

Review

Intervention studies on Mediterranean diet and cardiovascular risk

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The traditional Mediterranean diet, as studied in the 1950s to 1960s in the South of Europe, is characterized by moderate energy intake, low animal fat, high olive oil, high cereals, high legumes, nuts and vegetables, and regular and moderate wine. A Mediterranean-type diet is being developed to mimic the traditional one and fit with present life style. While numerous epidemiological studies have supported the concept that adherence to the traditional Mediterranean diet is beneficial for health and particularly protects against cardiovascular disease, the limited number of intervention studies in this field have not yet provided major support. Nevertheless, the dietary interventions performed until now have demonstrated that adoption of a Mediterranean-type diet reduces several cardiovascular risk factors in subjects at risk (primary prevention) and/or cardiovascular events or mortality in patients after a first cardiac event (secondary prevention). Among numerous foodstuffs characterizing the Mediterranean diet, virgin olive oil has been shown to display beneficial effects on a wide range of risk factors.

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1 Introduction

The concept of Mediterranean diet is now acknowledged by both medical professionals and the public. The scientific corpus on the beneficial health effects of a traditional Mediterranean diet was first established in the 1960s thanks to the Seven-Country epidemiological study, and has recently been firmly sustained by new epidemiological and intervention studies as reviewed elsewhere. Here we update available knowledge on the established relationship between Mediterranean diet and cardiovascular disease based on intervention studies.

2 The concept of Mediterranean diet and interventions studies

What is nowadays called a Mediterranean diet deserves special attention. Indeed, the traditional Mediterranean diets have been the result of important evolutions for more than

two millennia with key inputs from the Greeks, then Romans, Arabs, Africans, Asians and Americans [1]. The near and middle East provided wheat, onion, garlic, olives, peas, broad beans, figs, grapes, citrus, sheep and goat. Eggplant, cucumber, chickpeas, rice, peach, apricot and lemon came from India and Asia. Africa provided melons, while the discovery of America provided tomato, sweet pepper, squash, potato and corn. As a result, a huge diversity of foodstuffs have been cultivated, processed and consumed in countries around the Mediterranean sea. The present concept of Mediterranean diet is based on the recent traditional Mediterranean diet that was studied in the 1950s to 1960s in the South of Europe during the Seven-Country study [2–4]. Some variability has been found between the different Mediterranean locations studied (three in Italy, five in Yugoslavia, two in Greece) but general trends appeared as compared to other northern European countries (Netherlands, Finland) or other industrialized countries (Japan, USA). From these data, the traditional Mediterranean diet is characterized by moderate energy intake due to generally low economic levels, low animal fat, meat and meat product intakes because of reduced availability, moderate to high fish and poultry intakes, high olive oil consumption as almost the only added fat, moderate to high cereal intakes, high intake of legumes, vegetables and nuts, high intakes of

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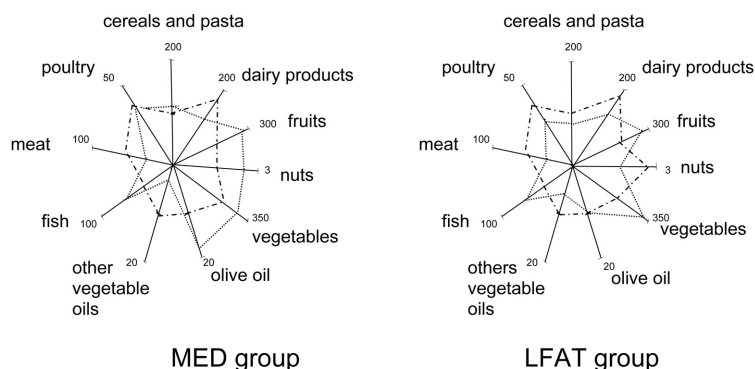


Figure 1. Mean intakes (g/day) of important food items at baseline and after 3-month diet intervention in the MED group (Mediterranean-type diet; $n = 88$) and in LFAT group (Low-fat diet; $n = 81$) at baseline (— · —) and (· · ·) after 3-month dietary intervention. From [7, 8].

garlic and herbs, moderate fruit intake and regular and moderate wine consumption. This dietary pattern has been recently popularized as the traditional Mediterranean diet pyramid [5].

By the second half of the twentieth century, daily diets markedly changed in the Mediterranean countries in such a way that westernization of traditional diets spread through the area. The result at present time is an important loss of the traditional Mediterranean diet, with variable impact in the various Mediterranean countries [6]. We have recently observed a situation similar to that seen in Greece, Italy or Spain in the area of Marseille in France [7], with dietary patterns typical of western industrialized countries, with important intakes of animal foods (meat, meat products, dairy products) and rather low intakes of vegetable foodstuffs (fruits, vegetable, cereals, nuts). This unbalanced pattern is characterized by high intakes of saturated fat and sugars and low intakes of micronutrients and fibers [7].

As a consequence, to perform intervention studies, it is now necessary to use the so-called Mediterranean-type diets, which are well-adapted versions of the traditional Mediterranean diet discussed above but based on presently available foodstuffs and suitable for modern type of life. An illustration of the food items either currently consumed or to be consumed as an intervention Mediterranean-type diet in the area of Marseille is given in Fig. 1 [7, 8].

3 Dietary intervention studies with Mediterranean-type diets

In addition to data obtained from ecological observation studies, it is necessary to perform intervention studies to demonstrate that Mediterranean-type diets can have a causal role in the observed long-term beneficial health effects, especially regarding cardiovascular risk. Such studies can be classified as “primary prevention study” when the subjects involved are healthy or at risk for disease, or as “secondary prevention study” when the subjects studied are in fact patients who already have a disease, *i. e.*, in our case angina pectoris or a first myocardial infarction or stroke.

Serra-Majem *et al.* [9] recently systematically reviewed available scientific evidence on interventions with the Mediterranean diet. We focus here on the most relevant studies performed.

3.1 Primary prevention intervention studies

3.1.1 Mediterranean-style diet in subjects with the metabolic syndrome, Italy

In this study recently performed in Italy by Esposito *et al.* [10], 180 subjects (99 men, 81 women) were subjects at risk for cardiovascular disease by having a so-called metabolic syndrome (NCEP-ATPIII; National Cholesterol Education Program-Adult Treatment Panel III) associating elevated waist circumference, blood pressure plasma triglycerides, plasma glucose and low-HDL cholesterol. The subjects were randomized in two dietary intervention groups: one group with a Mediterranean-type diet and the other with a usual low fat, low cholesterol diet. Subjects in the Mediterranean-type diet had a significantly higher intake of whole grains (198 vs. 102 g/day), fruit, vegetable and nuts (487 vs. 201 g/day), olive oil (26.7 vs. 15.9 g/day), MUFAs (12.4 vs. 9.6 g/day) and n-3 fatty acids (1.5 vs. 0.68 g/day) and fiber (32 vs. 17 g/day).

After a 2-year follow-up, the subjects on the low-fat, low-cholesterol diet did not show marked changes. Conversely, as illustrated in Fig. 2, significant changes were observed in the subjects under the Mediterranean-type diet such as a reduction in weight, BMI, glycemia, insulinemia and HOMA score, reduced plasma cholesterol and triglycerides, reduced inflammatory markers and increased endothelial function score. Overall, after the 2-year intervention with the Mediterranean-type diet or the low-fat diet, 40 and 78 subjects, respectively, still had features of the metabolic syndrome.

3.1.2 The Medi-RIVAGE study, France

Recently, the Medi-RIVAGE study was performed in the area of Marseille, South-East of France [7, 8], aimed at determining the effects of a Mediterranean-type diet or a low-fat diet on risk factors in 212 randomly allocated volun-

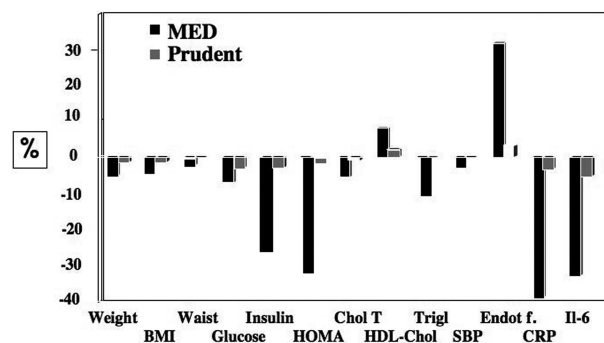


Figure 2. Effects (% relative changes from baseline) of a Mediterranean-type diet or a low-fat diet on cardiovascular risk factors in subjects with the metabolic syndrome after 2-year follow-up. Chol T: total cholesterol; Trig: triglycerides; SBP: systolic blood pressure; Endot f.: endothelial function; CRP: C reactive protein. From [10].

teers (men and women) with moderate risk factors for cardiovascular disease (35% with elevated BMI, 93% with hypercholesterolemia, 46% with hypertriglyceridemia, 21% with high blood pressure). Dietary questionnaires and plasma nutritional markers were used to test compliance. After the 3-month and 12-month dietary intervention, changes in a number of risk markers were evaluated.

After 3-months, changes in dietary habits were observed in both groups ($n = 169$), with an increase in fruit, vegetables, nuts, fish and olive oil in the Mediterranean diet group, as illustrated in Fig. 1. Increases in the intake of protein, carbohydrate (% energy) and fiber were observed, along with an improvement in fat quality (decreased saturated fat and increased MUFA and/or PUFA). Plasma markers of fruit and vegetable intake (beta-carotene, lycopene, folates) were significantly higher only in the Mediterranean diet group.

BMI, total cholesterol, LDL cholesterol and triglyceride-rich lipoprotein cholesterol, triglycerides and triglyceride-rich lipoprotein triglycerides, apolipoproteins A1 and B, insulinemia, glycemia and HOMA score were significantly lower after 3 months. The amplitude of reduction of some risk factors was more important in the Mediterranean diet group (total cholesterol: -7.4% vs. -4.4% ; LDL cholesterol: -9.8% vs. -5.4%) (Fig. 3). Reduction in total cholesterol, triglycerides and insulinemia remained significant after adjustment for BMI. In obese and overweight subjects, significant reductions in plasma triglycerides were observed in the Mediterranean diet group only. The data obtained after 3-month intervention predict a 15% reduction in cardiovascular risk with the Mediterranean diet (and a 9% reduction with the low-fat diet).

3.1.3 The PREDIMED Study, Spain

In this new intervention study by Estruch *et al.* [11], 772 adult subjects at high cardiovascular risk were involved and assigned either to one of two experimental diets mimicking

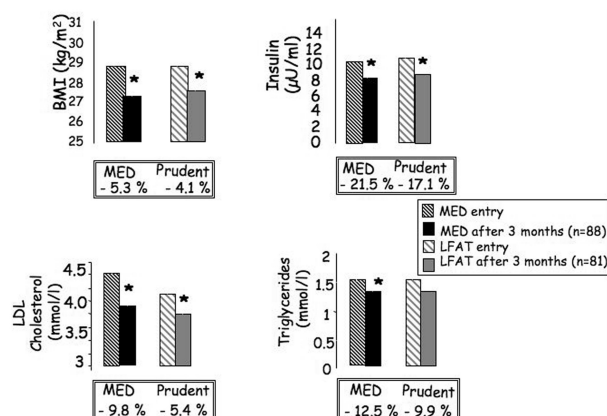


Figure 3. Effects (% relative changes from baseline) of a Mediterranean-type diet or a low-fat diet on cardiovascular risk factors in subjects at moderate cardiovascular risks after 3-month follow-up. * indicates a significant difference from baseline in a given group. From [8].

the Mediterranean diet: one likely rich in virgin olive oil (1 L/week) and the other providing a reasonably quantity of walnuts (30 g/day); or to a low-fat diet.

After 3-month follow-up, compared to the low-fat diet, the two Mediterranean-style diets promoted beneficial changes in most outcomes, such as -0.39 and -0.30 mmol/L, respectively, for fasting glucose; -5.9 and -7.1 mmHg, respectively, for systolic blood pressure; and -0.38 and -0.22 , respectively, for the cholesterol/HDL cholesterol ratio. The C-reactive protein was reduced (-0.54 mg/L) only by the olive oil-rich diet.

3.1.4 Other studies on some risk factors

Some studies have evaluated the influence of Mediterranean-type diets on specific risk factors for cardiovascular disease. Examples of such intervention studies are given below.

Perez-Jimenez *et al.* [12] investigated the effects of a diet enriched in MUFAs (Mediterranean diet) and a low-fat, high-carbohydrate diet (CHO) in 59 young subjects (men and women) for 28 days. In comparison to the saturated-fat diet, the Mediterranean and CHO diets induced a significant decrease of LDL-cholesterol and HDL-cholesterol. Steady-state plasma glucose significantly decreased and basal and insulin-stimulated 2-deoxyglucose uptake in peripheral monocytes increased in both diets, indicating an improvement in insulin sensitivity. This study showed that Mediterranean diet is an adequate way for improving glucose metabolism in healthy young adults.

Fuentes *et al.* [13] aimed at determining whether endothelial function in 22 hypercholesterolemic men is affected by replacing a saturated fat-enriched diet with a diet rich in MUFAs as in Mediterranean countries or a low-fat, low-saturated fat diet for 28 days. Compared with the saturated fat diet, flow-mediated dilatation increased during the Med-

Table 1 Brief overview of the main intervention studies on Mediterranean diet and cardiovascular health

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| Primary prevention studies | | | |
| Perez-Rimenez <i>et al.</i> [12], Spain | Mediterranean diet (or a low fat, high-carbohydrate diet), 4-week follow-up | 59 healthy young men or women | The Mediterranean diet decreased LDL-cholesterol and HDL-cholesterol and improved insulin sensitivity. |
| Esposito <i>et al.</i> [10], Italy | Mediterranean-type diet (or low-fat diet), 2-year follow-up | 180 men or women with the metabolic syndrome | The Mediterranean-type diet reduced weight and BMI, glycemia, insulinemia and HOMA score, plasma cholesterol and triglycerides, inflammatory markers. |
| Vincent-Baudry <i>et al.</i> [8], France | Mediterranean-type diet (or low-fat diet), 3- and 12-month follow-up | 212 men or women with =1 cardiovascular risk factor | The Mediterranean-type diet lowered BMI, total, LDL- and triglyceride-rich lipoprotein cholesterol, triglycerides and triglyceride-rich lipoprotein triglycerides, apolipoproteins A1 and B, insulinemia, glycemia and HOMA score. |
| Estruch <i>et al.</i> [11], Spain | Mediterranean-style diets either rich in virgin olive oil or walnuts, (or low-fat diet), 3-month follow-up | 772 adult subjects at high cardiovascular risk | The two Mediterranean-style diets promoted beneficial changes for fasting glucose, systolic blood pressure, the cholesterol/HDL cholesterol ratio. |
| Secondary prevention studies | | | |
| de Lorgeril <i>et al.</i> [15, 16], France | n-3 PUFA-rich Mediterranean-type diet or low-fat, high n-6 PUFA diet, 46-month follow-up | 605 men and women, aged <70 years, after myocardial infarction or angina pectoris | The number of patients with non-fatal myocardial re-infarction or cardiac death was 70% lower in the Mediterranean group than in the low-fat control group. |
| Barzi <i>et al.</i> [18], Italy | Advice to increase the consumption of Mediterranean foods, 6.5-year follow-up | 11 323 men and women after myocardial infarction | The odds ratio for the risk of death for those in the best score quarter was 0.51 compared with ones in the worst dietary score quarter. |

iterranean diet but not during the low-fat diet. In addition, levels of plasma cholesterol, LDL-cholesterol, apolipoprotein B, and P-selectin decreased during the Mediterranean and low-fat diets. It was concluded that diets rich in MUFAs improve endothelial function.

Mezzano *et al.* [14] compared the effect of an alcohol-free Mediterranean-type diet and a high-fat diet on variables of primary hemostasis [bleeding time, plasma von Willebrand factor (vWF) and platelet aggregation/secretion] in two groups of 21 healthy young males (22 ± 3.4 years) over 90 days. Total plasma cholesterol, HDL and LDL did not change significantly in either study group at any time point. After 30 days on each diet, individuals on the Mediterranean-type diet had longer bleeding time than those on high-fat diet (7.6 ± 2.8 vs. 5.8 ± 1.7 min; $p = 0.017$). Plasma vWF did not change significantly at 30, 60 or 90 days. Mediterranean-type diet intake was associated with a significant increase in platelet serotonin secretion and a non-significant increase in platelet aggregation after stimulation with epinephrine. The longer bleeding time in individuals on Mediterranean-type diet, obtained independently of red wine, denotes less interaction of platelets with the vascular wall, which could be beneficial from the point of view of

cardiovascular risk but his effect is not explained by changes in the measured hemostatic determinants of bleeding time (plasma vWF, *ex vivo* platelet function).

3.2 Secondary prevention intervention studies

3.2.1 The Lyon heart study

The Lyon heart study [15, 16] was a prospective, randomized secondary prevention study aimed at comparing the usually recommended low-fat, high-n-6 PUFA diet to a Mediterranean-type diet rich in oleic and alpha-linolenic acid for secondary prevention in patients (age <70 years) with coronary heart disease (angina pectoris or myocardial infarction). The patients were randomly assigned to the Mediterranean-type diet ($n = 302$) or the control low-fat group ($n = 303$). The follow-up lasted 5 years with a check every year. The patients in the Mediterranean-type diet group consumed significantly less fat (30.6% vs. 33.1% energy), saturated fat (8.3% vs. 11.8% energy), cholesterol (217 vs. 320 mg/day) and linoleic acid (3.6% vs. 5.4% energy) but more oleic acid (12.9% vs. 10.4% energy) and alpha-linolenic acid (0.83% vs. 0.28% energy) as confirmed by plasma fatty acid analyses.

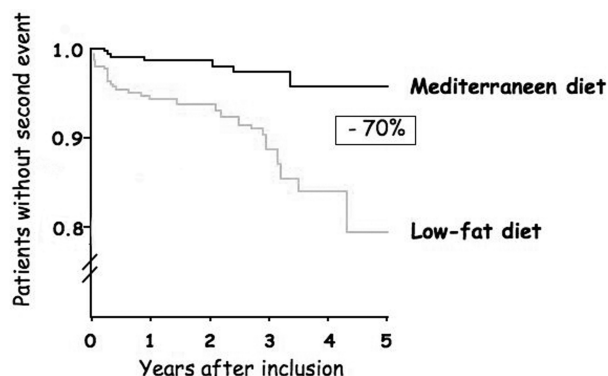


Figure 4. Effects of a Mediterranean-type diet or a low-fat diet on the cumulative number of cardiovascular events in patients suffering from cardiovascular disease. From [15, 16].

After a mean follow-up of 27 months, there were 16 cardiac deaths and 17 non-fatal myocardial infarction in the control low-fat group and only 3 and 5, respectively, in the Mediterranean-type diet group. A risk ratio for these two main endpoints combined of 0.27 was obtained after adjustment. No noticeable changes in plasma cholesterol parameters were observed. After a mean 46-month follow-up ($n = 219$ and 204), the number of patients with non-fatal myocardial re-infarction or cardiac death was 70% lower in the Mediterranean group than in the control group, demonstrating a very impressive preventive effect in this high-risk population (Fig. 4). Another worthwhile information obtained was that as soon as 6 months after the beginning of the dietary intervention, a significant reduction in coronary events was observed under the Mediterranean-type diet, which is of sounded relevance in term of public health.

3.2.2 The GISSI-Prevenzione clinical trial

Barzi *et al.* [17] aimed to ascertain whether simple dietary advice to increase the consumption of Mediterranean foods, given in a clinical setting, led to reduced mortality after a myocardial infarction. More specifically, this study aimed at evaluating the effects of vitamin E and n-3 long-chain fatty acids. A total of 11 323 men and women with myocardial infarction from 172 centers in Italy were included in the GISSI-Prevenzione clinical trial. All subjects received advice to increase their consumption of fish, fruit, raw and cooked vegetables and olive oil, and the intakes of the five foods were assessed at baseline, 6, 18 and 42 months. Associations of food intakes, a combined dietary score, and the risk of death over a 6.5-year follow-up were estimated after adjusting for several non-dietary variables. Subjects generally improved their diet according to the advice given. All foods were associated with a significant reduction in risk of death. Compared with people in the worst dietary score quarter, the odds ratio for those in the best score quarter was 0.51 (95% CI 0.44–0.59). It thus appears that in sub-groups defined by age, sex, smoking, randomized treatment and

concomitant drug therapy. It was concluded that myocardial infarction patients can respond positively to simple dietary advice, and that a Mediterranean-type diet has a marked protective effect leading to a substantial reduction in the risk of early death.

4 Conclusion

Intervention studies published until now on the relationship between Mediterranean diets and cardiovascular disease, although limited in number, indicate that Mediterranean diets are effective in reducing cardiovascular risk factors in subjects at risk, and are associated with a reduction in cardiovascular events or mortality. This is in very good agreement with the numerous epidemiological studies supporting the cardio-protective effect of the traditional Mediterranean diet as observed in the mid twentieth century as well as nowadays, as reviewed elsewhere.

The traditional Mediterranean diet pattern is based on numerous foodstuffs with reported health benefits, which includes virgin olive oil as the main fat intake. As recently reviewed in an international consensus report by Perez-Jimenez *et al.* [18], the health effects of virgin olive oil have been scientifically documented on numerous risk factors for cardiovascular disease, such as lipid and lipoprotein profile, insulin-mediated glucose metabolism, blood pressure, thrombotic profile, hemostasis, endothelial function, inflammation, and oxidative stress. These effects have been shown to result from either high levels of oleic acid or antioxidant compounds in virgin olive oil. Other foodstuffs characteristic of the traditional Mediterranean diet such as vegetables, legumes, fruits or seafood have also independently been shown to afford protection against the development of cardiovascular disease.

Unfortunately, during the last few decades, dietary habits around the Mediterranean sea have markedly changed, with more fat, meat, egg, dairy product and sugar and less cereals, legumes, vegetables and seafood being consumed in Southern Europe [1]. Three European countries have kept some important traits of traditional Mediterranean diet such as Greece (with very high intakes of olive oil, legumes, vegetables and fish), Italy (with very high intakes of vegetables, legumes, fruits, cereals, and olive oil) and Spain (with very high intakes of olive oil, vegetables, legumes, fruits and fish) [6]. Conversely, a Latin country such as France has no longer a Mediterranean-type diet [7, 19] except in older people in some southern areas. This could lead to a detrimental evolution in the health status in Mediterranean countries, as already observed, in line with the loss of the protective effect of the traditional Mediterranean diet. Thus, the challenge for the near future is to stop the present detrimental trend in the Mediterranean area and to rehabilitate the essential foodstuffs of the Mediterranean diet. This is in line with modern dietary recommendations [20] as

well as the ancient knowledge that “your diet should be your first medicine” since the time of Hippocrates (400 BC).

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