Chapter 40
The Mediterranean Diet: A Healthy Diet for the Modern Times

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Introduction

The Mediterranean diet (MD) is the dietary pattern commonly found in South European countries, such as Greece, Spain, Italy, and South France. Populations of Northern Africa and Middle East also influence the MD model.

This diet is widely embraced by medical doctors and nutritionists, as numerous studies have shown that adhering to the MD can reduce the risk of many diseases, such as cardiovascular disease (CVD), cancers, cognitive decline, and dementia. Adherence to the MD model is however challenged in the present times due to the Western diet model spreading across the world.

We now are aiming at providing an overview of the fundamentals of the MD model. We will summarize some important findings regarding its definition and health effects. The biological mechanisms explaining the health effects of the MD and the totality of epidemiological evidence supporting the benefits of the MD are not fully discussed in this text. Preedy and Watson have contributed an authoritarian text on this subject that encompasses the finer details of epidemiology, mechanism, and specific health advantages [1].

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What the Mediterranean Diet Is?

Historical Overview

The traditional MD diet is an eating pattern typical of the people living in the Mediterranean Sea areas. It likely originated before the modern eating habits emerged with energy-dense, highly processed, and mass-produced foods.

The MD was first defined by the controversial American biochemist Ancel Keys, who launched the Seven Countries Study in the 1950s [2]. The MD was the eating pattern of Italians and Greeks at that time with a very low risk of CVD and coronary heart disease (CHD) mortality especially among middle-aged men living in Crete and Corfu. The Seven Countries Study was in fact the first epidemiological study that examined whether CVD could be influenced by factors such as diet and lifestyle.

The main finding was that the farmers of Crete and Corfu, despite high intake of fat, had very low CHD mortality and the highest life expectancy in comparison to the other cohorts, in particular American and Northern European people. Only the Japanese cohort was comparable to the Greek, but because of the recent world war, the Japanese example did not attract the attention of Keys.

This quite surprising finding was first attributed by Ancel Keys to the low blood cholesterol levels of the people in Crete and Corfu. Ancel Keys was thinking that the reason of low cholesterol was the low intake of saturated fat and high intake of unsaturated fat. The MD being characterized by high consumption of olive oil (rich in unsaturated fat), along with low consumption of fatty meat and cow milk products (rich in saturated fat), the main advantage of the MD as seen by Ancel Keys was its effect on blood cholesterol. Thus, for Ancel Keys, the main finding of the Seven Countries Study was the role of blood cholesterol in CHD, a theory he had been defending for many years and before launching the Seven Countries Study. All the other aspects of the MD, including polyphenols of olive oil and wine (for instance), had no importance for Ancel Keys who was focusing almost exclusively on the cholesterol-lowering effect of the MD [2].

However, since that introduction, a great amount of work has been carried out highlighting the protective role of several components of the MD against chronic diseases, such as CHD and cancer.

This plethora of evidence on the positive health benefits of the MD, which is not present for other dietary patterns, led to the MD being recognized by the United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 2010 as an “intangible cultural heritage of humanity” [3].

The Traditional Mediterranean Diet

The traditional MD is characterized by abundant plant foods, such as fruits, vegetables, legumes, potatoes, nuts, seeds, and unrefined cereals (e.g., whole grain bread and pasta, brown rice). Olive oil is the principal source of fat, and intake of animal and plant saturated fat is low. Dairy products (mostly in the form of cheese and

yogurt), fish, and poultry are consumed in low to moderate amounts, and several eggs are consumed weekly. Red meat is consumed in low amounts, and wine is consumed in low to moderate amounts, normally with meals. Between-meal snacks are frequent with nuts, cheese, bread, and some alcoholic beverage. Fresh and dried fruit is often and seasonally consumed. The energy from fats of the MD can range according to the area; it could be high, around 40%, as in Greece, or moderate, around 30%, as in Southern Italy, but in any case, the intake of the monounsaturated fats, primarily originating from olive oil, is higher than the saturated fats [4–6].

What Is the Evidence on Health Benefits of the MD?

Cardiovascular Diseases

According to WHO, CHD and stroke remain the major causes of death around the globe. It is estimated that 15.2 million deaths occurred from CHD and stroke in 2016, out of which 9.4 million were due to CHD and 5.8 due to stroke [7].

Many epidemiological and ecological studies have examined the association between the MD and cardiovascular diseases (CVD). For instance, a meta-analysis of cohort studies up to 2010 assessed the relationship between the degree of adherence to the MD – using an MD score – and CVD mortality and morbidity. It was shown that a two-point increase in the MD score was associated with an 8% reduction in mortality and a 10% reduction in morbidity [8].

In 2011, a Spanish cohort of 13,000 participants concluded that participants with the highest MD score (>6 out of 9) had a lower CVD risk compared to those with the lowest adherence score (<3 out of 9). It was found that a 20% risk reduction for total CVD and a 26% risk reduction for CHD were associated with a two-point increase in the MD score [9].

Interestingly, the benefits of adhering to the MD are not confined to the Mediterranean populations. For instance, in the Dutch European Prospective Investigation into Cancer and Nutrition (EPIC)-NL cohort study, analyzing data from 40,000 participants, a two-point increase in the MD score (on a nine-point scale) was inversely associated with fatal CVD, total CVD, myocardial infarction, stroke, and pulmonary embolism [10].

Similarly, in the US cohort Northern Manhattan Study (NOMAS), investigators found that the MD score was inversely associated with the risk of ischemic stroke, myocardial infarction, and CVD death [11].

More importantly, data from randomized clinical trials (RCT) supported the epidemiological evidence. The Lyon Diet Heart Study was a single-blinded RCT aimed at testing secondary prevention with the MD on recurrence rates of myocardial infarction in comparison to the diet recommended in the Western world after myocardial infarction or other heart attacks. The study showed that the protective effect of the MD was considerable (70% reduction of the risk) and maintained up to 4 years after the first infarction [12, 13].

The Prevención con Dieta Mediterránea (PREDIMED) RCT investigated the effect of the MD on CVD risk in primary prevention. The researchers randomized 7.447 participants into an MD diet group supplemented with extra-virgin olive oil, an MD diet group supplemented with mixed nuts, or a control diet group. Results showed that the MD extra-virgin olive oil group had a 30% lower CVD risk and the MD nuts group a 28% lower risk compared with the control group. The results of multivariate analyses showed a similar protective effect of the two Mediterranean diet versions versus the control diet [14].

Taken together, a plethora of epidemiological, clinical, and meta-analytic evidence highlights the cardioprotective effect of the MD.

Cancer

Cancer is the second cause of death worldwide and in developed countries. According to WHO, about one-third of deaths due to cancer are attributed to deleterious lifestyle, i.e., low fruit and vegetable intake, lack of physical activity, and tobacco and alcohol use [15]. Therefore, a healthy dietary pattern can play an important role in cancer prevention.

The first randomized trial showing an anticancer effect of the MD was again the Lyon Diet Heart Study [16]. Revisiting the updated review and meta-analysis of Sofi et al. [8], data of the Lyon Diet Heart Study were confirmed, as it was found that adherence to the MD (assessed by an MD score) was associated with a lower cancer risk. Later, the Multicase-Control Study on Common Tumors in Spain (MCC-Spain), a study performed in seven Spanish provinces between 2008 and 2013, investigated the influence of environmental factors in certain tumors. They recently came up with data showing that high adherence to the MD is associated with a lower risk of aggressive prostate cancer [17]. Sub-analysis of the Adventist study found an association of eating red meat one or more times per week with nearly twice the risk of colon cancer. In the same population, an association of eating "white meat," both chicken and fish, one or more times per week was found to confer a risk with colon cancer over three times than that of nonmeat eaters. Eating legumes two or more times per week predicted half the risk [18].

Data on breast cancer are also supportive of the protective role of MD. Breast cancer is the leading type of cancer in European women, followed by colorectal and lung cancers [19]. The Greek EPIC cohort study followed up 14,807 women and found that adherence to the MD (assessed by an MD score) was associated with a lower breast cancer risk [20]. The same was found in an American case-control study, showing that a high MD score is associated with a decreased risk of breast cancer [21]. In the Nurses' Health Study cohort, investigators also found that high MD scores were associated with a lower risk of breast cancer [22]. The PREDIMED study showed a 62% lower risk of malignant breast cancer in the group of women receiving supplements of extra-virgin olive oil compared to the control group [23]).

In contrast, some other studies have not found an association between breast cancer and the MD. For instance, a British study with 33,731 women found no significant associations between the MD and breast cancer [24]. A similar result was reported in Sweden [25]. An important issue is the control of many confounding factors including genetic predisposition and lifestyle characteristics other than diet.

Taken together, the above scientific evidence, especially data from randomized trials (Lyon Diet Heart Study and PREDIMED), points toward a protective effect of the MD against several cancer types. Additionally, the association of excess body weight, often mitigated in a plant-based, MD-style diet, has been linked independently to a number of cancers including breast, colon, esophageal, liver, ovarian, and thyroid [26].

Cognitive Function

Cognitive aging has become an important concern of the modern times. It decreases the quality of life and is predictive of cognitive decline and dementia.

Dietary patterns, including the MD, have been investigated for their influence on cognitive function. Higher adherence to the MD appears to be associated with a lower risk of cognitive impairment. In subjects with mild cognitive impairment, adhering to the MD seems to reduce the risk of progressing to Alzheimer disease [27]. The MD has also been associated with a risk reduction of Alzheimer disease [28, 29]. A cohort study examined the relations between the MD score and cognitive performance [30]. It was found that higher MD scores are associated with slower cognitive decline. Another prospective study concluded that adherence to the MD is associated with lower subjective cognitive function [31]. Meta-analyses have also shown a protective effect of the MD against cognitive decline [32, 33]. Another meta-analysis provided evidence that adherence to the MD results in benefits on cognition in healthy adults [34]. Finally, the PREDIMED trial showed that in the MD group supplemented with extra-virgin olive oil, cognition scores were higher than the control group [35].

Thus, overall evidence indicates that the MD protects cognitive health. This is a critical finding in the context of aging population.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease in the developed world, and the patients who suffer from it have increased mortality and morbidity [36]. It will probably emerge as the leading cause of end-stage liver disease in the coming decades, with the disease affecting both adults and children [37]. NAFLD is characterized by the accumulation of fat in the liver, not related to alcohol drinking. The prognosis can vary in severity, from simple steatosis to hepatocellular carcinoma. Mechanisms of NAFLD are not well defined.

A diet high in refined sugars and saturated fats has been associated with NAFLD [38]. General advice however simply refers to weight loss. Interestingly, low adherence to the MD was associated with the severity of both NAFLD and insulin resistance [39].

A randomized 6-week dietary trial showed that the MD reduces liver steatosis and improves insulin sensitivity without weight loss [40]. Another study found that a low adherence to the MD and a high body mass index predict fatty liver disease in obese children [41]. More recently, in children 10–17 years of age, poor adherence to the MD was shown to be higher in patients with NAFLD [42].

Thus, the MD might be associated with a reduction in NAFLD risk and severity, but more studies, in particular randomized trials, are needed to confirm the point.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder that affects joints and causes pain, swelling, and stiffness. The main treatment is medications, which can provoke side effects. Dietary interventions can improve the symptoms of RA [43].

A diet rich in vegetables can improve the symptoms of RA. The MD, being primarily based on plant products and low in red meat, dairy foods, and alcohol, can decrease inflammatory activity in RA. It could also increase physical function and improve vitality [44]. The precise components of the MD that are responsible for the amelioration are not clearly defined.

A recent cohort study reported that the intake of MUFA, pulses, total vegetables, meat, milk, and other dairy products was significantly lower in RA patients than in controls [45]. In contrast, grain intake was higher in the RA group. Finally, it was found that monounsaturated fat was the main factor that decreases risk. The study has highlighted the importance of MUFA, which the MD is rich in [45].

Recent studies suggest a link to RA from *Proteus mirabilis*, a pathogenic bacterium potentially found in the urinary tract. Through molecular mimicry, the immune system reacting to an antigen of the *P. mirabilis*, an autoimmune reaction results in RA deposits and symptoms [46]. Potentially, switching to an MD-style plant-based diet can alter the microbiome of the urine and colon resulting in a decline in *P. mirabilis* leading to less onset and a decline in symptoms. This has been clinically supported by a study demonstrating a vegan then lactovegetarian diet resulting in significant decline in pain, morning stiffness, and improved function in patients with RA [47].

Chronic Respiratory Diseases

Among chronic respiratory diseases, one of the most common is asthma. In particular, it is the most common chronic disease in children. However, most asthma deaths occur in the elderly, and with the increasing aging population, deaths from asthma will considerably increase in the next 20 years.

Lifestyle characteristics, such as tobacco, air pollutants, and nutrition, are thought to play a role in asthma. Antioxidants, such as vitamins A, C, and E, carotenoids, and polyphenols, may be protective against asthma during childhood, because it is the time when airways are most vulnerable to oxidative stress [48].

Since the MD is high in antioxidants (fruit, vegetables, and extra-virgin olive oil), studies have investigated the relations of MD with asthma.

A study among 7–18-year-old children in Crete was performed to assess whether adherence to the MD is protective effect against allergic rhinitis, asthma, and atopy [49]. Another study showed that high adherence to the MD reduces by about 80% the risk of asthma in adults, in particular because of high intake of fresh fruit [50]. Three studies reported a protective effect of the MD for wheezing in children [51]; reduced asthma, wheezing, and rhinitis in Mexican children [52]; and a protective effect in girls aged 6–7 years with current severe asthma [53]. A cohort study showed that high adherence to the MD had a protective effect against persistent wheeze, atopic wheeze, and atopy [54]. In 2011, a Greek study found that high adherence to the MD was inversely associated with wheeze, in particular exercise wheeze. One-unit increase in the MD adherence score was associated with 14% lower risk of asthma [55].

Finally, a randomized trial, where asthmatic adults were allocated to an MD or a control diet, found improvements in the quality of life of patients in the MD group [56].

There appears to be a significant rate of misdiagnosis of asthmatics with over 30% demonstrating no objective evidence of asthma resulting in cessation of medication in 90% of the group [57]. Exercise-induced asthma is a misnomer as most cases are not asthmatic at all and are instead related to "exercise-induced laryngeal obstruction" or EILO. EILO occurs during physical activity and presents as inspiratory stridor, on inhalation, and not a "wheeze" as it is commonly described. This occurs from a hypersensitive larynx reflexively causing closure of the vocal folds and thus stridor, when stimulated. Treatment consists of trigger reduction of postnasal drip, laryngopharyngeal reflux, and exercise-induced laryngeal obstruction therapy and not asthma medication [58]. A diet-based approach using alkaline water and a plant-based MD with EILO therapy can improve symptoms significantly and avoid the long-term unnecessary use of medications, steroids, and other asthmatic treatments [59].

Given the scope of this book, only a few of the many benefits of an MD have been discussed. A plant-based, MD-style diet can result in significant improvement in glycemic control in diabetes, both type 1 and type 2. Decreased rates of cerebrovascular disease as well as neuropsychiatric diseases with better outcomes are seen in an MD. A mostly plant-based MD lifestyle leads to far less obesity. In fact, a mostly plant-based MD results in overall decline in morbidity and mortality. The authoritarian text by Preedy and Watson [1] encompasses the wide range of health benefits and disease improvements afforded by a mostly plant-based MD.

What Are the Main Foods of the Mediterranean Diet?

A synergistic effect of the different food components in the MD is suggested to play the main role in the protective effect of the MD. Studies have examined the effects of individual components of the MD. There is evidence that some components of

the MD are important. Most nutritional studies are observational and epidemiological in nature and thus exposed to multiple confounding factors and variables. Studies focusing on a specific nutrient or compound often miss the forest through the trees. The focus on the compound often does not take into account the complex interactions of the multitude of components within the whole food and the complex biochemical and biophysical reactions within the body during digestion and metabolism. The emphasis on a mostly plant-based, whole food MD should be the focus rather than the individual components of the particular foods in order to see the marked potential improvement in overall health.

Fish and Marine Omega-3 Polyunsaturated Fats

Marine long-chain omega-3 fatty acids (LCO3) are found in fatty fish and have been studied for their health effects. Fatty fish is a component of the MD. It is unknown so far whether the health effects of fatty fish are independent from full adherence to the MD. Conceivably, evidence from these studies may be skewed to represent a trend toward a healthier lifestyle that has incorporated far more fruits, vegetables, grains, and nuts into the diet.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the main LCO3 in fish and are thought to be partly responsible for the cardioprotective effect of marine foods. A systematic review of RCT showed that LCO3 reduce the risk of CVD by 23% [60]. A meta-analysis of RCT found a significant CHD risk reduction with LCO3 among high-risk populations, and from the analysis of cohorts, it found a statistically significant 18% reduced risk of CHD [61]. On the other hand, studies showed that supplementation with LCO3 had no significant effect on fatal and non-fatal cardiovascular complications [62].

However, it is important to distinguish between the consumption of fish and that of LCO3 supplements. The health benefits related to consuming fish/seafood are not limited to the consumption of LCO3. Sea and most freshwater fish contain in various amounts high-quality proteins, iodine, selenium, and vitamin D, all this in addition to LCO3, cholesterol, and other lipids. In other words, testing the benefits of fish is not equivalent to testing the effects of fish oil and/or LCO3 supplements [63].

However, there is not yet a published randomized trial testing the effect of fish, so one has to rely on epidemiological studies. Studies, such as the Zutphen [64] and Western Electric studies [65], showed an inverse association between fish and CHD mortality. The US Physicians Health Study also showed that one fish meal per week reduced the risk of sudden cardiac death by 52%, compared to a fish meal once a month [66]. The Nurses' Health Study reported that frequent fish consumption was associated with a lower risk of CHD [67]. A meta-analysis showed that an increased consumption of fish was associated with a 19% reduced risk of coronary heart disease [60].

In contradiction, other studies, such as the Health Professionals Follow-Up Study [68], the EPIC-Spain [69], and the EPIC-Germany cohort [70], found no association

between fish consumption and the risk of myocardial infarction and/or stroke. A meta-analysis found a nonsignificant trend toward decreased risk with fish consumption [71]. The reason for the nonsignificant results could be that the amount of fish was less than suggested by previous studies, for example, about 30 g/d in the study of Grosso versus more than 100 g/d from previous positive studies.

Importantly, fish consumption also results in lower risk of other diseases such as cancers. Studies have shown an inverse association between fish intake and various types of cancers [72–74]. However, as mentioned earlier, an increase rate of colon cancer was found among a population of Seventh-Day Adventists eating one or more serving of fish weekly [18].

Finally, in a randomized trial, high consumption of DHA was shown inversely associated with cerebral amyloidosis, a preclinical stage of Alzheimer [75].

The human body can process LCO3 into EPA and DHA bringing into question the amount required to be consumed on a daily basis. Chia seeds and walnuts are simple sources of LCO3, and as little as a tablespoon a day is sufficient to provide the sources required.

It is always important to balance the potential benefits and risks of any particular type of food material. The benefit of fish, though suggested in some studies, is not completely clear as other studies have shown potential risks. In addition, the majority of fish stocks are contaminated with heavy metals such as lead, mercury, and cadmium, organic pollutants such as dioxins and other polychlorinated, and polybrominated diphenyls, not to mention antibiotics, other pharmaceuticals, and most recently microplastics.

Keeping the consumption of fish to no more than one to two servings per week in the setting of a mostly plant-based diet can be a guide for those who choose to keep fish and marine animals in their diet.

Plant Omega-3 Fatty Acids

The traditional MD is rich in plant n-3 fatty acids, the main one being alpha-linolenic acid (ALA). This n-3 fatty acid is *essential* to humans, meaning that they cannot synthesize it independently. The major sources of ALA in the Western diet are vegetable oils (for instance, rapeseed oil and soybean oil), seeds (for instance, flaxseed), and nuts (mainly walnuts). In the traditional MD and besides walnuts, ALA is found in wild plants consumed by goats, sheep, chickens, and rabbits, products of which (eggs, fermented milk, meat) are then consumed by the Mediterraneans [76]. The intake of ALA is definitely associated with health benefits [77–79].

ALA is in fact a precursor molecule that can be converted into LCO3 such as EPA and DHA, discussed in the previous section [80, 81]. The enzymatic system acts through a series of elongation and desaturation steps. The conversion of ALA to EPA and DHA is influenced by genetic variations, hormonal status, and nutrient substrate competition [82–85]. This conversion efficiency is thought to be low in

non-Mediterranean populations, leading to the necessity of consuming certain amounts of LCO3.

Another interesting aspect lies in consumption of polyphenols, which seems to increase the conversion of ALA to DHA and EPA, as shown in epidemiological and animal studies [86–88]. These data were however not confirmed in human trials [89]. This might have been due to the fact that in these studies, the polyphenol ingestion was increased through supplementations and/or pure substances and not through the consumption of a healthy diet as in the positive studies [86–88]. This is a critical issue as the active forms of polyphenols – the substances that actually increase the synthesis of LCO3 from ALA – need a specific microbiota to be activated and acquisition of that specific microbiota needs specific nutrients (specific fibers in particular) absent from the supplements [90]. In other words, to get benefits from ALA intake and obtain more blood and tissue LCO3, the Mediterranean polyphenols and microbiota are both required.

Olive Oil

Olive oil is a traditional component of the MD. For a long time, olive oil has been the main source of fat for the Mediterranean population. Extra-virgin olive oil is obtained from the fruit of the olive tree, and more than 95% of if consists of fatty acids. Its fatty acids are mainly monounsaturated, such as oleic acid, whereas polyunsaturated fatty acids, such as linoleic acid, and saturated fatty acids, such as stearic or palmitic acid, are in very low amounts. Olive oil also contains major phenolic compounds, oleuropein being the most abundant one. Other minor components of olive oil may have a potential cardioprotective effect. The amounts of these compounds in the final olive oil depend on the cultivar, climate, and ripeness of the olives at harvesting.

Studies have found an inverse association between olive oil consumption and risk of cardiovascular diseases and also risk of various cancers, diabetes, and neurodegenerative disorders [91–95]. The most recent finding comes from the PREDIMED study reporting a 39% risk reduction of stroke in the group consuming extra-virgin olive oil. For each 10 g/day increase in olive oil consumption, mortality decreased by 7% [96].

The proposed mechanisms of the protective effect of olive oil are the improvement of insulin resistance, reduction of blood pressure, improvement of endothelial function, decrease of inflammatory markers, and reduction of coagulation factors and platelet aggregation [97]. Just as with fish, there are also studies suggesting the consumption of oils, including olive oils, can lead to increased endothelial stiffness lasting for hours potentially suggesting that overconsumption can lead to cardiovascular disease [98]. Evaluation of the Spanish cohort of the EPIC study, with over 40,000 people evaluated, demonstrated that although extra-virgin olive oil seemed to confer a slight advantage over regular olive oil with regard to cardiac events, neither significantly differed when controlled for other healthy diets including more

vegetables and fruits [99]. In fact, the benefits of olive oil consumption are related to the anti-inflammatory phytonutrients which are in far higher concentration in the olive itself, again suggesting the whole food is more important than an isolated component.

Fruit and Vegetables

Most healthy diet required high fruit and vegetable intake. Fruit and vegetable are major components of the MD. The Healthy Eating Plate created by the Harvard School of Public Health advices that ½ of our plate should consist of fruit and vegetables [100]. The American Heart Association also recommends five or more servings per day for adults [101]. This advice is based on epidemiological studies. In 2003, WHO concluded that the evidence on the preventive effect of fruit and vegetables against CHD is powerful enough and advised on an intake of about 500 g/day (5–6 portions of 80 g each) [102].

In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart, investigators found that fruit and vegetable consumption was associated with a 22% lower risk of fatal CHD for subjects consuming at least eight portions (80 g each) of fruits and vegetables a day, in comparison to those consuming fewer than three portions a day [103]. In the Health Survey of England data, there was inverse association between fruit and vegetable intake and all-cause, cancer, and cardiovascular mortality [104]. The cardioprotective effects of fruit and vegetables could be linked to their high content of antioxidant vitamins and phytochemicals [105–107].

Several meta-analyses have been conducted to examine the issue. Wang analyzed 16 studies and found a significant association between consumption of fruit and vegetables and all-cause and cardiovascular mortality [108]. The study found a threshold around five servings of fruit and vegetable per day, after which the effect of all-cause mortality does not persist. In the systematic review and meta-analysis, a reduced risk of CHD, stroke, cancer, and all-cause mortality was observed with increased intake of fruit and vegetables [109].

As expected, the results from RCTs regarding the health effects of fruit and vegetables are less evident. In a small trial, individuals consuming a standardized meal of 500 g of fruit and vegetables per day, as well as 200 ml of fruit juice per day, were compared to a group who consumed only 100 g of fruit and vegetables per day [110]. It was found that over a 4-week follow-up, the serum lipids, blood pressure, and hemostatic parameters were not modified. Conversely, in a 6-month RCT including 690 healthy individuals, those allocated in the intervention group (increased fruit and vegetable consumption) had higher plasma concentrations of carotenoids and ascorbic acid and a significant decrease of blood pressure, compared to the control group [111].

Studies examined the effects of specific fruits or vegetables. In a study where subjects had low intake of fruit and vegetables, consumption of blackcurrant juice (high in vitamin C and polyphenols) resulted in decreased oxidative stress and

improvement of vascular health, within a 6-week time frame [112]. Fruits and vegetables are the primary source of abundant antioxidants, phytochemicals, and other nutrients that can protect against oxidative stress and against a chronic inflammatory state.

Another study reported that high-sulforaphane broccoli sprouts reduced production of noxious nitric oxide metabolites in *H. pylori*-infected patients [113]. Obviously, we need RCT testing the intake of specific Mediterranean fruit and vegetables in the context of full adherence to the MD.

Nuts and Seeds

Nuts and seeds are nutrient-dense foods, high in vitamins and minerals, and they have been part of the MD diet since early times. These products contain, among other components, beneficial fatty acids and proteins. Main nuts of the MD are almonds, hazelnuts, walnuts, and pistachios [114]. Saturated fatty acids in these nuts are low, whereas mono- and polyunsaturated fatty acids are high. For instance, walnuts provide the omega-6 linoleic acid and the omega-3 ALA; both have been linked to health benefits. Nuts are also sources of fiber, protein, and micronutrients, such as potassium, calcium, magnesium, folate, antioxidant vitamins, and polyphenols [115].

Several studies have studied the association between nuts consumption and health outcomes. A summary of the data from the Adventist Health Study, Iowa Women's Health Study, Nurses' Health Study, and Physician's Health Study found a dose-response relationship, estimating an 8% reduction of CHD death for each weekly serving of nuts [116]. The cross-sectional Multi-Ethnic Study of Atherosclerosis found that frequent nut and seed consumption was associated with lower levels of inflammatory markers. This could explain the inverse association of nut consumption with cardiovascular disease and diabetes risk [117].

Clinical trials confirmed epidemiological studies. For example, in the PREDIMED trial, participants allocated to the intervention group with 30 g/day mixed nuts had a lower prevalence of high blood pressure, compared to the control group [118].

Nuts and seeds are integral components of the MD, and even though the specific mechanisms of their protective effects are still unclear, nut consumption is highly recommended, especially in individuals with a high risk of CHD.

Dietary Fiber

Dietary fiber traditionally refers to the indigestible part of plants. It is found in fruits, vegetables, legumes, nuts, seeds, and whole grain and cereals. Examples are lignin and polysaccharides. Oligosaccharides, such as inulin and resistant starches,

have been recently added to the definition of dietary fiber [119]. The recommended intake of fibers is 25–30 g/day.

Most available data are from epidemiological studies. A large body of evidence exists on the inverse association between dietary fiber intake and CHD, diabetes, and gastrointestinal disease. Knowledge on the effects of fiber on weight management and gastrointestinal health is more widespread than the benefits against CHD and diabetes.

High intake of dietary fiber has been associated with a decreased CHD and stroke risk. Early evidence came from the Iowa Women's Health Study where postmenopausal women with high intake of whole grains had a lower risk of CHD [120]. In the Nurses' Health Study, women in the highest quintile of whole grain consumption had a 30% lower risk of CHD than women in the lowest quintile [121]. Similar results were reported in subsequent studies [122]. An inverse association between fiber intake and risk of stroke was found in epidemiological studies and meta-analyses [123, 124].

Increased dietary fiber intake is useful in diabetes prevention [125, 126]. In addition, total grain and whole grain were inversely associated with the risk of type 2 diabetes [127]. In a randomized crossover study of participants following a diet with moderate amounts of fiber (24 g) or a high-fiber diet (50 g), improvement of glycemic control and decreased blood insulin were observed [128]. Finally, a meta-analysis found a dose-response relationship, where the risk of type 2 diabetes decreased by 6% for each 2 g/day increment in cereal fiber intake [129].

Wine

Wine is the preferred alcoholic drink of the Mediterranean population, except in Muslims. Wine consumption has been shown to reduce risk of CVD throughout the world. The first report of the possible protective effect of wine was in 1979 [130]. The term "French paradox" was used to describe the fact that French people, despite their high saturated fat intake and lifestyle characteristics often similar to other Western populations, have a low incidence of CHD [131–133]. Wine and ethanol drinking has been associated with several protective effects including antiplatelet [134, 135] and vasodilating action but also myocardial preconditioning [136, 137] and increasing plasma LCO3 (as discussed above in the fish section), all these factors being critical in the prognosis of heart attack and ischemic stroke.

Many studies have shown a cardioprotective effect of wine, including systematic reviews and meta-analyses. For instance, Di Castelnuovo analyzed 26 studies and found a J-shaped association between wine intake and CHD risk [138]. A subsequent meta-analysis included 84 prospective cohort studies and found that light to moderate alcohol consumption is linked to a reduced CHD risk [139].

One of the main principles of the MD is moderation. This implies that when wine is consumed in the setting of an MD, it is critical to respect the Mediterranean "way of drinking." That means in moderate quantities and most of the time during

the meals and not Saturday night binge drinking. Is there a safe amount of alcohol to consume? This question was addressed in a large multi-institutional study published in Lancet suggesting that the current limits for alcohol consumption should be lower than what is currently recommended. In over 600,000 studied, the risk of all causes of mortality, especially cancer, rises with increasing alcohol intake. Recommendations from this study suggest that "no level of alcohol consumption" should be considered safe [140]. Again, the epidemiological nature of this research is prone to confounding factors. Does alcohol use in a vegan or mostly plant-based MD population have less of a negative effect than in a more meat-heavy, standard American diet?

Is the MD Adapted to the Present Times?

Level of Adherence to the MD

To determine whether a population is adhering to the MD, we need a specific methodology. So far, the usual methodology to evaluate adherence to the MD has been the scoring of the dietary habits of sample populations. In most cases, higher score stands for higher adherence [141]. In the Greek EPIC cohort study, investigators used a Mediterranean Diet Score (MDS) and observe that a two-unit increase of the MDS was associated with a 25% reduction in mortality [142]. This MDS was based on nine major components of the MD: vegetables, legumes, fruits and nuts, cereals, fish and seafood, meat and meat products, dairy products, moderate alcohol intake, and MUFA/SFA ratio. A value of 0 or 1 was assigned to subjects whose consumption was below the median (value: 0) or at or above the median (value: 1). The MDS ranges from 0 to 9.

The Mediterranean Adequacy Index (MAI) is another MD score [143]. The reference MD was that from Nicotera (Southern Italy) in 1960, and the data for the calculation of the MAI were derived from the Seven Countries Study.

The MD 55 Score is based on the Greek ATTICA study and aimed at detecting clinical characteristics associated with cardiovascular disease [144]. Eleven main components of the MD (non-refined cereals, fruits, vegetables, potatoes, legumes, olive oil, fish, red meat, poultry, full-fat dairy products, and alcohol) are used. Scores from 0 to 5 are assigned depending on the frequency of consumption of each of these foods (from 0: no consumption to 5: daily). A score (from 0 to 55) is calculated. The study reported, for instance, that the score was 23.5 in hypertensive subjects versus 26.8 in normotensive subjects, 22.2 in diabetic subjects versus 26.2 in nondiabetic subjects, and 22.2 in obese subjects versus 26.5 in normal/overweight subjects.

The 14-point MD Adherence Screener (MEDAS) is another index created to provide a rapid control of compliance with the dietary intervention of the Spanish PREDIMED study (135). It consists of 14 food consumption frequency questions.

Each question is scored as 0 (no fulfillment) or 1 (fulfillment criterion). The study reported that for men, MEDAS was 8.7 ± 2.0 and 8.5 ± 2.0 for women [145].

Recently, a Spanish study developed a self-efficacy scale for adherence to the MD (SESAMeD) [146].

Challenges of Adhering to the MD

Despite the plethora of health benefits resulting from adherence to the MD, adherence can be challenging. Globalization and economic, urban, and technology-driven developments have led to a significant shift toward the Western diet high in refined sugars and saturated and industrial *trans* fats and low in fruits, vegetables, legumes, nuts, and seeds.

At present in many developed countries, the low-income groups show the highest prevalence in CVD, and it is thought that it is, at least partly, a result of the shift toward the Western diet. The higher prices of healthy, high-quality, and fresh foods, compared to the low prices of unhealthier snacks and fast food, also reduce adherence to the MD, as it has been found in the MOLI-SANI study, in which adherence to the MD was highly related to material resources [147].

The greater the income is, the higher the adherence to the MD. During the economic crisis in Italy (between 2008 and 2010), adherence to the MD decreased dramatically (18.3%) especially in the elderly, the less affluent, and the urban inhabitants [148].

Two additional factors that might be important for adhering to the MD are nutrition knowledge and exposure to media [149, 150]. Thus, it is likely that material resources are one of the most important factors influencing adherences to the MD. Other factors, such as mass media exposure and information, might play a role as well.

The Updated Mediterranean Diet Recommendations

Despite a general consensus in the scientific community on the characteristics of the MD, issues have been raised that the traditional MD should be updated to cover the changing lifestyle, as well as the environmental and health challenges of the modern society.

Main recommendations for a new (modernized) MD are food related. It is recommended to consume plant-based foods on a daily basis, such as fruit and vegetables, whole grain bread/pasta/rice, grains, cereals, and nuts. The overall goal is to obtain the vast amount of nutritional intake from a 90–95% whole food, plant-based, Mediterranean-style diet with only 10% of the dietary intake from any animal-based product. This translates to a diet of two to three meals out of twenty-one meals with snacks containing three to four ounces of any type of animal product, meat, or dairy.

These recommendations are in line with the most recent online dietary recommendations for the population of Canada [151].

To cover the intake of monounsaturated fatty acids, foods like extra-virgin olive oil (sparingly) and avocado can be consumed. Extra-virgin olive oil might be considered expensive compared to other oils, but due to its high caloric content, it does not need to be consumed in large amounts. Rapeseed canola oil can be used alternatively with olive oil, again sparingly. Selecting organic oils could be a major issue despite their costs. Nuts are recommended, as they are a rich source of important amino acids, unsaturated fats, fiber, and micronutrients. Mediterranean nuts include almonds, hazelnuts, pine nuts, pistachios, and walnuts. Walnuts especially are a rich source of ALA and have the highest level of phenolic compounds in comparison to other nuts [152].

Another important component of the MD is water. Hydration is important, and a daily intake of 1.5–2 L of water is strongly advised. This intake can be complemented with non-sugar herbal infusions, such as tea. Dairy products are recommended in moderate amounts, primarily in the form of yogurt, cheese, and other fermented dairy products though limited to the overall meal of less than five percent. For those who desire alcohol, a minimal consumption of wine during meals is recommended, but religious and social beliefs should be taken into account. On a weekly basis, it is suggested to consume fatty fish and seafood no more than two to three times per week, in line with a 95% whole food, plant-based MD-style diet. Fish can provide *essential* protein and lipids and other major nutrients such as iodine and selenium. Fish is a nonvegetarian source of LCO3, but until recently, vegetarians and vegans had only a few options, like flaxseeds and nuts to get ALA, but these options do not provide the LCO3 such as EPA and DHA. As the conversion of plant omega-3 to LCO3 is limited in humans in the absence of adequate microbiota and polyphenols, a solution could be algae, which is an emerging food rich in LCO3. By eating a mostly plant-based diet, adequate levels through endogenous conversion can be achieved.

White meat, such as poultry, rabbit, and eggs, can be consumed on a weekly basis, as they are sources of high-quality proteins, a major nutrient in the aging population but again limited to part of the two to three meals per week with three to four ounces per meal. Red and certainly processed meats should be consumed rarely, if at all, and in low amounts. Instead, legumes (lentils and chickpeas, for instance) and soy are alternatives.

Potatoes and other starches should be consumed weekly, as they often form a part of many traditional MD recipes. They should be consumed with moderation because of their high glycemic index, and the fried version should be consumed on an occasional basis. The seasonality of fruit and vegetables is a factor that should be taken into account. Fresh, seasonal, non-processed organic foods are the basis of the new and traditional MD. It is important to remember that it is not only about choosing a fruit but also considering its journey to the table and the way (organic or not) it has been produced, harvested, and stored.

Sweets and beverages high in sugars should be avoided, except for special occasions.

Socializing during meals is important, and sharing foods with family is recommended as a supportive factor of healthy eating and learning.

Sustainability

Adhering to sustainable diets is now a critical issue in modern societies. It is definitely recognized that the MD is not only a healthy dietary model but also a sustainable diet. In the first World Conference on the MD held in Milan in 2016, the International Mediterranean Diet Foundation illustrated the MD as a sustainable, human-centered dietary pattern.

The four sustainable benefits of the MD have been very well highlighted in a review article on the Med Diet 4.0 framework (142). These are as follows:

1. Major health benefits
2. Low environmental impact
3. High sociocultural values
4. Positive local economic returns

Regarding the lower environmental impact of the MD, many studies have documented it. As the MD is a plant-based diet with low animal product consumption, it has a small water footprint, low greenhouse gas emissions, and low energy consumption [153, 154].

The MD is a biodiverse diet, as it uses a large range of cereals, fruits, and vegetables that not only are cultivated but also can be wild; in the latter case, they come with specific local and traditional knowledge on their use.

The seasonality of the plant-based products of the MD is another important factor that contributes to its biodiversity.

Regarding the sociocultural value, the MD populations have had so many traditions and religious and cultural differences throughout their history, with values such as family and common meals all contribute to the MD being considered as an Intangible Cultural Heritage of Humanity.

Finally, about the positive local economic returns, it is clear that the MD encourages the sustainable development of rural areas producing local and traditional food products, with low dependence on external food imports. Local producers should be empowered, supported, and protected, and typical Mediterranean food products should be properly labelled, identified, and promoted [155].

Conclusions

The MD has definitely earned its title as a healthy-eating dietary pattern and a sustainable model. A plethora of medical studies, meta-analyses, and clinical trials supports the notion that the MD is a protective diet against several noncommunicable

diseases. Finally, the MD is not static but rather a dynamic model that brings together food, nutrition, sociocultural elements, and sustainability to create one of the world's most valuable lifestyles. Further exploration into the health benefits of a mostly plant-based, whole food, Mediterranean-style diet is encouraged with resources such as "The Mediterranean Diet" by Preedy and Watson [1], "How not to Die" by Michael Greger [156], and online resources such as "Forks over Knives" [157] that can be the basis for educated decisions on diet for the treatment and prevention of most chronic disease.

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