Original Research

Association Between Mediterranean Diet and Non-Fatal Cardiovascular Events, in the Context of Anxiety and Depression Disorders: A Case/Case-Control Study

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Key words:
Coronary heart disease, stroke, Mediterranean diet, anxiety, depression.

Introduction: The aim of this study was to investigate the effect of the Mediterranean diet on the likelihood of having a non-fatal cardiovascular outcome, taking into account anxiety and depression status.

Methods: This was a case-control study with individual matching by age and sex. During 2009-2010, 1000 participants were enrolled; 250 were consecutive patients with a first acute coronary syndrome (ACS), 250 were consecutive patients with a first ischemic stroke, and 500 were population-based control subjects, one-for-one matched to the patients by age and sex. Among other characteristics, adherence to the Mediterranean diet was assessed by the MedDietScore, anxiety was assessed with the Spielberger State-Trait Anxiety Inventory form Y-2, while depressive symptomatology was evaluated by the Zung Depression Rating Scale.

Results: Higher adherence to the Mediterranean diet was associated with a lower likelihood of ACS and ischemic stroke, even after adjusting for anxiety or depression (ACS: OR=0.92, 95%CI 0.87-0.98 and 0.93, 0.88-0.98, respectively; ischemic stroke: 0.91, 0.84-0.98 and 0.90, 0.83-0.97, respectively). For both ACS and stroke patients, anxiety and depression were associated with a higher likelihood of ACS and stroke. When stratifying for depression or anxiety status, the Mediterranean diet remained a significantly protective factor only for people with low levels of depression and anxiety for ACS, and only for people with low levels of anxiety, as far as stroke was concerned.

Conclusion: Anxiety and depression seem to play a mediating role in the protective relationship between adherence to the Mediterranean diet and the likelihood of developing cardiovascular events.

Manuscript received:
May 11, 2012;
Accepted:
November 26, 2012.

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Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in both developed and developing countries, as well as in Greece,[1] and its incidence is expected to increase dramatically within the next decade.[2] Consequently, research into and prevention of CVD is a major public health issue. During the last 20 years, specific dietary patterns have been associated with the development of CVD and the Mediterranean diet is considered the most protective of all.[3] According to the recent definition by UNESCO, the Mediterranean diet constitutes a set of skills, knowledge, practices and traditions ranging from the landscape to the table, including the crops, harvesting, fishing, conservation, processing, preparation and, particularly, consumption of food.[4] The Mediterranean diet, a nutri-

tional model that has remained unchanged over time and space, is mainly characterized by the consumption of olive oil, cereals, fresh or dried fruit and vegetables, a moderate amount of fish, dairy and meat, and many condiments and spices, all accompanied by wine or infusions, always respecting the beliefs of each community.[4] In the mid 1980s, the Seven Countries Study was one of the first that reported the protective role of a diet rich in olive oil against atherosclerosis.[5] In the 2000s, the retrospective CARDIO2000 study suggested that the adoption of the Mediterranean diet was associated with an adjusted 23% rate reduction in the likelihood of developing a first event of acute coronary syndrome (ACS),[6] whereas, almost 15 years after the report of the Seven Countries Study, the EPIC-Greek study highlighted the inverse association between adherence to the Mediterranean diet and death from coronary heart disease, studying approximately 22,000 people from various parts of Greece.[7] During all these years, several other observational and interventional studies have revealed the protective effect of adherence to the Mediterranean diet against CVD,[8] as well as various other cardiometabolic disorders.[9]

In contrast, trait disorders, such as anxiety and depression, have been well associated with an increased risk of CVD.[10-14] Activation of the sympathetic nervous system, which leads to a reduction in heart rate variability, elevated levels of pro-inflammatory cytokines, and hypercortisolemia,[14] might account for the augmented risk of CVD in anxiety and depression disorders. However, it has been suggested that anxiety and/or depression (both traits are strongly inter-correlated in the majority of studies), tend to be associated with unhealthy lifestyle behaviors, such as smoking, unhealthy diet, and physical inactivity.[15-17] Therefore, the independent protective role of the Mediterranean diet on CVD risk could be altered by emotional disorders.

Taking into account the aforementioned considerations, the aims of the present study were: (a) to evaluate the effect of dietary habits on ACS or ischemic stroke, after controlling for the participants' anxiety and depression status, and (b) to evaluate the independent role of depression and anxiety in the aforementioned outcomes.

Methods

Design

This was a case-control study with individual (one-to-one) matching by age (within ± 3 years) and sex.[18]

Bioethics

The study was approved by the Ethics Committee of the University Hospital of Ioannina and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Before the collection of any information, participants were informed about the aims and procedures of the study and provided their signed consent.

Sampling procedure

From October 2009 to December 2010, 500 of the 615 consecutive patients with a first ACS event (n=250; 209 acute myocardial infarction, 41 unstable angina), or ischemic stroke (n=250), and without any suspicion of previous CVD, who were admitted to the cardiology, pathology clinics or the emergency units of three major general hospitals in Greece, agreed to participate (participation rate 81%). For the ACS patients, clinical symptoms were evaluated at hospital entry and a 12-lead electrocardiogram was recorded. Evidence of myocardial cell death was assessed with blood tests and measurement of the levels of troponin I and the MB fraction of total creatinine phosphokinase (CPK).[19] Unstable angina was defined as the occurrence of one or more anginal episodes, at rest, within the preceding 48 h, corresponding to class III of the Braunwald classification.[20] Ischemic strokes were defined as symptoms of neurologic dysfunction of acute onset of any severity, consistent with focal brain ischemia, and imaging/laboratory confirmation of an acute vascular ischemic pathology.[21] For the stroke patients who were unable to communicate (speech disorders, aphasia, memory problems), the information was obtained from a valid surrogate respondent (first degree relative living in the same home with the patient and being aware of the participant's dietary habits and medical history). Five hundred control subjects (250 matched one-for-one with ACS patients, and another 250 matched one-for-one with stroke patients) were selected concurrently with the patients on a volunteer, population basis, and from the same region as the patients. Controls had no clinical symptoms or suspicions of CVD in their medical history, as assessed by a physician. Subjects with chronic neoplastic disease or chronic inflammatory disease, as well as individuals with recent changes in their dietary habits, were not enrolled in the study.

Based on *a priori* statistical power analysis, a sample size of 500 patients (250 ACS, 250 stroke) and

500 age- and sex-matched healthy subjects, was adequate to evaluate two-sided odds ratios equal to 1.20, achieving a statistical power greater than 0.80 at a probability level (p-value) of 0.05.

Investigated parameters

Socio-demographic, clinical, anthropometric and lifestyle characteristics

The socio-demographic variables recorded were: age, sex (for the matching procedure), and financial status, evaluated indirectly using an index measuring how satisfied the participant was by his/her income (i.e. from 1, meaning not at all satisfied, to 9, meaning very satisfied). Current smokers were defined as those who smoked at least one cigarette per day, former smokers as those who had stopped smoking more than one year previously and the rest of the participants were defined as non-current smokers. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) index,[22] which has been validated for the Greek population.[23] Body mass index (BMI) was calculated as weight (in kilograms) divided by standing height (in meters squared); overweight and obesity were defined as BMI 25.0-29.9 kg/m^2 and >29.9 kg/m^2, respectively.

In all participants a detailed medical history was recorded, including family history of CVD, as well as personal history of hypertension, hypercholesterolemia, hypertriglyceridemia and diabetes. Patients whose average blood pressure levels were ≥140/90 mmHg or were under antihypertensive medication were classified as having hypertension. Hypercholesterolemia was defined as total serum cholesterol levels >200 mg/dL or the use of lipid-lowering agents; and diabetes mellitus was defined as fasting blood glucose >126 mg/dL or the use of antidiabetic medication.

Psychological assessment

Anxiety was assessed using the translated and validated version of the Spielberger Trait Anxiety Inventory (STAI form Y-2), which is a 20-item self-reported questionnaire, evaluating how the respondent feels generally.[24] The 20 items were rated from 1 to 4 according to frequency of their feelings (i.e. almost never, sometimes, often, almost always). The total theoretical range of the score is 20-80. Values between 20-39 suggest low anxiety, 40-59 moderate anxiety, and values >59 suggest severe anxiety.[24]

Depression was evaluated using the translated and validated version of the Zung Depression Rating Scale (ZDRS).[25] The ZDRS is a self-rating scale consisting of 20 items that cover affective, psychological, and somatic symptoms for the measurement of depression, and was originally developed in order to assess depression symptoms without the bias of an administrator affecting the results. The individual specifies the frequency a symptom is experienced (i.e. little, some, a good part of the time, or most of the time). The total theoretical range of the score is 20-80. Scores 20-49 are considered normal, scores of 50-59 indicate mild depression, scores of 60-69 moderate to marked depression, while scores of 70-80 denote severe depression.[25]

Dietary assessment and evaluation of adherence to the Mediterranean diet

Dietary habits of the past year were assessed through a 90-item, validated semi-quantitative food-frequency questionnaire (FFQ) that has been described previously.[18,26] The level of adherence to the Mediterranean diet was evaluated using an 11-item large-scale, composite index, the MedDietScore.[27] In brief, for the consumption of foods presumed to be part of the Mediterranean pattern (i.e. those suggested on a daily basis or more than four servings per week, such as non-refined cereals, fruits, vegetables, legumes, olive oil, fish, and potatoes), lower scores were assigned when participants reported no, rare or moderate consumption, while higher scores were assigned when the consumption was according to the rationale of the Mediterranean pattern. For the consumption of foods presumed not to be part of the Mediterranean pattern (i.e. consumption of meat and meat products, poultry, and full-fat dairy products), scores were assigned on a reverse scale. For alcohol, score 5 was assigned for consumption of less than 3 wineglasses per day, score 0 for consumption of more than 7 wineglasses per day and scores from 4 to 1 for consumption of 3, 4-5, 6 and 7 or 0 wineglasses per day, respectively. The theoretical range of the MedDietScore was 0-55. Higher values of this diet score indicate greater adherence to the Mediterranean diet. The validation properties of the MedDietScore have been presented elsewhere in the literature.[27]

Statistical analysis

Normally distributed continuous variables (age, BMI,

STAI-Y2, ZUNG-DRS and MedDietScore) are presented as mean values ± standard deviation, and categorical variables (sex, smoking habits, medical history, BMI categories, physical activity, financial status, MedDietScore categories, STAI-Y2 and ZUNG-DRS categories) as frequencies. Associations between categorical variables were tested using the chi-square test. Comparisons of mean values of normally distributed continuous variables by clinical outcome were performed using Student's t-test. Correlations between continuous variables were evaluated using Pearson's r or Spearman ϱ coefficients. The normality of the variables was tested using P-P plots. Estimations of the relative odds of having ACS or stroke according to the level of adherence to the Mediterranean diet, ZUNG-DRS or STAI, and other covariates were performed through conditional logistic regression analysis; results are presented as odds ratios (OR) and the corresponding 95% confidence intervals (CI). Collinearity diagnostics were based on VIF (Variance Inflation Factor) values. The Hosmer–Lemeshow statistic was calculated to evaluate the model's goodness of fit. All reported p-values were based on two-sided hypotheses. SPSS 18.0 software (SPSS Inc., Chicago, Il, USA) was used for all the statistical calculations.

Results

The demographic, clinical, psychological and nutritional characteristics of the subjects under study are shown in Table 1. Traditional CVD risk factors differed between patients—with either non-fatal ACS or stroke—and their corresponding controls. Compared with controls, patients with ACS and stroke tended to adhere less to the Mediterranean diet ($p<0.001$) and presented higher anxiety and depression scores ($p<0.001$) (Table 1). Moreover, MedDietScore was inversely correlated with STAI-Y2 ($r=-0.22$, $p=0.007$) and ZUNG-DRS ($r=-0.28$, $p=0.001$) scales in stroke patients, as well as among controls (STAI-Y2: $r=-0.21$, $p=0.02$, and ZUNG-DRS: $r=-0.2$, $p=0.03$), but not in ACS patients (STAI-Y2: $r=-0.1$, $p=0.174$, and ZUNG-DRS: $r=-0.07$, $p=0.32$). In addition, STAI-Y2 and ZUNG-DRS scales showed strong correlations in all subgroups of the participants (i.e. controls: $p<0.001$, ACS-patients: $p<0.001$, and stroke-patients: $p<0.001$).

In the next step of analysis, variables that differed significantly between cases and controls, as well as biologically relevant variables, were incorporated into multivariable models for ACS and stroke. Table 2 summarizes the independent predictors of a non-fatal ACS. MedDietScore was inversely associated with the likelihood of ACS, even after adjusting for anxiety (*model 1*) or depression levels (*model 2*). Since a strong correlation between the STAI-Y2 score and the ZUNG-DRS scale was detected, because of collinearity both variables could not be entered in the model at the same time. However, as can be seen in *models 1* and *2* (Table 2), each unit increase in STAI-Y2 scale led to a 3% increase of the likelihood of having an ACS event; and every unit of increase in ZUNG-DRS scale was associated with 5% higher odds of having an ACS, after adjusting for various potential confounders. Factors also associated with ACS were physical activity, smoking habits, hypertension, hypercholesterolemia, and diabetes mellitus (Table 2).

The previous analysis was repeated for non-fatal stroke events (Table 3). In the multivariable *model 1*, which included STAI-Y2 but not ZUNG-DRS, MedDietScore was inversely associated with the likelihood of having a non-fatal stroke event, while in *model 2*, which included ZUNG-DRS, but not STAI-Y2, MedDietScore was still inversely associated with the likelihood of having a non-fatal stroke event (Table 3). Moreover, for every unit increase in STAI-Y2, a 5% increase in the likelihood of having a stroke event was observed (*model 1*, Table 3), and every unit of increase in ZUNG-DRS scale was associated with 6% higher odds of having a stroke event, after adjusting for various potential confounders. Other factors associated with non-fatal ischemic stroke events were hypertension and financial status (Table 3).

The analysis was further stratified by depression and anxiety status. Specifically, the effect of the MedDietScore on ACS and stroke was tested in participants who had median scores on STAI-Y2 <38 and >38 for ACS patients, and STAI-Y2 <41 and >41 for stroke patients, adjusting for depression status; similarly for subjects who had median scores on ZUNG-DRS <36 and >36 for ACS patients and ZUNG-DRS <41 and >41 for stroke patients, adjusting for anxiety status. All factors taken into account were the same as in the aforementioned models. It was observed that every unit increase in the MedDietScore was associated with 11% lower odds of being an ACS (95%CI 0.83-0.97) or a stroke patient (95%CI 0.81-0.99), but only for people with STAI-Y2 <38 or STAI-Y2 <41 respectively, when adjusting for all potential confounders and ZUNG-DRS. Moreover, each unit increase in the MedDietScore was associated with 13% (95%CI

Table 1. Socio-demographic, lifestyle and clinical characteristics of the study participants (n=1000).

	ACS patients n=250	ACS controls n=250	Stroke patients n=250	Stroke controls n=250
Age	60 ± 12	60 ± 12	77 ± 9	73 ± 9
Male sex	208 (83.2%)	208 (83.2%)	139 (55.6%)	139 (55.6%)
Smoking habits:				
Never smoker	56 (22.4%)†	108 (43.2%)	151 (60.4%)	139 (55.8%)
Current smoker	127 (50.8%)	63 (25.2%)	49 (19.6%)	47 (18.9%)
Former smoker	67 (26.8%)	79 (31.6%)	50 (20%)	63 (25.3%)
Physical activity	150 (64.1%)†	203 (82.5%)	99 (47.1%)†	181 (74.8%)
Family history of CVD	81 (36.2%)†	39 (16.7%)	51 (31.3%)†	38 (16.7%)
Hypertension	148 (62.2%)†	90 (37.7%)	206 (84.4%)†	137 (56.8%)
Hypercholesterolemia	165 (71.4%)†	100 (45.5%)	159 (68.5%)*	119 (54.1%)
Diabetes mellitus	58 (26.1%)†	29 (12.4%)	71 (32.9%)*	50 (21.5%)
Body mass index (kg/m^2):	27.82 ± 4.29	27.23 ± 3.50	26.72 ± 3.57	27.35 ± 4.24
Normal weight (18.5-24.9)	57 (24.9%)	63 (26.3%)	79 (33.1%)	73 (30%)
Overweight (25-29.9)	116 (50.7%)	132 (55%)	124 (51.9%)	120 (49.4%)
Obese (>30)	56 (24.5%)	45 (18.8%)	36 (15.0%)	50 (20.6%)
Financial status satisfaction:				
Not satisfied (1-3)	50 (22.7%)†	19 (8.1%)	74 (35.9%)†	35 (14.6%)
Satisfied (4-6)	118 (53.6%)	154 (65.3%)	114 (55.3%)	157 (65.7%)
Very satisfied (7-9)	52 (23.6%)	63 (26.7%)	18 (8.7%)	47 (19.7%)
MedDietScore (range 0-55):	30.67 ± 5.02†	32.50 ± 4.41	29.99 ± 3.79†	32.03 ± 4.08
1st tertile (0-29)	86 (41.1%)†	50 (21.9%)	94 (49.5%)†	60 (26.8%)
2nd tertile (30-33)	66 (31.6%)	79 (34.6%)	64 (33.7%)	82 (36.6%)
3rd tertile (34-55)	57 (27.3%)	99 (43.4%)	32 (16.8%)	82 (36.6%)
STAI-Y2 (range 20-80):	40.52 ± 10.05†	36.55 ± 9.26	45.66 ± 7.17†	38.65 ± 9.86
20-39: low anxiety	109 (48.7%)†	158 (64.5%)	37 (17.9%)†	135 (54.9%)
40-59: moderate anxiety	105 (46.9%)	84 (34.3%)	167 (80.7%)	106 (43.1%)
60-80: severe anxiety	10 (4.5%)	3 (1.2%)	3 (1.4%)	5 (2%)
ZUNG-DRS (range 20-80):	38.50 ± 8.50†	35.07 ± 7.90	46.30 ± 8.23†	38.01 ± 8.57
20-49: normal	203 (89.4%)*	233 (94.7%)	121 (57.1%)†	224 (91.8%)
50-59: mild depression	22 (9.7%)	12 (4.9%)	86 (40.6%)	18 (7.4%)
60-69: moderate to mild depression	2 (0.9%)	1 (0.4%)	5 (2.4%)	2 (0.8%)
70-80: severe depression	0	0	0	0

Data are expressed as mean ± SD or frequencies (n, %). p-values are derived from Student's t-test or the chi-square test.
*p<0.05, †p<0.001 compared with the ACS or Stroke control group, respectively.
ACS – acute coronary syndrome; CVD – cardiovascular disease; MedDietScore – Mediterranean Diet Score; BMI – body mass index; ZUNG-DRS – Zung Depression Rating Scale; STAI-Y2 – Spielberger Trait Anxiety Inventory.

Table 2. Results from the multiple conditional logistic regression analysis that was developed to evaluate the likelihood of having an ACS (outcome) according to MedDietScore, depression and anxiety levels, among 250 ACS cases and 250 controls.

	Model 1		Model 2	
MedDietScore (per 1/55 unit)	0.93	(0.88-0.98)	0.92	(0.87-0.98)
Body mass index (per 1 kg/m^2)	1.00	(0.93-1.07)	1.00	(0.93-1-07)
Physical activity (Y/N)	0.34	(0.18-0.66)	0.34	(0.18-0.67)
Ever smoker (Y/N)	3.44	(1.89-6.23)	3.47	(1.91-6.32)
Hypertension (Y/N)	3.07	(1.73-5.47)	3.03	(1.69-5.45)
Hypercholesterolemia (Y/N)	2.66	(1.58-4.47)	2.89	(1.71-4.88)
Diabetes mellitus (Y/N)	2.18	(1.05-4.51)	2.42	(1.15-5.11)
Financial status (per 1/9 unit)	0.90	(0.78-1.04)	0.87	(0.75-1.00)
ZUNG-DRS (per 1/80 unit)	1.05	(1.01-1.08)		–
STAI-Y2 (per 1/80 unit)		–	1.03	(1.00-1.05)

Results are presented as odds ratio (95% confidence interval) obtained from multiple conditional logistic regression.
Abbreviations as in Table 1.

Table 3. Results from the multiple conditional logistic regression analysis that was developed to evaluate the likelihood of having an ischemic stroke (outcome) according to MedDietScore, depression and anxiety levels, among 250 stroke cases and 250 controls.

	Model 1		Model 2	
MedDietScore (per 1/55 unit)	0.90	(0.83-0.97)	0.91	(0.84-0.98)
Body mass index (per 1 kg/m2)	0.93	(0.86-1.00)	0.92	(0.85-0.99)
Physical activity (Y/N)	0.51	(0.26-1.00)	0.45	(0.23-0.87)
Ever smoker (Y/N)	0.55	(0.27-1.12)	0.54	(0.27-1.10)
Hypertension (Y/N)	2.54	(1.26-5.12)	2.46	(1.21-5.01)
Hypercholesterolemia (Y/N)	1.74	(0.92-3.29)	1.64	(0.87-3.12)
Diabetes mellitus (Y/N)	1.53	(0.77-3.04)	1.56	(0.78-3.13)
Financial status (per 1/9 unit)	0.78	(0.65-0.95)	0.80	(0.66-0.96)
ZUNG-DRS (per 1/80 unit)	1.06	(1.02-1.10)		-
STAI-Y2 (per 1/80 unit)		-	1.05	(1.01-1.09)

Results are presented as odds ratio (95% confidence interval) obtained from multiple conditional logistic regression.
Abbreviations as in Table 1.

0.80-0.95) lower odds of having an ACS, only for people with ZUNG-DRS score <36, when adjusting for the aforementioned confounders and the STAI-Y2 score. No other significant associations were observed between adherence to the Mediterranean diet and the likelihood of having an ACS or stroke event.

Discussion

The results of the present work confirmed the protective role of adherence to the Mediterranean diet as far as CVD outcomes (i.e. ACS and ischemic stroke) were concerned. However, further examination according to depression and anxiety status indicated that this protective role seems to remain important only for people with low depression or anxiety levels. Moreover, it was observed here that both anxiety and depression were positively associated with the likelihood of a first ACS or stroke event. Although the role of the investigated disorders has long been associated with ACS, especially myocardial infarction,[11,28] the emerging association between anxiety or depression and stroke incidence has not been well studied and understood.[29-30] This is one of the first studies to reveal the effect of these disorders on stroke, especially taking dietary habits into consideration. Nevertheless, future prospective studies are warranted in order to address the relationship between cerebrovascular diseases *per se* and dietary patterns, and to delineate the underlying multi-potent regulation of cardiovascular homeostasis through metabolic pathways triggered by Mediterranean nutritional ingredients.

The Mediterranean diet has been implicated in a variety of metabolic pathways that could induce counterbalancing effects against adverse cardiovascular sequelae of emotional disorders. High content of dietary fiber, mono-unsaturated fatty acids, beta-carotene, polyphenols, as well as vitamins C and E, constitute the cornerstone of healthy dietary habits and might improve endothelial function by decreasing low-density lipoprotein cholesterol, triglycerides and fibrinogen levels, as well as lipid oxidation.[31] The independent association of the Mediterranean diet with favorable CVD outcomes in the present study, even when taking into account anxiety or depression status, further implies the potential existence of residual mechanisms. The fact that the Mediterranean diet did not retain its protective role for people with high levels of depression or anxiety shows that the beneficial effects of this pattern probably cannot compensate for the aggravating role of psychological disorders on the cardiovascular system.

The detrimental role of anxiety and depression on the cardiovascular system is attributed to complex interactions along a chain of pathophysiological events. Neuroendocrinologic alterations in the stress-response system, higher concentrations of circulating catecholamines, increased total body sympathetic activity, arterial vasomotor dysfunction and autonomic nervous system dysfunction—including diminished heart rate variability and increased QT variability—are some of the sites along this chain.[32] Pathophysiologic links may also include surges of sympathetic nervous system activity, blood pressure and heart rate that predispose to plaque rupture, enhanced platelet aggregation and thrombosis, while emotional disorders directly correlate with a higher prevalence and clustering of traditional CVD risk factors.[33]

On the basis of the aforementioned links, the association of anxiety and depression disorder with ACS

is broadly recognized.[11,34] Recent data suggest that the clinical utility of depression measures in terms of CVD prediction may be improved by using them in combination with measures of anxiety.[35] On the other side of the spectrum, depression disorders have been independently linked to cerebrovascular disease[29] and stroke incidence, while relevant associations for anxiety trait are lacking or have been established only indirectly through composite cardiovascular endpoints (combining myocardial and cerebrovascular incidents).[30] In this context, the present work corroborates the accumulating evidence for the updated role of psychological factors in terms of primary CVD prevention and their interactions with dietary habits.

Limitations

The present study has certain limitations. Its retrospective nature does not offer proof of causality for the associations reported and in addition it could have been susceptible to systematic errors of selection and recall bias. To minimize the selection bias, only cases with a first event were enrolled, and to minimize recall bias, accurate and detailed data from all participants during the first 3 days of hospitalisation were obtained. For the dietary evaluation, an FFQ was administered; although these tools may entail measurement error and be less accurate (especially in energy and nutrient assessment) as compared with a diary, an effort was made to reduce these errors and inaccuracies of dietary reporting with its application by trained dieticians through face-to-face interviews. Over-/underestimation in reporting may also exist, especially in the measurement of diet, smoking habits and the onset of CVD risk factors. However, every effort was made to retrieve accurate information from participants' medical records, as well as their relatives. Anxiety and depression measures were estimated through questionnaires. Although the tools have been validated for the referent population,[18,24-25] examining psychological traits (e.g. anxiety and/or depression) rather than specific anxiety and depression disorder subsets, such as generalized anxiety disorder and phobic anxiety, may create a different pattern of associations. Furthermore, regarding the stroke patients, self-reported information was obtained from 76% of the sample, while for 60 patients (24%) who were unable to answer the interviewer because of their condition, data were collected from a valid surrogate respondent. In addition, the coronary and stroke patients who died at hospital entry or the following day were not included in the study (survivor bias); thus, the results should be generalised only to CVD survivors. Finally, the inclusion of patients and controls from only two regions may limit the generalization of the findings to the whole country; nevertheless, it should be noted that Athens metropolitan area and Ioannina city in western Greece represent a vast majority of the Greek urban and rural population.

Conclusion

In conclusion, adherence to the Mediterranean diet tends to exert its protective role against adverse CVD events in subjects with low anxiety and depression levels. For this reason, personality traits or emotional disorders should be taken into account for the primary prevention of apparently healthy individuals with CVD risk factors, allowing health professionals to focus on dietary changes according to the psychological status of the subjects. Finally, for people with depressive or anxious symptomatology, nutritional care should be provided combined with psychological treatment for synergistic action.

Acknowledgments

The authors would like to thank the field investigators of the study: Kallirroi Kalantzi, Aggeliki Ioannidi, Markella Symeopoulou, Zoe Konidari, Eirini Trichia, Stavroula Bitsi, Vissarion Euthimiou, Dimitrios Kantas, Eftychia Bika, Vaia Salma, Antonis Kramvis, Glykeria Papagiannopoulou, Alexandra Litsardopoulou, Alexia Katsarou, Fani Lioliou, Labros Papadimitriou, Konstantina Siganou, Ioanna Kousoula, Eleni Koroboki, Anastasia Vemmou, Paraskevi Savvari and Vassiliki Vlachaki.

Christina-Maria Kastorini has received scholarships for her PhD thesis from the National Scholarships Foundation and the Hellenic Atherosclerosis Society.

This study was supported financially by the Hellenic Cardiological Society (2012-2013).

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