



Applied nutritional investigation

Effect of adherence to Mediterranean diet on first ST-elevation myocardial infarction: Insights from multiethnic case-control study



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ARTICLE INFO

Article History:

Received 8 November 2018

Received in revised form 21 March 2019

Accepted 26 March 2019

Keywords:

ST-elevation myocardial infarction

Dietary habits

Mediterranean diet

Risk factors

ABSTRACT

Objective: This study aimed to assess the protective role of dietary habits and Mediterranean diet adherence in first acute myocardial infarction in patients enrolled in the multicenter and multiethnic FAMI (First Acute Myocardial Infarction) study.

Methods: In this study we analyzed a multiethnic case-control population of 1478 individuals (858 from Europe and 620 from China): 739 patients with ST-elevation myocardial infarction (STEMI) without previous history of coronary artery disease who were admitted to the Emergency Department within 6 h of symptoms onset, and 739 age- and sex-matched healthy controls. Dietary habits were collected with a food frequency questionnaire from which we calculated the FAMI Mediterranean Diet Score, according to the adherence to Mediterranean diet.

Results: European patients with STEMI had significantly lower adherence to Mediterranean diet than controls. Among Chinese populations, there was no association between FAMI Mediterranean Diet Score and STEMI prevalence. The distribution of the main food types suggested that our questionnaire was not an effective tool to study dietary habits in the Chinese population.

In the European population, higher adherence to Mediterranean dietary pattern was associated with a protective effect on the risk of STEMI, independently of global cardiovascular risk factor profile. Furthermore, high fruit and vegetable consumption was associated with a significant reduction of STEMI risk.

Conclusions: The study found a protective effect of the Mediterranean diet and high fruit and vegetable consumption on the risk of first STEMI, regardless of traditional cardiovascular risk factors in the European population.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in industrialized countries, with an increasing contribution to mortality also in middle- and low-income countries. Each year more than 17 million deaths are recorded globally, and this figure is expected to reach 23.6 million by 2030 [1]. Therefore innovative and multi-dimensional prediction, prevention, and treatment strategies are needed.

Acute coronary syndrome (ACS) is the most lethal among CVDs. Acute coronary syndrome refers to a spectrum of clinical conditions caused by myocardial ischemia and includes unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment

elevation myocardial infarction (STEMI). These conditions are predominantly provoked by atherosclerotic plaque instability and rupture and consequent endoluminal thrombosis [2].

Since the publication of data in the Seven Countries Study by Ancel Keys in 1980 [3], several authors have investigated how different dietary habits may influence the risk of myocardial infarction through their effects on blood pressure, lipid profile, and inflammation [4–6]. Currently diet is acknowledged as one of the modifiable risk factors for CVD disease, and increasing evidence indicates that dietary patterns high in fruit, vegetable, pulses, whole grains, fish, nuts, and low-fat dairy products have a protective effect against development and progression of atherosclerosis [7–9].

The Mediterranean diet brings together these dietary features. Accordingly, epidemiologic studies have indicated lower cardiovascular mortality in Mediterranean countries compared with Northern European countries and the United States [10].

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In the present study we analyzed the dietary habits and the adherence to a Mediterranean diet in patients with first STEMI and healthy controls, and we assessed the effects of diet on the risk of first STEMI in European and Chinese populations.

Methods

Study population

The analysis was performed within the framework of the FAMI (First Acute Myocardial Infarction) Study, a multiethnic, multicentric, observational, prospective study. The FAMI study enrolled individuals with STEMI occurring as their first manifestation of coronary heart disease (CHD) and age- and sex-matched healthy controls from urban areas of Italy, Scotland, and China. The study was approved by the appropriate regulatory and ethics committees in all participating centers. All participants provided informed consent before enrollment. The rationale and design of the FAMI study have been described elsewhere [11].

A total of 2190 subjects (both STEMI patients and control subjects) were enrolled between October 2002 and April 2007. All patients who arrived in hospital within 6 h from the onset of symptoms were screened, and those who had electrocardiographic evidence of STEMI, without previous history of CHD, were enrolled in the study. A control subject, matched for age (≤ 5 y old), sex, and environment (enrolled from the same city), was recruited for each index case. Controls were recruited only in case of negative history of CHD or exertional chest pain.

After screening for the inclusion criteria, 739 patients and 739 matched controls were included in this analysis. Among the 739 patients and their respective controls, 272 were Italian, 157 Scottish, and 310 Chinese. Italian and Scottish individuals were grouped into the European population.

Variables and risk assessment

At the enrollment visit a standardized structured questionnaire was administered and physical examinations were undertaken in the same manner in cases and controls. Self-reported information on personal or family history of CHD, traditional cardiovascular risk factors (smoking, diabetes, dyslipidemia, hypertension), and therapy were collected.

Blood pressure was measured in a stable phase, after recovery from the acute phase or just before hospital discharge. Non-fasting blood samples (50 mL) were collected on admission before reperfusion strategies within 6 h from symptoms onset to minimize acute event-related changes in plasma lipid profile. After separation, micro aliquots of serum, sodium-citrate plasma, heparin plasma, and whole blood were immediately frozen at -80°C . Fasting blood samples were drawn from each control subject and processed similarly. Serum samples from all countries were centrally analyzed at the Università Vita-Salute San Raffaele core laboratory for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triacylglycerols, ApoB lipoprotein, and ApoA₁ lipoprotein. We considered hypercholesterolemic patients those with total cholesterol levels >200 mg/dL because the prevalence of dyslipidemia based on self-reported information was largely underestimated.

Using the continuous Adult Treatment Panel III-Framingham Risk Score (ATP-III/FRS) risk prediction model [12] based on age, systolic blood pressure, treatment of hypertension, total and HDL cholesterol levels, and current smoking status, we calculated the 10-y risk of severe CHD. The risk thresholds used for categorization were 10% and 20%, corresponding to the cutoff points for intermediate- and high-risk categories, respectively, according to the ATP-III guideline.

Individuals with diabetes mellitus or other clinical forms of atherosclerotic disease were considered to carry a risk for major coronary events equal to that of established CHD (i.e., $>20\%$ per 10 y).

Dietary assessment

Dietary habits during the year preceding the enrollment were assessed by a semiquantitative food frequency questionnaire in all participants, both cases and controls. The adherence to Mediterranean diet was evaluated with the FAMI Mediterranean Diet (FAMI MD) Score, a continuous score adapted from the MedDiet-Score [13,14], based on the available food categories included in our questionnaire (Table 1).

The FAMI MD Score was calculated by assigning a number from 0 to 5 for increasing consumption of each food consistent with the Mediterranean diet as displayed in Table 1; conversely, a decreasing score from 5 to 0 was given for increasing consumption of a food known to diverge from the Mediterranean diet pattern. The FAMI MD Score ranged from 0 to 45.

Both cases and controls were divided into quintiles according to the MD FAMI Score distribution. Also, they were divided into the following three categories: subjects with MD FAMI score between the 25th and the 75th percentile and subjects at the opposite extremes of the distribution, with a score ≤ 25 th percentile and ≥ 75 th percentile.

Table 1
FAMI Mediterranean Diet Score

	Frequency of consumption					
	Never	1–6	7–12	13–18	19–31	>32
Non-refined cereals	0	1	2	3	4	5
Fruits, juices and nuts	Never	1–4	5–8	9–15	16–21	>22
	0	1	2	3	4	5
Raw vegetables	Never	1–6	7–12	13–20	21–32	>33
	0	1	2	3	4	5
Cooked Vegetables	Never	1–4	5–8	9–12	13–18	<18
	0	1	2	3	4	5
Fish	Never	<1	1–2	3–4	5–6	>6
	0	1	2	3	4	5
Red meat	≤ 1	2–3	4–5	6–7	8–10	>10
	5	4	3	2	1	0
Poultry	≤ 3	4–5	5–6	7–8	9–10	>10
	5	4	3	2	1	0
Full-fat dairy products	≤ 10	11–15	16–20	21–28	29–30	>30
	5	4	3	2	1	0
Use of olive oil in cooking	Never	Rare	<1	1–3	3–5	Daily
	0	1	2	3	4	5

MD, Mediterranean Diet

The consumption of at least four servings of fresh fruits and vegetables per day was also considered.

Statistical analysis

Continuous variables are presented as mean and standard deviation (\pm SD) or as median and interquartile range (25th–75th), as appropriate.

Continuous variables, which are normally distributed, were compared using the Student *t* test for independent samples. When the variable distribution was not normal, Mann-Whitney *U* test for independent samples was used.

The proportion of categorical variables were compared using a χ^2 analysis or Fisher exact test, as appropriate.

Univariate analysis was presented as estimated odds ratios and accompanying 95% confidence intervals (95% CI) for each class of variables in relation to the referent class. Multivariate logistic regression analysis was performed to identify the independent risk of STEMI.

A *P* value < 0.05 was considered statistically significant. Statistical analysis and graphics were produced with JMP (Version 11, SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Baseline clinical characteristics of the whole study population and each ethnic group are presented in Table 2.

In the study population the prevalence of traditional risk factors was significantly higher in patients than in controls. Patients with STEMI had a higher prevalence of positive family history of myocardial infarction ($P=0.0004$), higher LDL ($P < 0.0001$), and triacylglycerols ($P=0.0016$) levels and lower HDL levels ($P < 0.0001$). There was no statistically significant difference in anthropometric parameters, such as body mass index and abdominal circumference.

European and Chinese patients with STEMI had different baseline characteristics. Cardiovascular risk factors were similar between the two cohorts, even if the proportion of current smokers was higher in the Chinese than in the European cohort in both patients (59.7% versus 47.1%) and controls (37.4% versus 14.2%). The frequency of hypertension in the Chinese population was lower in patients than in controls, who, however, were more often treated with anti-hypertensive therapy. CAD equivalents, such as peripheral artery disease and chronic renal disease, were significantly different among patients and controls only in the European population. The frequency of peripheral artery disease was higher in the Chinese cohort in both patients (11.6% versus 8.4%) and controls (8.7% versus 3.5%).

Table 2
Baseline characteristics of patients and controls, overall and for each ethnic group

	Overall (n = 1478)			European (n = 858)			Chinese (n = 620)		
	STEMI (n = 739)	Controls (n = 739)	P	STEMI (n = 429)	Controls (n = 429)	P	STEMI (n = 310)	Controls (n = 310)	P
Age (y)	60.6 ± 11.9	60.7 ± 11.8	ns	60.9 ± 11.6	61.2 ± 11.6	ns	60.2 ± 12.3	59.9 ± 11.9	ns
Males, n (%)	574 (77.7)	574 (77.7)	ns	334 (77.9)	334 (77.9)	ns	240 (77.4)	240 (77.4)	ns
CV risk factors									
Familiar history of MI, n (%)	126 (17.1)	78 (10.6)	0.0004	101 (23.5)	60 (14.0)	0.0004	25 (8.1)	18 (5.9)	ns
Hypertension, No. (%)	320 (43.3)	337 (45.6)	ns	178 (41.5)	140 (32.6)	<0.0001	142 (45.8)	197 (63.5)	<0.0001
Current smoking, n (%)	387 (52.4)	177 (24.0)	<0.0001	202 (47.1)	61 (14.2)	<0.0001	185 (59.7)	116 (37.4)	<0.0001
Diabetes mellitus, n (%)	92 (12.4)	47 (6.4)	<0.0001	41 (9.6)	22 (5.1)	0.0179	51 (16.5)	25 (8.1)	0.0020
Systolic BP (mm Hg)	137.6 ± 13.8	132.4 ± 11.6	<0.0001	137.6 ± 13.6	130.7 ± 11.6	<0.0001	137.5 ± 14.2	134.9 ± 12.7	0.0166
Anthropometric parameters									
BMI (kg/m ²)	26.2 ± 3.8	26.2 ± 3.9	ns	26.9 ± 4.1	26.8 ± 4.1	ns	25.1 ± 3.2	25.3 ± 3.5	ns
Abdominal circumference (cm)	92.3 ± 12.2	92.0 ± 11.3	ns	94.9 ± 12.4	94.9 ± 11.4	ns	88.9 ± 11.0	88.0 ± 9.9	ns
Lipid profile									
Total C (mg/dL)	224.1 ± 52.3	219.0 ± 48.1	ns	234.8 ± 53.9	227.0 ± 46.0	0.0231	209.4 ± 46.2	207.9 ± 48.7	ns
HDL-C (mg/dL)	40.8 ± 11.0	47.1 ± 11.8	<0.0001	41.9 ± 12.3	49.8 ± 12.1	<0.0001	39.3 ± 8.7	43.3 ± 10.1	<0.0001
LDL-C (mg/dL)	156.2 ± 52.6	142.1 ± 48.6	<0.0001	166.6 ± 55.8	149.1 ± 51.1	<0.0001	141.7 ± 43.8	132.3 ± 43.2	0.0070
CAD equivalents									
Triacylglycerols (mg/dL)	126.9 (86.4–179.8)	117.8 (80.8–161.4)	0.0016	122.9 (82.1–175.3)	112.6 (76.6–153.3)	0.0015	132.9 (88.8–193.2)	124.9 (86.8–175.7)	ns
Peripheral artery disease, n (%)	72 (9.7)	42 (5.7)	0.0045	36 (8.4)	15 (3.5)	0.0035	36 (11.6)	27 (8.7)	ns
Chronic kidney disease, n (%)	88 (11.9)	48 (6.5)	0.0004	60 (14.0)	32 (7.5)	0.0027	28 (9.0)	16 (5.2)	ns
Therapy									
Statin treatment, n (%)	37 (5.0)	77 (10.4)	<0.0001	28 (6.5)	61 (14.2)	0.0003	9 (2.9)	16 (5.2)	ns
Antihypertensive treatment, n (%)	217 (29.4)	271 (36.7)	0.0034	128 (29.8)	119 (27.7)	ns	89 (28.7)	152 (49.0)	<0.0001

BMI, body mass index; BP, blood pressure; C, cholesterol; CAD, coronary artery disease; CV, cardiovascular; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; ns, not significant. Values are expressed as mean ± SD, median (25th–75th percentile), or n (%).

Both in European and in Chinese populations, the mean ATP-III/FRS was significantly higher in STEMI patients than in controls (European STEMI versus controls: ATP-III/FRS 16.4% ± 8.3% versus 11.3% ± 7.2%; $P < 0.0001$; Chinese STEMI versus controls: ATP-III/FRS 16.1% ± 8.2% versus 12.6% ± 7.9%; $P < 0.0001$).

High-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) were significantly higher in STEMI patients than controls both in European (European STEMI versus controls: CRP 2.5 mg/L [1.7–5.3] versus 1.4 mg/L [0.7–3.2]; $P < 0.0001$; IL-6 4.6 pg/mL [2.7–8.8] versus 1.3 pg/mL [0.7–2.7]; $P < 0.0001$) and in Chinese population (Chinese STEMI versus controls: CRP 2.5 mg/L [1.0–5.6] versus 1.0 mg/L [0.5–2.4]; $P < 0.0001$; IL-6 4.7 pg/mL [1.6–10.0] versus 1.4 pg/mL [0.8–2.5]; $P < 0.0001$).

Food frequency questionnaire

Significant differences between European STEMI patients and controls were found in the consumption of bread and rice (χ^2 10.6; $P = 0.014$), cooked (χ^2 13.7, $P = 0.0033$) and raw (χ^2 22.3; $P < 0.0001$) vegetables, fruit (χ^2 34.3; $P < 0.0001$), lard (χ^2 13.4; $P = 0.0062$), and dairy products (χ^2 11.6; $P = 0.009$). The differences in the consumption of olive oil (χ^2 7.7; $P = 0.05$) and eggs (χ^2 7.8; $P = 0.05$) were of borderline significance.

In the Chinese population an unusual distribution of the leading food types was identified, although patients with STEMI had lower consumption of fish (χ^2 15.4; $P = 0.018$), soy (χ^2 16.6; $P = 0.0009$), and olive oil (χ^2 8.6; $P = 0.035$) and higher intake of white meat (χ^2 19.4; $P = 0.0002$) and cooked (χ^2 7.8; $P = 0.049$) and raw vegetables (χ^2 28.9; $P < 0.0001$) than controls.

FAMI Mediterranean Diet Score

The whole study population was divided into quintiles based on the FAMI MD Score. Figure 1 shows the percentage distribution of European (panel A) and Chinese (panel B) patients with STEMI and controls by the FAMI MD Score quintiles.

The prevalence of patients with STEMI tended to be significantly lower with the increasing quintiles of Mediterranean diet adherence ($P = 0.0002$) in the European population only (Fig. 1, panel A). Conversely, in the Chinese population (Fig. 1, panel B), no significant differences in the proportion of STEMI and controls were identified across FAMI MD Score quintiles ($P = 0.751$).

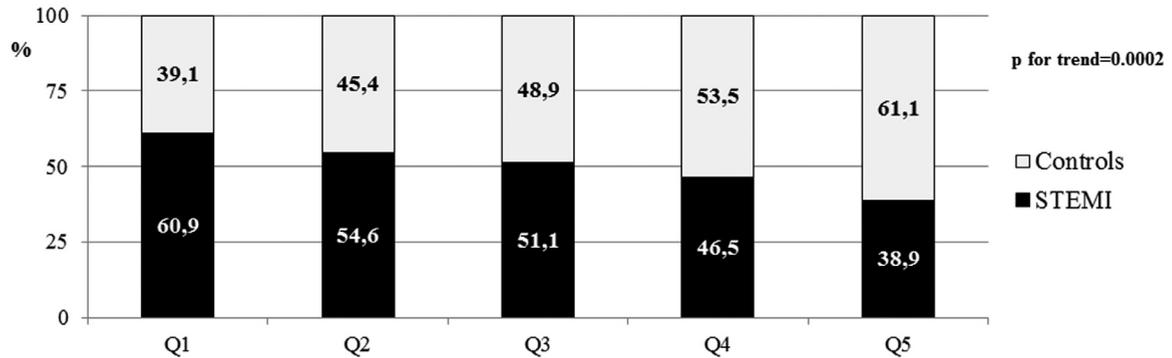
In the European population a progressive reduction of risk of STEMI occurrence was identified across increasing quintiles of FAMI MD Score (odds ratio [95% confidence interval] fifth quintile FAMI MD Score versus first quintile FAMI MD Score: 0.41 [0.27–0.6], $P < 0.0001$) (Table 3).

The two groups at the extremes of the FAMI MD Score distribution (≤ 25 th and ≥ 75 th percentile) were analyzed against the reference group within the 25th to 75th percentiles of the score. Compared with the reference group, individuals at the lower extreme of FAMI MD Score (≤ 25 th) exhibited 1.5-fold increase in the risk for STEMI, whereas participants with a FAMI MD Score > 75 th percentile had a reduction of 37% of the risk of STEMI (Table 3).

In the European population, consumption of at least four servings of fruits and vegetables per day was associated with a significant reduction of STEMI risk (odds ratio [95% confidence interval] 0.59 [0.45–0.78]; $P < 0.0001$) (Table 3).

Finally, multivariate logistic regression analysis indicated that both the MD FAMI Score and the consumption of fruits and vegetables were significantly associated with the risk of first STEMI independently of the risk factor profile assessed by the ATP-III/FRS model (Fig. 2 and Table 3).

A. EUROPE



B. CHINA

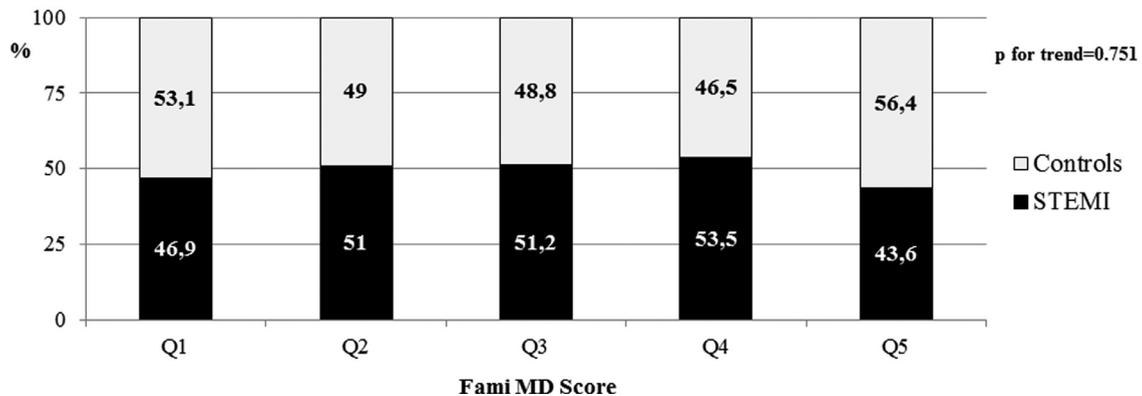


Fig. 1. The percentage distribution of case and controls according to FAMI MD Score in European (panel A) and Chinese (panel B) population. Among the European population, the prevalence of STEMI indicates a statistically significant reduction as FAMI MD Score increases.

No significant association between STEMI prevalence and FAMI MD Score emerged in the Chinese population. MD, Mediterranean Diet, STEMI, ST-elevation myocardial infarction.

Table 3

Association among Mediterranean diet, fruit and vegetable (F&V) consumption, and risk of acute myocardial infarction in the European population

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
FAMI MDS quintiles						
1	Ref.			Ref.		
2	0.77	0.48–1.26	0.3	0.78	0.47–1.31	0.35
3	0.67	0.45–1.0	0.05	0.67	0.43–1.02	0.06
4	0.56	0.37–0.85	0.0063	0.52	0.33–0.80	0.0031
5	0.41	0.27–0.6	<0.0001	0.36	0.24–0.55	<0.0001
FAMI MDS						
25th–75th percentiles	Ref.			Ref.		
<25th	1.46	1.03–2.06	0.033	1.47	1.03–2.14	0.033
≥75th	0.63	0.46–0.86	0.0035	0.58	0.41–0.81	0.0012
F&V consumption						
<4 times/d	Ref.			Ref.		
≥4 times/d	0.59	0.45–0.78	0.0002	0.55	0.42–0.74	<0.0001

CI, confidence interval; MDS, Mediterranean Diet Score; OR, odds ratio

Discussion

In this case-control study we investigated the relationship between dietary habits and adherence to the Mediterranean diet and the risk of first STEMI in European and Chinese populations.

In the European population, patients with STEMI had significantly lower adherence to the Mediterranean diet and lower consumption of fruit and vegetable compared with controls. The

effects of the Mediterranean diet on the occurrence of STEMI were more evident in European than in Chinese population, possibly because of differences in dietary and daily living habits between these two ethnic groups.

In the European population the results of our study identified a correlation between an increasing FAMI MD score and a reducing risk of STEMI, thus confirming the protective role of the Mediterranean diet on acute myocardial infarction. Interestingly, traditional cardiovascular risk factors, assessed by ATP-III/FRS, did not influence

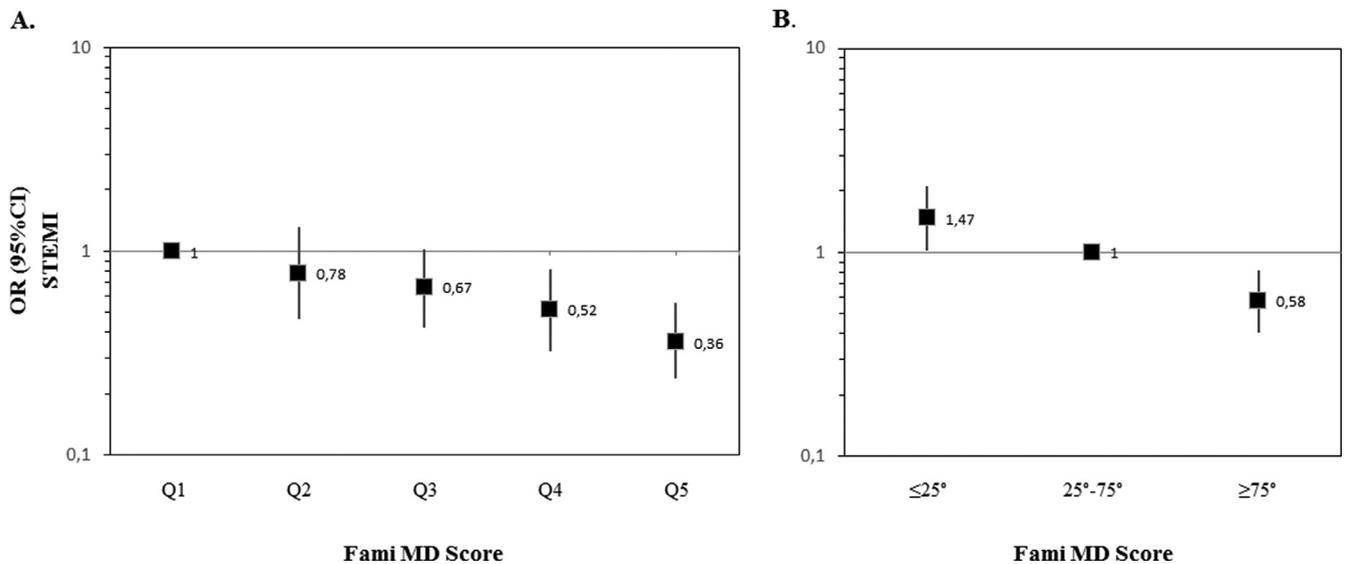


Fig. 2. Among European population, the risk of first STEMI according to quintiles of FAMI MD Score (panel A) and the risk of first STEMI at the extremes of the FAMI MD Score distribution (≤ 25 th and ≥ 75 th percentiles) against the reference group within the 25th to 75th percentiles of the FAMI MD Score (panel B). CI, confidence interval; MD, Mediterranean Diet; OR, odds ratio; Q, quarter; STEMI, ST-elevation myocardial infarction.

the effects of dietary habits, as indicated by the similar odd ratios resulted from the univariate and multivariate analyses.

In previous observational and secondary prevention studies, adherence to the Mediterranean diet had important benefits in cardiovascular prevention to be protective against CHD [15,16]. In the PREDIMED study the energy-unrestricted Mediterranean diet supplemented with either extra-virgin olive oil or nuts reduced the absolute risk of three major cardiovascular events in 1000 person-years [17]. The risk of stroke was consistently reduced in both enriched Mediterranean diets, which could explain the lower cardiovascular mortality in Mediterranean countries compared with Northern European countries and the United States [17]. Higher survival rates have been associated to specific characteristics of the Mediterranean diet, including moderate consumption of ethanol (mostly from wine), low consumption of meat and meat products, and high consumption of vegetables, fruits, nuts, legumes, fish, and olive oil [18–20]. The food frequency questionnaire used in this study gathered similar information. Therefore, although further prospective studies are necessary to validate this tool, the FAMI MD Score seems useful to identify patients who are at higher risk for cardiovascular disease and who may benefit from educational programs on improving dietary habits.

In this study the effect of the Mediterranean diet was less relevant in the Chinese population, and no association was identified between the risk for STEMI and FAMI MD Score. The unusual distribution of the main types of food suggests that the questions and the structure of our questionnaire were not effective to investigate Chinese dietary habits and the relationship with cardiovascular risk. Nonetheless, we confirmed that the consumption of fruit and vegetable, rice, fish, and white meat also reduced the cardiovascular risk in this population.

Over the past decade, along with rapid economic growth and social changes, the traditional diet of the Chinese population has remarkably changed: Grain intake has decreased, whereas fat intake has dramatically increased; moreover, daily intake of salt is currently much higher than that recommended, and intake of fruit and vegetable is insufficient [21]. The imbalances in dietary intake may explain the increased morbidity and mortality from diabetes, hypertension, dyslipidemia, and cardiovascular diseases recently reported in China [22,23]. The main differences in nutrient intake

between Chinese and Mediterranean populations are lower daily intakes of fibers, calcium, phosphorus, potassium, selenium, vitamin A, vitamin B1, vitamin B2, and vitamin C in the Chinese diet compared with the Mediterranean diet [24]. These nutrients are involved in many processes, including inflammation [25,26], LDL oxidation [27], and endothelial function [26]. Therefore their high content in the Mediterranean diet may at least partially explain its protective role in atherosclerosis and cardiovascular disease.

The study has some limitations. First, the study population was recruited between 2002 and 2007, and in the last decade dietary habits may be changed both in European and Chinese population. Second, one questionnaire was used for all participants, and it was not able to effectively describe Chinese dietary habits. In this population the distribution of food frequency intake was not uniform, and it was difficult to generalize the impact of the Mediterranean Score in the Chinese population.

Conclusions

The food frequency intake questionnaire was a valuable tool to identify patients at potential risk of cardiovascular disease. The study confirmed that the Mediterranean diet had a protective effect on the risk of first acute myocardial infarction in the European population, independently of traditional cardiovascular risk factors.

Acknowledgments

The authors thank Elisa Sala, Ph.D., professional medical writer, for her medical editorial assistance with our report.

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