

The effects of Mediterranean Diet on Cardiovascular diseases: a systematic review

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Abstract

Background: Diet and lifestyle-related factors may be responsible for the different geographical distribution of cardiovascular disease incidence. The aim of our study is to conduct a systematic review of the effect of Mediterranean Diet on cardiovascular diseases (CVD), in terms of prevention of both cardiovascular mortality and cardiovascular events.

Methods: We undertook a scientific literature search using MEDLINE, Embase and the Cochrane database for systematic reviews. We selected studies that evaluate the association between mortality and morbidity due to CVD and Mediterranean diet considered as primary or secondary prevention intervention, and found 16 articles concerning 13 studies (2 case-control, 3 cohort studies and 8 randomised clinical trials).

Results: The analyzed studies indicate a reduction of adverse cardiovascular events by about 30% and 40%, in terms of primary and the secondary prevention, respectively. Concerning the reduction of mortality, a larger corpus of data is available, demonstrating that the Mediterranean diet significantly reduces mortality by 50% or 70% in terms of secondary prevention, and by about 30% for primary prevention.

Conclusions: The Mediterranean diet has positive effects over the CVD both in primary and secondary prevention settings. The estimate of the effect is different in different settings and such variability is attributable to the heterogeneity of the enrolled population, which is obviously lower in the general population compared to those who have already had an adverse cardiovascular event.

Key words: mediterranean diet, cardiovascular diseases, primary prevention, secondary prevention, systematic review

Introduction

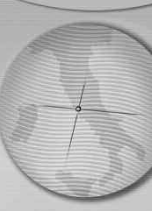
Cardiovascular diseases (CVD) represent one of the main causes of death and disability in the United States of America (USA) and most European countries. Geographic differences in the incidence of CVD have been demonstrated in many epidemiological studies. Diet and lifestyle-related factors may be responsible for these differences. The observation of a lower incidence of CVD among the Mediterranean countries (Italy, Spain, France and Greece) has raised the hypothesis that the diet commonly consumed by people in these regions may have a cardio-protective effect. In 1950 an epidemiological study conducted by Keys and coll. [1] focused on the association between diet and CVD in different populations and concluded that the overall mortality due to CVD was significantly lower in Mediterranean regions than in the Northern European countries and in the USA.

Because of the geographic extension of the Mediterranean area, it is not possible to formulate a single definition of the Mediterranean diet. In fact different cultural, ethnic, religious, economic and

agricultural situations result in different dietary styles, although, as several authors have previously underlined, the various Mediterranean diets are linked together by a common *dietetic pattern* [2]. Such a pattern is characterized by the following:

- a) high intake of vegetables, legumes, fruit and cereals;
- b) medium-high intake of fish;
- c) low intake of meat and saturated fat;
- d) high intake of unsaturated fat (particularly olive oil);
- e) medium-low intake of dairy produces (mainly yogurt and cheese),
- f) additionally, a moderate intake of wine.

Prevention programmes must therefore consider dietary style as have been recognized in the current American Heart Association guidelines [3], which highlights that dietary interventions play a key role in both the prevention and treatment of CVD. The diet recommended by the current guidelines includes, expressed here in terms of percentage of overall caloric intake: carbohydrates 50%-60%, proteins 15% and lipids 30%, with no more than 10%



of this being attributable to saturated fats. Such a diet allows for a reduction in body weight and better control of dyslipidemia, diabetes and hypertension.

A review paper [4] concerning 147 studies on metabolism, cohort studies and clinical investigations, suggests that at least three dietary strategies are effective for the prevention of CVD. These include: a) the replacement of the saturated fats with unsaturated non-hydrogenated fats; b) the increase of the intake of omega-3 fats available in fish, cod-liver oil and vegetal oils; c) the intake of fruit, vegetables, walnuts and whole grains.

The Mediterranean diet emphasizes all of these elements, thus provides many protective aspects which may explain its positive effects.

As reported in the scientific literature [5, 6], the presence in these foods of antioxidants, selenium, glutathione, omega-3 fats and the balance between the contents of omega-3 and omega-6 fats may be associated with reduced mortality, reduced cardiovascular risk and less risk of developing some neoplastic diseases.

The Mediterranean diet would appear to provide better results than the AHA's Step I diet, but randomized clinical trials and systematic reviews of literature are needed before these data can lead to the revision of the guidelines.

The aim of our study is to conduct a systematic review of the effect of Mediterranean Diet on cardiovascular diseases prevention, in terms of prevention of both cardiovascular mortality and cardiovascular events.

Methods

Identification of relevant studies

We conducted a scientific literature search using MEDLINE, Embase and the Cochrane Database for Systematic Reviews, using the keywords Mediterranean diet, heart OR cardiovascular diseases, mortality, primary OR secondary prevention. Online bibliographic databases were searched as of March 2007.

The search was refined using the references from systematic reviews and meta-analyses and from selected articles in order to find potential studies.

We selected studies that evaluated the association between mortality or morbidity due to CVD and Mediterranean diet, in terms of primary or secondary prevention intervention, which aimed to prevent death and/or diseases in a general population and in a group of patients.

Results

We selected 16 articles - 2 case-control (for each study we found two publications) [7-10], 3 cohort

studies [11-13] and 8 randomised clinical trials (for one trial, we found two publications) [5, 14-21].

As far as the case-control studies were concerned, the main outcome was represented by acute coronary syndrome (ACS) and acute myocardial infarction (AMI), while in the cohort studies and the randomised clinical trials different outcomes were taken into consideration (overall and cardiovascular mortality rates, cardiovascular diseases, recurrent adverse cardiac events after a previous AMI); furthermore they considered patients with different baseline characteristics (metabolic syndrome, diabetes, elderly, primary prevention in moderate and high cardiovascular risk population). The following paragraphs provide further details of these results.

Observational studies

Case-control studies

In table 1 the results of case-control studies are summarised.

The CARDIO2000 study [7] is a multicentric, case-control study undertaken in Greece, aimed at clarifying the relationship between cardiovascular risk factors and actual risk of ACS development.

In this study, 18% of patients with a first adverse cardiovascular event followed a Mediterranean diet vs. 28% of the hospitalized control patients. Individuals who had adopted a Mediterranean diet had a decrease in coronary risk compared to individuals who followed a western dietary pattern (OR = 0.80).

The risk was reduced by 19% among those who practiced systematic physical activity more than three times a week.

In the same case-control study, the adoption of the Mediterranean diet was associated with a 23% reduction of coronary risk, even in the subgroup of patients with metabolic syndrome. This suggests that the Mediterranean diet potentially lowers the risk of adverse cardiovascular events even in high-risk subjects [8].

A case-control study conducted by Martinez-Gonzalez et al. [9] has quantified the reduction of risk of AMI associated to the Mediterranean diet. They correlate the risk of AMI to a score that measures the compliance to the Mediterranean diet, as it has been previously demonstrated that an inverse correlation exists between risk of AMI and this score. They showed that there is an 8% reduction in the risk of AMI if a *a priori* score is used and a 45% reduction if the *post hoc* score is used.

The same Authors demonstrated an inverse association between AMI and intake of olive oil. The risk of AMI is reduced by 86% if the outer quintiles are compared. As explained by the

**Table 1. Case-control studies on Mediterranean Diet and Cardiovascular Prevention**

Authors	Country and population size	Year of publication	Main results
Panagiotakos et al ⁷	Greece 848 cases 1078 controls	2003	Individuals who had adopted a Mediterranean diet had a 20% decrease of coronary risk compared to individuals who followed a Western dietary pattern
Pitsavos et al ⁸	Greece 848 cases 1078 controls	2003	The adoption of the Mediterranean diet was associated to a reduction of coronary risk by 23% even in the subgroup of patients with metabolic syndrome
Martinez-Gonzalez et al ⁹	Spain 171 cases 171 controls	2002	An inverse correlation exists between the risk of acute myocardial infarction (AMI) and the score that measures the compliance to the Mediterranean diet. The reduction of the risk of AMI is between 8% and 45%
Fernandez-Jarne et al ¹⁰	Spain 171 cases 171 controls	2002	An inverse association between AMI and intake of olive oil exists. The risk of AMI is reduced by 86% comparing the extreme quintiles

authors, such a strong association should be mostly attributed to the heterogeneity of olive oil intake in the Spanish population, but also to the reduction of statistical power due to comparison of the outer quintiles [10].

Cohort studies

In table 2 the results of cohort studies are shown.

In a large prospective study performed in Greece, with a cohort of 22,043 adults, Trichopoulou et al. [11] investigated the relationship between the Mediterranean diet and mortality rate. During a 44-month follow-up period it was shown that the higher the compliance to the Mediterranean diet, the larger the reduction of both overall and cardiovascular mortality. Dietary compliance was quantified by a

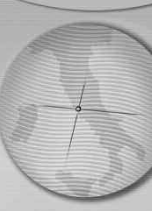
score based upon nine components (range 0 to 9.9 indicating the maximum compliance). An increase in the score of 2 points was associated with a 25% reduction in the overall mortality and a 33% reduction in cardiovascular mortality. However, when the study population was stratified into age classes then significant results appeared only for those individuals in the age group ≥ 55 yrs, in contrast with younger individuals.

When foods were considered separately, a statistically significant association emerged only for fruit, walnuts and the unsaturated-to-saturated fats ratio. No significant reduction in mortality was observed for other foods.

The HALE Project (Healthy Ageing: a Longitudinal Study in Europe) [12] investigated

Table 2. Cohort studies on Mediterranean Diet and Cardiovascular Prevention

Authors	Country/Continent and population size	Year of publication	Main results
Trichopoulou et al ¹¹	Greece 22043 adults	2002	Compliance to the Mediterranean diet was measured by a score based upon nine components (range 0 to 9, 9 indicating the maximum compliance). Higher compliance is associated to larger reduction of both overall and cardiovascular mortality. The increase of the score by 2 points was associated with a 25% reduction in the overall mortality and a 33% reduction in cardiovascular mortality
Knoops et al ¹²	Europe 1507 apparently healthy men and 832 women	2004	After a ten-years observation period, a 39% and 29% reduction in the risk of ischemic heart disease and of overall CVD, respectively, was evidenced among those who followed the Mediterranean diet (modified Mediterranean diet score ≥ 4 according to Trichopoulou et al ¹⁰)
Trichopoulou et al ¹³	Europe 74607 men and women	2005	The higher was the Trichopoulou's score, the lower was the overall mortality, with a mean 8% reduction of mortality per 2-units increase in the score. The mortality was reduced by 17% among those who displayed the maximum compliance to the Mediterranean diet (score 6 to 9) in comparison to the elderly having the lower score (0-3)



the effects of the Mediterranean diet in an elderly European population. After a ten-year observation period, a reduction of 39% in the risk for ischemic heart disease and a 29% reduction in overall CVD was demonstrated amongst those who followed the Mediterranean diet, i.e. a modified Mediterranean diet score ≥ 4 according to Trichopoulos et al. [11]. The coexistence of three additional protective factors (moderate alcohol consumption, regular physical activity and no cigarette smoking) reduced the risk of coronary heart disease and CVD by about 70%. The benefits of a healthy lifestyle were evident also on the global mortality-rate and the risk of cancer, with the reduction of risk being directly correlated with the number of the protective factors.

A large prospective study conducted in 10 European States was undertaken to determine the association between diet and survival in elderly individuals who were from CVD, *ictus cerebri* and cancer at the time of their enrolment into the study [13]. The compliance to the Mediterranean diet was quantified according to the Trichopoulos score [11]. In order to apply the same score to the non-Mediterranean populations, the mono-unsaturated fats were replaced with the unsaturated fats. This study found that the higher the score, the lower the overall mortality was, with a mean 8% reduction of mortality per 2-units increase in the score. The mortality was reduced by 17% among those who displayed maximum compliance with the Mediterranean diet (score 6 to 9) in comparison to those elderly who had a lower score (0-3). There were no statistically significant differences among the States, although the relationship between the diet and the mortality rate was more evident in Greece and absent in The Netherlands and Germany.

Randomized clinical trials

In table 3 the results of experimental studies are briefly described.

The combination of different components of the Mediterranean diet may reduce the risk of CVD through the reduction of the systemic inflammatory status and the endothelial dysfunction, which are known to be associated with metabolic syndrome. After a two-years follow-up, only the 44.4% of patients diagnosed with metabolic syndrome who had followed the Mediterranean diet still presented the features of the syndrome, vs. the 86.6% in the control group (made up by patients randomized to follow a 'prudent' diet: 50%-60% carbohydrates, 15-20% proteins and <30% fat, <10% saturated). In contrast to these control individuals, the treated patients presented a significant reduction of

circulating inflammatory markers (C reactive protein, IL-6, IL-7 and IL-18), of insulin resistance and of the HOMA score [14].

The Lyon Heart Study [15], a large randomized, double-blind clinical trial, investigated the benefits of the Mediterranean diet on the risk of recurrent adverse cardiac events after a previous AMI. The patients were randomized to a Mediterranean-like diet, enriched with alpha-linoleic acid, or to a 'prudent' western diet. At the end of the follow-up (mean duration: 46 months), no difference could be observed in the lipid profile between the two groups, while a 72% reduction was observed for the primary composite outcome (cardiac death plus non-fatal AMI). This trend confirmed the previous results of the mid-term analysis (27-months follow-up); this indicates that the protective effect of the Mediterranean diet is maintained even 4 years after the first ischemic event. The lack of differences in the main cardiovascular risk factors between the study groups supports the idea that the effect of the Mediterranean diet on CVD is independent from the reduction of blood pressure and the levels of blood cholesterol and triglycerides.

Shingh et al. [16] evaluated the cardioprotective effects of the Indo-Mediterranean diet in Southern-Asian patients with ischemic heart disease and/or with high cardiovascular risk. The patients were randomized into two groups: the first group received a diet enriched with alpha-linoleic acid and composed mainly by cereals, fruit, vegetables, walnuts and almonds (intervention group), and the second one received the conventional diet recommended by the National Cholesterol Education Program (control group). Although there were no significant differences among groups in cardiovascular risk factors at the time of their enrolment, by the end of a two-years follow-up the reduction of blood total cholesterol, LDL cholesterol and triglycerides levels were higher in the intervention group. The Indo-Mediterranean diet was shown to be more effective in the prevention of total cardiac events in comparison to the conventional NCEP diet (7.8% vs. 15.2%, $p < 0.001$). In particular, the risk of non-fatal AMI, fatal AMI and sudden cardiac death was reduced by 37%, 67% and 33%, respectively.

The GISSI prevention trial [17], a multicentre Italian study, was designed to evaluate the benefits of the supplementation with omega-3 unsaturated fats and with vitamin E in patients who had experienced a recent AMI. Furthermore, it was evaluated whether the simple dietary advice of increasing the intake of Mediterranean-diet food led to the reduction of mortality-rate after AMI. After they had been advised to increase their intake

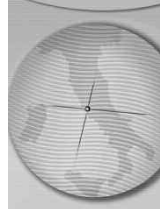
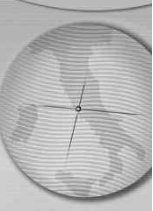


Table 3. Randomised clinical trials on Mediterranean Diet and Cardiovascular Prevention

Authors	Country/Continent and population size	Year of publication	Main results
Esposito et al ¹⁴	Italy 180 patients (99 men and 81 women)	2004	After a two-years follow-up, 44.4% of patients with the metabolic syndrome who had followed the Mediterranean diet still presented the features of the syndrome, vs 86.6% in the control group (made up by patients randomized to follow a 'prudent' diet)
de Lorgeril et al ¹⁵	France 413 patients	1999	At the end of the follow-up (mean duration: 46 months), a 72% reduction was observed for the primary composite outcome (cardiac death plus non-fatal AMI) in the group randomised to the Mediterranean diet, as far as for the risk of unstable angina, <i>ictus cerebri</i> , heart failure
Shingh et al ¹⁶	Asia 499 patients	2002	At the end of a two-years follow-up the reduction of blood total cholesterol, LDL cholesterol, triglycerides levels, BMI and blood pressure was higher in the intervention group (Indo-Mediterranean diet, enriched with alpha-linoleic acid and composed mainly by cereals, fruit, vegetables, walnuts and almonds). This diet resulted more effective in the prevention of total cardiac events in comparison to the conventional National Cholesterol Education Program diet (7.8% vs. 15.2%). The risk of non-fatal AMI, fatal AMI and sudden cardiac death was reduced by 37%, 67% and 33%, respectively
GISSI prevention trial ¹⁷	Italy 11324 patients	1999	After a 6.5 years follow-up, the patients who had the highest compliance to the Mediterranean diet had a significantly lower mortality risk. The reduction of mortality was by 31%, 34% and 49% for the second, third and fourth quartiles in comparison to the lower quartile
Vincent-Baudry et al ¹⁸	France 212 healthy volunteers	2005	After a three-months follow-up a reduction in BMI, HOMA score, blood glucose, insulinemia, blood triglycerides, blood total and LDL cholesterol could be evidenced in the patients randomised to the Mediterranean diet and in those randomised to a low fat-content diet, and a reduction of cardiovascular risk was observed in 15% and 9%, respectively
Bemelmans et al ^{19,20}	Denmark 124 men and 158 women	2000, 2002	At the end of the follow-up (2 years) no differences in the BMI and blood cholesterol levels and in the incidence of cardiovascular disease at ten years were seen in both the intervention (daily supplementation with margarine with high alpha-linoleic acid content) and the control group (Mediterranean diet)
Tobert et al ²¹	USA 279 women	2003	Post-menopausal women with type 2 diabetes mellitus were randomized to either a Mediterranean lifestyle (intervention group) or to traditional treatment (control group), with evidence of a non statistically significant reduction of the blood pressure and a significant reduction of the BMI and an improvement of the glycaemic control
Sondergaard ⁵	Denmark 131 patients	2003	In patients with coronary heart disease and hypercholesterolemia, after a 1-year treatment, the brachial artery vasoreactivity was significantly better among the individuals randomized to the Mediterranean diet in comparison to controls (statin therapy alone)

of fruit, vegetables, fish and olive oil, all patients improved their diet. After a 6.5 years follow-up, the patients who had the highest compliance to the

Mediterranean diet had a significantly lower mortality risk. The reduction in mortality was 31%, 34% and 49% for the second, third and fourth



quartiles in comparison to the lower quartile. The supplementation with omega-3 fats, but not with vitamin E, further determined a reduction of the risk of death and non-fatal AMI. Patients who received supplementation with omega-3 fats had overall and cardiovascular mortality-rates lower by the 14% and 17%, respectively, in comparison to those who received no supplementation. Such data were much more compelling if globally evaluated (analysis of all the 4 randomized study groups), displaying a reduction by 20% and 30%, respectively. No differences have emerged with regards to non-fatal cardiovascular events. There were no major changes in the values of blood cholesterol and glucose with respect to baseline.

The Medi-RIVAGE study (Mediterranean diet, Cardiovascular Risks and Gene Polymorphisms) [18] addressed the benefits of the diet within the primary prevention in subjects with moderate cardiovascular risk factors who underwent no anti-diabetic or cholesterol-lowering therapy. The aim of this study was the assessment of the reduction of the cardiovascular risk in patients randomized to either the Mediterranean diet or to a low fat-content diet. After a three-months follow-up a reduction in BMI, HOMA score, blood glucose, insulinemia, blood triglycerides, blood total and LDL cholesterol could be evidenced in both groups. Although there was no statistically significant reduction among the groups, the objective reduction of the risk factors (in particular of the blood cholesterol) implies a reduction of cardiovascular risk by 9% with the low-fat diet and by 15% with the Mediterranean diet.

The MARGARIN study (Mediterranean Alpha-linoleic acid enriched Groningen diet/ARY INtervention) [19, 20] conducted in a primary prevention setting in a high cardiovascular risk population, evaluated the effects of the Mediterranean diet (control group) as well as the daily supplementation of margarine with a high alpha-linoleic acid content in the Danish population, over a two-years period. At the end of the follow-up no differences in the BMI and blood cholesterol levels were seen in both the intervention and the control group. The latter received the diet recommended by the German guidelines. Additionally, no significant difference was observed in the incidence of cardiovascular disease at ten years using the Framingham score. Although these results are apparently in contrast with the conclusions of the previous studies, actually they strengthen the concept of the Mediterranean diet as cardioprotective by mechanisms which are not necessarily dependent on the reduction of the risk factors.

Tobert and coll. [21] tested the efficacy of a Mediterranean lifestyle for the reduction of the cardiovascular risk factors in women affected by type 2 diabetes mellitus. The post-menopausal women were randomized to either a Mediterranean lifestyle (intervention group) or to traditional treatment (control group). The study evidenced a non statistically significant reduction of the blood pressure and a significant reduction of the BMI ($p = 0.009$), and a significant improvement of the glycaemic control (reduction of the glycated haemoglobin levels).

The anti-inflammatory, anti-thrombotic and vasodilating properties are tightly linked to the endothelial function, which is known to be altered in patients with coronary heart disease. Sondergaard et al. [5] found that the association of the Mediterranean diet and the treatment with statins ameliorates the endothelial function in patients with coronary heart disease and hypercholesterolemia. After a 12-months treatment, the brachial artery vasoreactivity (an index of endothelial dysfunction) was significantly better among the individuals randomized to the Mediterranean diet in comparison to controls (statin therapy alone). Due to the statin therapy, in both groups a significant reduction of blood LDL cholesterol levels could be evidenced in both groups, while a significant reduction of the blood triglycerides was found only in the treatment group. This suggests that it is closely linked to the diet.

Discussion

Several studies after the Seven Country Study [1] indicate that the Mediterranean diet is of benefit to human health, in terms of both primary and secondary prevention of CVD. The present review of literature underlines that the adoption of a Mediterranean diet style actually has the potential to reduce the risk of cardiovascular mortality and morbidity.

The analyzed studies show a reduction in adverse cardiovascular events by about 30% and 40%, in relation to primary and secondary prevention, respectively. As far as the reduction of mortality is concerned, a larger corpus of data is available demonstrating that the Mediterranean diet significantly reduces the mortality by 50% [15] or 70% (14) for secondary prevention, while the reduction is about 30% for primary prevention [11]. Such variability is attributable to the heterogeneity of the enrolled population and is obviously lower in the general population [11] compared to those who have already had an adverse cardiovascular event.



Regardless, the relationship between diet and the CVD is very complex, as it involves a large range of dietary elements. It is therefore very unlikely that it can be determined by a single food. In some investigations the high intake of fruit, vegetables and a unsaturated/saturated fats ratio > 2 was statistically associated with the reduction in cardiovascular events. Nonetheless, no single food can be considered cardioprotective. An interesting aspect of the Lyon Diet Heart Study [14, 22] is the lack of a significant association concerning the majority of the foods included in the score, despite a strong inverse correlation between diet and mortality. The effect of the single nutrients or foods may be too small to be measured, and this may explain the observations cited above. Meanwhile, the cumulative effect of the multiple dietary components becomes substantial and influential. It is also probable that a synergistic or interactive effect exists between the different foods which are included in the score.

Many previous studies that investigate the association between diet and the CVD showed that the reduction of the risk factors as their main objective. Such an event did not occur in the studies in terms of compliance to the Mediterranean diet for secondary prevention.

The reduction of the risk of coronary events appears to be independent from the reduction of blood lipoproteins in patients with ischemic heart disease [14]. Even though the prevalence of the major cardiovascular risk factors is reduced, there are multiple and not completely clarified mechanisms to explain the cardioprotective effect of the Mediterranean diet. The evidence in the scientific literature indicates that the arrangement of different dietary components has the potential to lower the levels of some coronary disease markers and consequently reduces the adverse cardiovascular events. In his study, Esposito [12] has demonstrated that a Mediterranean lifestyle may actually reduce the prevalence of the metabolic syndrome and the associated cardiovascular risk. The proposed mechanism for this is a reduction of the circulating inflammatory markers (C reactive protein, IL-6, IL-7 and IL-18), body weight and of the insulin resistance. In the ATTICA study a higher compliance to a traditional Mediterranean diet was independently associated to a reduction of the indexes of inflammation and of activation of the coagulation system, resulting in a reduced risk for developing metabolic syndrome [23, 24].

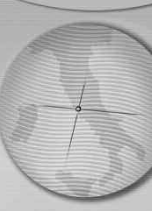
Besides the reduction of the inflammatory markers, it has been hypothesized that the Mediterranean diet has a direct protective effect

on the cardiovascular system, due to its antioxidant properties. It has been documented that compliance to the Mediterranean diet is directly proportional to its antioxidant potential [25]. The high content of cereals, vegetables, fruit and olive oil guarantee a considerable delivery of vitamins E, C, B6, B12, beta-carotene, folic acid and phenols. The olive oil is in particular enriched with antioxidants, mainly phenols. *In-vitro* studies have documented that these have the potential to preserve the LDL from lipid peroxidation, to promote the rising of endogenous antioxidant defences and reduce the endothelial dysfunction. The latter is a major contributor to the development of hypertension and to the destabilization of atherosclerotic plaques [26]. As Martinez-Gonzalez and Sanchez-Villegas underline [27], not all of the components of the Mediterranean diet are actually protective, or at least not all of them can provide the same level of protection. The balancing of the different dietary elements and their multiple-vitamins content are the elements that determine the protective effects of the Mediterranean diet. In the GISSI prevention trial [16] the administration of vitamin E supplements alone did not provide an additional reduction of the cardiovascular risk.

The evidences in literature then indicate that the Mediterranean diet improves the blood lipid profile, decreases the risk of thrombosis, ameliorates the endothelial function and insulin resistance, reduces the omocystein plasma concentration and the ventricular arrhythmias [16, 28]. Taking into consideration other literature reviews [29-31] on the Mediterranean diet, some limitations emerge in the analysis of the effects of diet on health:

- Because of the complexity of the dietary modifications, it is very difficult to conduct double-blind studies aimed to investigate the effects on health [28];
- The differences in the dietary habits and in the nutritional objectives represents a limitation to the comparison of studies conducted in different countries [28];
- As the questionnaire is the main tool used to collect accurate data on food consumption, we have to consider the issue of validity and reproducibility of the tool in different settings.
- The comparison between the different dietary components is difficult due to the different intake ranges assigned per each food in the different studies. The number of dietary components taken into consideration in each study is also different.

Even the different methods used to define the intervention groups represents a limitation to the



comparison of different studies. Some authors characterize the Mediterranean diet as enriched with unsaturated fats, or with supplements of walnuts or wine, while few authors employ a standard score system and a Mediterranean diet pattern.

Finally, the compliance to new alimentary habits is difficult to obtain, while often the difficulties to obtain some kind of food in non Mediterranean regions is a further limitation to nutrition studies in these areas.

Recent studies have highlighted that the adoption and the compliance to new dietary customs can be successfully achieved if adequate information is provided to the patients and their families, and if a professional surveillance is performed [14]. An experimental project based in Scotland has proven that the Mediterranean diet can be promoted even in the Northern Europe countries [32], mainly if the communication media are properly used. In this study the nutrition program obtained higher compliance if it was diffused by the Internet rather than by brochures. After a six-month follow-up period, modifications to dietary style and of plasma lipids were already evident among healthy adult participants.

In comparison of the diet recommended by the current AHA guidelines (NCEP Step I and Step II diet) the Mediterranean diet does not present major differences in relation to macro- and micronutrients. Both diets emphasize the intake of carbohydrates, fruit and vegetables, but in the Mediterranean diet does not fulfil the same numeric criteria for lipid intake, fat less than 30%, with <10% saturated and is its main constituents are olive oil and the omega-3. As Hu and Willett have underlined [4], that compliance with the criteria outlined in the AHA guidelines is often poor, while the Mediterranean diet is accepted by many patients and in such a way it represents an additional and alternative nutritional approach.

From our review it has emerged that the strongest association between the Mediterranean diet and mortality rate can be found in the elderly, and it is stronger as the age increases [11, 17]. Such a tendency is due, on one side, to the cumulative exposition effect and, on the other side, to the relatively low number of deaths in the subgroup of younger individuals. Both a lower incidence of CVD and a lower compliance to the Mediterranean diet can be seen among younger patients.

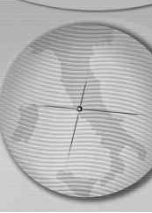
In recent years we have faced a progressive change in our alimentary habits, with the trend towards a progressive 'westernisation'. A French study [33] has shown that the traditional Mediterranean diet is a dietary model limited to the rural zones and mainly to the older age groups. In

fact, compliance to the Mediterranean dietary style is the highest among the elderly. This is due to both a higher attention to their health status and to their connection with traditional foods. However, it is those who are younger who represent a group at risk and hence are the primary target of a campaign of nutritional prevention.

The implementation of prevention strategies requires a practical, systematic approach in order to identify the priorities for intervention and the distribution of resources. On the basis of the scientific evidence, in 2001 the AHA scientific committee stated that the Mediterranean diet has positive effects on CVD and that the current guidelines may be improved by the introduction of the Mediterranean diet. Regardless, such recommendations are part of a healthy lifestyle, and in a secondary prevention setting they may be used in conjunction with conventional drug therapy. The results of the study INTERHEART indicate that lifestyle modifications have the potential to reduce the risk of coronary heart disease by 80% and has main importance for both genders, at all ages, independent of geographical area [34].

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