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Mediterranean diet and CHD: the Greek European Prospective Investigation into Cancer and Nutrition cohort

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Abstract

Adherence to the Mediterranean diet (MD) has been reported to improve CHD prognosis and to be inversely associated with CHD mortality. The aim of the present study was to investigate the association of adherence to the MD with CHD incidence and mortality in the Greek European Prospective Investigation into Cancer and Nutrition cohort, a population with traditional Mediterranean roots. In a general population sample of 23 929 adult men and women with no CVD or cancer at enrolment, a validated FFQ was interviewer-administered, sociodemographic, physical activity and other characteristics were recorded, and arterial blood pressure and anthropometric characteristics were measured. In a median period of 10 years, 636 incident CHD cases and 240 CHD deaths were recorded. Associations of adherence to the MD, operationalised through a nine-component score (0, poor; 9, excellent), with CHD incidence and mortality were evaluated through Cox regression controlling for potentially confounding variables. A two-point increase in the MD score was associated with lower CHD mortality by 25 % (95 % CI 0·57, 0·98) among women and 19 % (95 % CI 0·67, 0·99) among men. The association of adherence to the MD with CHD incidence was again inverse, but weaker (hazard ratios 0·85 (95 % CI 0·71, 1·02) among women and 0·98 (95 % CI 0·87, 1·10) among men). With respect to score components, only meat among men (positively) and fruits and nuts among women (inversely) were associated with both the incidence of and mortality from CHD. The MD, as an integral entity, is inversely associated with CHD incidence and, particularly, mortality.

Key words: Mediterranean diet: CHD: European Prospective Investigation into Cancer and Nutrition: Greece

In the early 1960s, Ancel Keys introduced the concept of the traditional Mediterranean diet (MD) and reported its strong ecological association with a low incidence of CHD, attributing this association largely to the low content of the MD in saturated lipids[(1)]. About two decades later, the traditional MD pattern drew again the attention of the scientific community[(2)] and in the mid-1990s, Trichopoulou *et al.*[(3)] introduced a scoring concept to assess conformity with the salient characteristics of this diet. Several score variants have since been introduced[(4–8)] and used in observational studies to assess the relationship between conformity with the MD and various health outcomes, including total mortality[(4,6–9)], incidence of or mortality from stroke[(10)], as well as incidence of or mortality from cancer overall[(4,7,8,11)] and from specific cancer sites[(12–15)].

With respect to CHD, a condition intimately linked to the diet[(16)], there have been prospective studies reporting that conformity with the MD is inversely associated with CHD mortality[(4,10,17)]. There has also been at least one randomised trial[(18)], indicating that a closer adherence to the MD or its key elements may improve CHD prognosis[(19,20)]. Furthermore, three studies have examined the association of conformity with a traditional MD pattern with the incidence of CHD, one in the USA, in the major Nurses' Health Study[(10)], and two in Spain, notably one in the Spanish component of the European Prospective Investigation into Cancer and Nutrition (EPIC)[(21)] and the second in the Seguimierto Universtiy of Navarra (SUN) Project cohort[(22)]; they all indicated an inverse association of adherence to the MD with CHD incidence.

We have studied the association of adherence to the MD with the incidence of and mortality from CHD in the Greek component of the EPIC cohort. Greece is one of the countries in which Keys and his colleagues undertook their original

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; MD, Mediterranean diet.

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work, and a Mediterranean country in which large segments of the population still adhere to the traditional MD pattern.

Methods

Study population

The EPIC cohort comprises about 520 000 participants from twenty-three centres in ten European countries. It provides data on diet, anthropometry, lifestyle, socio-economic variables, as well as genetic and biomarker data in relation to cancer and other chronic diseases[23]. The EPIC cohort in Greece consists of 28 572 volunteers (11 954 men and 16 618 women) aged 20–86 years recruited between 1994 and 1999 from all over Greece. Participants were actively followed up through telephone interviews by specially trained health professionals (next of kin interviewed, in the case of death of a participant).

For the present study, of the 28 572 Greek volunteers, 3118 subjects with prevalent CVD or cancer at recruitment were excluded. From the remaining subjects, another 1525 were excluded for not having any follow-up data at all as of 31 December 2009 or not having information for one or more of the study variables. Thus, a total of 23 929 subjects were included in the present investigation. The procedures implemented in the EPIC study were in accordance with the Declaration of Helsinki on the Ethical Principles for Medical Research involving Human Subjects of 1975 as revised in 1983. All study participants signed an informed consent form and the study protocol was approved by the ethics committees of the International Agency for Research on Cancer and the Medical School of the University of Athens.

Dietary information

Dietary habits of the study participants were assessed at baseline through a validated interviewer-administered semi-quantitative FFQ[24,25]. The FFQ reflected the frequency of consumption of about 200 foods and recipes that are common in Greece. The quantification of dietary intake was performed with the use of photographs of usual portion sizes. Nutrient and energy intakes were estimated through the Greek Food Composition Tables[26].

Conformity with the traditional MD was assessed through a MD score (range 0–9 points), as described by Trichopoulou *et al.*[4]. The score relies on nine dietary components, frequent or less frequent consumption of which is typical of the traditional MD. A value of 0 or 1 is assigned to each component of the score as follows: for components frequently consumed in the traditional MD (vegetables, legumes, fruits and nuts, cereals, fish and seafood, as well a high ratio of monounsaturated:saturated lipids), subjects whose consumption was above the sex-specific median are assigned a value of 1 or 0 otherwise; for components less frequently consumed in the traditional MD (dairy, as well as meat and meat products), subjects whose consumption is equal to or lower than the sex-specific median are assigned a value of 1 or 0 otherwise. A value of 1 is also given to subjects consuming a moderate amount of alcohol (i.e. between 5 and 25 g/d for women and between 10 and 50 g/d for men) or a value of 0 otherwise. Thus, the total MD score can take values from 0 (minimal adherence to the traditional MD) to 9 (maximal adherence to the traditional MD).

Non-dietary information

A number of sociodemographic and lifestyle characteristics, including years of schooling, smoking and physical activity, were recorded at enrolment. An overall metabolic equivalent task-h/d index, expressing the average daily energy expenditure level, was calculated on the basis of the frequency and duration of participation in occupational and leisure-time physical activities[27,28]. Anthropometric measurements were also undertaken using standardised procedures and allowing for the calculation of BMI (kg/m^2). Arterial blood pressure was measured by trained physicians, through a mercury sphygmomanometer (Baumanometer; W.A. Baum Company Inc.) and following international protocols[29]. The averages of two readings for both systolic and diastolic blood pressure were used. For the present study, hypertension was defined as systolic blood pressure of 140 mmHg or higher, or a diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medication.

Study outcomes

Self-reporting of a CHD event during the follow-up was confirmed through hospital discharge data, medical records or death certificates, and was classified according to the 10th revision of the International Classification of Diseases (ICD)[30]. The following three manifestations of CHD were considered: myocardial infarction (ICD-10 codes I21, I22, I23, Z95.1 and I46), angina (ICD-10 code I20) and CHD other than angina or myocardial infarction (ICD-10 codes I24, I25, Z95.5, Z95.8 and Z95.9, which include other acute and chronic IHD, presence of coronary angioplasty implant and graft)[31]. For the calculation of CHD incidence, the first CHD event was considered, even if that event was death from CHD. For the calculation of CHD mortality, death from CHD was considered, irrespectively of whether a CHD event had occurred in the past or not.

Statistical analysis

Statistical analyses were performed using the Stata Statistical Software, release 11 (StataCorp. 2009, StataCorp LP). We calculated sex-specific distributions of the study participants, person-time at risk, incident CHD cases and CHD deaths by participants' personal characteristics (excluding the diet), as well as hazard ratios for CHD incidence and mortality, mutually adjusting for energy and non-nutritional variables. We also calculated daily intakes (means and percentiles) of the key dietary components by sex. Associations between dietary intakes and CHD incidence and mortality were next evaluated through Cox regression. The statistical models were fitted: (1) adjusting only for age and energy intake;

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Table 1. Distribution of the study participants, person-time at risk, incident CHD cases and CHD deaths, and hazard ratios (HR) for CHD incidence and mortality by participants' personal characteristics: the Greek European Prospective Investigation into Cancer and Nutrition cohort – men

(Hazard ratios and 95 % confidence intervals)

					CHD incidence*		CHD mortality*	
	Study participants (*n*)	Person-years at risk†	Incident CHD cases (*n*)	CHD deaths (*n*)	HR	95 % CI	HR	95 % CI
All	9740	89 716	426	150				
Age (years)								
< 45	3511	31 648	50	9	1·0		1·0	
45–54	2419	22 792	89	16	2·32	1·62, 3·32	1·99	0·86, 4·61
55–64	1975	19 049	115	24	3·48	2·39, 5·08	3·04	1·31, 7·06
≥ 65	1835	16 227	172	101	5·69	3·79, 8·54	13·75	6·03, 31·36
Years of schooling								
≤ 6	4603	42 173	278	124	1·0		1·0	
> 6	5137	47 543	148	26	1·05	0·82, 1·34	0·64	0·39, 1·05
Height (cm)								
< 165	2048	18 896	130	61	1·0		1·0	
165–169	2471	22 713	134	41	1·11	0·87, 1·42	0·88	0·59, 1·32
170–174	2591	24 042	88	31	0·88	0·66, 1·17	0·96	0·61, 1·50
≥ 175	2630	24 065	74	17	0·99	0·72, 1·35	0·84	0·47, 1·49
BMI (kg/m^2)								
< 25	1909	17 572	61	29	1·0		1·0	
≥ 25 and < 30	5143	47 548	209	68	1·26	0·95, 1·68	0·93	0·60, 1·45
≥ 30	2688	24 596	156	53	1·58	1·16, 2·13	1·17	0·73, 1·86
Physical activity level (MET-h/d)								
< 35	5250	47 392	272	100	1·0		1·0	
≥ 35	4490	42 324	154	50	0·83	0·68, 1·02	0·96	0·67, 1·37
Alcohol intake (g/d)								
< 5	2936	26 519	150	61	1·0		1·0	
≥ 5 and < 25	4163	38 756	174	50	0·85	0·68, 1·07	0·65	0·44, 0·95
≥ 25	2641	24 441	102	39	0·75	0·57, 0·98	0·74	0·48, 1·15
Smoking								
Never	2467	23 504	91	33	1·0		1·0	
Former smokers	3048	28 475	144	56	1·25	0·96, 1·63	1·35	0·88, 2·08
Current smokers	4225	37 737	191	61	2·01	1·56, 2·61	2·22	1·43, 3·43
Arterial blood pressure								
Normal	5647	52 372	147	40	1·0		1·0	
High‡	4093	37 344	279	110	1·63	1·30, 2·03	1·62	1·09, 2·40

MET, metabolic equivalent of tasks.

* Mutually adjusted for the variables indicated in the table plus daily energy intake in the following four categories: < 6276 kJ (1500 kcal); ≥ 6276 kJ (1500 kcal) and < 8368 kJ (2000 kcal); ≥ 8368 kJ (2000 kcal) and < 10 460 kJ (2500 kcal) and ≥ 10 460 kJ (2500 kcal).

† For the CHD incidence analysis.

‡ High blood pressure was defined as systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medication.

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Table 2. Distribution of the study participants, person-time at risk, incident CHD cases and CHD deaths, and hazard ratios (HR) for CHD incidence and mortality by participants' personal characteristics: the Greek European Prospective Investigation into Cancer and Nutrition cohort – women

(Hazard ratios and 95 % confidence intervals)

	Study participants (*n*)	Person-years at risk†	Incident CHD cases (*n*)	CHD deaths (*n*)	CHD incidence*		CHD mortality*	
					HR	95 % CI	HR	95 % CI
All	14 189	140 179	210	90				
Age (years)								
< 45	4539	43 668	5	0	1·0		1·0	
45–54	3454	35 439	10	3	1·0		1·0	
55–64	3475	35 363	64	18	5·72	3·09, 10·59	9·26	2·54, 33·80
≥ 65	2721	25 709	131	69	12·18	6·51, 22·82	36·14	10·02, 130·39
Years of schooling								
≤ 6	8584	84 595	189	82	1·0		1·0	
> 6	5605	55 584	21	8	0·71	0·42, 1·19	0·75	0·33, 1·71
Height (cm)								
< 150	1953	18 977	56	30	1·0		1·0	
150–154	3577	35 097	82	35	1·19	0·85, 1·68	1·00	0·61, 1·64
155–159	4206	42 192	46	17	0·89	0·59, 1·32	0·68	0·37, 1·25
≥ 160	4453	43 913	26	8	0·95	0·58, 1·55	0·66	0·29, 1·50
BMI (kg/m^2)								
< 25	3567	35 061	22	9	1·0		1·0	
≥ 25 and < 30	5301	52 699	79	33	1·19	0·74, 1·92	1·20	0·57, 2·54
≥ 30	5321	52 419	109	48	1·09	0·68, 1·76	1·14	0·54, 2·37
Physical activity level (MET-h/d)								
< 35	6768	65 752	147	70	1·0		1·0	
≥ 35	7421	74 427	63	20	0·79	0·58, 1·08	0·62	0·37, 1·04
Alcohol intake (g/d)								
< 5 g/d	11 046	108 891	184	81	1·0		1·0	
≥ 5 g/d	3143	31 288	26	9	0·77	0·50, 1·17	0·62	0·31, 1·26
Smoking								
Never	10 181	101 171	183	78	1·0		1·0	
Former smokers	1121	10 987	10	5	1·52	0·79, 2·93	1·92	0·75, 4·91
Current smokers	2887	28 021	17	7	1·89	1·10, 3·23	2·35	1·03, 5·34
Arterial blood pressure								
Normal	8469	84 435	35	16	1·0		1·0	
High‡	5720	55 844	175	74	2·62	1·76, 3·90	1·88	1·05, 3·34

MET, metabolic equivalent of tasks.

* Mutually adjusted for the variables indicated in the table plus daily energy intake in the following four categories: < 6276 kJ (1500 kcal); ≥ 6276 kJ (1500 kcal) and < 8368 kJ (2000 kcal); ≥ 8368 kJ (2000 kcal) and < 10 460 kJ (2500 kcal) and ≥ 10 460 kJ (2500 kcal).

† For the CHD incidence analysis.

‡ High blood pressure was defined as systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medication.

Table 3. Intakes of the indicated food groups, nutrients and energy, by sex: the Greek European Prospective Investigation into Cancer and Nutrition cohort

(Mean values and standard deviations; percentiles)

	Men (n 9740)					Women (n 14 189)				
Nutritional variables	Mean	SD	25th percentile	50th percentile	75th percentile	Mean	SD	25th percentile	50th percentile	75th percentile
Potatoes (g/d)	98	63	57	87	120	73	47	39	65	95
Vegetables (g/d)	582	233	434	547	682	535	231	389	499	634
Legumes (g/d)	10	7	6	9	13	8	6	4	7	10
Fruits and nuts (g/d)	387	216	249	356	480	380	207	249	351	468
Dairy foods (g/d)	224	149	118	198	303	218	147	112	194	294
Cereals (g/d)	190	81	134	176	231	145	55	107	139	175
Meat (g/d)	129	61	87	121	163	95	45	64	90	120
Fish (g/d)	26	20	14	24	34	22	15	13	19	28
Eggs (g/d)	19	13	10	16	24	16	10	9	14	20
Sugar and confectioneries (sweets) (g/d)	26	20	12	22	35	23	18	11	19	30
Non-alcoholic beverages (g/d)	386	247	220	334	490	294	205	163	251	376
Olive oil (g/d)	53	24	38	52	66	45	22	31	44	57
Saturated lipids (g/d)	33	13	24	31	40	27	11	19	26	33
Monounsaturated lipids (g/d)	57	20	43	54	67	47	17	36	45	57
Polyunsaturated lipids (g/d)	16	10	10	13	19	14	9	8	11	16
Monounsaturated:saturated lipid ratio	1·82	0·51	1·47	1·77	2·10	1·85	0·54	1·47	1·80	2·16
Energy intake (kJ/d)	9954	2950	7866	9602	11 673	7927	2368	6297	7636	9205

(2) adjusting for age, energy intake and non-nutritional variables; and (3) adjusting for age, non-nutritional variables and other dietary intakes, but excluding total energy intake to avoid collinearity. Continuous non-nutritional variables included in the models were age, years of schooling, height, BMI and physical activity level. Categorical variables included in the models were as follows: smoking status in three categories (never, former or current smokers), levels of arterial blood pressure in two categories (normotensives or hypertensives) and alcohol intake in three categories for men (<5 g/d, ≥ 5 and <25 g/d or ≥ 25 g/d) and two categories for women (<5 g/d or ≥ 5 g/d). The nutritional variables studied were the components of the MD score (fruits and nuts, vegetables, legumes, cereals, dairy products, meat and meat products, fish and seafood, alcohol and ratio of MUFA:SFA), as well as potatoes, eggs, sweets, non-alcoholic beverages, olive oil, saturated, mono- and polyunsaturated lipids (adjusted as indicated in Tables 4 and 5). Lastly, the association of the MD score (both in categories and as an ordered variable per two-point increment) with CHD incidence and mortality was evaluated by sex and overall (controlling for sex), also controlling for the non-nutritional variables and energy intake.

Results

Of the study, 636 participants (426 males and 210 females) developed CHD in the course of the study. Among them, 240 died from the disease (150 males and ninety females). The follow-up time ranged between 1 month and 15·8 years with a median of 10 years. Tables 1 (men) and 2 (women) present the distributions of participants, person-time at risk, incident CHD cases and CHD deaths by sociodemographic, anthropometric and lifestyle variables, as well as the hazard ratios for CHD incidence and mortality, mutually adjusting for the non-nutritional variables, as well as for alcohol and energy intake. The studied population included more women than men and a high proportion of the participants were of a relatively low education level. The majority of participants of both sexes were either overweight or obese. Most men were light to moderate alcohol drinkers, in contrast to women who largely did not drink alcohol at all. Smoking was very common, particularly among men. The associations of traditional risk factors for CHD with the incidence of and mortality from the disease are evident in the data for the Greek EPIC cohort presented in Tables 1 and 2.

Table 3 presents daily intakes (means and percentiles) of various food groups (including the nine components of the MD score, as well as potatoes, eggs, sweets, non-alcoholic beverages and total energy intake) by sex. The data in this table provide the dietary background of the study population, which still reflects the traditional MD.

Tables 4 (men) and 5 (women) present hazard ratios for the incidence of and mortality from CHD per 1 standard deviation increment of the indicated dietary compounds. Estimates were derived from three models: one controlling for age and energy intake; another also controlling for the non-nutritional variables; a third model in which dietary variables were also mutually adjusted for (without controlling for energy intake).

Table 4. Hazard ratios (HR) for CHD incidence and mortality from CHD per 1 standard deviation increment for the corresponding nutritional variable: the Greek European Prospective Investigation into Cancer and Nutrition cohort – men

(Hazard ratios and 95 % confidence intervals)

	Age and energy intake adjusted*				Adjusted for age, energy intake and non-nutritional variables†				Adjusted for age, nutritional and non-nutritional variables‡			
	CHD incidence		CHD death		CHD incidence		CHD death		CHD incidence		CHD death	
Nutritional variables	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Potatoes (g/d)	1·03	0·92, 1·14	0·95	0·76, 1·17	1·01	0·91, 1·13	0·92	0·74, 1·14	1·01	0·90, 1·13	0·92	0·73, 1·16
Vegetables (g/d)	1·11	0·98, 1·24	0·92	0·73, 1·17	1·12	0·99, 1·27	0·96	0·75, 1·22	1·15	0·95, 1·39	0·96	0·66, 1·40
Legumes (g/d)	0·97	0·88, 1·08	1·02	0·85, 1·21	0·98	0·88, 1·08	1·04	0·87, 1·24	0·96	0·86, 1·07	1·07	0·89, 1·29
Fruits and nuts (g/d)	0·90	0·79, 1·01	0·68	0·54, 0·87	0·93	0·83, 1·05	0·73	0·57, 0·92	0·94	0·84, 1·06	0·77	0·61, 0·97
Dairy foods (g/d)	0·98	0·88, 1·09	1·03	0·86, 1·23	0·99	0·88, 1·11	1·06	0·88, 1·27	1·04	0·90, 1·19	0·93	0·73, 1·19
Cereals (g/d)	1·01	0·90, 1·12	0·94	0·77, 1·15	0·98	0·87, 1·09	0·91	0·74, 1·11	1·01	0·91, 1·12	0·95	0·79, 1·14
Meat (g/d)	1·18	1·05, 1·32	1·26	1·04, 1·54	1·13	1·01, 1·27	1·18	0·96, 1·44	1·13	1·00, 1·27	1·09	0·89, 1·35
Fish (g/d)	1·04	0·97, 1·12	1·05	0·92, 1·20	1·03	0·95, 1·11	1·04	0·91, 1·20	1·02	0·93, 1·11	1·05	0·90, 1·23
Eggs (g/d)	1·00	0·91, 1·10	1·12	0·98, 1·27	1·00	0·91, 1·10	1·11	0·97, 1·26	1·00	0·91, 1·11	1·10	0·97, 1·26
Sugar and confectioneries (sweets) (g/d)	0·93	0·83, 1·04	0·85	0·69, 1·05	0·92	0·82, 1·03	0·83	0·67, 1·03	0·94	0·83, 1·06	0·89	0·71, 1·11
Non-alcoholic beverages (g/d)	1·11	1·00, 1·24	0·95	0·76, 1·19	1·06	0·95, 1·18	0·90	0·72, 1·14	1·08	0·97, 1·20	0·95	0·75, 1·21
Olive oil (g/d)	1·10	0·98, 1·23	1·07	0·88, 1·31	1·09	0·97, 1·23	1·11	0·91, 1·36		–		–
Saturated lipids (g/d)	1·05	0·87, 1·26	1·34	0·97, 1·85	1·00	0·82, 1·21	1·37	0·97, 1·95	0·93	0·73, 1·20	1·39	0·89, 2·15
Monounsaturated lipids (g/d)	1·14	0·97, 1·33	1·05	0·80, 1·39	1·13	0·96, 1·34	1·08	0·81, 1·44	1·01	0·76, 1·33	0·99	0·59, 1·68
Polyunsaturated lipids (g/d)	0·97	0·87, 1·08	0·94	0·78, 1·13	0·97	0·87, 1·08	0·92	0·77, 1·11	0·95	0·81, 1·10	0·90	0·69, 1·19
Monounsaturated:saturated lipid ratio	1·01	0·92, 1·11	0·93	0·79, 1·09	1·02	0·92, 1·12	0·95	0·80, 1·12	0·96	0·83, 1·12	0·90	0·69, 1·17
Energy intake (kJ/d)	1·03	0·94, 1·14	1·06	0·89, 1·26	1·05	0·95, 1·17	1·09	0·90, 1·31		–		–

* Age and energy intake entered in the model as continuous variables.

† Age, BMI, height, physical activity, years of schooling and energy intake entered as continuous variables. Alcohol consumption, smoking status and arterial blood pressure entered categorically in the categories indicated in Tables 1 and 2.

‡ Variables as entered in footnote †, mutually adjusted for all variables in the table (per 1 standard deviation increment), except olive oil and energy intake that were not included in the model. For the monounsaturated:saturated lipid ratio values, the model was run without controlling for saturated and monounsaturated lipids.

Table 5. Hazard ratios for (HR) CHD incidence and mortality from CHD, per 1 standard deviation increment for the corresponding nutritional variable: the Greek European Prospective Investigation into Cancer and Nutrition cohort – women

(Hazard ratios and 95 % confidence intervals)

	Age and energy adjusted*				Adjusted for age, energy intake and non-nutritional variables†				Adjusted for age, nutritional and non-nutritional variables‡			
	CHD incidence		CHD death		CHD incidence		CHD death		CHD incidence		CHD death	
Nutritional variables	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Potatoes (g/d)	1·12	0·91, 1·39	1·29	0·94, 1·77	1·11	0·89, 1·38	1·29	0·93, 1·78	1·02	0·81, 1·29	1·15	0·82, 1·61
Vegetables (g/d)	1·10	0·88, 1·36	1·17	0·84, 1·63	1·10	0·87, 1·38	1·17	0·83, 1·66	0·89	0·62, 1·29	1·00	0·56, 1·78
Legumes (g/d)	0·89	0·72, 1·09	0·86	0·61, 1·19	0·88	0·71, 1·09	0·85	0·61, 1·19	0·83	0·67, 1·03	0·78	0·56, 1·10
Fruits and nuts (g/d)	0·63	0·50, 0·79	0·60	0·42, 0·86	0·66	0·52, 0·84	0·64	0·45, 0·92	0·66	0·53, 0·83	0·66	0·46, 0·93
Dairy foods (g/d)	1·10	0·94, 1·30	1·13	0·88, 1·45	1·12	0·95, 1·33	1·16	0·90, 1·50	1·08	0·87, 1·33	1·13	0·81, 1·57
Cereals (g/d)	0·95	0·75, 1·20	0·85	0·58, 1·23	0·89	0·70, 1·14	0·79	0·54, 1·16	0·83	0·67, 1·05	0·79	0·55, 1·13
Meat (g/d)	1·29	1·01, 1·64	1·36	0·93, 1·98	1·21	0·94, 1·55	1·24	0·84, 1·84	1·02	0·79, 1·32	1·04	0·70, 1·56
Fish (g/d)	1·13	0·99, 1·30	1·14	0·93, 1·40	1·14	1·00, 1·31	1·17	0·95, 1·45	1·08	0·94, 1·26	1·06	0·84, 1·34
Eggs (g/d)	1·08	0·91, 1·29	1·28	1·05, 1·56	1·07	0·89, 1·27	1·26	1·03, 1·55	1·02	0·85, 1·23	1·25	1·01, 1·54
Sugar and confectioneries (sweets) (g/d)	0·82	0·65, 1·03	0·74	0·52, 1·07	0·82	0·65, 1·04	0·73	0·50, 1·05	0·83	0·65, 1·05	0·84	0·58, 1·22
Non-alcoholic beverages (g/d)	1·09	0·88, 1·36	0·79	0·53, 1·20	1·11	0·88, 1·39	0·77	0·50, 1·18	1·12	0·90, 1·40	0·80	0·52, 1·24
Olive oil (g/d)	1·05	0·86, 1·29	1·37	0·98, 1·91	1·10	0·90, 1·34	1·42	1·02, 1·96		–		–
Saturated lipids (g/d)	1·44	1·00, 2·08	1·54	0·87, 2·71	1·39	0·95, 2·03	1·46	0·80, 2·65	0·85	0·54, 1·33	0·79	0·38, 1·64
Monounsaturated lipids (g/d)	1·20	0·88, 1·64	1·84	1·13, 2·99	1·25	0·92, 1·70	1·87	1·16, 3·01	1·33	0·78, 2·27	1·46	0·62, 3·41
Polyunsaturated lipids (g/d)	1·12	0·93, 1·34	0·89	0·64, 1·23	1·05	0·87, 1·26	0·82	0·59, 1·14	1·16	0·87, 1·55	0·94	0·58, 1·53
Monounsaturated:saturated lipid ratio	0·95	0·84, 1·08	1·05	0·88, 1·26	0·98	0·86, 1·10	1·07	0·89, 1·27	1·02	0·84, 1·23	1·04	0·78, 1·38
Energy intake (kJ/d)	0·72	0·59, 0·89	0·73	0·53, 1·00	0·76	0·62, 0·94	0·80	0·58, 1·10		–		–

* Age and energy intake entered in the model as continuous variables.

† Age, BMI, height, physical activity, years of schooling and energy intake entered as continuous variables. Alcohol consumption, smoking status and arterial blood pressure entered categorically in categories indicated in Tables 1 and 2.

‡ Variables as entered in footnote †, mutually adjusted for all variables in the table (entered per 1 standard deviation increment), except olive oil and energy intake that were not included in the model. For the monounsaturated:saturated lipid ratio values, the model was run without controlling for saturated and monounsaturated lipids.

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Table 6. Overall and sex-specific hazard ratios (HR)* for CHD incidence and death from CHD by Mediterranean diet (MD) score (categorically (0–3, 4–5 and 6–9) and per two-point increment): the Greek European Prospective Investigation into Cancer and Nutrition cohort

(Hazard ratios and 95 % confidence intervals)

	Men (n 9740)						Women (n 14 189)						All (23 929)†					
	CHD incidence (426 cases)			CHD mortality (150 cases)			CHD incidence (210 cases)			CHD mortality (90 cases)			CHD incidence (636 cases)			CHD mortality (240 cases)		
MD score	HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P
4–5 v. 0–3	0·80	0·64, 1·01	0·055	0·80	0·55, 1·15	0·223	1·02	0·76, 1·36	0·918	0·89	0·57, 1·39	0·604	0·86	0·72, 1·03	0·098	0·82	0·62, 1·09	0·169
6–9 v. 0–3	0·90	0·70, 1·16	0·415	0·62	0·39, 0·98	0·040	0·62	0·39, 0·99	0·043	0·39	0·17, 0·88	0·024	0·82	0·66, 1·02	0·077	0·54	0·37, 0·81	0·003
Two-point increment	0·98	0·87, 1·10	0·678	0·81	0·66, 0·99	0·043	0·85	0·71, 1·02	0·084	0·75	0·57, 0·98	0·038	0·92	0·84, 1·02	0·115	0·78	0·66, 0·92	0·003

* Age, BMI, height, physical activity, years of schooling and energy intake entered as continuous variables. Smoking status was entered in three categories (never, former or current smokers) and arterial blood pressure in two categories (normal or high, with high being defined as systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medication).
† Adjusted for sex as well as for the aforementioned variables.

Given the number of associations evaluated in Tables 4 and 5, the results should be interpreted cautiously. Only with respect to meat among men (positive) and fruits and nuts among women (inverse) is there somewhat consistent evidence for an association with both the incidence of and mortality from CHD.

Table 6 shows overall and sex-specific hazard ratios for CHD incidence and mortality by level of conformity with the traditional MD as assessed through the MD score, both categorically and per two-point increment. Overall, increased conformity with the traditional MD was associated with a suggestive reduction in CHD incidence ($P=0·115$) and a statistically significant reduction in mortality ($P=0·003$) from CHD. The results were generally more evident among women than among men and for CHD mortality rather than for CHD incidence. A two-point increase in the MD score was associated with a reduction in CHD mortality by 25 % (95 % CI 0·57, 0·98) among women and 19 % (95 % CI 0·66, 0·99) among men.

To further probe the associations observed, we undertook a series of sensitivity analyses. In particular, we repeated the analysis presented in Table 6 focusing first on participants being overweight or obese (i.e. with BMI ≥ 25 kg/m^2) at baseline, since the MD has been reported to reduce the risk of obesity and the metabolic syndrome[32–34]. Second, events of angina without any revascularisation procedure were excluded from the incident CHD cases, in order to reduce possible misclassification bias in the outcome. Third, we excluded cases occurring in the first 2 years of follow-up to accommodate a possible longer latency. Lastly, to allow for possible changes in participants' diet over time, we only considered events occurring in the first 8 years after recruitment. No difference was evident when participants of normal weight at baseline were excluded. When cases of angina were excluded, the apparent effect of the MD on CHD incidence was somewhat more evident, particularly among men. When CHD deaths occurring in the first 2 years of follow-up were excluded, we found a stronger inverse association of the MD with CHD mortality, but only among women (for a two-point increase in the MD score, the HR changed from 0·75 to 0·69). When follow-up observations were censored at the 8th year, we noticed only among men a stronger inverse association between the MD score and CHD incidence (the HR changed from 0·98 to 0·96, per two-point increment of the MD score) or CHD mortality (the HR changed from 0·81 to 0·76 for the same increment of the score).

Discussion

In a population-based cohort study of 23 929 apparently healthy women and men in Greece, followed for a total of 229 894 person-years for CHD incidence and 231 725 person-years for CHD mortality, 636 incident cases of CHD and 240 deaths from this disease were recorded. After controlling for possible confounding influences by traditional non-nutritional risk factors for CHD, conformity with the traditional MD, as operationalised through a widely used MD score, was significantly inversely associated with mortality from CHD and not significantly, but suggestively, associated with incidence of the disease. The inverse association with respect to both the incidence of and mortality from CHD was stronger among women than among men, possibly because women, the traditional housekeepers in Greece, have a better recollection and provide more accurate reporting of nutritional habits. In sensitivity analyses aiming to reduce misclassification of the diet during prolonged follow-up (more than 8 years), we found among men a somewhat stronger inverse association, whereas exclusion of deaths occurring during the first 2 years of follow-up resulted in stronger inverse associations among women. Of note, nutritional variables, including those that are part of the MD score, even after mutual adjustment, were inconsistently related to CHD incidence and mortality. Thus, the present results support the view that in the study of its association with health and disease, the traditional MD should be viewed and evaluated as an integral entity.

The present results are consistent with those of previous investigations evaluating individual dietary factors, as well as conformity with the MD in relation to CHD mortality and incidence[35]. In an early study based on the Greek EPIC cohort, relying on a total of fifty-four CHD deaths, a two-point increase in the MD was associated with a significant decrease in CHD mortality by 33 %[4]. In a large American study, relying on the American Association of Retired Persons cohort, and including 3451 CVD deaths, in comparison with those with low adherence (0–3 units), those with high adherence (score 6–9 units) had significantly 22 and 19 % lower cardiovascular mortality, among men and women, respectively. In an analysis of data from the Nurses' Health Study, which included 2391 incident CHD cases and 794 CHD deaths, significant inverse trend associations were noted, with those in the fifth quintile having 29 % lower incidence and 42 % lower mortality in comparison with those in the first (low-adherence) quintile. In the first analytical epidemiological study of adherence to the MD in relation to the incidence of CHD in a Mediterranean population, Spanish EPIC cohort participants with high adherence to the MD had a significant 40 % lower risk of CHD in comparison with those with low adherence. Of note, in the Spanish study, only vegetables ($P=0·01$) and olive oil and alcohol ($P=0·05$) were significantly inversely associated with CHD risk, even though the inverse association of the MD score with CHD was highly significant ($P<0·001$). In a recent publication based on the Spanish SUN Project cohort with 13 609 participants with no prevalent CVD, who were followed for about 5 years, a two-point increment in a similar MD score was significantly associated with a 26 % lower CHD risk[22]. In a systematic review of prospective cohort studies or randomised trials investigating dietary exposures in relation to CHD, evidence supported inverse associations for a limited number of dietary factors (notably vegetables, nuts and MUFA) with CHD risk. The MD pattern was the only dietary exposure with strong evidence of protection from both cohort and randomised trials[35].

A frequent misconception, which leads to a form of circular reasoning, is that the MD score assesses adherence to an *a priori* defined, 'optimal' health-protecting diet[4]. It should be clear that what the MD score assesses is adherence to the dietary pattern which was traditionally followed in the olive oil-growing areas of the Mediterranean up to the early 1960s[36,37]; it just so happens that this traditional dietary pattern turned out to have favourable health effects. The key components of the traditional MD, including olive oil and wine, are plant-derived and the traditional MD is essentially a plant-derived diet which, however, does not dogmatically exclude meat or dairy products. In the present data, as in the data from the earlier study in a Mediterranean population[21], the MD scores tend to generate fairly consistent results with respect to CHD, whereas results on their component foods or food groups were largely inconsistent. When a single food – rather than a multi-component, yet unidimensional, score – is evaluated, chance, non-differential misclassification and residual confounding may have more important consequences for several reasons. Chance is more likely to disruptively operate on a single food group rather than simultaneously on several components of a score. Moreover, in analyses focusing on individual components, effects are examined against the background of average risk associated with other nutritional components, whereas a dietary score can account for extremes of converging exposures with a minimal confounding influence of other major nutritional effects[4,38,39].

The strengths of the present investigation are its cohort design, the use of a validated dietary evaluation instrument and reliance in a population where the MD has deep roots. An argument for the validity of the results is that traditional risk factors for CHD incidence and mortality were evident in the data. Limitations are the long interval between the assessment of exposure and outcome, allowing for possible changes in the diet that would lead to exposure misclassification and effect underestimation. When follow-up observations were censored at the 8th year to minimise the opportunity for changes in the diet, we noticed a stronger inverse association between the MD score and CHD events among men. The weak inverse associations observed, particularly in relation to adherence to the MD and CHD incidence among men, could be attributed to the use of a MD score which may not be nuanced enough to allow observing the differential effect of certain foods on the study outcome. Another limitation is that we have no information on blood cholesterol, which, however, can be thought of as an intermediate factor that does not necessarily require controlling for.

In conclusion, in a population in which the traditional MD has long-standing roots, we found that adherence to this diet is associated with a lower incidence of and mortality from CHD, a leading cause of death in most countries, including Greece. The traditional MD pattern could represent a feasible, easy to adhere to option for the preservation of coronary health.

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V. D., P. L. and A. N. drafted the paper and all authors contributed in the development of the manuscript. A. T. had primary responsibility for the final content of the manuscript. D. T. was epidemiological consultant and A. T. is the principal investigator of the EPIC-Greece study. The authors declare that they have no conflicts of interest.

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