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Can a Mediterranean diet moderate the development and clinical progression of coronary heart disease? A systematic review

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Summary

Background:

It has been suggested that adherence to a Mediterranean diet reduces all causes of mortality, especially death rates due to coronary heart disease. In this review we summarize the findings of observational studies that evaluated the effect of the Mediterranean dietary pattern in the primary and secondary prevention of coronary heart disease.

Matreial/Methods:

We retrieved published results from prospective and case-control studies which evaluated the association between adherence to a Mediterranean diet and the occurrence of coronary heart disease outcomes.

Results:

The benefits from the Mediterranean diet were significant in all studies. The reduction in the risk of coronary heart disease varied from 8% to 45%, depending on the increment used by the investigators in the presentation of their results.

Conclusions:

The systematically reviewed studies reveal a cardio-protective effect of the Mediterranean diet and point to this dietary pattern as highly appropriate for public health objectives.

key words:

risk • coronary heart disease • Mediterranean diet • olive oil

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BACKGROUND

There is increasing scientific evidence that there are protective health effects from diets which are high in fruits, vegetables, legumes, and whole grains and which include fish, nuts, and low-fat dairy products. Such diets need not be restricted in total lipid intake as long as there is no excess of energy intake over expenditure and vegetable oils are emphasized that are low in saturated fats and partially hydrogenated oils [1]. The traditional Mediterranean diet, whose principal source of dietary lipids ("fat") is olive oil, encompasses these dietary characteristics [2]. During the past decades a large body of evidence has related adherence to a Mediterranean diet to all causes mortality as well as incidence of coronary heart disease and some types of cancer [3–5].

What is the Mediterranean diet?

Although different regions in the Mediterranean basin have their own diets, it is legitimate to consider these as variants of a single entity, the Mediterranean diet. Indeed, the dietary patterns that prevail in the Mediterranean region have many common characteristics, most of which stem from the fact that olive oil occupies a central position in all of them. Olive oil is important not only just because it has several beneficial properties, but also because it allows the consumption of large quantities of vegetables in the form of salads and equally large quantities of legumes in the form of cooked foods. Thus, it might be convenient, if not wholly accurate, to define the Mediterranean diet as the dietary pattern found in the olive-growing areas of the Mediterranean region in the late 1950s and early 1960s, when the consequences of World War II had been overcome, but the fast-food culture had not yet invaded the area. Other essential components of the Mediterranean diet are wheat, olives, and grapes, and their various derivative products. Total lipid intake may be high, as in Greece (around or in excess of 40% of total energy intake), or moderate, as in Italy (around 30% of total energy intake). In all instances, however, the ratio of monounsaturated to saturated fats is much higher than in other places of the world, including northern Europe and North America. The Italian variant of the Mediterranean diet is characterized by a higher consumption of pasta, whereas in Spain, fish consumption is particularly high.

The traditional Mediterranean diet, and in particular the Greek version of it, may be thought of as having 9 components [6]: a high consumption of olive oil, legumes, cereals, fruits, and vegetables; a moderate to high consumption of fish; a moderate consumption of wine, dairy products, mostly as cheese and yogurt; and a low consumption of meat and meat products. In particular, this dietary pattern implies: (a) daily consumption of unrefined cereals and cereal products (whole grain bread, pasta, brown rice, etc.), vegetables (2–3 servings/day), fruits (4–6 servings/day), olive oil (as the main added lipid), and nonfat or low-fat dairy products (1–2 servings/day), (b) weekly consumption of potatoes (4–5 servings/week), fish (4–5 servings/week), olives, pulses, and nuts (>4 servings/week), and, more rarely, poultry (1–3 servings/week), and eggs and sweets (1–3 servings/week), and (c) monthly consumption of red meat and

meat products (4–5 servings/month). It is also characterized by a moderate consumption of wine (1–2 wineglasses/day) and a high monounsaturated-to-saturated fat ratio (>2). In addition, although the intake of milk is moderate, the consumption of cheese and yogurt is relatively high. Feta cheese is regularly added to salads and accompanies vegetable stews. The high content in the diet of vegetables, fresh fruits, and cereals, and the liberal use of olive oil guarantee an adequate intake of β -carotene, vitamin C, tocopherols, α -linolenic acid, various important minerals, and several possibly beneficial non-nutrient substances such as polyphenols and anthocyanines. Wine is consumed in moderation and almost always during meals. This diet is low in saturated fat (less than about 9% of energy), with total lipid intake ranging from less than 30 to more than 40% of energy from one area to another. The monounsaturated-to-saturated fat ratio is greater than two [2]. It has become customary to represent the Mediterranean diet in the form of a triangle ("pyramid"), the base of which refers to foods which are to be consumed most frequently and the top to those to be consumed rarely, with the remaining foods occupying intermediate positions (Figure 1).

Epidemiological data regarding mortality statistics provided evidence that something unusual was favorably affecting the health status of Mediterranean populations. Although health care for many of the Mediterranean populations has been inferior to that of the northern European and North American populations, and the prevalence of smoking is high in the Mediterranean region, the death rates in this region tend to be lower than in many economically more developed countries [7]. Mediterranean populations, Greeks and Italians in particular, have been reported to have long life expectancies and among the lowest overall mortality rates. Results from the Seven Countries Study confirmed that the two Greek and the three Italian cohorts had the lowest death rates from all causes from among the European and US cohorts in the study [8]. Results from the 25-year follow-up of the Seven Countries Study indicate that the occurrence of cardiovascular disease was much lower in southern European countries than in northern European countries [9]. WHO statistics indicate that the standardized mortality rates from heart disease varies from 180 to 270 per 100,000 people from 1970 to 1995 in the United Kingdom, and from 50 to 100 per 100,000 people in Greece and Italy [7]. Although ecological interpretations of these data are beset by difficulties, a potential explanation of the lower cardiovascular mortality rates among Mediterranean populations is their traditional diet.

In this systematic review we summarize the findings from six observational studies evaluating the effect of the Mediterranean dietary pattern in the primary or secondary prevention of coronary heart disease.

MATERIAL AND METHODS

We studied the results from six observational studies (two prospective, one case-control, and three sub-studies). The criteria for the selection of these studies were: (i) the assessment of the Mediterranean diet should be based on the recent Nutrition Guidelines of the Greek Ministry of Health [6] or the diet pyramid presented by Willett and colleagues

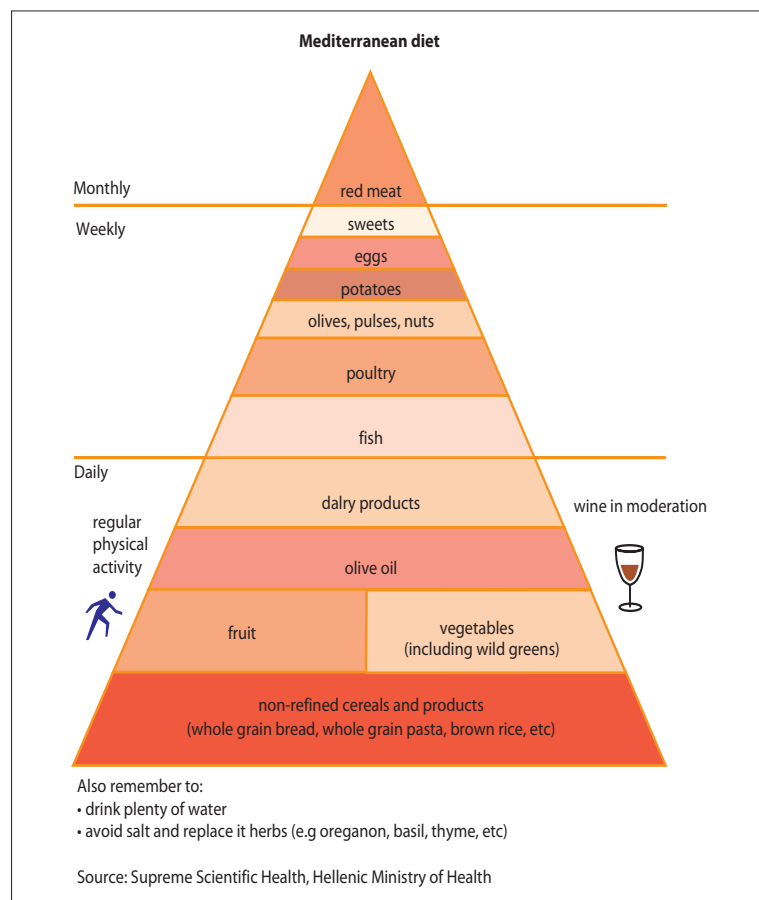


Figure 1. The traditional Mediterranean diet pyramid.

es [10]; (ii) the outcome in all these studies was the occurrence of coronary heart disease [11]; and (iii) the measurements of the effect (odds ratio, relative risk or rate ratio) of the diet on coronary heart disease, as well as their 95% confidence intervals, should be available in the abstract or the text of these articles. Thus we collected published information from: (a) the Seven Countries Study [2], which prospectively followed up 12763 men aged 40–59 from seven countries (Greece, Italy, the Netherlands, Finland, former Yugoslavia, Japan, and the United States of America) since the early 1960s; (b) the CARDIO2000 study [12], which studied 661 patients with a first event of an acute coronary syndrome and 661 age- and sex-matched controls from various areas of Greece. Sub-studies of the previous study included: (c) hypertensive [13], (d) hypercholesterolemic patients [14], and (e) people with the metabolic syndrome [15]. We also studied (f) a Greek prospective study [16] that enrolled 22043 middle-aged men and women and followed them for 44 months; and (g) a case-control study [17] that included 171 patients who suffered their first acute myocardial infarction and 171 matched controls. Although the ascertainment of the adoption of a Mediterranean diet differed among studies, a common dietary pattern as described by either the Nutrition Guidelines of the Greek Ministry of Health [6] or Willett and colleagues [10] was assessed in all studies.

The effect measurements are presented as rate ratios, relative risks, or odds ratios (and 95% confidence intervals), depending on the study's design.

RESULTS

The Seven Countries Study [2] represents a major investigation contributing to the knowledge about the benefits of the Mediterranean diet on mortality. The Study's investigators (based on the two Greek cohorts of Corfu and Crete) reported that the protective role of the Mediterranean diet against atherosclerosis was partially explained due to the reduction in blood pressure levels. Moreover, at the end of the 25-year follow-up, the same investigators showed that differences in mortality from coronary heart disease rates among the 16 cohorts of the study were strongly associated with population differences in the intake of saturated fatty acids and flavonoids [8]. However, to the best of our knowledge there is no data available from this study as regards the total risk reduction that the adoption of this diet may impart for cardiovascular disease.

The CARDIO2000 investigators studied a sample of 661 middle-aged patients with a first event of myocardial infarction or unstable angina and 661 age- and sex-matched controls from various Greek regions. They reported that the adoption of a Mediterranean diet was related with an adjusted 16% reduction in the risk of developing a first event of acute coronary syndromes [12]. Moreover, in a sub-study of the CARDIO2000 study, and after taking into account the effect of several potential confounders, the investigators reported that the adoption of a Mediterranean diet was associated with a 7% to 10% reduction in coronary risk in treated, untreated, or uncontrolled hypertensive

Table 1. A summary of studies that assessed the effect of Mediterranean diet on coronary heart disease.

Study	Population	Type of study	Outcome	Odds ratio or relative risk
Panagiotakos et al. [12]	661 with ACS and 661 controls	Case - control	First event of ACS	0.84; 0.73–0.96
Pitsavos et al. [13]	534 with ACS and 399 controls with hypercholesterolemia	Case - control	First event of ACS	0.88; 0.82–0.94
Pitsavos et al. [14]	418 with ACS and 303 controls with hypertension	Case - control	First event of ACS	0.92; 0.85–0.98
Pitsavos et al. [15]	307 with ACS and 198 controls with metabolic syndrome	Case - control	First event of ACS	0.64; 0.44–0.95
Trichopoulou et al. [16]	22034 men and women adults	Population based prospective	Fatal CHD	0.67; 0.47–0.94
Martinez-Gonzalez MA et al. [17]	171 with AMI and 171 controls	Case-control	First event of AMI	0.55; 0.42–0.73

ACS – acute coronary syndromes; CHD – coronary heart disease; AMI – acute myocardial infarction

subjects [13]. Furthermore, when the CARDIO2000 investigators studied the group of hypercholesterolemic subjects they found that the adoption of a Mediterranean diet was also associated with a 12% reduction in coronary risk, independent of cholesterol levels and the other cardiovascular factors [14]. Finally, the same investigators [15] reported that adoption of this dietary pattern was associated with a 35% reduction in coronary risk in the sub-group of subjects with metabolic syndrome, after adjusting for age, sex, educational and financial level, and the conventional cardiovascular risk factors.

Recently, in a large prospective survey involving 22043 middle-aged and older adults from Greece, Trichopoulou and colleagues [16] (from the Greek cohort of the EPIC Study) reported that an inverse association with greater adherence to the Mediterranean diet was observed for death due to coronary heart disease. In particular, approximately a 2/9 increment in the Mediterranean diet-score was associated with a 25% reduction in total mortality and a 33% reduction in coronary heart disease mortality. These associations were evident irrespective of sex, smoking status, level of education, body mass index, and level of physical activity. It is notable that the relation between the applied Mediterranean diet-score and mortality was significant among participants 55 years of age or older, but not among younger participants. This association might reflect increasing cumulative exposure to a more healthy diet, i.e. the Mediterranean diet.

Martinez-Gonzalez et al. [17], in a case-control study that included 171 patients and 171 matched controls, quantified the risk reduction of the incidence of myocardial infarction provided by a Mediterranean dietary pattern. The investigators reported that the higher the Mediterranean diet-score, the lower the odds ratio of myocardial infarction (Table 1). Moreover, a significant linear trend between the diet-score and the risk of myocardial infarction was observed after adjustment for the main cardiovascular risk factors. Their data support the hypothesis that the Mediterranean diet was an effective means of reducing the risk of myocardial infarction; however, they propose the exclusion of refined cereals with a high glycemia index as unhealthy elements of this pattern.

Table 1 summarizes the findings from the several observational studies (and sub-studies) that evaluated the effect of the Mediterranean diet on coronary heart disease. At this point it should be mentioned that differences in the effect of the Mediterranean diet depending on the investigated outcome are related to the increment that was used by the investigators in the presentation of their results.

DISCUSSION

The findings support the hypothesis that a Mediterranean diet that emphasizes olive oil, fiber, fruits, vegetables, fish, and alcohol and reduces meat and meat products can be an effective measure for reducing the risk of coronary heart disease. The benefits of the Mediterranean diet were significant in all studies. The reduction in the risk of coronary heart disease varied from study to study, but this also reflects the different increments used, explicitly or implicitly, in these studies. To our knowledge there are no studies that have shown a detrimental or non-significant impact of the Mediterranean diet on cardiovascular disease.

A pathophysiological explanation

The Mediterranean diet is low in saturated fat, high in monounsaturated fat (mainly from olive oil), high in complex carbohydrates (from legumes), and high in fiber (mostly from vegetables and fruits). Total fat may be high ($\approx 40\%$ of total energy intake), but the monounsaturated-to-saturated fat ratio is around 2. The high content of vegetables, fresh fruits, cereals, and olive oil guarantee a high intake of β -carotene, vitamins C and E, polyphenols, and various important minerals. These key elements have been suggested to be responsible for the beneficial effect of diet on human health, and especially cardiovascular disease. Moreover, during the last years many researchers have related the Mediterranean diet with improvements in the blood lipid profile (especially LDL cholesterol and triglycerides), decreased risk of thrombosis (i.e. fibrinogen levels), improvement in endothelial function and insulin resistance, reduction in plasma homocysteine concentrations, and decrease in ventricular irritability [1,18–21].

Furthermore, antioxidants represent a common element in the Mediterranean pattern and antioxidant action provides a plausible explanation for the apparent benefits [21]. It is known that wild edible greens frequently eaten in the form of salads and pies contain very high quantities of flavonoids. Although there is no direct evidence that these antioxidants are central to the benefits of the Mediterranean diet, indirect evidence from epidemiological data and the increasing understanding of their mechanisms of action suggest that antioxidants may play a role.

Ansel Keys, in one of his last reviews [22], admitted that his concern about diet as a public health problem began in the early 1950s, when they observed very low incidences of coronary heart disease associated with what we later came to call the "good Mediterranean diet". These observations led him and his colleagues in the Seven Countries Study to adopt the notion that saturated fats are the major dietary "villains".

Simopoulos [23] suggested that the Mediterranean dietary pattern showed a number of protective substances, such as selenium, glutathione, a balanced ratio of (n-6): (n-3) essential fatty acids, high amounts of fiber, antioxidants (especially resveratrol from wine and polyphenols from olive oil), as well as vitamins E and C, which may be associated with lower risks of coronary heart disease and cancer.

Can the Mediterranean diet be implemented in other cultures?

Despite the large body of scientific evidence regarding the benefits of the Mediterranean diet, some investigators suggest that the effect of this diet on human health may be explained by potential geographic, social, and other cultural differences among the investigated populations [24]. Moreover, other investigators suggest that this traditional dietary pattern is difficult to adopt by other populations due to differences in cultural and environmental conditions. On the other hand, Trichopoulou and her co-workers suggest that the Mediterranean dietary pattern can easily be translated into other cultures, since it can use other food options for increasing the intake of mono-unsaturated fats and, as a consequence, lead to similar effects in the health status of people [16,25,26]. For example, in a clinical trial involving an Indian population [27] who were at high cardiovascular risk, the investigators reported that the Indo-Mediterranean diet reduced the rate of fatal myocardial infarction by one third and the rate of sudden death from cardiac causes by two thirds.

CONCLUSIONS

Growing evidence demonstrates that the Mediterranean diet is beneficial to human health, although there are voices that dispute this suggestion. It is difficult to compare dietary findings from epidemiological and clinical studies, because different approaches were used to identify adherence to the investigated diet. Nevertheless, the presented studies highlight the cardio-protective effects of the Mediterranean diet, through various mechanisms. These findings render this dietary pattern attractive for public health purposes. The observed inter-study variability may be explained by the cultural differences in the populations studied, the outcome measured (i.e. manifestations of coronary heart disease), the methods that were

used to evaluate adherence to the Mediterranean diet, and the increments that were explicitly or implicitly utilized.

REFERENCES:

1. World Health Organization Study Group: Diet, Nutrition, and the Prevention of Chronic Diseases. Geneva, Switzerland: World Health Organization; Technical Report Series, 2003, 916
2. Trichopoulou A, Lagiou P: Healthy traditional Mediterranean diet - An expression of culture, history and lifestyle. *Nutr Rev*, 1997; 55: 383-89
3. Trichopoulou A, Kouris-Blazos A, Wahlqvist M et al: Diet and overall survival in elderly people. *Br Med J*, 1995; 311: 1457-60
4. Keys A, Menotti A, Karvonen MJ et al: The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol*, 1986; 124: 903-15
5. Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D: Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev*, 2000; 9: 869-73
6. Supreme Scientific Health Council, Ministry of Health and Welfare of Greece. Dietary guidelines for adults in Greece. *Archives of Hellenic Medicine*, 1999; 16: 516-24
7. World Health Organization. Health for all - statistics database. WHO, Regional office for Europe, 1997
8. Toshima H, Koga Y, Blackburn H: (Eds) Lessons from the Seven Countries Study. In Dontas A. CVD Risk factors and Trends in Greece. Springer Verlag Tokyo, 1994
9. Menotti A, Lanti N, Puudu PE, Kromhout D: Coronary heart disease incidence in northern and southern European populations: A reanalysis of the seven countries study for a European coronary risk chart. *Heart*, 2000; 84: 238-44
10. Willett WC, Sacks F, Trichopoulou A et al: Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr*, 1995; 61: 1402S-1406S
11. Braunwald E: Heart Disease. 5th Ed. WB Saunders Company, London, UK, 1995
12. Panagiotakos DB, Pitsavos C, Chrysohoou C et al: The role of traditional Mediterranean-type of diet and lifestyle, in the development of acute coronary syndromes: preliminary results from cardio2000 study. *C Eur J Pub Health*, 2002; 1-2; 7-11
13. Pitsavos C, Panagiotakos DB, Chrysohoou C et al: The benefits from Mediterranean diet on the risk of developing acute coronary syndromes, in hypercholesterolemic subjects: a case-control study (CARDIO2000). *Cor Artery Dis*, 2002; 13: 295-300
14. Pitsavos C, Panagiotakos DB, Chrysohoou C et al: The effect of the combination of Mediterranean diet and leisure time physical activity on the risk of developing acute coronary syndromes, in hypertensive subjects. *J Hum Hypert*, 2002; 16: 517-524
15. Pitsavos C, Panagiotakos DB, Chrysohoou C et al: The adoption of Mediterranean diet attenuates the development of acute coronary syndromes in people with the metabolic syndrome. *Nutr J*, 2003; 3: 9
16. Trichopoulou A, Costacou T, Bamia C et al: Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*, 2003; 348: 2599-608
17. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M et al: Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score. *Eur J Nutr*, 2002; 41: 153-60
18. Ruit-Gutierrez V, Muriana FJG, Guerrero A: Plasma lipids, erythrocyte membrane lipids and blood pressure of hypertensive women after ingestion of dietary oleic acid from two different sources. *J Hypertens*, 1996; 14: 1483-90
19. Assmann G, de Basker G, Bagnara S et al: International Consensus statement on olive oil and the Mediterranean diet: implications for health in Europe. *Eur J Cancer Prev*, 1997; 6: 418-21
20. Strazullo P, Ferro-Luzzi A, Saini A et al: Changing the Mediterranean diet: effects on blood pressure. *J Hypertension*, 1986; 4: 407-12
21. Knapp HW: Dietary fatty acids in human thrombosis and hemostasis. *Am J Clin Nutr*, 1997; 65: 1687S-1698S
22. Keys A: Mediterranean diet and public health: personal reflections. *Am J Clin Nutr*, 1995; 61: 1321S-1323S
23. Simopoulos AP: The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence. *J Nutr*, 2001; 131: 3065-73S

24. Robertson RM, Smaha L: Can a Mediterranean style diet reduce heart disease? *Circulation*, 2001; 103: 1821–22
25. Trichopoulou A, Vasilopoulou E: Mediterranean diet and longevity. *Br J Nutr*, 2000; 84: S205–209
26. Kouris-Blazos A, Gnardellis Ch, Wahlqvist ML et al: Are the advantages of the Mediterranean diet transferable to other populations? A cohort study in Melbourne, Australia. *Brit J Nutr*, 1999; 82: 57–61
27. Singh RB, Dubnow G, Niaz MA et al.: Effect of Indo-Mediterranean diet on progression of coronary disease in high risk patients: a randomized single blind trial. *Lancet*, 2002; 360: 1455–61

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