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ORIGINAL CONTRIBUTION

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Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score

Summary *Background* Although an important secondary prevention trial reported an impressive protection by a Mediterranean dietary pattern on reinfarction and cardiovascular death, scarce direct epidemiologic evidence is currently available regarding the role of the Mediterranean diet in the aetiology of coronary heart disease. *Aims* The aim of the study was to quantify the risk reduction of *incident* myocardial infarction provided by a Mediterranean dietary pattern. *Methods* We included 342 subjects (171 patients who suffered their first acute myocardial infarction and 171 matched controls) in a case-control study. A validated semi-quantitative food frequency questionnaire (136 items) was used. We defined an *a priori* Mediterranean dietary pattern. We assessed six food items that we considered protective: 1) olive oil, 2) fiber, 3) fruits, 4)vegetables, 5) fish and 6) alcohol. For each of these six dietary factors, we calculated the distribution according to quintiles within the study and assigned each participant a score of 1 to 5 corresponding to the quintile of intake, with 1 representing the lowest and 5 representing the highest quintile. We also estimated the quintiles of two other elements assumed to be associated with a higher risk: 7) meat/meat products and 8) some items with high glycaemic load (white bread, pasta and rice). For these two elements we inversely ranked the score, with 1 representing the highest and 5 representing the lowest quintile. Finally, we summed up the eight quintile values for each participant.

A second score (*post hoc* pattern) was built using only a single cut-off point for these eight elements. The cut-off points for each element in this *post hoc* pattern were decided according to the dose-response relationships between the consumption of each food item and the risk of myocardial infarction observed in the analyses that used quintiles of each food item. *Results* For both patterns, we found that the higher the score, the lower the odds ratio of myocardial infarction. A significant linear trend was apparent after adjustment for the main cardiovascular risk factors. For each additional point in the *a priori* Mediterranean pattern (observed range: 9–38) the odds ratio (95 % confidence intervals) was 0.92 (0.86–0.98). This estimate was 0.55 (0.42–0.73) when we used the *post hoc* pattern (range: 0–8). *Conclusions* Our data support the hypothesis that a Mediterranean diet (that emphasizes olive oil, fiber, fruits, vegetables, fish and alcohol and reduces meat/meat products) can be an effective measure for reducing the risk of myocardial infarction. However, our results support the exclusion of refined cereals with a high glycaemic load as healthy elements of this pattern.

Key words myocardial ischemia – olive oil – glycaemic load – white bread – nutritional epidemiology – case control

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Introduction

The term Mediterranean diet refers to dietary patterns found in olive-growing areas of the Mediterranean region and described in the 1960s and beyond. In these countries, there are some common features in the consumption of specific foods and nutrients, such as olive oil as the main source of fat, abundant plant foods, fresh and varied fruits as the main and usual dessert, frequent consumption of fish, moderate but consistent wine consumption with meals and relatively low amounts of meat. Among the common components that can be identified are: high monounsaturated/saturated fat ratio; ethanol intake at moderate levels; high intakes of fiber, vitamins, folate and natural antioxidants; and low intake of animal protein [1–4]. Dietary patterns from the Mediterranean region have been postulated as protective against coronary heart disease (CHD) [1, 2, 5]. It has been suggested that a Mediterranean diet could be more beneficial for cardiovascular health than the Step-I diet [6]. This recommendation from the American Heart Association was motivated because a secondary prevention trial demonstrated a very impressive reduction in the risk of reinfarction or death among survivors of a first myocardial infarction [7]. However, the statement of the American Heart Association also indicates that further evidence is needed [6, 8]. In fact, scarce direct epidemiologic evidence is apparently available regarding the effect of a Mediterranean dietary pattern on CHD risk.

A public health recommendation promoting this dietary pattern needs to be solidly based on epidemiologic findings conducted in populations where there is a high consumption of the typical food items in this pattern.

The aim of our study was to evaluate the reduction in risk of a first Acute Myocardial Infarction (AMI) that can be obtained by following a Mediterranean diet.

Subjects and methods

We defined as cases all male or female subjects, aged under 80, with their first definite AMI who were admitted to one of the three tertiary hospitals of Pamplona (Spain) within the periods October 1999–June 2000 or October 2000–February 2001. These subjects had to fulfill the criteria [9] for definite AMI of the MONICA project (two or more ECGs showing specific changes; ECGs showing probable changes plus abnormal cardiac enzymes; or typical symptoms plus abnormal enzymes). In addition, exclusion criteria were a previous history of angina pectoris, a previous diagnosis of CHD or other prior diagnosis of major cardiovascular disease. Informed consent was obtained from the patients and the project was approved by the Institutional Review Board of the University of Navarra Medical School. We identified 180 eligible cases. Nine eligible subjects refused to participate (participation proportion = 95 %).

To each case, we matched a control subject of the same age (5-year bands), gender and hospital. Eligible controls were patients admitted to the same hospital during the same month for a wide variety of diseases assumed to be unrelated to diet. A current or previous history of angina pectoris, CHD or other major cardiovascular disease were exclusion criteria for controls. We decided to select hospital controls instead of population controls to ensure comparability regarding level of participation and aiming to capture the level of exposure in the population giving rise to cases. Eight eligible controls refused to participate (participation: 96 %) and each of these was replaced by other patients of similar characteristics for matching variables.

Four trained physicians conducted face-to-face interviews with cases and controls in a standard way and using the same questionnaire. The same physician who interviewed a case patient also interviewed the respective matched control. The physician approached the patients, invited them to participate and provided them with the self-administered questionnaire, including a semi-quantitative food-frequency questionnaire, previously validated in Spain [10], that was slightly expanded for this study (the original version included 118 items, the current version was expanded to 136 items, both including vitamin supplements). For each food item, a commonly used portion size was specified, and participants were asked how often they had consumed that unit on average over the previous year. This way of recording was already used in the original version of the questionnaire [10]. Emphasis was paid to ensure that the answers were related to long-term dietary exposures and not to recent changes in diet. Nine options for frequency of consumption were possible. The nine response categories ranged from "never/almost never" to "six or more times per day."

The type of fat used in frying was specifically assessed. A dietitian updated the nutrient data bank using the latest available information included in the food composition tables for Spain. Total energy-adjusted intakes were computed using the residuals method [11].

The participants reported in the questionnaire their usual time spent practicing 19 activities during their leisure time. This questionnaire about physical activity had been previously validated [12]. We assigned a multiple of resting metabolic rate (MET score) to each activity [13, 14]. With this information, we computed an activity metabolic equivalent index (METs-h/week) which represents both the amount and relative intensity of physical exercise during the week for each participant.

The physician clarified any questions that the patient may have had in completing the questionnaire, and subsequently conducted a face-to-face interview about coronary risk factors (smoking, diabetes, high blood pressure, high blood cholesterol, recent weight changes) and family history of cardiovascular disease. Systolic and fifth-phase diastolic blood pressure readings were recorded for each participant. The average of two readings measured with a mercury-column sphygmomanometer by a physician while the subject was seated was recorded. Weight and height were directly measured according to a standardized protocol, with the subject barefooted and dressed in light clothing. For each participant, we calculated the Body Mass Index (BMI) as the weight in kilograms divided by the squared height in meters (kg/m^2).

Most cases (166/171) were interviewed in the cardiology ward once they had been discharged from the coronary unit. Three of them were interviewed in the Coronary Care Unit and two were interviewed in their homes after being discharged from the hospital. All control subjects were interviewed in hospital wards, except one who was interviewed at home. If there was any missing value, we re-contacted the patients. All missing values were thus corrected. Therefore, the statistical analyses and multivariate modeling were run with complete data for all variables on all participants.

We analyzed the association with AMI for the following eight food groups: olive oil, fiber, fruits, vegetables, fish, alcohol, meat (or meat products) and the combination of white bread + rice + pasta. For each food group, we calculated the distribution according to energy-adjusted quintiles (we did not adjust for energy the intake of alcohol). To appraise the dose-response relationship between consumption of each food item and the risk of myocardial infarction we used conditional logistic regression with matched data of 171 case-control pairs. Adjusted odds ratios and their respective confidence intervals were computed for each of the four upper quintiles using the first quintile as the reference. The following potential confounders were introduced in multivariable models: smoking (six categories), body mass index (kg/m^2, adding a quadratic term to account for non-linearity), high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METS-h/week, adding a quadratic term), family history of CHD before 60 years, aspirin intake, and socioeconomic status (study level, four categories). We selected confounders by taking into account previous published literature about coronary risk factors and avoided reliance on p values or stepwise approaches.

We combined the eight elements to build a combined score (hereafter, *a priori* Mediterranean pattern) associated with a beneficial effect against CHD. We computed this *a priori* pattern simply summing the quintile value of the eight elements. A higher quintile value represented a higher consumption for olive oil, fiber, fruits, vegetables, fish and alcohol, while we inverted the quintile values for meat/meat products and for the sum of white bread, rice and pasta (i. e., for these two factors, quintile 1 was given a value of 5, quintile 2 a value of 4, and so on). For each participant, the quintile values for each of the eight characteristics were summed. The possible range of this variable was, therefore, 5–40.

We computed for each participant an alternative variable (hereafter, *post hoc* pattern) after observing the results obtained using quintiles of each of the eight elements. We dichotomized each element in two categories using the cut-off points that better represented the observed dose-response relationships. When participants were above the cut-off point for the consumption of olive oil, fiber, fruits, vegetables, fish and alcohol, we assigned them one point for each element. When participants were *below* the cut-off point for the consumption of meat (and meat products) or for the combination of white bread + rice + pasta, we assigned them one point for each of these characteristics. Therefore, the range for this score was 0–8.

Tests for trend were done using the absolute value of each score as a continuous variable. We added a quadratic term to evaluate departure from linearity. We plotted the adjusted ORs for each observed value using both the linear and quadratic terms for the score. We used the covariance matrix to estimate the confidence intervals for these estimates [15]. Reported p-values are two-tailed; values < 0.05 were considered significant.

Results

As expected, cases were more likely to be current smokers, have a higher BMI and a prior history of hypertension, diabetes or high blood cholesterol (Table 1).

We found important reductions in relative risks (odds ratios lower than 1) associated with a high consumption of olive oil, fiber, fruits, vegetables, fish and alcohol (Table 2). With the exception of vegetables and ethanol, these associations were statistically significant. When we adjusted for non-dietary confounders, the estimated ORs for the three upper quintiles represented a relative reduction in risk greater than 50 % for all items except alcohol. For most of these items we observed an L-shaped dose-response trend, with a substantial reduction in risk for those in the second (or third) quintile as compared with those in the first quintile, but no further important reduction was observed with even higher consumption (Table 2). Nevertheless, as we have reported elsewhere, we did observe a significant linear trend for olive oil consumption and for dietary fiber intake [16, 17].

On the other hand, point estimates for the odds ratios higher than 1 were found for a high consumption of meat/meat products and for the highest consumption of the combination of factors with high glycaemic index (white bread + rice + pasta). When we only adjusted for non-dietary risk factors, the highest OR was found for

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Table 1 Characteristics of case and control participants

	Cases (n = 171)	Controls (n = 171)
Age (years, mean)	61.7	61.4
Gender (% men)	81	81
Educational level (%)		
< Primary	28	29
Primary	44	45
Secondary	12	16
University	16	10
Occupational level (%)		
White collar	21	25
Blue collar	18	16
Retired	44	46
Housewife	12	10
Other	5	3
Smoking (%)		
Never	32	44
Ex-smoker (< 2 years)	17	26
Ex-smoker (≥ 2 years)	12	6
Currently	40	23
< 15 cig/day	14	12
15–34 cig/day	18	11
> 34 cig/day	8	1
Body mass index (kg/m^2, mean)	27.7	27.3
History of hypertension (%)	42	30
History of diabetes (%)	16	8
High blood cholesterol in last 5 years (%)	19	11
Leisure-time physical activity (METS-h/week, mean)	31.5	34.5

the fifth quintile of the combination of these items (white bread + rice + pasta). The addition of potatoes to this group did not improve the prediction of the CHD risk and only slightly increased the explained variability in the total glycaemic load (data not shown).

When we adjusted the model to include each of the seven variables as independent terms, the direction of most of the associations was maintained, although they tended to reflect lower effects and wider confidence intervals, losing statistical significance. The most important change in the point estimate was observed for meat/meat products (with an increased estimate), whereas the protective effect of alcohol was clearer and the effect of fiber did not substantially change. In another analysis, we separated poultry, pork, veal, other red meats and processed meats, but we did not find specific differences for the consumption of each type of meat (data not shown).

Among our participants, the observed values for the *a priori* defined pattern ranged between 9 and 38. Most participants (69 %) scored between 20 and 29 points. When we introduced this score in the multivariable conditional logistic regression model, we found a very important and significant reduction in the *odds ratio* for those scoring 20 points or higher (Table 3). When we used alternative cut-off points (< 15; 15–19; 20–24; 25–29; ≥ 30) for the *a priori* Mediterranean pattern we also found important and significant reductions for those in the upper part of the distribution (the respective point-estimates of the ORs were: 1.00 [ref.], 0.09; 0.03; 0.03 and 0.04) in the fully adjusted analyses. The differences between those scoring 9–14 and those scoring 15–19 were borderline significant ($p = 0.06$). The differences between those scoring 15–19 and 20 or higher were statistically significant (OR = 0.25; 95 % CI: 0.09–0.66). We found no significant differences within the range 25–38 points. When we used the *a priori* Mediterranean pattern as a continuous variable to assess the linear trend, we found a monotonic risk reduction, i. e., the higher the score, the lower the risk. Nevertheless, when we also introduced a quadratic term for this score in the model, we found a statistically significant improvement, indicating that an L-shaped pattern better reflected the dose-response relationship between the adherence to the Mediterranean pattern and the odds ratio of AMI (Fig. 1). The interpretation of this finding suggested that, for scores higher than 16 in the *a priori* pattern, the *odds ratio* approached 0 and the dose-response curve was almost flat with increasing scores.

To build the alternative *post hoc* score we used the cut-off points suggested by the results of the quintile analyses and shown in Table 4. For olive oil, fruits, vegetables, fish, alcohol and meat we merged the four upper quintiles in a single category. For fiber we merged the three upper quintiles. For the combination of white bread, pasta and rice we merged the four lower quintiles.

As shown in Table 4, using this classification, we found adjusted ORs for the eight elements ranging from 0.35 (for a high fruit consumption) to 0.64 (for a low meat consumption). The upper limits of all confidence intervals were lower than one, with the exception of alcohol and meat consumption. However, when we additionally adjusted for the other food items, the OR for low meat consumption was 0.33 (95 % CI: 0.13–0.79) but it did not substantially change for alcohol.

Among our participants, the *post hoc* pattern ranged between 0 and 8. We observed that increasing values of this pattern were associated with a monotonic reduction in the *odds ratio* of AMI (Table 5). The association was highly significant and showed a great magnitude (OR = 0.55; 95 % CI: 0.42–0.73 for each additional point in this score). In fully adjusted models, we found statistically significant differences between participants scoring 0–2 and those scoring 3–4 ($p = 0.04$) and between participants with 3–4 points and those scoring 5–6 ($p = 0.02$). We did not find differences for those scoring 7–8 points when they were compared with participants scoring 5–6 (OR = 0.88; 95 % CI: 0.46–1.70). When we tried a quadratic term in the model for this pattern, it did not significantly improve the model, showing that the dose-response relationship was best defined as a linear trend.

Table 2 Odds ratios (95 % confidence intervals) of a first myocardial infarction according to each one of the food items included in the Mediterranean dietary pattern

Item consumption (quintiles, energy adjusted[1])	Adjusted ORs (95 % CI)[2]	Adjusted ORs: the three upper vs. the lower quintile[2]	Additionally adjusted ORs: the three upper vs. the lower quintile[3]
Olive oil (g/day): < 10	1 (ref.)		
10–18	0.34 (0.12–0.97)		
18–26	0.43 (0.18–1.06)		
27–38	0.56 (0.20–1.61)	0.43 (0.19–0.99)	0.60 (0.22–1.63)
> 38	0.22 (0.07–0.73)		
Fiber (g/day): < 24	1 (ref.)		
24–27	0.70 (0.27–1.86)		
27–32	0.25 (0.08–0.76)		
32–38	0.38 (0.13–1.09)	0.36 (0.14–0.91)	0.33 (0.07–1.57)
> 38	0.46 (0.16–1.35)		
Fruits (g/day): < 175	1 (ref.)		
175–252	0.28 (0.08–0.91)		
252- 364	0.38 (0.13–1.10)		
365–570	0.32 (0.11–0.97)	0.37 (0.14–0.96)	0.65 (0.16–2.61)
> 570	0.43 (0.14–1.34)		
Vegetables (g/day): < 347	1 (ref.)		
347–482	0.42 (0.16–1.08)		
482–583	0.36 (0.13–0.98)		
583–744	0.61 (0.23–1.57)	0.46 (0.21–1.04)	0.71 (0.23–2.17)
> 744	0.42 (0.15–1.20)		
Fish (g/day): < 60	1 (ref.)		
60–77	0.41 (0.15–1.10)		
77–106	0.28 (0.10–0.77)		
106–142	0.55 (0.20–1.51)	0.36 (0.15–0.87)	0.37 (0.13–1.03)
> 142	0.31 (0.11–0.85)		
Alcohol (g/day): 0	1 (ref.)		
> 0–7	0.49 (0.18–1.32)		
7–13	0.57 (0.24–1.39)		
14–34	0.47 (0.17–1.29)	0.54 (0.24–1.22)	0.42 (0.16–1.14)
> 34	0.57 (0.19–1.72)		
Meat/meat products (g/day)			
< 107	1 (ref.)		
107–130	2.27 (0.97–5.33)		
130–163	0.91 (0.35–2.36)		
164–208	1.19 (0.46–3.08)	1.28 (0.61–2.70)	2.16 (0.83–5.63)
> 208	2.04 (0.80–5.38)		
White bread + rice + pasta			
(g/day): < 84	1 (ref.)		
84–138	1.64 (0.61–4.41)		
138–180	0.97 (0.35–2.68)		
181–252	0.80 (0.32–2.02)	1.11 (0.50–2.44)	0.97 (0.36–2.64)
> 252	3.00 (0.96–9.40)		

[1] With the exception of alcohol intake, all the other food items shown in the table are adjusted for total energy intake (residuals method)
[2] Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking, body mass index, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METS-h/week) and socioeconomic status (study level)
[3] Additionally adjusted for all the other food items shown in the table

Discussion

In a Mediterranean population, our case-control study, after controlling for the main risk factors, found important relative reductions in the risk of myocardial infarction for a high consumption of olive oil, fiber, fruits, vegetables, fish and alcohol. On the other hand, we found a positive association of myocardial infarction occurrence with high meat consumption and with the highest consumption of refined cereals and food items with a high glycaemic load (white bread, pasta and white rice) which are currently consumed in high amounts and frequently recommended in Mediterranean countries. When we combined these elements in a single variable representing a healthy Mediterranean dietary pattern, we found important reductions in the odds ratio.

Some limitations of our study need to be recognized.

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Table 3 Odds ratios (95 % confidence intervals) of a first myocardial infarction according to the *a priori* defined Mediterranean dietary pattern (directly built summing up the energy-adjusted quintiles for the eight items)

Score (points)	Controls/cases (n)	Multivariate adjusted OR[1] (95 % CI)	p
< 20	17/41	1 (ref)	
20–24	72/56	0.17 (0.06–0.51)	0.001
25–29	58/50	0.14 (0.04–0.47)	0.001
≥ 30	24/24	0.21 (0.06–0.73)	0.01
For each additional point	(index as a continuous variable)	0.92 (0.86–0.98)	0.01

[1] Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking (six categories), body mass index (adding a quadratic term to account for non-linearity), high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METS-h/week, adding a quadratic term), family history of CHD before 60 years, aspirin intake and socioeconomic status (study level)

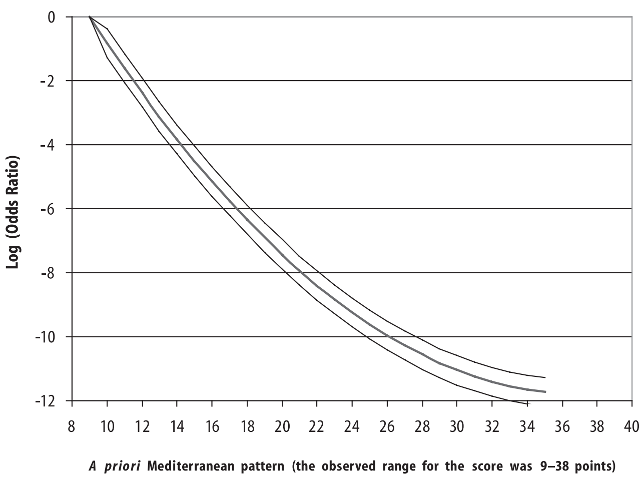

Fig. 1 Log (Odds Ratio) and 95 % confidence intervals of a first myocardial infarction according to the *a priori* defined Mediterranean dietary pattern (directly built summing up the energy-adjusted quintiles for the eight items)

Table 4 Score system used to build the post hoc pattern

Item	Points	Adjusted OR (95 % CI)[1]
Olive oil		
< 10 g/day (Q1)	0	
≥10 g/day (Q2 to Q5)	1	0.41 (0.18–0.92)
Fiber		
< 27 g/day (Q1 and Q2)	0	
≥27 g/day (Q3 to Q5)	1	0.44 (0.21–0.92)
Fruits		
< 175 g/day (Q1)	0	
≥175 g/day (Q2 to Q5)	1	0.35 (0.14–0.89)
Vegetables		
< 347 g/day (Q1)	0	
≥347 g/day (Q2 to Q5)	1	0.45 (0.21–0.98)
Fish and marine items		
< 60 g/day (Q1)	0	
≥60 g/day (Q2 to Q5)	1	0.38 (0.17–0.87)
Alcohol		
No consumption (Q1)	0	
Any consumption (Q2 to Q5)	1	0.53 (0.24–1.17)
Meat and meat products		
< 107 g/day (Q1)	1	0.64 (0.32–1.27)[2]
≥107 g/day (Q2 to Q5)	0	
White bread + rice + pasta		
< 252 g/day (Q1 to Q4)	1	0.38 (0.15–0.93)
≥ 252 g/day (Q5)	0	

[1] Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking (six categories), body mass index (adding a quadratic term to account for non-linearity), high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METS-h/week, adding a quadratic term), family history of CHD before 60 years, aspirin intake and socioeconomic status (study level)
[2] When it was additionally adjusted for the other seven food items, the odds ratio was 0.33 (95 % CI: 0.13–0.79)

Table 5 Odds ratios (95 % confidence intervals) of a first myocardial infarction according to the post hoc pattern (score system shown in Table 4).

Score (points)	Controls/cases (n)	Multivariate adjusted OR[1] (95 % CI)	p
0–4	24/46	1 (ref)	
5–6	87/74	0.17 (0.06–0.48)	< 0.001
7–8	60/51	0.15 (0.05–0.44)	< 0.001
For each additional point	(index as a continuous variable)	0.55 (0.42–0.73)	< 0.001

[1] Conditional logistic regression (age-, hospital- and gender-matched pairs), adjusted for smoking (six categories), body mass index (adding a quadratic term to account for non-linearity), high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METS-h/week, adding a quadratic term), family history of CHD before 60 years, aspirin intake and socioeconomic status (study level)

The case-control design has inherent drawbacks, the use of hospitalized patients might be seen as controversial, and our sample size was not very large. All of these weaknesses support the need for further evidence. These studies would ideally come from large prospective cohort studies with a repeated dietary assessment conducted in Mediterranean populations.

Some doubts may be raised concerning the relevance for validity of slightly expanding the food frequency questionnaire from 118 to 136 items because a new validation study has not been formally conducted. Ordinarily, in nutritional epidemiology, it has been shown that the more comprehensive the questionnaire, the higher the validity, although a ceiling of validity may exist for food frequency questionnaires somewhat near correlations of 0.7 [18]. The published validation study showed acceptable performance for this questionnaire [10] and it is likely that in any case this validity may have improved with the slight expansion of the questionnaire, moreover, when most of the new items came from splitting some of the merged items of the previous version (red meats, processed meats, sausages, some groups of fruits, types of wine, fats and oils used for cooking).

The same physician was responsible for assessing both the case and the matching control subject. A potential concern could be interviewer bias because physicians were not blinded to the case-control status of the patient. However, this bias is very unlikely in our study because the food-frequency questionnaire was self-administered. The interviewing physicians did not ask any questions to the case or control subject regarding food consumption, they simply provided him/her with the self-administered questionnaire, and the patient answered the questionnaire by him/herself.

Finding a statistically significant linear trend usually reinforces the causal interpretation in epidemiology. Our data suggest an L-shaped pattern for most of the individual items. In addition, when we adjusted for all other food items, the statistical significance for each food item was lost. All this could lead us to see our results with some skepticism. However, the lack of statistical significance is more likely to be associated with the large number of independent terms simultaneously introduced in the model (Table 2, last column) together with our limited sample size. In this context, more important than statistical significance may be the magnitude of the reduction in risk. This magnitude was essentially maintained for some food items (fiber, fish, alcohol). We think that this is per se a relevant finding of our study. Moreover, in spite of the lack of statistical significance or the L-shaped pattern for individual food items, we did find a very significant association for the overall pattern and a significant linear trend for both patterns (Tables 3 and 5). In spite of the limitations derived from the size of our case-control study, the findings are, therefore, interesting and in any case they will be available for future meta-analyses which would overcome the problem of statistical power.

Desirably, future similar studies with larger sample size are needed to confirm our findings.

Nevertheless, our findings are consistent with previous epidemiologic studies that have assessed the potential protective role of the Mediterranean dietary pattern, even though these studies did not specifically have CHD incidence as the outcome and considered all cereals as beneficial elements [7, 19–22]. Our results are also consistent with previous hypotheses suggesting that a higher intake of total fat or monounsaturated fat is not necessarily associated with a higher risk of CHD [23] while a very high glycaemic load may have an adverse effect [25].

A previous case-control study in Greece did not find any significant association between fat intake and CHD [24]. The same group [19] found that an *a priori* defined Mediterranean dietary pattern was associated with advantageous survival in a cohort of elderly people. Three other small studies have consistently reported similar results in Australia [20], Spain [21] and Italy [22] using analogous methodologies. However, the outcome in all of these four studies included every cause of death and no information was reported about specific associations with CHD risk. If the primary benefit of the Mediterranean diet is exerted on CHD risk, then some degree of misclassification of the outcome may arise when the end-point is overall mortality. In spite of this potential non-differential misclassification which tends to blur the effect, the four studies [19–22] found important benefits for a Mediterranean diet. In fact, they would have been consistent with an even higher benefit had they used CHD specifically as the outcome. Therefore, our estimates of odds ratios cannot be considered as exaggerated.

Our results are also consistent with the high magnitude of the relative reduction in risk reported in the randomized secondary prevention trial conducted in France [7]. Our findings go beyond secondary prevention, also showing a clear protection by the Mediterranean diet on the incidence of a first coronary event. The results arising from our study thus meet the call for further evidence made by the American Heart Association [6].

The high consumption of cereals in the Mediterranean diet has usually been considered to be a healthy element of this pattern, but evidence was sparse. Interestingly, the investigators of the Greek elderly cohort [19] *a priori* considered the group of "cereals" as a beneficial factor to build their score, but the point estimate they found for the hazard ratio was not protective (although statistically non-significant). The use of refined cereals is increasing worldwide, which is also the case in Mediterranean countries where there is already a high consumption of cereals. The three cereal products summed together as one factor in the score (white bread, rice and pasta) are usually consumed in high amounts in the Mediterranean countries. We decided to merge them as a single group because they represent an indicator food which can be easily used to elaborate food-based dietary guidelines. The three of them accounted for 45 % of the variability in the glycaemic load in our sample. Glycaemic load has been shown as a strong risk factor for CHD [25]. This study adds further evidence to support this adverse effect and to suggest not to include refined cereals as healthy elements of the Mediterranean diet.

A growing interest currently exists in nutritional epidemiology to study dietary patterns [26–28]. This approach is based on the rationale that nutrients and foods are eaten in combination, and their joint effects are more appropriately investigated by considering a composite pattern than by assessing single nutrients or individual foods, thus taking advantage of the fact that nutrients are correlated. The lower mortality rate by CHD found in Asia and Mediterranean countries has attracted the attention toward their respective dietary patterns. Both share many common features with the empirically identified "prudent" patterns in large American cohorts which have been reported to be associated with a lower incidence of CHD [27–29]. Therefore, the lower consumption of meats and the higher consumption of olive oil, fiber, fruits, vegetables, fish and alcohol found in Mediterranean countries could explain the lower mortality by CHD in these countries. Our results support this hypothesis.

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