

# Primary prevention of acute coronary events through the adoption of a Mediterranean-style diet

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الوقاية الأولية من الأمراض القلبية التاجية الحادة بالالتزام بنظام غذائي لمنطقة البحر المتوسط  
ديوسثينيس باناغيويتاكوس، كريستوس بتسافوس، كريستين خريسو، كريستودولوس ستيفاناديس،  
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**الخلاصة:** تم تقييم دور نظام غذائي متبع في منطقة البحر المتوسط في الوقاية من المتلازمات القلبية التاجية الحادة. وتم استخدام معطيات من الدراسة المعروفة باسم CARDIO 2000، وهي دراسة استيعابية للحالات مضبوطة بالشواهد شاركت فيها عدة مراكز بحثية لاستقصاء الارتباط بين المتلازمات القلبية التاجية الحادة من جهة، وبين العوامل الديموغرافية والتغذية والعوامل المتعلقة بنمط الحياة والمخاطر الطبية من جهة أخرى. وتمت دراسة 661 مريضاً أدخلوا المستشفى نتيجة للظهور الأول لمتلازمة تاجية حادة، مع استخدام 661 مريضاً آخرين كشواهد لا تظهر عليهم علامات سريرية يشتبه معها في إصابتهم بأمراض قلبية وعائية. ودلت النتائج على أن النظام الغذائي المتبع في بلدان البحر المتوسط يقلل مخاطر حدوث المتلازمات التاجية الحادة بنسبة 16%. ويظل الارتباط قوياً في حالة وجود فرط ضغط الدم، أو فرط كوليسترول الدم، أو نمط الحياة الخالية من النشاط، أو مرض السكري، أو مزيج من اثنين أو أكثر من عوامل الاختطار القلبية الوعائية هذه. وتبين نتائج الدراسة أهمية اتباع النمط الغذائي المتوسطي في الوقاية الأولية من الحالات التاجية الحادة.

**ABSTRACT** We evaluated the role of a Mediterranean-style diet in preventing acute coronary syndromes (ACS). Data from CARDIO2000, a multi-centre retrospective case-control study investigating the association between ACS and demographic, nutritional, lifestyle and medical risk factors were used. We studied 661 patients hospitalized for a first ACS event and 661 matched controls without clinical suspicion of cardiovascular disease. The Mediterranean diet significantly reduced (by 16%) the risk of developing ACS. The association remained significant in the presence of hypertension, hypercholesterolaemia, sedentary lifestyle, diabetes mellitus or a combination of two of these cardiovascular risk factors. Our findings illustrate the importance of the Mediterranean diet in the primary prevention of acute coronary events.

## Prévention primaire des événements coronaires aigus par l'adoption d'un régime alimentaire de type méditerranéen

**RESUME** Nous avons évalué le rôle d'un régime alimentaire de type méditerranéen dans la prévention des syndromes coronariens aigus. Les données de CARDIO2000, une étude cas-témoins rétrospective, multicentrique examinant l'association entre les syndromes coronariens aigus et des facteurs de risque démographiques, nutritionnels, médicaux et liés aux modes de vie, ont été utilisées. Nous avons étudié 661 patients hospitalisés pour un premier événement lié à un syndrome coronarien aigu et 661 témoins appariés sans suspicion clinique de maladie cardio-vasculaire. Le régime méditerranéen réduit significativement (de 16 %) le risque de survenue des syndromes coronariens aigus. L'association demeure significative en présence d'hypertension, d'hypercholestérolémie, de sédentarité, de diabète sucré ou d'une combinaison de deux de ces facteurs de risque cardio-vasculaire. Nos conclusions montrent l'importance du mode d'alimentation méditerranéen dans la prévention primaire des événements coronariens aigus.

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## Introduction

There is extensive scientific evidence of the association between diet and incidence of coronary heart disease, various types of cancer and other diseases [1-4]. Dietary factors exert their influence largely through their effect on blood lipids and lipoproteins, as well as on other established modifiable risk factors, with the exception of cigarette smoking [2,3]. Based on the results of the Seven Countries Study of the early 1970s [1] and the Lyon Diet Heart Study of the late 1990s [2], many investigators have recognized the beneficial role of a Mediterranean-style diet (Mediterranean diet) in cardiovascular diseases, metabolic disorders and several types of cancer [2,3,5-7].

The effects of a Greek-style Mediterranean diet on overall mortality or morbidity have been evaluated using the results of the Seven Countries Study (which included two rural male populations from Crete and Corfu) or other local studies (including sub-groups from rural and urban Greek areas) [3,8,9]. However, due principally to the small number of enrolled subjects, these latter studies lacked the power to clarify the relationship between a Mediterranean diet and the risk of acute coronary syndromes.

We evaluated whether the adoption of a Mediterranean diet was associated with a reduction in the risk of developing acute coronary syndromes, independent of the conventional cardiovascular risk factors. Stratified, random sampling from all Greek regions ensured representation of various cultural, socioeconomic and behavioural characteristics that clustered in the population and might have influenced the results.

## Methods

The CARDIO2000 was a multicentre retrospective case-control study that investigat-

ed the association between several demographic, nutritional, lifestyle and medical risk factors with the risk of developing acute coronary syndromes. From January 2000 to March 2001, 661 cardiac patients and 661 hospitalized controls without any past or present clinical symptoms or suspicions of cardiovascular disease were enrolled in the study. This number of subjects was used to give the study sufficient power to evaluate differences in coronary risk  $> 7\%$  (statistical power  $> 0.80$ ; significance level,  $P < 0.05$ ).

In order to reduce any unbalanced distribution of measured or unmeasured confounders, patients and controls were randomly selected. A sequence of random numbers (1 or 0) was applied to hospital admission listings. Coronary patients assigned a '1' were enrolled in the study. The same procedure was used for controls, after taking into account matching criteria. Only patients hospitalized for an acute first event of coronary heart disease (acute myocardial infarction or unstable angina) were eligible as cases. Stable angina patients were excluded. Specific inclusion criteria for cardiac patients were a first event of acute myocardial infarction diagnosed by two or all of typical electrocardiographic changes, compatible clinical symptoms or specific diagnostic enzyme elevations or by unstable angina, not previously diagnosed, corresponding to class III of the Braunwald classification.

For each patient, a control was randomly selected from hospitalized patients without any clinical symptoms and signs or suspicions of cardiovascular disease in their medical history. Controls were matched to cases by age ( $\pm 3$  years), sex and region. Controls were drawn mainly from patients in surgical clinics (urology, ophthalmology or orthopaedic clinics). They attended, as far as possible, the same

hospital at the same time as the coronary cases. In a few cases, particularly in country hospitals, where the available number of hospitalized controls was insufficient for the matching procedure, we enrolled into the study friends or colleagues of the coronary patients. We used hospitalized controls to obtain more accurate medical information, to eliminate the potential adverse effect of several unknown confounders, to increase the likelihood that cases and controls would share the same study base and to reduce the problem of misclassification [5]. Medical information was retrieved through hospital or insurance records. Demographic and lifestyle data were obtained through a confidential questionnaire that included structured questions concerning lifestyle habits and sociodemographic background factors. Interviews took place after the third day of hospitalization. The same physicians who took the medical history and gave the physical examination also evaluated the controls.

Hypertension was defined by systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or by special anti-hypertensive medication [6]. Hypercholesterolaemia was defined as cholesterol levels > 220 mg/dL [6] and diabetes as glucose concentrations greater than 125 mg/dL. Body mass index (BMI) was calculated at entrance by dividing the subject's weight by height squared ( $\text{kg/m}^2$ ). According to the collected medical records, the majority of controls (78%) and patients (72%) had at least one laboratory measurement during the past 12 months. In addition, we took total cholesterol and blood glucose measurements during the first 12 hours of hospitalization. Quantification of smoking status was based on the calculation of pack years adjusted for nicotine content equal to 0.8 mg per cigarette. The

physically active were defined as those who reported engaging in non-occupational physical activity more than once per week. The rest were considered physically inactive, i.e. leading a sedentary lifestyle.

At least 16 countries that border the Mediterranean Sea can be defined as 'Mediterranean' countries. Between these populations, many cultural, ethnic, religious, economic and agricultural differences may exist, resulting in different dietary habits and precluding a single definition of a 'Mediterranean diet'. The evaluation of nutritional habits was based on guidelines from the Department of Nutrition of the National School of Public Health [8]. In particular, we investigated the average consumption during the past year of red meat, chicken, fish, vegetables, legumes, pasta, salads, cereals, dairy products, sweets and fruits. For each of the fourteen food items, the frequency of consumption was quantified approximately in terms of the number of times per month the food was consumed [9]. Thus, weekly consumption was multiplied by a factor of 4 and a value of 0 was assigned to food items rarely or never consumed. In order to perform an objective assessment of nutritional characteristics, food frequencies were calculated as quantities (g/day) on the basis of standard portion size estimations [9].

The traditional Mediterranean diet is characterized by olive oil as an important fat source, high intake of fruits, vegetables, bread, other cereals, potatoes, poultry, beans, nuts, fish, little red meat, dairy products and moderate consumption of alcohol. The pattern is based on food patterns typical of many regions in Greece and southern Italy [2,3]. To describe the total diet, we used composite scores, which are necessary for the evaluation of epidemiological associations [9].

The Mediterranean diet can be scored in terms of eight component characteristics:

- high monounsaturated to saturated fat ratio;
- high consumption of legumes;
- high consumption cereals (including bread and potatoes);
- high consumption of fruits;
- high consumption of vegetables;
- moderate consumption of ethanol;
- low consumption of red meat products;
- low consumption of dairy products.

We defined subjects as consumers of this type of diet by using as cut-off points the median values of the monthly food consumption score [9]. Finally, alcohol consumption was measured by daily ethanol intake in wine glasses (100 cc, 12% ethanol).

Continuous variables are presented as mean values  $\pm$  one standard deviation, while qualitative variables are presented as absolute and relative frequencies. The Pearson correlation coefficient was applied to measure associations between the continuous variables. Contingency tables with calculation of chi-squared test and application of Student *t*-test evaluated associations between categorical and continuous variables. The chi-squared test for homogeneity was applied to check differences within the investigated groups. Estimation of the relative risks of developing acute coronary syndromes under several hypotheses was performed by calculating the odds ratio (OR) and corresponding confidence intervals (CI) through multiple conditional logistic regression analysis. A final model was developed through stepwise elimination procedures for the selection of variables, using 5% for the probability for entering a variable and 10% for the probability of removing it from the model. Deviance residuals were used to evaluate the model's

goodness-of-fit [10]. All reported *P*-values are two-sided and have a significance level of 5%. STATA 6 software was used for the calculations (STATA Corp., College Station, Texas, United States of America).

## Results

Table 1 presents subjects' demographic profiles, the prevalence of smoking habit, hypertension, hypercholesterolaemia, obesity, diabetes mellitus and physical activity status. In our study, 393 (59%) coronary patients and 492 (74%) controls were consumers of a Mediterranean diet. Stratified analysis showed that patients and controls from rural areas more commonly consumed the Mediterranean diet than subjects from rural-urban and urban areas (73%–86% versus 54%–72% and 48%–58% respectively,  $P = 0.035$ ). There was no gender difference in either patients or controls (males: 58% versus 62%; females: 73% versus 76%,  $P > 0.7$ ). There was no association between consumption of the diet and income or educational level ( $\chi^2 = 18.67$ ,  $P = 0.465$ ;  $\chi^2 = 19.67$ ,  $P = 0.523$  respectively).

Table 2 shows the effect of the Mediterranean diet on the prevalence of hypertension, hypercholesterolaemia, diabetes mellitus, sedentary life and BMI among the groups of study.

## Multivariate analysis

Adoption of the Mediterranean diet has been shown to be inversely associated with the incidence of acute coronary syndromes and the prevalence of conventional cardiovascular risk factors in both groups in the study. To test the hypothesis that the effect of the Mediterranean diet on coronary risk is independent of other risk factors, we developed multivariate risk models, adjusted for sex, age and region by design, BMI,

**Table 1 Sociodemographic profile and risk factor distribution of the study subjects**

Variable	Subjects (n = 661)		Controls (n = 661)		P-value
	No.	%	No.	%	
<b>Sex</b>					
Males	535	81	535	81	
Females	126	19	126	19	
<b>Income (US\$)</b>					
Low (< 4750)	29	4	12	2	0.045
Moderate (4750–8500)	356	54	285	43	
Good (8500–14 500)	260	39	345	52	
Very good (> 14 500)	16	2	19	3	
<b>Education</b>					
None—primary school	169	26	160	24	0.002
High school or technical institute	235	36	188	28	
Senior high or college	181	27	202	31	
University	76	11	111	17	
<b>Residence</b>					
Urban	345	52	343	52	
Rural—urban	191	29	190	29	
Rural	125	19	128	19	
<b>Current smoking</b>					
	443	67	271	41	0.023
<b>Other conventional risk factors</b>					
Hypertension	322	49	148	22	0.009
Hypercholesterolaemia	397	60	191	29	0.011
Obesity	245	37	190	29	0.002
Diabetes mellitus	171	26	35	5	0.003
Sedentary lifestyle	450	68	374	57	0.034

The mean age  $\pm$  standard deviation for male subjects and controls was  $56.4 \pm 3$  years and  $55.8 \pm 21$  years respectively ( $P = 0.841$ ).

The mean age  $\pm$  standard deviation for female subjects and controls was  $65.3 \pm 2$  years and  $66.2 \pm 3$  years respectively ( $P = 0.712$ ).

Mean number of pack years  $\pm$  standard deviation among the subjects and controls was  $44 \pm 11$  and  $31 \pm 13$  respectively ( $P = 0.010$ ).

physical activity level, smoking habit, blood pressure and cholesterol levels. Consuming a Mediterranean diet led to an adjusted 23% reduction of coronary risk (OR = 0.77, 95% CI: 0.69–0.85,  $P = 0.003$ ). However, stratifying our analysis by region (rural, rural-urban and urban), we found significant

differences in the estimated OR ( $F$ -test = 4.59,  $P = 0.012$ ). Thus, the corrected OR was equal to 0.84 (95% CI: 0.73–0.96,  $P = 0.041$ ).

Further analysis showed that adoption of the Mediterranean diet was associated with a reduction in the risk of developing

**Table 2 Assessment of body mass, hypercholesterolaemia, hypertension, sedentary lifestyle and diabetes mellitus by group of diet and group of study**

Variable	Subjects (n = 661) Mediterranean diet				Controls (n = 661) Mediterranean diet				P-value*
	Yes (n = 393)		No (n = 268)		Yes (n = 492)		No (n = 169)		
	No.	%	No.	%	No.	%	No.	%	
Age (years)	61.1 ± 9		53.2 ± 11 <sup>b</sup>		62.3 ± 10		53.4 ± 11 <sup>b</sup>		Not significant
Hypercholesterolaemia	192	48	205	76 <sup>c</sup>	118	24	73	43 <sup>c</sup>	< 0.001
Hypertension	154	39	168	62 <sup>c</sup>	101	21	47	28 <sup>b</sup>	< 0.001
Diabetes mellitus	73	19	98	36 <sup>c</sup>	21	4	14	8 <sup>b</sup>	< 0.001
Sedentary life	196	50	254	94 <sup>c</sup>	234	48	140	83 <sup>c</sup>	0.542
Body mass index (kg/m <sup>2</sup> )	26.4 ± 3.3		27.8 ± 2.6 <sup>c</sup>		25.3 ± 3.8		26.2 ± 3.2 <sup>c</sup>		< 0.001
Smoking (pack years)	44 ± 11		43 ± 10		32 ± 13		31 ± 10		< 0.001

\*Comparisons between groups of study, in subjects who adopted the Mediterranean-type diet.

<sup>b</sup>Significant differences at 5% level, within groups of study, between subjects who adopted or did not adopt the Mediterranean-type diet.

<sup>c</sup>Significant differences at 1% level, within groups of study, between subjects who adopted or did not adopt the Mediterranean-type diet.

acute coronary syndromes in the presence of several unhealthy conditions such as hypertension, hypercholesterolaemia, diabetes mellitus and sedentary lifestyle. Conversely, in current smokers, adoption of the Mediterranean diet did not significantly influence coronary risk. Further, in the presence of a combination of three or more risk factors, the effect of Mediterranean diet lost its significance.

## Discussion

In this study, we evaluated the effect of the Mediterranean diet on the risk of developing acute coronary syndromes. Coronary patients and controls that consistently consumed this type of diet had a lower prevalence of hypertension, hypercholesterolaemia and diabetes mellitus and had lower BMI (Table 1). These findings may partially explain the beneficial effect of diet on car-

diovascular disease. However, multivariate analysis, after taking into account the presence of the aforementioned risk factors, provided evidence that an *a priori* defined nutritional pattern, i.e. the Mediterranean diet, favourably affected coronary risk, independent of the presence of several cardiovascular risk factors (Figures 1 and 2).

World Health Organization mortality statistics have documented the long survival of people in southern European Mediterranean countries despite a high prevalence of smoking and gaps in available health services [11]. Many investigators have attributed this outcome to several cultural and behavioural differences between the populations, including nutritional particularities, to provide a plausible explanation for what is widely considered an 'ecological paradox' [9]. Based on the results of the Seven Countries study in the late 1970s [1,3,10-13], the protective role of the Mediterra-

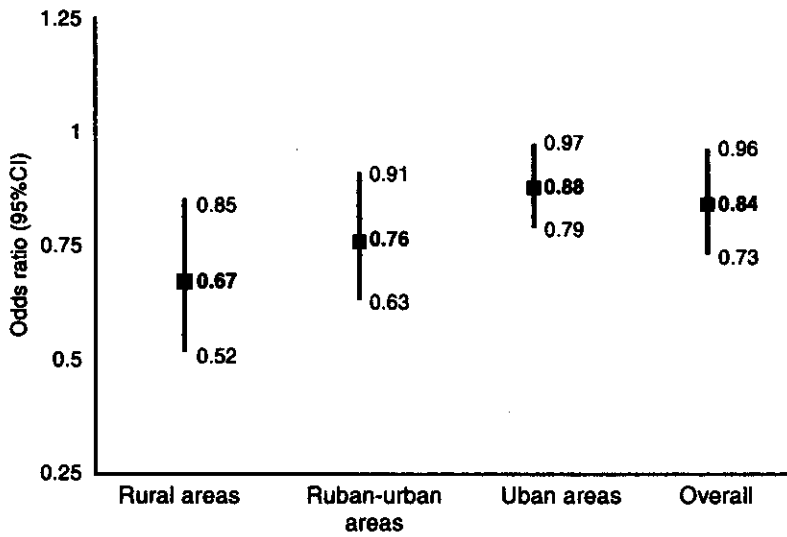


Figure 1 The adjusted effect of the adoption of a Mediterranean-type diet on the risk of developing acute coronary syndromes by type of region (*P*-value for the test of homogeneity = 0.012)

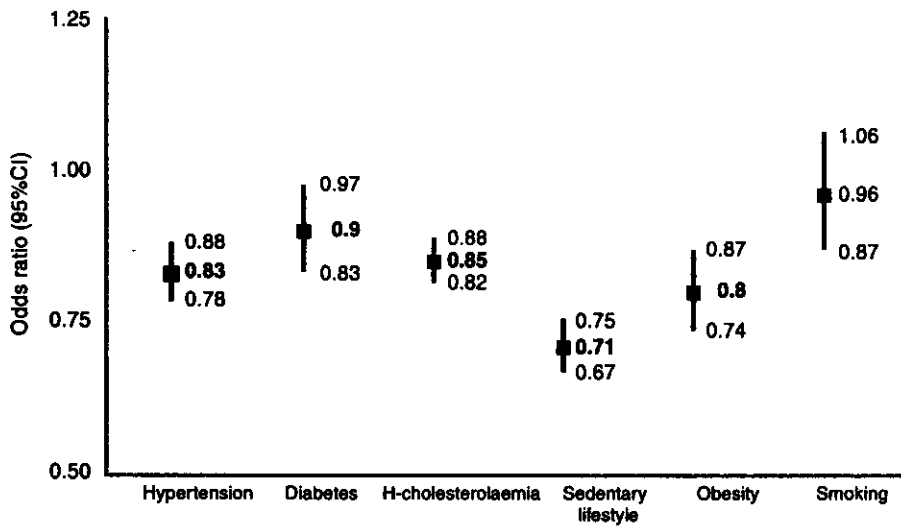


Figure 2 The effect of the adoption of Mediterranean diet on the risk of developing acute coronary syndromes (adjusted for the conventional risk factors) in hypertensive, diabetic, hypercholesterolaemic, physically inactive, obese and smoker subjects

nean diet against atherosclerosis has been partially explained by lower cholesterol and blood pressure levels. Similar results were observed in the present study, where subjects who had adopted this type of diet were observed to have a lower BMI and lower blood glucose concentrations. Recent findings of the Lyon Diet Heart Study highlight the potential importance of the Mediterranean dietary pattern within the context of the American Heart Association (AHA) Step I diet, compared to other recommended diets [2,14]. The Lyon study concluded that subjects who consumed a Mediterranean diet had a 50%–70% lower risk of recurrent heart disease, compared to those who followed a diet similar to the AHA Step I diet [2,11]. These results accord with results from the Seven Countries study [1,14,15], the Italian Nine Communities study [16] and from studies involving Finnish [17] and Scottish groups [18]. All confirm a plausible pathway by which diet might influence coronary risk.

The Greek type of Mediterranean diet is low in saturated fat, high in monounsaturated fat (mainly from olive oil), high in complex carbohydrates from legumes and high in fibre, mostly from vegetables and fruits. Total fat intake may be high (about 40% of total energy intake), but the monounsaturated:saturated fat ratio is around 2. Daily foods include large quantities of bread, pasta, legumes, vegetables, cooked meals, soups and salads rich in olive oil. Intake of milk is rather low, but the consumption of feta cheese and yoghurt is high. Also, people prefer to consume fish rather than meat, especially in the rural and rural-urban areas. The high content of vegetables, fresh fruits, cereals and olive oil guarantee a high intake of beta-carotene, vitamins C and E, polyphenols and various important minerals. Finally, wine is consumed in moderation and almost always

during meals [9,11–13]. According to several investigators, these are the key elements responsible for the beneficial effects of diet on human health [1–3,9]. Others believe that the effect of the Mediterranean diet on coronary risk may be explained through a number of confounders, such as geographic and other non-measured cultural and social differences of the particular populations under study [19].

Our study showed an association between the Mediterranean diet and a lower prevalence of the conventional cardiovascular risk factors (with the exception of smoking) in both subjects and controls. However, after taking into account the effect of these risk factors and the confounding effect of region (probably due to several cultural, behavioural and psychosocial differences between the investigated areas), we found that subjects who consumed a Mediterranean diet had a 16% ( $P < 0.01$ ) lower risk of developing acute coronary syndromes compared to those that did not. In addition, the effect of diet on coronary risk was associated with 10%–24% lower coronary risk in the presence of several cardiovascular risk factors (Figures 2 and 3). An association between diet and coronary risk independent of conventional risk factors needs further investigation. In recent years, there have been attempts to understand the Mediterranean diet in relation to emerging cardiovascular risk factors such as thrombogenic factors (i.e. fibrinogen levels), homocysteine, elevated serum triglycerides and low-density lipoprotein cholesterol. The diet has also been associated with an improvement in endothelial function, decreased inflammation, decreased oxidation of lipids and improved insulin resistance [4,16,17,21]. Clearly, to provide causal evidence much remains to be learned about the biological mechanisms underlying these associations.



In summary, the present study, in addition to confirming the previously established relationship between diet and conventional cardiovascular risk factors, raises the issue of an independent association between the Mediterranean diet and lower risk of acute coronary syndromes. Prospective studies are needed in order to confirm our findings by identifying the factors, i.e. the pathway, by which Mediterranean diet and olive oil are associated with lower coronary risk.

### Limitations of the study

In this type of study, two main errors may occur: selection and recall bias. To eliminate selection bias, we sought to set objective criteria for both patients and controls. To minimize recall bias, we made use of detailed data from patients' medical records. However, recall bias may still exist, especially in the measurement of nutritional habits, smoking and the onset of cardiovascular risk factors. We sought to minimize the potential effect of uncon-

trolled or unknown confounders through multivariate analysis and by using the same study base for patients and controls.

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