European Heart Journal Supplements (2023) **25** (Supplement B), B166–B170
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad097

ESC
European Society
of Cardiology

Cardiovascular prevention: Mediterranean or low-fat diet?

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KEYWORDS
Mediterranean Diet;
Cardiovascular prevention;
Saturated fats

The international scientific community has long agreed on the fact that a low-fat diet is actually able to bring benefits to cardiovascular health and beyond. By low-fat diet, experts mean a diet where the average calories assimilated daily are made up of no more than 30% fat. The Mediterranean Diet, on the other hand, identifies a nutritional model inspired by the traditional eating habits of the countries bordering the Mediterranean Sea. It began to be studied scientifically in the 1950s and it is still today one of the diets that have a positive impact on our health when associated with correct lifestyles. Although epidemiological and mechanistic studies show similar results, there is no evidence from large-scale, long-term clinical trials on the efficacy of the Mediterranean Diet compared with another active group, particularly in secondary prevention. A convincing response has been obtained from the recent CORDIOPREV study (CORonary Diet Intervention with Olive oil and cardiovascular PREVention) which randomized ~1000 patients with documented coronary artery disease to a Mediterranean Diet or a low-fat dietary intervention. In a 7-year follow-up, the Mediterranean Diet was superior to the low-fat diet in the prevention of major cardiovascular events.

'Eat well and stay well.'

Ancel & Margaret Keys

The benefits of a low-fat diet

The composition of the optimal diet for cardiovascular prevention has evolved over the past few decades. The international scientific community has long agreed on the fact that a low-fat diet is actually able to bring benefits to cardiovascular health and beyond. By low-fat diet, experts mean a diet where the average calories assimilated daily are made up of no more than 30% fat. Some advise keeping around an average of 10–15% of fat intake in a whole day, others suggest a daily caloric intake of saturated fats not exceeding 7–10%.

Low-fat diets are often recommended for people who need to lose weight because foods high in fat have higher calories per gram than proteins and carbohydrates (nine calories per gram for fat vs. four calories per gram for proteins and carbohydrates). As demonstrated in a large meta-analysis including 33 randomized trials and 10 cohort studies, lower total fat intake leads to small but statistically and clinically significant reductions in body weight in adults with a baseline fat intake of 28–43% of energy intake and maintained for at least six months to more than eight years.[1]

The first studies on low-fat diets were conducted by scientists who believed that saturated fat was the main cause of heart disease. In 1977, the first edition of 'The Dietary Goals for the United States' was published in an attempt to reduce the incidence of diet-related diseases, such as cardiovascular disease and diabetes.[2] Although numerous dietary changes were recommended to improve health, reducing dietary fat was identified as a contributing factor. Although well intentioned, the US low-fat guidelines issued in 1977 ended up causing a change in the behaviours of the food industry on the one hand and in the average American's perception of a healthy diet on the other, paradoxically contributing to an increase in the national obesity rate and incidence of related diseases, rather than the expected opposite result. Unfortunately, it had been accepted as a

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fact that reducing dietary fat was the panacea for a wide variety of ailments.

Although several experts have tried to question these conclusions, the international food recommendations of the following decades have often been aimed at discouraging people from eating foods rich in saturated fats (such as eggs, red meat, and dairy products). Even the health authorities—or at least most of them—have continued to support this thesis. In fact, in the early 2000s, reducing fat intake was the standard approach to prevent the onset of cardiovascular disease or its recurrence. This approach was based on two main guidelines: the National Cholesterol Education Program II and the Adult Treatment Panel III (ATP III).[3,4] In the latter, as part of a multifactorial approach to reduce cardiovascular disease, an essential role was attributed to a diet low in saturated fats (<7% of total calories), polyunsaturated fats (up to 10% of total calories), monounsaturated (up to 20%) and in which, in any case, the total fat content should not exceed 35% of the total calories (*Table 1*). All associated with a weight loss and an increase in aerobic physical activity. ATP III emphasized the type of carbohydrates (e.g. complex carbohydrates) used to replace saturated fat and correct fibre composition. However, the guideline did not increase the recommended lower limit for fat, keeping it at 25% (desirable limits are 25–35%). Therefore, a low-fat diet was the recommended option and has remained so for many years.

The origins of the Mediterranean Diet

The Mediterranean Diet identifies a nutritional model inspired by the traditional eating habits of the countries bordering the Mediterranean Sea. It began to be studied scientifically in the 1950s and it is still today one of the diets that have a positive impact on our health when associated with correct lifestyles. The paternity of the research on the Mediterranean Diet can be attributed to the nutritionist Lorenzo Piroddi who in 1939 hypothesized the connection between eating habits and the onset of metabolic diseases. To treat his patients, Piroddi elaborated a first version of the Mediterranean Diet, which limited the consumption of animal fats favouring vegetable ones. However, the first major observational study on the Mediterranean Diet, which later became known as the 'Seven Countries Study', was conducted by the American biologist and physiologist Ancel Keys. Sent in the wake of the troops during the Second World War, he was responsible for a large programme on nutrition on behalf of the Ministry. During his stay in Italy, he participated in the first 'Conference on Food' held in Rome in the early 1950s. Keys were struck by the data on the low incidence of cardiovascular pathologies and the Campania region and the island of Crete. To try to explain this situation, he was the promoter of a first pilot study in which the inhabitants of Nicotera in Calabria were subjected to analysis. Later, Keys moved to Pioppi, Cilento, which became the headquarters of his studios. Between 1958 and 1964, Keys and co-workers conducted the Seven Countries Study, which enroled men aged 40–59 in one of sixteen cohorts from seven countries (Finland, Greece, Italy, Yugoslavia, Japan, the United States, and Italy). For Italy, the sample came from Nicotera (Calabria), Crevalcore (Emilia), Montegiorgio (Marche), and Pioppi (Cilento).[5] After decades of investigations, he concluded that a diet based on bread, pasta, fruit, vegetables, legumes, extra-virgin olive oil, fish, and very little meat was mainly responsible for the protective effect on cardiovascular events, and not only, in that population. This type of diet was called the 'Mediterranean Diet' and had an extraordinary media and scientific impact. In fact, in 1975, Keys and his wife published a book entitled: 'How to eat well and stay healthy. The Mediterranean way' which talks about their revolutionary discoveries on nutrition and which immediately became a best seller in the Anglo-American world. After a 15-, 25-, and 50-year follow-up, a strong positive relationship between saturated fat intake and coronary heart disease mortality and a negative relationship with the Mediterranean Diet was observed. Keys remained in Pioppi in Italy for over 20 years and died in 2004 at the age of 100, confirming the favourable impact of 'his' Mediterranean Diet on himself.

Table 1 Adult Treatment Panel III recommended nutrient composition

Nutrients	Recommended intake
Saturated fats	<7% of total calories
Polyunsaturated fats	Up to 10% of total calories
Monounsaturated fats	Up to 20% of total calories
Total fats	25–35% of total calories
Carbohydrates	50–60% of total calories
Protein	~15% of total calories
Total calories	Balance energy intake and expenditure to maintain ideal body weight

Modified from Ref. 4.

The traditional Mediterranean Diet

A single definition of the Mediterranean Diet is not easy, given that in the Mediterranean area coexist countries with different cultural backgrounds, different ethnic and religious roots, different social and economic statuses, and different agricultural production, which lead to different food choices. In fact, there is no a single Mediterranean Diet, but a common 'Mediterranean' dietary pattern that has the same main characteristics. The main characteristics of the Mediterranean Diet defined by Ancel Keys, on the basis of the eating habits of the populations of the Mediterranean basin in the 1950s and 1960s, were a low consumption of meat and meat-derived products, with very low consumption of red meats (beef, pork, and lamb were reserved only for special occasions), very low or no consumption of cured meats, butter, creams, or other whole milk products (only fermented milk products, cheeses, and yoghurts were consumed in moderate quantities). It had a relatively high-fat profile due to the heavy consumption of olive oil, along with a high intake of lightly processed, locally grown vegetables, fruits, nuts, legumes, and grains (mostly unrefined). An important source of protein was a moderate consumption of fish and shellfish, which varied according to proximity to the sea. The main sources of fat and alcohol in the traditional Mediterranean Diet were mainly extra virgin olive oil and red wine, respectively. Red wine and extra virgin olive oil contain

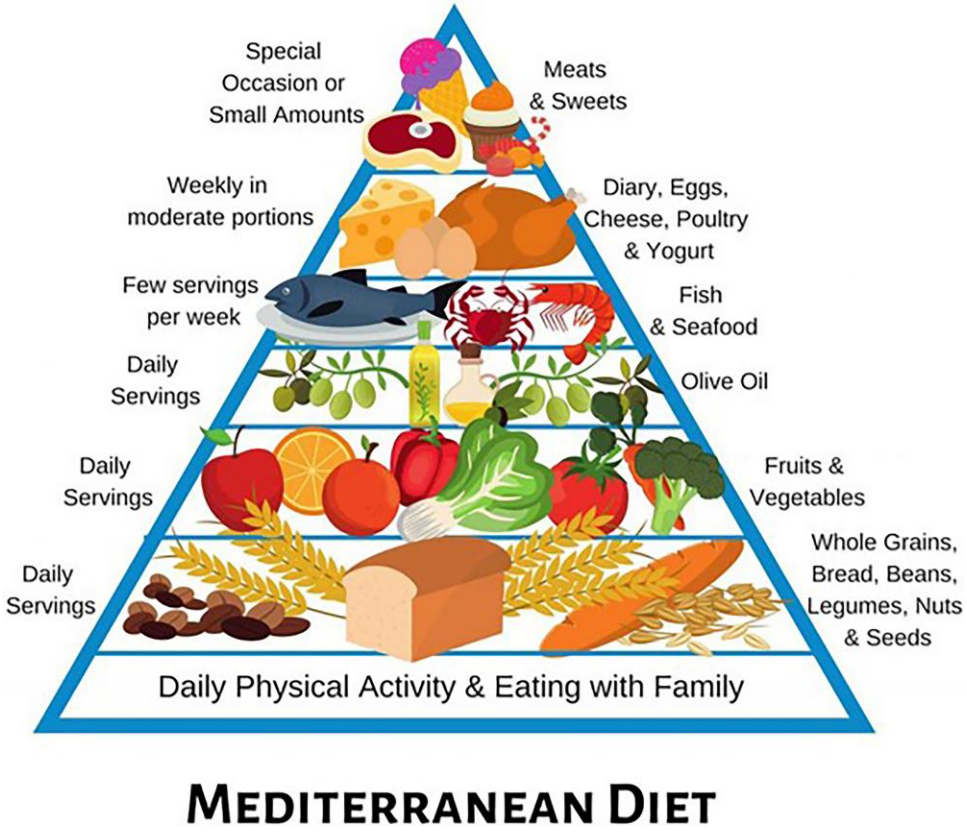

Figure 1 The Mediterranean Diet pyramid built by Oldways. www.oldwayspt.org.

several bioactive polyphenols (hydroxytyrosol and tyrosol, oleocanthal and resveratrol) with supposed anti-inflammatory properties.[6] The presumed antiatherogenic properties of olive oil would have been attributed to its high content of monounsaturated fats[7] and some more recent investigations also suggest that the bioactive polyphenols, present only in extra virgin olive oil, but not in the common variety of refined olive oil, may contribute to these cardioprotective actions.[8] An example of the Mediterranean Diet is represented in the Oldways pyramid (*Figure 1*).

Strengths and limitations of the Mediterranean Diet

Many of the scholars who are currently strong advocates of the Mediterranean Diet were born, live, or have ancestors in Mediterranean countries. This could represent a limitation because they may be biased in selecting the evidence that best fits their image of what a healthy diet should be.[9]

It is known that there is a significant association between pharmaceutical industry sponsorship and some scientific research conclusions. Recently, similar influences on research results have also been documented from the food industry. Furthermore, the regulations are stricter for pharmaceutical research than for nutritional research.[10]

A limitation from the scientific point of view is also constituted by the fact that there are more systematic reviews than the original studies. In 2016, an assessment of the quality of systematic reviews relating the Mediterranean Diet to cardiovascular outcomes was published. In their evaluation, the authors included 24 meta-analyses and systematic reviews.[11] In 2015, Martínez-González *et al.*[12] included 37 meta-analyses or systematic reviews evaluating the association between adherence to the Mediterranean Diet and cardiovascular events. Subsequently, in 2017 and 2018, a further five new meta-analyses were published. Thus, paradoxically, the literature appears to contain more reviews than original studies. In addition, Huedo-Medina's quality assessment found that, on average, systematic reviews on the Mediterranean Diet and cardiovascular health had a low-quality score, and 60% of the 24 meta-analyses had severe limitations because they did not report the details on research or used inappropriate statistical methods.[11]

As far as randomized trials are concerned, the French Lyon Diet Heart was a seminal study in evaluating the impact of diet on cardiovascular health.[13] It is a secondary prevention study aimed at reducing the risk of cardiovascular death and recurrence of myocardial infarction by means of diet modification in 605 patients who survived a previous infarction, enroled between 1988 and 1992, and randomized to a Mediterranean Diet (302 patients) or the control group (303 patients). The study showed a dramatic reduction in major coronary events and deaths over 4 years of follow-up. In an interim analysis at 27 months of follow-up, there was a 73% reduction in coronary events and a 70% reduction in total mortality and the study was terminated prematurely. The results of the

Lyon Diet Heart Study were therefore impressive, but the intervention did not exactly correspond to the traditional Mediterranean Diet.

In 2002, the results of the Indo-Mediterranean trial were published in the Lancet[14] which showed a drastic reduction in cardiovascular events in 499 patients randomly assigned to a diet similar to the Mediterranean one compared with 501 controls assigned to a similar diet to the low-fat one recommended by the National Cholesterol Education Program. However, in 2005, the Lancet published a note of 'concern' due to the unavailability of the original research data, resulting in the study being largely discredited.[15]

More recently, the Spanish study PREDIMED (Prevención con Dieta Mediterránea)[16] included 7447 participants at high cardiovascular risk assigned to three types of diet: a Mediterranean Diet supplemented with extra virgin olive oil, a Implemented Diet supplemented with mixed nuts or a control diet (with reduced use of all dietary fat subtypes). The study was prematurely terminated after 4.8 years following the termination rules established a priori in the protocol. The incidence of cardiovascular events (myocardial infarction, stroke, or cardiovascular death) in the Mediterranean Diet groups was reduced by 30% compared with the control diet. PREDIMED remains to date the largest dietary intervention study to evaluate the effects of the Mediterranean Diet on the prevention of cardiovascular disease. However, a review published in 2017 identified some inconsistencies in the study that led the authors to withdraw their original paper and simultaneously republish it in the same journal[17] in a new version where the mentioned inconsistencies were discussed and edited.

Low-fat diet or Mediterranean Diet in cardiovascular prevention?

Although epidemiological and mechanistic studies show similar results, there is no evidence from large-scale, long-term clinical trials on the efficacy of the Mediterranean Diet on secondary cardiovascular prevention, especially when compared with another active group. In fact, there is little evidence on the effects of a Mediterranean Diet in the secondary prevention of cardiovascular disease. Two works have highlighted the need for clinical data from randomized trials. A report by the Cochrane Library evaluated the current knowledge on the effects of the Mediterranean Diet in primary and secondary prevention.[18] The authors concluded that there is a paucity of evidence specifically for secondary prevention. In addition, a 2019 critical review analyzing the effects of the Mediterranean Diet highlighted the need for new data on secondary prevention, because the only two existing significant studies were either too short[13] or had some important limitations.[14] Thus, although several guidelines also recommend the Mediterranean Diet for secondary prevention, no clinical studies have been conducted in the last 20 years to support this recommendation. A convincing answer was obtained from the recent CORDIOPREV (CORonary Diet Intervention with Olive oil and cardiovascular PREVention) study.[19] The CORDIOPREV trial is a randomized (single centre) clinical trial conducted in Spain. Approximately 1000 patients with documented coronary artery disease were randomly assigned in a 1:1 ratio to receive a Mediterranean Diet or low-fat dietary intervention, with a 7-year follow-up. The primary endpoint was a composite of major cardiovascular events, including myocardial infarction, revascularization, ischaemic stroke, peripheral arterial disease, and cardiovascular death. The primary endpoint occurred in 198 participants: 87 in the Mediterranean Diet group and 111 in the low-fat group (log-rank $P = 0.039$). The multivariate adjusted hazard ratios of the different models ranged from 0.719 (95% CI 0.541–0.957) to 0.753 (0.568–0.998) in favour of the Mediterranean Diet. In conclusion, in secondary prevention, the Mediterranean Diet was superior to the low-fat diet in the prevention of major cardiovascular events. The results of the CORDIOPREV study are relevant for clinical practice and support the use of the Mediterranean Diet also in secondary prevention.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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