adherence to the Relative Mediterranean Diet in the EPIC-Spain Cohort

rMED Score[a]	Male (*n* = 15,335)				Female (*n* = 25,422)				Total (*N* = 40,757)[b]			
	No. of Cases	HR	95% CI[c]	*P*-Trend	No. of Cases	HR	95%CI[c]	*P*-Trend	No. of Cases	HR	95% CI[c,d]	*P*-Trend
Low	115	1.00	Referent		33	1.00	Referent		148	1.00	Referent	
Medium	257	0.84	0.67, 1.05		68	0.85	0.55, 1.30		325	0.86	0.70, 1.04	
High	108	0.58	0.44, 0.76	<0.001	25	0.67	0.39, 1.16	0.16	133	0.60	0.47, 0.77	<0.001
1-Unit increase in score[e]	480	0.94	0.91, 0.97	<0.001	126	0.93	0.87, 0.99	0.04	606	0.94	0.91, 0.97	<0.001

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; rMED, relative Mediterranean diet.

[a] Low score, 0–6; medium score, 7–10; high score, 11–18.

[b] Excluded were 321 participants (including 3 cases) because of missing information on smoking, diabetes, hypertension, and/or hyperlipidemia status.

[c] Cox proportional hazards regression models were stratified by center and age and were adjusted for education; physical activity; body mass index; smoking status; diabetes, hypertension, and hyperlipidemia status; and total calorie intake.

[d] Model were also stratified by sex.

[e] Index as a continuous variable.

almost identical reduction in CHD risk for every 2-unit increase in both scores.

DISCUSSION

A large sample of healthy individuals from a Mediterranean population was followed up for more than 10 years, and, after adjustment for important confounders, high adherence to an rMED was associated with a 40% reduced risk of a first CHD event. Previous prospective studies have shown that adhering to this dietary pattern protects against CHD mortality in healthy individuals (20), and in patients with CHD (23, 24), and against incidence of CHD and stroke in women in the United States (22). The present study expands on this evidence by showing that a Mediterranean diet, as followed by a Mediterranean population, can protect against incidence of CHD in healthy populations.

Previous research on the Mediterranean diet and CHD

Because this cohort study is one of the first to investigate whether the Mediterranean diet is associated with a first CHD event, the findings can be only tentatively compared with those from other cohort studies whose outcomes are total mortality or CHD mortality. In addition, quantitative comparisons with results from studies using different Mediterranean diet scores can be problematic, especially since many different Mediterranean diet scores are now in use (7), with variations in the type and number of components included. The range of intakes and absolute amounts of food consumed also vary between study populations, which means that different cutoff points are used to define Mediterranean diet adherence. However, to try to make our results more comparable with previous studies that applied the original Mediterranean diet score, developed by Trichopoulou et al. (21), we constructed this same Mediterranean diet score. The overall strength of the protective effect of the Mediterranean diet (applying both scores) on incidence of coronary events is within the range of results from previous studies in this area (20).

Our results are also in line with the findings from the Lyon Diet Heart Study trial that highlighted the value of the Mediterranean diet in secondary prevention of coronary events (36). Our study goes beyond this point by underscoring the importance of this diet in primary prevention as well. Indeed, a recent overview of research on the Mediterranean diet concluded that a healthy diet such as the traditional Mediterranean diet, along with frequent physical activity and avoiding tobacco smoke, could prevent 80% of CHD (37). Mediterranean diet trials also provide insight into potential mechanistic pathways through which the Mediterranean diet may reduce the risk of cardiovascular diseases, including its ability to reduce systolic blood pressure (16), apolipoproteins A-I and B, insulinemia, glycemia (14), and vascular inflammation and to improve endothelial dysfunction (38).

Methodological considerations

In our study, the beneficial effect of the rMED was more evident when measured by a dietary score rather than measuring each of the components separately. This occurrence is common and is also the impetus behind measurement of overall dietary patterns using scores (39). The use of Mediterranean diet scores is also advantageous because they 1) capture the effect of individual food groups whose health effect may be undetectable alone, 2) overcome issues of nutritional collinearity and confounding, and 3) capture biologic interactions between food groups.

The rMED score was also based on energy-adjusted tertiles of intake for each component, to take into account the quantity consumed relative to an individual's total daily energy intake. The advantage of constructing the score by using tertiles is that it discriminates better between the variations of intakes within the study population, and, although

Table 6. Sensitivity Analyses for Risk of Coronary Heart Disease According to Level of Adherence to the Relative Mediterranean Diet in the EPIC-Spain Cohort[a]

Sensitivity Analyses	No. of Cases	No. of Participants	rMED[b] Score								
			Categorical[c]						Continuous[d]		
			Low	Medium		High		P-Trend	1-Unit Increase in Score[d]		P-Trend
				HR	95% CI	HR	95% CI		HR	95% CI	
Censoring											
CHD cases and at-risk participants in the first 2 years of follow-up	530	40,040	1 (referent)	0.84	0.68, 1.04	0.57	0.44, 0.74	<0.001	0.93	0.90, 0.96	<0.001
CHD cases classified as unstable anginas[e]	466	40,151	1 (referent)	0.86	0.69, 1.08	0.61	0.46, 0.81	<0.001	0.94	0.90, 0.97	<0.001
Excluding											
Participants with diabetes at baseline	536	38,212	1 (referent)	0.93	0.75, 1.14	0.65	0.50, 0.84	0.001	0.95	0.92, 0.98	0.001
Granada EPIC-center	561	32,542	1 (referent)	0.83	0.68, 1.02	0.56	0.44, 0.73	<0.001	0.93	0.90, 0.96	<0.001
									2-Unit Increase in Score[d]		
Mediterranean diet score comparisons									HR	95% CI	
rMED score[f] (energy-adjusted tertiles)	606	40,151	1 (referent)	0.86	0.70, 1.04	0.60	0.47, 0.77	<0.001	0.88	0.83, 0.93	<0.001
Mediterranean diet score[g] (sex-specific medians)	606	40,151	1 (referent)	0.89	0.74, 1.07	0.79	0.63, 0.98	0.034	0.89	0.81, 0.97	0.017

Abbreviations: CHD, coronary heart disease; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; rMED, relative Mediterranean diet.

[a] Hazard ratios for an incident CHD event. The model was stratified by center and age and was adjusted for education; physical activity; body mass index; smoking status; diabetes, hypertension, and hyperlipidemia status; and total calorie intake (321 participants were excluded previously (including 3 cases) because of missing information on smoking, diabetes, hypertension, and/or hyperlipidemia status).

[b] Includes 9 components—vegetables, legumes, fruit, cereals, fresh fish, olive oil, alcohol, meat, and dairy products—from EPIC-Spain dietary questionnaire data.

[c] Low score, 0–6; medium score, 7–10; high score, 11–18.

[d] Index as a continuous variable, with a 1-unit or 2-unit increase in score.

[e] Unstable anginas requiring a revascularization procedure.

[f] Energy-adjusted tertiles were used as cutoffs (except for alcohol, for which sex-specific ranges were used).

[g] Nine-component score, as developed by Trichopoulou et al. (21), using sex-specific medians as cutoffs for legumes, cereals, fruits and nuts, vegetables, fish, meat and poultry, dairy, a ratio of monounsaturated lipids to saturated lipids, and sex-specific ranges for alcohol. Low score, 0–3; medium score, 4–5; high score, 6–9.

the hazard ratios for the association between the Mediterranean diet and CHD were relatively similar when we applied the Mediterranean diet score with tertiles and with medians, the *P* values did vary. In addition, our rMED score included intake of olive oil instead of monounsaturated fat, which is a proxy for olive oil but is also an indication of meat intake, especially in non-Mediterranean countries.

Further strengths of this study include its prospective design, involving a long follow-up of a large sample of healthy individuals. The study was also conducted in a Mediterranean country, where foods that form part of the Mediterranean diet are commonly eaten. There were also a reasonably large number of incident CHD cases, which were confirmed by international standards. In addition, to ensure good specificity, probable CHD events were not considered cases of CHD.

Although there is regional variability in CHD incidence rates across Spain (28), the number of CHD cases in Granada is probably an underestimate, resulting in lower sensitivity. Theoretically, with high specificity, nondifferential sensitivity of disease misclassification would not bias the estimated relative risk (40), and there is no reason to believe that there would be differential misclassification of disease because of lower coverage among subjects with higher adherence to the Mediterranean diet. In fact, the main consequence would be a reduction in the total number of cases and decreased statistical power to detect associations. However, in a sensitivity analysis excluding subjects from Granada, very similar results were observed. The number of prevalent cases (which were excluded at baseline) could also have been underestimated, although possible inclusion of prevalent cases in the censored population would have little impact in a cohort study of this size.

There were fewer female than male cases; however, it is well documented that the incidence of myocardial infarctions in Spain, as in other industrialized countries, is lower among females (2). The rMED score also has limitations; above all, similar weight is given to each component, assuming that the components (and the foods constituting them) have equivalent effects on health. For example, most Mediterranean diet scores (including ours because of a lack of detailed information) use a cereal group that includes refined and whole-grain cereals, which are scored as beneficial even though their effects on health are distinct (41, 42). In contrast, there is increasingly convincing evidence for the cardioprotective role of olive oil and nuts (19, 43, 44). A recent study on the anatomy of health effects of the Mediterranean diet within the EPIC-Greece cohort clearly shows considerable differences in the relative contribution of each Mediterranean diet component in reducing total mortality (45).

A potential study bias is that some CHD cases may have been aware of early symptoms or of CHD risk factors related to their disease and may have altered their diet, perhaps to a more Mediterranean-style diet, as a consequence. A further bias could have originated from inclusion of the unstable anginas requiring revascularization procedures. These potential biases would probably lead to an underestimation of the observed association. Nevertheless, there were no notable differences in the results after we censored cases diagnosed during the first 2 years of follow-up or cases with unstable anginas.

In the descriptive analysis, we observed that participants with diabetes, hypertension, and hyperlipidemia had a higher rMED score, which may be due to medical dietary advice. However, this proportion of the study population was relatively small, and we adjusted for these medical disorders in the analysis. We also carried out a sensitivity analysis by excluding diabetic patients at baseline, and a similar association between the rMED and CHD was observed. There could also be residual confounding by factors not measured in the study, such as psychosocial status (46), and by variables that were adjusted for but were measured with error. However, the information on diet was assessed by using a validated dietary history questionnaire (31, 32) with fewer measurement errors than with food frequency questionnaires (47). The physical activity questionnaire has also been validated (48).

Conclusion

Our study shows that high adherence to an rMED is associated with a 40% reduction in the risk of CHD. Also of public health relevance is that even a 2-unit increase in rMED score, which requires less drastic and more feasible dietary changes, has a protective effect on myocardial infarction risk. The results of this study complement the existing literature on the health benefits of the Mediterranean diet (10, 12, 22) by providing evidence on its importance in primary prevention of incident coronary events in healthy individuals. Understanding which and how key components of the Mediterranean diet provide this cardioprotective effect is an important focus for future research (45). It is also relevant when translating this diet to non-Mediterranean countries and when trying to preserve the traditional diets of Mediterranean countries, where dietary habits are becoming increasingly westernized (49,50).

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REFERENCES

1. Cardiovascular diseases (CVDs). Geneva, Switzerland: World Health Organization, 2007. Fact sheet no. 317. (http://www.who.int/mediacentre/factsheets/fs317/en/index.html). (Accessed December 17, 2007).
2. Marrugat J, Elosua R, Aldasoro E, et al. Regional variability in population acute myocardial infarction cumulative incidence and mortality rates in Spain 1997 and 1998. *Eur J Epidemiol*. 2004;19(9):831–839.
3. Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000;343(1):16–22.
4. 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(6):903–915.

5. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. *Lancet*. 1999;353(9164):1547–1557.
6. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. *BMJ*. 1995;311(7018):1457–1460.
7. Bach A, Serra-Majem L, Carrasco JL, et al. The use of indexes evaluating the adherence to the Mediterranean diet in epidemiological studies: a review. *Public Health Nutr.* 2006;9(1A):132–146.
8. Serra-Majem L, Trichopoulou A, Ngo de la Cruz J, et al. Does the definition of the Mediterranean diet need to be updated? *Public Health Nutr.* 2004;7(7):927–929.
9. Mente A, de Koning L, Shannon HS, et al. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med*. 2009;169(7):659–669.
10. de Lorgeril M, Salen P. Mediterranean type of diet for the prevention of coronary heart disease. A global perspective from the Seven Countries Study to the most recent dietary trials. *Int J Vitam Nutr Res.* 2001;71(3):166–172.
11. Panagiotakos DB, Pitsavos C, Polychronopoulos E, et al. Can a Mediterranean diet moderate the development and clinical progression of coronary heart disease? A systematic review. *Med Sci Monit.* 2004;10(8):RA193–RA198.
12. Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean diet: a systematic review. *Nutr Rev.* 2006;64(2 pt 2):S27–S47.
13. Martinez-Gonzalez MA, Bes-Rastrollo M, Serra-Majem L, et al. Mediterranean food pattern and the primary prevention of chronic disease: recent developments. *Nutr Rev.* 2009;67(suppl 1):S111–S116.
14. Vincent-Baudry S, Defoort C, Gerber M, et al. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr.* 2005;82(5):964–971.
15. 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.
16. 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.
17. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. *Am J Clin Nutr.* 2000;71(4):987–992.
18. Martínez-González MA. The SUN cohort study (Seguimiento University of Navarra). *Public Health Nutr.* 2006;9(1A):127–131.
19. Fernández-Jarne E, Martínez-Losa E, Prado-Santamaría M, et al. Risk of first non-fatal myocardial infarction negatively associated with olive oil consumption: a case-control study in Spain. *Int J Epidemiol*. 2002;31(2):474–480.
20. Sofi F, Cesari F, Abbate R, et al. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ*. 2008;337(112):a1344–a1350.
21. Trichopoulou A, Costacou T, Bamia C, et al. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348(26):2599–2608.
22. Fung TT, Rexrode KM, Mantzoros CS, et al. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation*. 2009;119(8):1093–1100.
23. Iestra J, Knoops K, Kromhout D, et al. Lifestyle, Mediterranean diet and survival in European post-myocardial infarction patients. *Eur J Cardiovasc Prev Rehabil*. 2006;13(6):894–900.
24. Trichopoulou A, Bamia C, Norat T, et al. Modified Mediterranean diet and survival after myocardial infarction: the EPIC-Elderly study. *Eur J Epidemiol*. 2007;22(12):871–881.
25. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26(suppl 1):S6–S14.
26. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr.* 2002;5(6B):1113–1124.
27. Bingham S, Riboli E. Diet and cancer—the European Prospective Investigation into Cancer and Nutrition. *Nat Rev Cancer.* 2004;4(3):206–215.
28. Larrañaga N, Moreno C, Basterretxea M, et al. Incidence of acute myocardial infarction in the Spanish epic cohort. *An Sist Sanit Navar.* 2009;32(1):51–59.
29. Danesh J, Saracci R, Berglund G, et al. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. *Eur J Epidemiol*. 2007;22(2):129–141.
30. Burke B. The dietary history as a tool in research. *J Am Diet Assoc.* 1947;23:1041–1046.
31. Relative validity and reproducibility of a diet history questionnaire in Spain. I. Foods. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26(suppl 1):S91–S99.
32. Relative validity and reproducibility of a diet history questionnaire in Spain. II. Nutrients. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26(suppl 1):S100–S109.
33. Slimani N, Deharveng G, Unwin I, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr.* 2007;61(9):1037–1056.
34. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108(20):2543–2549.
35. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev.* 2007;16(1):36–42.
36. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779–785.
37. Willett WC. The Mediterranean diet: science and practice. *Public Health Nutr.* 2006;9(1A):105–110.
38. Esposito K, Ciotola M, Giugliano D. Mediterranean diet, endothelial function and vascular inflammatory markers. *Public Health Nutr.* 2006;9(8A):1073–1076.
39. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3–9.

40. Greenland S, Lash TL. Bias analysis. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
41. Martínez-González MA, Fernández-Jarne E, Serrano-Martínez M, et al. Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score. *Eur J Nutr*. 2002;41(4):153–160.
42. Martínez-González MA, Sánchez-Villegas A. The emerging role of Mediterranean diets in cardiovascular epidemiology: monounsaturated fats, olive oil, red wine or the whole pattern? *Eur J Epidemiol*. 2004;19(1):9–13.
43. Fitó M, Cladellas M, de la Torre R, et al. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial. *Eur J Clin Nutr*. 2008;62(4):570–574.
44. Salas-Salvadó J, Garcia-Arellano A, Estruch R, et al. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur J Clin Nutr*. 2008;62(5):651–659.
45. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. *BMJ*. 2009;338:b2337(DOI: 10.1136/bmj.b2337).
46. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ*. 1999;318(7196):1460–1467.
47. Bingham SA, Gill C, Welch A, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol*. 1997;26(suppl 1):S137–S151.
48. Cust AE, Smith BJ, Chau J, et al. Validity and repeatability of the EPIC physical activity questionnaire: a validation study using accelerometers as an objective measure. *Int J Behav Nutr Phys Act*. 2008;5:33.
49. Garcia-Closas R, Berenguer A, González CA. Changes in food supply in Mediterranean countries from 1961 to 2001. *Public Health Nutr*. 2006;9(1):53–60.
50. da Silva R, Bach-Faig A, Raidó Quintana B, et al. Worldwide variation of adherence to the Mediterranean diet, in 1961–1965 and 2000–2003. *Public Health Nutr*. 2009;12(9A):1676–1684.