American Journal of Epidemiology

Vol. 176, No. 12
DOI: 10.1093/aje/kws205
Advance Access publication:
November 27, 2012

Original Contribution

Relation of the Traditional Mediterranean Diet to Cerebrovascular Disease in a Mediterranean Population

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Initially submitted February 15, 2012; accepted for publication April 10, 2012.

The authors aimed to evaluate the association of the traditional Mediterranean diet and major food groups with incidence of and mortality from cerebrovascular disease (CBVD) in a Mediterranean population. The study population was a cohort of 23,601 participants from the Greek segment of the EPIC Study (European Prospective Investigation into Cancer and Nutrition) who were free of cardiovascular diseases and cancer at baseline (1994–1999). Diet was assessed by means of a validated food frequency questionnaire. A 10-point scale integrating key Mediterranean diet characteristics was used to assess the participants' degree of adherence to this diet. During a median follow-up period of 10.6 years (1994–2009), 395 confirmed incident cases and 196 deaths from CBVD were recorded. Using Cox proportional hazards regression and adjusting for potential confounders, increased adherence to the Mediterranean diet, as measured by 2-point increments in score, was inversely associated with CBVD incidence (adjusted hazard ratio = 0.85, 95% confidence interval: 0.74, 0.96) and mortality (adjusted hazard ratio = 0.88, 95% CI: 0.73, 1.06). These inverse trends were mostly evident among women and with respect to ischemic rather than hemorrhagic CBVD and were largely driven by consumption of vegetables, legumes, and olive oil. These data provide support for an inverse association of adherence to the Mediterranean diet with CBVD incidence and mortality.

cerebrovascular disease; Mediferranean diet; olive oil; stroke

Abbreviations: CBVD, cerebrovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision.

Cerebrovascular diseases (CBVDs) are listed by the World Health Organization as a leading cause of mortality in Greece, with the percentage of CBVD deaths (out of all deaths) being 22.9% in women and 14.7% in men (1). In the absence of a national stroke registry, data on the incidence of CBVD in Greece are sparse and rely mostly on studies that have been conducted at a regional level (2, 3).

The link between diet and CBVD has been studied mainly with respect to specific food items or food groups. Positive associations have been reported for salt (4) and red meat (5) consumption, whereas inverse associations have been reported for fruits and vegetables (6), whole grains (7), light-to-moderate consumption of alcohol (8), and fish (9). For dietary fat (10) and dairy products (11, 12), the results are inconclusive. Relatively few studies, however, have examined the associations between dietary patterns, more specifically the Mediterranean dietary pattern, and CBVD risk. The results of those studies point to a potentially protective effect of this diet (13–15).

We investigated the association of the traditional Mediterranean dietary pattern and major food groups with incidence of and mortality from CBVD, controlling for established risk factors for these conditions (16), in the Greek segment of a European prospective cohort study. Large segments of the Greek population still adhere to the traditional Mediterranean diet (17, 18).

MATERIALS AND METHODS

Participants and follow-up

The data used in the present analysis were collected in the context of the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC is a multicenter, prospective cohort study aiming to investigate the role of biologic, dietary, lifestyle, and environmental factors in the etiology of cancer and other chronic diseases, including CBVD. Twenty-three centers from 10 European countries participate in EPIC, and the total study population exceeds 520,000 men and women. The rationale, population, and design of the EPIC Study have been described in detail elsewhere (19–21).

The Greek EPIC cohort consists of 28,572 participants from all over Greece, covering a wide range of socioeconomic strata. The study population is comprised of volunteers invited from the general adult population, since random samples of defined populations were not required; response rates could not be ascertained. Participants were recruited from 1994 to 1999 and have been actively followed up since 1997 to record changes in health status, diet, and lifestyle by means of telephone interviews or next of kin in cases of a participant's death. Specifically, during follow-up, participants were asked to report any health problem they had developed since the last contact, the date of diagnosis, and the place of hospitalization if applicable. For a large fraction of the participants, information on lifestyle changes was not available for analyses.

When an incident cerebrovascular event or death from CBVD was reported, the information was verified through pathology reports, medical records, discharge diagnoses, or death certificates. The cause and date of death of deceased participants were obtained from the death certificates, which were searched at the local death registries. Details on the procedures used for verification of self-reported cases of cardiovascular disease are reported elsewhere (22).

All participants provided signed informed consent forms. The EPIC study protocol was approved by the Ethics Committee of the International Agency for Research on Cancer (Lyon, France), and for EPIC-Greece it was also approved by the University of Athens Medical School Bioethics Committee (Athens, Greece). All procedures were in accordance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Collection of data on diet and lifestyle

At recruitment, participants were asked by trained interviewers to report their dietary habits using a validated semiquantitative food frequency questionnaire. For validation, 42 men and 38 women aged 25–67 years completed 2 self-administered semiquantitative food frequency questionnaires, spaced approximately 1 year apart. Within this 1-year interval, participants visited the study center monthly and completed an interviewer-administered 24-hour dietary recall questionnaire (23, 24). The EPIC-Greece study participants were asked about the frequency and quantity of consumption of approximately 150 food and drink items. Nutrient and total energy intakes were calculated for each participant using a food composition database modified to accommodate the particularities of the Greek diet (25).

Data on medical history, medication use, smoking habits, and physical activity at work and during leisure time were also collected at recruitment. For physical activity, 24-hour energy expenditure was estimated using metabolic equivalents (26). Anthropometric and blood pressure measurements were also undertaken by trained personnel. During the baseline interview, participants were specifically asked to report medically documented health problems they had already encountered, notably any type of cancer, diabetes, or cardiovascular disease, including CBVD. Whenever these conditions were indicated, they were considered to be prevalent at enrollment.

On the basis of the information collected and the blood pressure measurements taken, a binary variable was generated for hypertension. A subject was considered hypertensive if, for 2 consecutive measurements, mean systolic blood pressure was above 140 mm Hg or mean diastolic blood pressure was above 90 mm Hg or if the subject was under hypertensive treatment, regardless of blood pressure values at baseline. Participants were considered diabetic at enrollment if they indicated a medical diagnosis of the disease or were taking antidiabetic medication.

Assessment of adherence to the traditional Mediterranean diet

The traditional Mediterranean diet is characterized by a high ratio of monounsaturated fatty acids to saturated fatty acids; high consumption of vegetables, legumes, fruits and nuts, and cereals; moderate-to-high consumption of fish; low consumption of dairy products and meat; and moderate consumption of ethanol (mostly wine during meals) (27, 28).

A 10-point scale, as described by Trichopoulou et al. (28), was used to assess the degree of adherence to the traditional Mediterranean diet in the cohort. A value of 0 or 1 was assigned for each of the components indicated above, using the sex-specific median as the cutoff value to define high/low categories. For components frequently consumed in the context of the traditional Mediterranean diet (i.e., vegetables, legumes, fruits and nuts, cereals, and fish), participants were assigned a value of 0 for consumption below the component sex-specific median and a value of 1 for consumption at or above the component sex-specific median. For components not frequently consumed in the context of the traditional Mediterranean diet (i.e., meat and meat products and dairy products), the value of 0 was assigned for consumption at or above the component sex-specific median, while the value of 1 was assigned otherwise. For ethanol, a value of 1 was assigned to men consuming 10–<50 g/day and to women consuming 5–<25 g/day and 0 otherwise (moderate consumption of alcohol is common in the traditional Mediterranean diet (27)). For lipid intake, a value of 1 was assigned to persons with a monounsaturated-to-saturated lipid ratio at or above the median. Thus, through summation of the values for each component, the Mediterranean diet score ranged from 0 (minimal adherence) to 9 (maximal adherence).

Endpoint ascertainment

In the present analysis, the endpoints considered were those classified under *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), codes I60 to I69 (CBVDs), as well as those classified under ICD-10 codes G45 and G46 (transient cerebral ischemic attack and vascular syndromes of the brain) (Table 1).

Only verified first-ever CBVD cases were included in the analysis of incident cases. These were confirmed either through medical records for nonfatal first events or, in the case of first events that were fatal, through death certificates (22). For the analysis of mortality from CBVD, all deaths with CBVD listed as the underlying cause on the death certificate were included.

From the initial cohort of 28,572 EPIC-Greece participants, we excluded 3,075 participants with prevalent CBVD and/or other prevalent cardiovascular disease and/or prevalent cancer at enrollment. Of the remaining 25,497 subjects, 1,048 were excluded because they could not be traced during follow-up. Finally, for 848 additional participants, information was missing for one or more of the sociodemographic, dietary, anthropometric, or lifestyle variables used in the present analysis. Thus, the final sample used for this analysis consisted of 23,601 persons. As of December 2009, the median follow-up time for the 23,601 persons included in this study was 10.6 years, ranging from 10 days to 15.8 years.

Statistical analysis

Simple tabulations were made for sociodemographic data, and mean values and standard deviations were calculated for the dietary variables.

Cox proportional hazards regression models were used to analyze time-to-occurrence data, when incident CBVD was the event of interest. In these models, the time variable was the interval between the date of enrollment and the date of diagnosis of CBVD (for cases), or the date of death for participants who died without having been diagnosed with CBVD (censored), or the date of last follow-up for those who were alive as of the date of last contact without previous diagnosis of CBVD (censored). With the Cox regression models, we estimated the association of study variables, particularly the Mediterranean diet score, with the incidence of CBVD. The Mediterranean diet score was grouped into 3 categories: scores 0–3, scores 4 and 5, and scores 6–9. The grouping was considered necessary because there were some categories (score 0 and score 9) that had very few observations ($n = 127$ and $n = 57$, respectively). In all analyses, we controlled for sex, age (<55, 55–64, or ≥65 years), education (categorical; none, completion of primary school, completion of secondary school, or higher education), smoking status (never smoker, former smoker, or current smoker), body mass index (weight (kg)/height (m)^2; categorical), level of physical activity as measured in metabolic equivalents (in ordered quartiles), hypertension, diabetes, and total energy intake (in ordered quartiles). Nelson-Aalen cumulative hazard curves were used to assess the proportionality of hazards for each variable and to check that there were no crossing hazards for the Mediterranean diet score or any of the other main covariates. The analysis for incidence of CBVD was also conducted separately for ischemic (ICD-10 codes I63 and G45) and hemorrhagic (ICD-10 codes I60, I61, and I62) CBVD.

Similar analyses were undertaken for mortality from CBVD. Observations were censored at the date of death or the date of last follow-up for participants who were alive as of the date of last contact. Analyses were performed

Table 1. ICD-10 Codes Used in a Study of Adherence to the Traditional Mediterranean Diet and Risk of Cerebrovascular Disease, EPIC-Greece, 1994–2009

ICD-10 Code	Category of Cerebrovascular Disease	No. of Incident Cases	No. of Deaths
I60	Subarachnoid hemorrhage	12	6
I61	Intracerebral hemorrhage	43	27
I62	Other nontraumatic intracranial hemorrhage	4	3
I63	Cerebral infarction	65	5
I64	Stroke, not specified as hemorrhage or infarction	228	153
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	5	0
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	3	0
I67	Other cerebrovascular diseases	3	1
I68	Cerebrovascular disorders in diseases classified elsewhere	0	0
I69	Sequelae of cerebrovascular disease	1	1
G45	Transient cerebral ischemic attacks and related syndromes	30	0
G46	Vascular syndromes of brain in cerebrovascular diseases	1	0
	Total	395	196

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision.

Table 2. Numbers of Incident Cases of Cerebrovascular Disease and Deaths from Cerebrovascular Disease and Associated Mutually Adjusted[a] Hazard Ratios, According to Selected Participant Characteristics, EPIC-Greece, 1994–2009

	No. of Observations	No. of Incident CBVD Cases	No. of CBVD Deaths	Incidence		Mortality	
				HR	95% CI	HR	95% CI
Sex							
Male	9,617	204	92	1	Reference	1	Reference
Female	13,984	191	104	0.55	0.43, 0.71	0.72	0.50, 1.05
Age, years							
<55	13,703	44	14	1	Reference	1	Reference
55–64	5,377	93	30	3.32	2.22, 4.97	3.56	1.77, 7.15
≥65	4,521	258	152	9.29	6.21, 13.88	17.50	8.97, 34.15
Smoking status							
Never smoker	12,501	229	117	1	Reference	1	Reference
Former smoker	4,105	91	44	1.12	0.83, 1.50	1.25	0.81, 1.92
Current smoker	6,995	75	35	1.23	0.90, 1.68	1.50	0.96, 2.36
Body mass index[b]							
<25	5,372	57	36	1	Reference	1	Reference
25–29.9	10,325	160	73	1.04	0.77, 1.42	0.77	0.51, 1.15
≥30	7,904	178	87	1.20	0.88, 1.65	0.90	0.60, 1.36
Education							
Some primary school (not completed)	4,495	180	103	1	Reference	1	Reference
Completion of primary school	8,569	161	69	0.76	0.61, 0.95	0.63	0.46, 0.86
Completion of secondary school	6,226	35	15	0.55	0.37, 0.82	0.52	0.29, 0.94
Higher education	4,311	19	9	0.53	0.31, 0.90	0.60	0.28, 1.28
Quartile of physical activity level							
1	5,892	184	108	1	Reference	1	Reference
2	5,899	80	33	0.72	0.55, 0.94	0.52	0.35, 0.78
3	5,909	77	37	0.86	0.66, 1.14	0.79	0.54, 1.16
4	5,901	54	18	0.76	0.55, 1.05	0.54	0.32, 0.91
Quartile of energy intake							
1	5,900	188	104	1	Reference	1	Reference
2	5,900	93	43	0.76	0.59, 0.97	0.66	0.46, 0.95
3	5,900	71	36	0.77	0.58, 1.03	0.80	0.54, 1.18
4	5,901	43	13	0.66	0.45, 0.94	0.43	0.24, 0.78
Hypertension							
No	13,850	104	48	1	Reference	1	Reference
Yes	9,751	291	148	1.39	1.09, 1.77	1.35	0.95, 1.93
Diabetes mellitus							
No	19,992	263	132	1	Reference	1	Reference
Yes	3,609	132	64	1.44	1.16, 1.79	1.32	0.97, 1.79

Abbreviations: CBVD, cerebrovascular disease; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a] Adjusted for all other covariates in the table and for Mediterranean diet score (as a categorical variable in 3 groups: 0–3, 4–5, or 6–9).

[b] Weight (kg)/height (m)^2.

Table 3. Cox Regression-derived Hazard Ratios[a] for Incidence of and Mortality from Cerebrovascular Disease in Relation to Degree of Adherence to the Mediterranean Diet, EPIC-Greece, 1994–2009

Category of Mediterranean Diet Score	No. of Observations	No. of Incident CBVD Cases	No. of CBVD Deaths	Incidence		Mortality	
				HR	95% CI	HR	95% CI
0–3	7,627	172	89	1	Reference	1	Reference
4–5	10,182	154	74	0.80	0.64, 1.00	0.79	0.57, 1.08
6–9	5,792	69	33	0.72	0.54, 0.97	0.76	0.50, 1.16
Per 2-point increment				0.85	0.74, 0.96	0.88	0.73, 1.06

Abbreviations: CBVD, cerebrovascular disease; CI, confidence interval; EPIC, European Investigation into Cancer and Nutrition; HR, hazard ratio.

[a] Adjusted for sex, age (<55, 55–64, or ≥65 years), education (categorical; none, completion of primary school, completion of secondary school, or higher education), smoking status (categorical; never smoker, former smoker, or current smoker), body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30), level of physical activity as measured in metabolic equivalents (in ordered quartiles), hypertension (yes vs. no), diabetes (yes vs. no), and total energy intake (in ordered quartiles).

separately for men, women, and the total study population, controlling for sex. Because of the small number of observations (there were only 5 deaths from ischemic CBVD confirmed through death certificates), separate analysis for different subtypes of CBVD was not performed.

Finally, analyses for major food groups and their association with incidence of and mortality from CBVD were also performed, adjusting for the same potentially confounding factors. Since consumption of food groups was measured in grams per day, rounded numbers close to the standard deviations for each measure were used as increments in the regression models in order to obtain meaningful estimates. Data were analyzed using the STATA SE statistical package, 11th edition (StataCorp LP, College Station, Texas).

RESULTS

During follow-up, 227,448 person-years were accrued, and 395 first-ever CBVD events occurred. Among the 1,446 deaths that occurred, 196 (13.6%) were due to CBVD (Table 1).

The distribution of participants by selected baseline characteristics is shown in Table 2. Table 2 also shows the association of each of these factors, after mutual adjustment among them, with incidence of and mortality from CBVD. In the analysis for incidence, positive associations were found for age, smoking, body mass index, hypertension, and diabetes; negative associations were noted for educational level, physical activity, and energy intake. Men appeared to have increased risk of incident CBVD compared with women. All of the indicated associations were plausible, and most of them were also statistically significant (except those for body mass index, smoking, and physical activity). Additionally, in the analysis for mortality, all associations pointed in the expected direction (except for body mass index), though they were generally not significant.

Tables 3 and 4 show fully adjusted hazard ratios for incidence of and mortality from CBVD in relation to the Mediterranean diet score, overall (Table 3) and by sex (Table 4). Results suggested that increasing conformity to the traditional Mediterranean diet was associated with lower incidence of and mortality from CBVD. However, the results were statistically significant only with respect to CBVD incidence overall (for a 2-point increment,

Table 4. Cox Regression-derived Hazard Ratios[a] for Incidence of and Mortality from Cerebrovascular Disease in Relation to Degree of Adherence to the Mediterranean Diet, by Sex, EPIC-Greece, 1994–2009

Category of Mediterranean Diet Score	Men				Women			
	Incidence		Mortality		Incidence		Mortality	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
0–3	1	Reference	1	Reference	1	Reference	1	Reference
4–5	0.71	0.52, 0.98	0.63	0.39, 1.02	0.90	0.66, 1.23	0.93	0.61, 1.42
6–9	0.78	0.53, 1.14	0.88	0.50, 1.55	0.61	0.38, 0.99	0.60	0.31, 1.16
Per 2-point increment	0.88	0.74, 1.04	0.94	0.72, 1.23	0.81	0.67, 0.98	0.82	0.64, 1.06

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

[a] Adjusted for age (<55, 55–64, or ≥65 years), education (categorical; none, completion of primary school, completion of secondary school, or higher education), smoking status (categorical; never smoker, former smoker, or current smoker), body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30), level of physical activity as measured in metabolic equivalents (in ordered quartiles), hypertension (yes vs. no), diabetes (yes vs. no), and total energy intake (in ordered quartiles).

Table 5. Cox Regression-derived Hazard Ratios[a] for Incidence of Ischemic and Hemorrhagic Cerebrovascular Disease, by Degree of Adherence to the Mediterranean Diet, EPIC-Greece, 1994–2009

Category of Mediterranean Diet Score	Overall CBVD ($n = 395$)		Ischemic CBVD ($n = 95$)		Hemorrhagic CBVD ($n = 59$)	
	HR	95% CI	HR	95% CI	HR	95% CI
0–3	1	Reference	1	Reference	1	Reference
4–5	0.80	0.64, 1.00	0.77	0.50, 1.21	1.25	0.69, 2.26
6–9	0.72	0.54, 0.97	0.54	0.29, 1.01	0.86	0.40, 1.87
P for trend	0.016		0.048		0.831	

Abbreviations: CBVD, cerebrovascular disease; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

[a] Adjusted for sex, age (<55, 55–64, or ≥65 years), education (categorical; none, completion of primary school, completion of secondary school, or higher education), smoking status (categorical; never smoker, former smoker, or current smoker), body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30), level of physical activity as measured in metabolic equivalents (in ordered quartiles), hypertension (yes vs. no), diabetes (yes vs. no), and total energy intake (in ordered quartiles).

hazard ratio = 0.85, 95% confidence interval: 0.74, 0.96) and among women (for a 2-point increment, hazard ratio = 0.81, 95% confidence interval: 0.67, 0.98).

Table 5 shows Cox regression-derived results for ischemic and hemorrhagic CBVD. The inverse association between Mediterranean diet score and CBVD was evident and marginally significant with respect to ischemic CBVD but virtually absent with respect to hemorrhagic CBVD. Notably, however, no information about the ischemic or hemorrhagic nature of the underlying pathology was available for the majority of incident CBVD events.

The results of the analysis for selected food groups are presented in Table 6. In this table, the dietary variables were not mutually adjusted. Regarding the occurrence of a first-ever CBVD event, the food groups that had a statistically significant inverse association were vegetables and legumes, olive oil, and monounsaturated lipids. Fish and cereals seemed to have little or no effect, whereas dairy products, meat, eggs, and saturated lipids appeared to be positively associated with CBVD incidence, albeit not significantly so. For mortality, the results were less striking, the only significant association (inverse) being for vegetables.

DISCUSSION

In the present study, we found evidence that closer adherence to the traditional Mediterranean diet was associated with lower CBVD incidence. This finding is in line with

Table 6. Mean Consumption of Selected Food Groups and Associated Hazard Ratios[a] for Incidence of and Mortality From Cerebrovascular Disease, per Increment[b] Increase in Consumption, EPIC-Greece, 1994–2009

Food Group	Mean Consumption, g/day	Increment, g/day	Incidence		Mortality	
			HR	95% CI	HR	95% CI
Vegetables	553.5	231	0.84	0.72, 0.98	0.76	0.60, 0.96
Legumes	8.9	6.5	0.86	0.75, 0.99	0.83	0.68, 1.02
Fruits and nuts	382.2	209	0.88	0.76, 1.02	0.93	0.75, 1.15
Dairy products	220.2	147	1.12	1.00, 1.26	1.16	0.99, 1.37
Cereals	163.4	70	1.02	0.89, 1.16	0.97	0.79, 1.19
Meat	108.9	54	1.08	0.94, 1.25	0.95	0.76, 1.19
Fish	23.7	17	0.99	0.89, 1.10	0.99	0.85, 1.16
Olive oil	48.1	23	0.80	0.70, 0.90	0.89	0.73, 1.08
Alcohol	10.4	19	1.05	0.94, 1.17	1.02	0.85, 1.23
Monounsaturated lipids	51.1	18	0.75	0.63, 0.89	0.80	0.62, 1.03
Saturated lipids	29.5	12	1.10	0.91, 1.34	1.01	0.75, 1.36
Eggs	17.0	11	1.07	0.98, 1.18	1.01	0.86, 1.17

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

[a] Adjusted for sex, age (<55, 55–64, or ≥65 years), education (categorical; none, completion of primary school, completion of secondary school, or higher education), smoking status (categorical; never smoker, former smoker, or current smoker), body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30), level of physical activity as measured in metabolic equivalents (in ordered quartiles), hypertension (yes vs. no), diabetes (yes vs. no), and total energy intake (in ordered quartiles).

[b] Increments were chosen to be a rounded-up number close to the standard deviation of overall consumption in each food group.

results from earlier studies (13–15), two of which (13, 14) were undertaken in the United States, whereas one was based on 5 cohorts in northern, central, and southern Italy. The traditional Mediterranean diet has been and is still prevalent in large segments of the population of Greece (17, 18), so our results directly addressed the issue under investigation. Several studies have shown associations between distinct components of the Mediterranean diet and CBVD, and it is possible that a combination of these components adds up to the apparently beneficial effect of the Mediterranean diet against CBVD. Thus, the combination of low consumption of saturated fatty acids, high intake of monounsaturated fatty acids (mainly from olive oil), and high intake of antioxidant compounds (from fruits, vegetables, olive oil, and wine) could underlie the inverse association of this diet with CBVD risk. Furthermore, studies have shown that closer adherence to the traditional Mediterranean diet improves the blood lipid profile (29), decreases oxidative stress (30), and reduces endothelial damage (31, 32), which are all possible mechanisms for a protective effect of the traditional Mediterranean diet against CBVD.

In our study, we also found evidence that the apparently protective effect of the Mediterranean dietary pattern against CBVD was mostly manifested against ischemic CBVD. This was an unexpected finding and, notwithstanding statistical significance, needs to be replicated in studies with larger numbers of events. It should be noted, however, that there is overwhelming evidence from several studies linking adherence to the traditional Mediterranean diet with reduced incidence of coronary heart disease (see review by Mente et al. (33)), a disease which is largely of an ischemic nature.

With respect to findings related to the other covariates evaluated in the present study (e.g., hypertension and diabetes), those are essentially compatible with the findings reported in previous investigations, a fact that provides indirect support to the validity of the current results. The inverse association of adherence to the traditional Mediterranean diet with CBVD was significant only with respect to CBVD incidence, whereas for CBVD mortality, although the association was of the same order of magnitude, it did not reach statistical significance. However, the number of deaths in this analysis was relatively small, which translates into power limitations.

The main advantage of this study was that it examined an association that has not yet been adequately investigated. The prospective nature of the study, besides ensuring the temporal relation between the exposure and disease, minimized the likelihood of information bias, which is possible when dietary habits are being recorded retrospectively after a disease has manifested. However, there are some issues arising both from the nature of the study (prospective) and from the exposure of interest (diet). Since this is an ongoing study and diet is a modifiable factor, we cannot be sure that the dietary habits of the cohort as recorded at baseline were steady throughout the follow-up period. Nevertheless, such changes would be more likely to lead to underestimation of the identified associations. We used only 1 scale assessing adherence to the traditional Mediterranean diet, whereas several others have been proposed (34); yet this score has been shown in previous studies to adequately capture population adherence to this diet (28). Another weakness of our study was the difficulty of evaluating possible differential effects of adherence to the Mediterranean diet in strata defined by levels of available covariates, because of power limitations imposed by the number of confirmed (rather than simply reported) incident cases of CBVD. Moreover, we did not have information about dyslipidemia for many of the participants, but we assumed that dyslipidemia is, to a large extent, an intermediate variable between diet and CBVD and as such might not have to be controlled for. Lastly, we did not have good information on salt intake, but we controlled for hypertension, the nosologic entity most closely related to increased consumption of salt.

In conclusion, in a general population-based cohort study undertaken in a setting in which the traditional Mediterranean diet is still prevalent, we found evidence that closer adherence to this diet was associated with reduced incidence of CBVD. Moreover, we found suggestive evidence that the inverse association between adherence to the Mediterranean diet and occurrence of CBVD referred mostly to ischemic CBVD, which is in line with almost conclusive evidence that adherence to the Mediterranean diet conveys protection against ischemic heart disease.

ACKNOWLEDGMENTS

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This work was supported by the Stavros Niarchos Foundation and the Hellenic Health Foundation.

Conflict of interest: none declared.

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