The Mediterranean diet contributes to the preservation of left ventricular systolic function and to the long-term favorable prognosis of patients who have had an acute coronary event\(^1,2\)

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**ABSTRACT**

**Background:** The effect of the cardioprotective Mediterranean diet on the development of cardiac abnormalities and prognosis of cardiac patients has rarely been investigated.

**Objective:** We sought to evaluate the relation between the Mediterranean diet, the development of left ventricular systolic dysfunction (LVSD) at hospitalization, and the 2-y prognosis of patients who have had an acute coronary syndrome (ACS).

**Design:** During 2006–2009, 1000 consecutive patients with ACS were enrolled; of these patients, 459 had LVSD (ejection fraction 40%) at hospitalization [367 men with a mean (±SD) age of 64 ± 14 y, and 92 women aged 71 ± 12 y], whereas 541 had preserved left ventricular systolic function [421 men aged 62 ± 12 y, and 120 women aged 67 ± 12 y]. Adherence to the Mediterranean diet was assessed by the validated Mediterranean Diet Score (MedDietScore; theoretical range: 0–55).

**Results:** The MedDietScore was associated with less likelihood of developing LVSD at hospitalization [odds ratio (OR) per 1/55 unit: 0.93; 95% CI: 0.88, 0.99; \(P = 0.04\)], less likelihood of remodeling (ie, ejection fraction <50% at 3 mo follow-up; OR: 0.90; 95% CI: 0.78, 1.03; \(P = 0.06\)], and less likelihood of recurrent cardiovascular disease events during the 2 y of follow-up (OR: 0.88; 95% CI: 0.80, 0.98; \(P = 0.04\)), after adjustment for various confounders.

**Conclusions:** Greater adherence to the Mediterranean diet seems to preserve left ventricular systolic function and is associated with better long-term prognosis of patients who have had an ACS. *Am J Clin Nutr* 2010;92:47–54.

**INTRODUCTION**

During the past decades, several observational studies and clinical trials have provided scientific evidence that the Mediterranean diet, which is rich in fruit, vegetables, legumes, whole grains, fish, and low-fat dairy products and with olive oil as the principal source of fat, is associated with lower incidence of cardiovascular disease (CVD) and some types of cancer (1–8). Several pathophysiologic mechanisms have been proposed to explain the apparent beneficial effects of the Mediterranean diet on the cardiovascular system, such as the diet’s antithrombotic, antiinflammatory, and antioxidant effects as well as its inverse relation with blood pressure and endothelial dysfunction markers (5, 6, 9–12). In terms of nutrients, the traditional Mediterranean diet is rich in oleic acid, omega-3 fatty acids, fiber, B-group vitamins, and various antioxidants but low in saturated and polyunsaturated fats (13–15), although all of the aforementioned components have shown, to some extent, an association with CVD risk and markers.

Although there is a lot of evidence on the protective effect of the Mediterranean dietary pattern or its components on the primary prevention of CVD, results from longitudinal studies that have assessed the influence of this traditional diet on the severity and prognosis of cardiac disease after an acute coronary syndrome (ACS) are limited. Therefore, the aim of this work was to evaluate the relation between adherence to the Mediterranean diet and the following: 1) the development of left ventricular systolic dysfunction (LVSD) at hospitalization, 2) left ventricular remodeling in a 3-mo period, and 3) the short-term (30-d) and long-term (death or rehospitalization due to CVD events during the 2 y after the event) prognosis of the patients.

**SUBJECTS AND METHODS**

**Study sample and inclusion criteria**

From May 2006 to March 2009, 1000 of the 1257 consecutive patients who were hospitalized at First Cardiology Clinic, University of Athens, for an ACS [first or recurrent acute myocardial infarction (MI) or unstable angina (UA)] were enrolled in the study (participation rate: 80%); nonparticipants were patients who declined to provide the requested information or who died during the first 48 h of hospitalization. Of the enrolled patients, 788 were men (mean ± SD age: 63 ± 13 y) and 212 women (age: 69 ± 12 y). For the determination of ACS, a 12-lead electrocardiogram was performed at hospital entry, and clinical symptoms were evaluated in all patients by a cardiologist. Moreover, blood tests were performed to detect evidence of myocardial cell death (troponin I and the MB fraction of total creatinine phosphokinase). Acute MI was defined according to

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Received November 23, 2009. Accepted for publication April 21, 2010. First published online May 19, 2010; doi: 10.3945/ajcn.2009.28982.
the latest guidelines on the basis of electrocardiogram findings and the aforementioned blood tests (16), whereas unstable angina was defined by the occurrence of one or more angina episodes, at rest, within the preceding 48 h, corresponding to class III of the Braunwald classification (17).

**Diagnosis of outcome measures: LVSD, remodeling, and 2-y follow-up**

Systolic function of the left ventricle was evaluated from the 2-dimensional 2- and 4-chamber view measurement of the end-diastolic and end-systolic volumes of the left ventricle by a Hewlett-Packard 5500 Sonos (Sonos 5500 Ultrasound system; Hewlett-Packard Hellas, Athens, Greece) with a multifrequency transducer (2.5–4 MHz). This was measured at entry and repeated before hospital discharge. LVSD was defined as an ejection fraction <40% according to the recent European Society of Cardiology guidelines for the diagnosis and treatment of acute heart failure (18). For the purposes of this study, patients were categorized into 2 main categories according to the systolic function of the left ventricle after the cardiac episode at discharge. In particular, 367 male (age: 64 ± 14 y) and 92 female (age: 71 ± 12 y) patients were classified into the group who had developed LVSD, whereas 421 male (age: 62 ± 12 y) and 120 female (age: 67 ± 12 y) patients were classified into the group who had preserved left ventricular systolic function. Remodeling of left ventricular function was defined as the maintenance or worsening of the left ventricular ejection fraction in values <50% in the echocardiographic evaluation that was performed (18).

To evaluate the short-term (30-d and 3-mo) and long-term (2-y) prognosis of enrolled patients, a follow-up examination was performed (median follow-up time: 23 mo; first, third quartiles: 6 and 24 mo). The loss-to-follow-up rates were 10% for the 30-d, 15% for the 3-mo, and 25% for the 2-y reevaluations. Patients lost to follow-up were considered missing cases. No differences were observed regarding age, sex, and medical history distribution and medication prescription between those who were lost to follow-up and the rest of the patients. Follow-up of the patients included evaluation for vital status (death from CVD or other cause) and rehospitalization due to ACS (acute MI or UA as defined above) or other cardiac symptoms (arrhythmias and stable angina). Moreover, ejection fraction was measured during a prearranged hospital visit at 3 mo after discharge.

**Clinical and biochemical measurements at baseline examination**

In all patients, a detailed medical history was recorded including previous hospitalization for CVD (coronary heart disease or stroke), history and management of hypertension (defined as systolic or diastolic blood pressure >140/90 mm Hg or use of antihypertensive medication), hypercholesterolemia (defined as fasting serum total cholesterol >200 mg/dL or use of lipid-lowering agents), diabetes mellitus (defined as fasting glucose >125 mg/dL or use of special treatment), as well as patients’ medical family history of CVD. Furthermore, the clinical course of all patients during hospitalization was recorded including medication (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, aldosterone antagonist, and b- or a- and b-blockers), coronary angiography results and number of coronary vessels involved, thrombolysis, type of revascularization (primary angioplasty and coronary artery bypass grafting), and time delay from the onset of symptoms to the arrival at the hospital.

In addition to the clinical information, white blood cell counts and uric acid were measured at the time of hospital admission, and C-reactive protein concentrations were also measured during the first 12–18 h of hospitalization. A latex-based immunoassay (Dade Behring, Newark, DE) was used to measure the concentrations of C-reactive protein in the blood, whereas uric acid was measured with an enzymatic colorimetric test according to the uricase-peroxidase method (UA Plus; Roche Diagnostics, Mannheim, Germany). The measurement range was 0.2–25 mg/dL, and the inter- and intraassay variability was 0.5% and 1.7%, respectively. Units used were mg/dL (1 mg/dL = 59.48 µmol/L). Total cholesterol, HDL cholesterol, blood glucose, and triglycerides were also measured in all participants at the time of hospital admission according to a colorimetric enzymatic method in a Technicon automatic analyzer RA-1000 (Dade-Behring Marburg GmbH, Marburg, Germany). LDL cholesterol was calculated with the Friedewald formula: total cholesterol − HDL cholesterol − 1/5 × triglycerides. An internal quality control was in place for assessing the validity of cholesterol and triglyceride methods. The intra- and interassay CVs of cholesterol and triglyceride concentrations were ≤4%. Renal function was evaluated with the baseline creatinine clearance rate calculated with the Cockcroft-Gault formula: creatinine clearance rate = [(140 − age) × weight]/(72 × serum creatinine)] for men; for women, the result of the above equation was multiplied by 0.85. All biochemical measurements were made with a Roche/Hitachi modular analyzer (Roche Diagnostics). Biochemical evaluations were performed in the same laboratory following the criteria of the World Health Organization Lipid Reference Laboratories. Samples were immediately processed for the determination of all biochemical variables.

**Demographic, anthropometric, and lifestyle characteristics at baseline examination**

Sociodemographic characteristics included age and sex. Height and weight were measured to the nearest 0.5 cm and 100 g, respectively. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. Obesity was defined as a BMI (in kg/m²) ≥29.9. To evaluate physical activity status of the patients during the past year, a modified version of a self-reported questionnaire provided by the American College of Sports Medicine was used (19). On the basis of this questionnaire, the frequency (in times/wk), duration (in min/time), and intensity of sport or occupation-related physical activity were evaluated. Patients who did not report any physical activities were defined as sedentary. Current smokers were defined as those who smoked ≥1 cigarettes/d or who had stopped cigarette smoking during the past 12 mo. Former smokers were defined as those who had stopped smoking >1 y previously. The rest of the patients were defined as never smokers or rare smokers.

**Dietary assessment and evaluation of adherence to the Mediterranean diet at baseline examination**

The dietary examination took place after the third day of hospitalization. Usual dietary intake over the year preceding
hospitalization was assessed in all patients by a repeatable and validated (in our laboratory) semiquantitative food-frequency questionnaire, which included 75 items (foods and beverages commonly consumed in Greece and dietary habits). Portion sizes were included in the food-frequency questionnaire to assist patients in reporting accurate information and to quantify dietary habits. Alcohol consumption was measured by the glass (100 mL) and quantified by ethanol intake (g/drink). One glass equaled 12 g ethanol concentration. The Mediterranean Diet Score (MedDietScore; see Appendix A under “Supplemental data” in the online issue) was calculated for each participant to evaluate the level of adherence to the Mediterranean diet (20, 21). In particular, intake of 10 food groups was evaluated (nonrefined cereals and products, fruit, nuts, vegetables, potatoes, dairy and its products, fish and seafood, poultry, red meat or meat products, and use of olive oil) as was consumption of alcohol. The diet score was calculated as follows: for consumption of items presumed to be close to the Mediterranean pattern (nonrefined cereals and products, fruit and nuts, vegetables, olive oil, nonfat or low-fat dairy, fish, potatoes, and pulses), a score of 0 was assigned when a patient reported no consumption, 1 when reported consumption was 1–4 times/mo, 2 for 5–8 times/mo, 3 for 9–12 times/mo, 4 for 13–18 times/mo, and 5 for >18 times/mo. In contrast, for consumption of foods presumed not to be consumed on a daily or weekly basis (such as meat or meat products, eggs, poultry, and dairy), reverse scores were assigned (eg, 0 when a patient reported almost daily consumption to 5 for rare or no consumption). Regarding alcohol intake, a score of 5 was assigned for consumption of <3 glasses/d; 0 for none or consumption >7 glasses/d; and scores of 4, 3, 2, and 1 for the consumption of 3, 4, 5, and 6, and 7 glasses/d, respectively. This nonmonotonic scoring followed the rationale of the Mediterranean dietary pattern that suggests an intake of 15–30 g ethanol/d (20). Higher values of this diet score indicate greater adherence to the Mediterranean diet (theoretical range: 0–55) (21). Moreover, the MedDietScore has been shown to be an accurate tool in predicting future CVD events (22) and has already been validated against CVD risk and markers (21) such as hypertension, hypercholesterolemia, obesity, and diabetes in previous analyses as well as consumption of fatty acids (23).

Bioethics

The study was approved by the Medical Research Ethics Committee of the First Cardiology Clinic, University of Athens, and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All patients were informed of the aims and procedures of the study and gave their consent.

Statistical analysis

Power analysis showed that the number of enrolled participants (n = 1000) was adequate to evaluate a 2% change in the odds of developing LVSD per 1% of change in the MedDietScore used, achieving a statistical power >85% at a 5% significance level.

Normally distributed continuous variables are presented as means ± SDs, skewed variables are presented as median and quartiles, whereas categorical variables are presented as absolute and relative (%) frequencies. Normality was evaluated with the Shapiro-Wilk test. Cross-sectional associations between normally distributed continuous variables and group of patients were evaluated through the Student’s t test or analysis of variance after equality of variances (homoscedasticity) with the Levene test was controlled for. Associations between skewed variables (troponin I, brain natriuretic peptide, glucose, triglyceride, and C-reactive protein concentrations) and group of patients were evaluated by Mann-Whitney or Kruskal-Wallis tests. Cross-sectional associations between categorical variables were tested by the use of the chi-square or Fisher’s exact tests, without the correction of continuity, whereas correlations between continuous variables were evaluated by Pearson’s correlation coefficient for normally distributed and by Spearman’s ρ coefficient for ordinal or skewed variables. The association between adherence to the Mediterranean diet and the development of LVSD as opposed to preserved systolic function, development of acute MI as opposed to unstable angina, in-hospital death, 30-d, 1-y, and 2-y vital outcomes, and left ventricular remodeling were evaluated by multiple logistic regression analyses after sociodemographic, clinical, and biochemical characteristics of the patients were controlled for. Appropriate tests for goodness-of-fit (Hosmer-Lemeshow and deviance residuals) were applied in all models. Results are presented as odds ratios (ORs) and their corresponding CIs. Multiple linear regressions were used to evaluate the association between patients’ characteristics and ejection fraction during hospitalization and at 3 mo reevaluation. Plots of the standardized residuals as compared with fitted values were used to assess assumptions of the linear regression models. Variables entered in all multiajusted models were those that showed a significant association (P < 0.1) at exploratory analysis or those that were considered as potential confounders in the investigated relations. Results are presented as b-coefficients and SE of the coefficient. All statistical calculations were performed by using SPSS version 14.0 software (SPSS Inc, Chicago, IL).

RESULTS

Development of LVSD in patients with ACS at hospitalization

The prevalence of LVSD at hospitalization was 459 cases out of 1000 hospitalized patients with ACS. Regarding in-hospital mortality, 4.3% of the patients with ACS died during hospitalization. The follow-up evaluation of the patients showed that 18.6% had a CVD event during the first 30 d after hospitalization (14.7% were rehospitalized and 3.9% died). CVD events (fatal or nonfatal) during the 1- and 2-y after hospital discharge were 30.6% (n = 306) and 46.4% (n = 464), respectively (for the 2-y evaluation events occurred during the first year were also considered as an outcome of interest). The 2-y recurrent CVD event rate was 26 cases per 1000 person-months of observation. Of the patients with ACS who had a recurrent cardiac event 135 (13.5%) were fatal; 72 of them occurred during the first year of follow-up. Patients with LVSD had higher CVD event risk during the first 30-d, 1-, and 2-y after hospital discharge (P < 0.001). Specifically, after adjusting for age and sex, the development of LVSD was associated with a 7.16-fold (95% CI: 2.37, 21.56) higher risk of death during hospitalization with
a 3.21-fold (95% CI: 1.91, 5.40) higher risk of 30-d CVD events, as well as with 2.17-fold (95% CI: 1.41, 3.34) and 2.23-fold (95% CI: 1.51, 3.31) higher risks of 1- and 2-y CVD events, respectively. Finally medication prescribed was similar to those who had and had not developed LVSD ($P > 0.10$).

### Adherence to the Mediterranean diet and development of LVSD at hospitalization

MedDietScore was lower in those who had developed LVSD compared with the rest of patients (17.8 ± 3.6 compared with 19.5 ± 4.7; $P < 0.001$). Moreover, a positive correlation was observed between MedDietScore and ejection fraction of the patients at hospital admission ($\rho = 0.267$, $P < 0.001$), whereas patients in the highest tertile of the diet score had on average 18% higher ejection fraction during hospitalization compared with those in the lowest tertile (Table 1). Patients’ characteristics in relation to Mediterranean diet adherence are presented in Table 1.

However, residual confounding may exist; thus, multiple linear regression analysis was applied and showed that MedDietScore was still positively associated with ejection fraction ($\beta \pm SE$: 0.65 ± 0.13; $P = 0.001$), even after adjustment for age, sex, BMI, physical activity status, smoking habits, and history of CVD, hypertension, hypercholesterolemia, and diabetes. Moreover, a 1-unit increase (1/55) in the diet score was associated with 6% lower odds of having LVSD at hospital admission (Table 2). In addition, compared with the lower tertile, patients in the upper tertile of the MedDietScore had less likelihood of developing LVSD at hospitalization (OR: 0.34; 95% CI: 0.20, 0.59). The additive models that were estimated revealed that the association of MedDietScore with LVSD was not influenced by the number of adjustments made (Table 2).

Then, the MedDietScore was recalculated without taking into account the alcohol intake component the analysis was repeated and showed that an increase in the diet score was still associated with reduced likelihood of developing LVSD at hospitalization (OR per 1/50 unit increase: 0.89; 95% CI: 0.85, 0.95). Regarding the patients’ other characteristics, troponin I and C-reactive protein concentrations at entry were associated with more likelihood of LVSD at hospitalization, whereas physical activity, smoking cessation for $\geq 1$ y, revascularization at hospital admission, and a higher creatinine clearance rate were associated with less likelihood of LVSD (Table 2).

### Adherence to the Mediterranean diet, in-hospital mortality, and 2-y follow-up of patients with ACS

Crude comparisons showed that patients in the highest tertile of the MedDietScore as compared with those in the lowest, had a lower risk of in-hospital mortality (0% compared with 2%; $P = 0.009$), a 31% lower risk of recurrent CVD events during the first month after hospitalization ($P = 0.09$), and 47% and 37% lower risks of CVD events during the 1- and 2-y follow-ups,

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**Table 1**

Lifestyle, behavioral, and clinical characteristics and prognosis of the patients with acute coronary syndrome ($n = 1000$) by tertiles of the Mediterranean Diet Score (MedDietScore).

<table>
<thead>
<tr>
<th></th>
<th>Low (&lt;16)</th>
<th>Moderate (17–20)</th>
<th>High (≥21)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>33.3</td>
<td>33.5</td>
<td>33.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65 ± 15a</td>
<td>65 ± 14</td>
<td>62 ± 12</td>
<td>0.007</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>77</td>
<td>73</td>
<td>90**</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of MI at hospital admission (%)</td>
<td>79</td>
<td>76</td>
<td>69</td>
<td>0.17</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>38 ± 10</td>
<td>40 ± 10</td>
<td>45 ± 9**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous history of CVD (%)</td>
<td>60</td>
<td>60</td>
<td>65</td>
<td>0.70</td>
</tr>
<tr>
<td>Family history of CVD (%)</td>
<td>46</td>
<td>42</td>
<td>44</td>
<td>0.79</td>
</tr>
<tr>
<td>Troponin I at entry (ng/mL)</td>
<td>12.8 ± 39</td>
<td>11.4 ± 31</td>
<td>12.1 ± 46</td>
<td>0.78</td>
</tr>
<tr>
<td>Troponin I maximum (ng/mL)</td>
<td>27.01 ± 61</td>
<td>26.7 ± 58</td>
<td>32.5 ± 57</td>
<td>0.73</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.3 ± 1.9</td>
<td>6.6 ± 2.0</td>
<td>6.2 ± 1.8</td>
<td>0.28</td>
</tr>
<tr>
<td>WBC count (no. cells)</td>
<td>10,223 ± 3347</td>
<td>10,057 ± 3138</td>
<td>10,039 ± 3379</td>
<td>0.89</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>45 ± 55</td>
<td>30 ± 43</td>
<td>41 ± 69</td>
<td>0.11</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>76 ± 36</td>
<td>75 ± 36</td>
<td>86 ± 31*</td>
<td>0.03</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>22</td>
<td>28</td>
<td>28</td>
<td>0.47</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 4.5</td>
<td>28.1 ± 5.1</td>
<td>28.0 ± 5.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>47</td>
<td>46</td>
<td>52</td>
<td>0.57</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>50</td>
<td>57</td>
<td>76**</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>56</td>
<td>63</td>
<td>63</td>
<td>0.45</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>200 ± 46</td>
<td>202 ± 52</td>
<td>195 ± 58</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>124 ± 40</td>
<td>123 ± 38</td>
<td>127 ± 47</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>65</td>
<td>64</td>
<td>61</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>34</td>
<td>39</td>
<td>24</td>
<td>0.08</td>
</tr>
</tbody>
</table>

a MI, myocardial infarction; CVD, cardiovascular disease; WBC, white blood cell. Comparisons between groups of patients were made by using ANOVA for normally distributed variables (age, BMI, and MedDietScore), Kruskal-Wallis test for continuous variables that were not normally distributed, and chi-square test for categorical variables (obesity, smoking, physical activity, hypertension, diabetes, hypercholesterolemia, and history of CVD). *$P < 0.05$ and **$P < 0.01$ for high compared with low adherence, after correction for multiple comparisons by using the Bonferroni rule.

b Mean ± SD (all such values).
respectively \((P < 0.001)\). Multiadjusted analyses showed that a one-unit increase \((1/55)\) in the diet score was associated with an 11% less likelihood of having recurrent fatal or nonfatal CVD events during the 2 y after discharge when controlled for the factors presented in Table 3. In addition, compared with the lower tertile of the MedDietScore, patients in the upper tertile had less likelihood of having recurrent CVD events during 2 y after discharge \((\text{OR}: 0.43; 95\% \text{ CI}: 0.19, 0.96)\), after the factors presented in Table 3 were controlled for (Figure 1). Moreover, when different types of medication were also taken into account \((\text{data not shown in text or tables})\) to those observed in the aforementioned results. No significant association with MedDietScore was observed when the analysis was focused only on fatal CVD events. In addition, the MedDietScore without the alcohol intake component was still inversely associated with the risk of having recurrent CVD events \((\text{OR per 1/55 unit: 0.90; 95\% CI: 0.78, 0.95})\) after adjustment for age, sex, traditional CVD risk factors \((\text{data not shown in text or tables})\) to those observed in the previous models.

Adherence to the Mediterranean diet and left ventricular remodeling at 3-mo follow-up examination

Multiple linear regression showed that greater adherence to the Mediterranean diet was associated with increased ejection fraction at 3 mo after the cardiac event \((\beta \pm SE: 0.45 \pm 0.24; P = 0.02)\) after adjustment for age, sex, traditional CVD risk factors \((\text{hypertension, hypercholesterolemia, diabetes, obesity, smoking, and physical activity})\), discharge diagnosis \((\text{MI or UA})\), and the use of statins, angiotensin-converting enzyme inhibitors, and \(b\)-blockers or carvedilol. With regard to remodeling, 53% \((\text{or } n = 413)\) of the 780 patients with an ejection fraction <50% at initial hospitalization maintained this value at 3-mo follow-up examination. Multiadjusted analysis showed that greater adherence to the Mediterranean diet was borderline associated with less likelihood of remodeling \((\text{OR per 1/55 unit: 0.90; 95\% CI: 0.78, 1.03})\) after adjustment for several patients’ characteristics listed in Table 3 and the use of statin, angiotensin-converting enzyme inhibitors, and \(b\)-blockers or carvedilol.

**DISCUSSION**

The present article suggests that greater adherence to the Mediterranean diet results in a less severe acute coronary event (in
Left ventricular systolic function and the Mediterranean diet

Among various predictors for the prognosis of patients hospitalized with an ACS, the presentation of LVSD has a significant effect on their prognosis (24, 25). In this context, the evaluation of factors, especially modifiable ones associated with the development of LVSD and eventually systolic heart failure in patients with ACS, is considered challenging and useful for the patients’ management.

Although the Mediterranean dietary pattern has already been associated with reduced mortality and morbidity from CVD and cancer (1–8), there is little evidence concerning its association with the severity and prognosis of patients with ACS. The present work assessed long-term dietary habits of patients experiencing an ACS, revealing that greater adherence to the Mediterranean dietary pattern is related to a lesser likelihood of remodeling at 3 mo after hospital discharge and fewer major adverse cardiac events (eg, death or rehospitalization due to a new ACS) during the 2-y follow-up after the initial event. Of the overall dietary pattern, only consumption of vegetables, salads, and nuts was associated with lower risk of recurrent cardiac events. It has already been observed that overall and not specific dietary habits play a role in all-cause and cardiovascular mortality and

terms of developing LVSD) and left ventricular remodeling as well as fewer hospital deaths and CVD events during the 2 y of follow-up among patients who have had an ACS. These findings were unaltered after several patients’ characteristics, such as lifestyle behaviors, medical history, and biological and clinical factors at hospital admission, were controlled for. It is of interest that there was a long-term protective association of Mediterranean diet on cardiac event recurrence regardless of patients’ left ventricular systolic function after the event. Despite the potential limitations of the study, the above-mentioned results state new hypotheses regarding the pathophysiologic mechanisms by which a healthy diet may affect human health and particularly the cardiovascular system. The latter is of major importance. Although there are several studies during the past decades suggesting the protective effect of Mediterranean diet on human health, the underlying mechanisms are not fully understood or appreciated.

Left ventricular systolic function and the Mediterranean diet

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Although the Mediterranean dietary pattern has already been associated with reduced mortality and morbidity from CVD and cancer (1–8), there is little evidence concerning its association with the severity and prognosis of patients with ACS. The present work assessed long-term dietary habits of patients experiencing an ACS, revealing that greater adherence to the Mediterranean dietary pattern is related to a lesser likelihood of remodeling at 3 mo after hospital discharge and fewer major adverse cardiac events (eg, death or rehospitalization due to a new ACS) during the 2-y follow-up after the initial event. Of the overall dietary pattern, only consumption of vegetables, salads, and nuts was associated with lower risk of recurrent cardiac events. It has already been observed that overall and not specific dietary habits play a role in all-cause and cardiovascular mortality and

**TABLE 3**

Results from multiple logistic regression analysis that evaluated the association between adherence to the Mediterranean diet and 2-y cardiovascular disease (CVD) events of patients who had an acute coronary syndrome (n = 750)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>Odds ratio</td>
</tr>
<tr>
<td><strong>Sociodemographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 1 y)</td>
<td>1.02</td>
<td>0.99, 1.04</td>
<td>1.03</td>
</tr>
<tr>
<td>Males vs females</td>
<td>0.98</td>
<td>0.46, 2.07</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>Lifestyle variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (yes vs no)</td>
<td>0.94</td>
<td>0.44, 1.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Ever smoking (yes vs no)</td>
<td>1.85</td>
<td>0.73, 4.70</td>
<td>1.63</td>
</tr>
<tr>
<td>MedDietScore (per 1/55 unit)</td>
<td>0.91</td>
<td>0.84, 0.98</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Medical history variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (per 1 kg/m²)</td>
<td>0.95</td>
<td>0.87, 1.03</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension (yes vs no)</td>
<td>1.00</td>
<td>0.45, 2.22</td>
<td>1.31</td>
</tr>
<tr>
<td>Hypercholesterolemia (yes vs no)</td>
<td>0.83</td>
<td>0.39, 1.71</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>0.60</td>
<td>0.28, 1.28</td>
<td>0.93</td>
</tr>
<tr>
<td>History of CVD (yes vs no)</td>
<td>1.72</td>
<td>0.78, 3.78</td>
<td>0.96</td>
</tr>
<tr>
<td>Family history of CVD (yes vs no)</td>
<td>1.18</td>
<td>0.58, 2.40</td>
<td>1.24</td>
</tr>
<tr>
<td><strong>Hospitalization variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization (yes vs no)</td>
<td>1.25</td>
<td>0.53, 2.98</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (per 1 unit)</td>
<td>0.96</td>
<td>0.93, 0.99</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance at entry (per 1 mL/min)</td>
<td>0.99</td>
<td>0.98, 1.01</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein at entry (per 1 mg/L)</td>
<td>1.008</td>
<td>1.00, 1.02</td>
<td></td>
</tr>
<tr>
<td>Discharge diagnosis (MI vs UA)</td>
<td>1.28</td>
<td>0.67, 2.46</td>
<td></td>
</tr>
</tbody>
</table>

MedDietScore, Mediterranean Diet Score; MI, myocardial infarction; UA, unstable angina.

**FIGURE 1.** Kaplan-Meir survival functions for cardiovascular disease (CVD) events (fatal or nonfatal) of the 1000 patients with acute coronary syndrome, according to their level of adherence to the Mediterranean diet (survival functions are fully adjusted for the variables presented in Table 3). MedDietScore, Mediterranean Diet Score.
morbidty (4). Jacques and Tucker (26) suggested previously that it is difficult to separate and understand the specific effects of nutrients or foods despite the common practice of examining the role of single nutrients or foods in relation to disease risk (26). Food- or nutrient-specific analyses in relation to the characteristics of people or incidence of a disease share many methodologic limitations, such as high collinearity of food variables that may influence the robustness of the predicted models, unknown synergistic effects of the foods, and so forth. In contrast, overall diet assessment represents a broader picture of food and nutrient consumption of real life and has been suggested to be more predictive of disease risk than individual foods or nutrients because dietary patterns capture the extremes of dietary habits, preempt nutritional confounding, possibly affect modification among nutritional variables through the same procedure, and do not tend to be biased (27–29).

Potential mechanisms regarding the beneficial effect of Mediterranean diet on the cardiovascular system

Many studies have shown the mechanisms through which the Mediterranean diet exerts its favorable effect on the cardiovascular system in healthy individuals as well as in diabetic and hypertensive subjects (30–34). The present work showed, for the first time in the literature to our knowledge, another mechanism by which long-term adherence to the Mediterranean diet may prove beneficial for the preservation of left ventricular systolic function. However, whether this is a direct cause-and-effect relation or a side-effect, is difficult to conclude with the present study design. Nevertheless, it could be speculated that a key mechanism is the antiinflammatory properties of the Mediterranean diet that already have been reported by the ATTICA study investigators (5). Inflammation and oxidative stress accompanies the clinical presentation and course of an ACS, thus affecting infarct size. Infarct size, in contrast, is a major determinant of postinfarction survival and prognosis and it is the most important factor that affects the ventricular remodeling process. Olive oil, which is the main source of fat in the Mediterranean diet, is rich in oleuropein, which has been shown to possibly reduce infarct size in experimental models (35–37) and to protect a reperfused myocardium from oxidative damage in vivo. However, in the present work, there was no association between inflammatory markers measured at hospital admission and adherence to Mediterranean diet, probably due to the exaggerated response of inflammation at the onset of an acute coronary event, which can mask any preexistent beneficial effect of this type of diet on the inflammation process.

Left ventricular systolic function and other patients’ lifestyle characteristics

The present analysis showed that adoption of a physically active lifestyle was associated with less likelihood of developing LVSD at hospitalization. Exercise training has been associated with a substantial improvement in myocardial contractile performance and infarct size during experimental ischemia-reperfusion in animal models (38, 39). Regarding the other patients’ characteristics, smoking cessation for ≥1 y, reduced the risk of LVSD. Smoking has long been associated with increased risk of CVD in almost all populations studied, whereas smoking cessation seems to confer a protection, especially with long-term abstinence (40). Finally, it is of interest that several established CVD risk factors (e.g., hypertension, hypercholesterolemia, and diabetes) were not associated with LVSD. It could be speculated that treatment of these conditions (statin use, antihypertensive medication, etc) that has already been associated with improvements in the prognosis of patients with ACS in previous studies, as well as the synergistic effect of lifestyle variables with the participants’ treatment, may have affected the strength of the associations between traditional CVD risk factors for and development of LVSD, or prognosis of patients with ACS.

Limitations

The present study has several strengths as mentioned above but also some limitations. In particular, only survivors of ACS were studied; thus, there is no information on patients who died during the first 2 d of hospitalization (~2% of total hospitalizations). The design and measured characteristics of this study do not allow for in-depth pathophysiologic explanations and cannot provide cause-and-effect relations.

Conclusions

Nonpharmacologic interventions, such as dietary pattern modification, are extremely important in primary and secondary prevention of ACS. The results of the present study extend previous scientific knowledge that greater adherence to the Mediterranean diet has a beneficial association with the severity of an ACS by preserving left ventricular ejection fraction, as well as on its long-term prognosis, in a “free-eating” population. Furthermore, the aforementioned association is independent of conventional cardiovascular risk factors and can be supported by the Mediterranean diet’s unique mechanisms of protection discussed above. At the population level, a Mediterranean dietary pattern with the potential of favorably modifying both the severity and the prognosis of ACS could be invaluable. As a result, a comprehensive strategy to decrease cardiovascular morbidity and mortality should primarily include a cardioprotective diet that contains the favorable characteristics of the Mediterranean diet.

We thank the field investigators of the study: George Metallinos, Athanasios Aggelis, Katerina Liontou, Stefanos Tyrovolas, Andria Christofi, and Vassiliki Sinopoulou as well as all the participants for their time spent in the interview. The authors’ responsibilities were as follows—CC: designed the study and wrote the manuscript; DBP: performed data analyses and wrote the manuscript; PA, C-MK, and IK: supervised the field investigation; and CP and CS: provided substantial consultation. None of the authors declared a conflict of interest.

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