

# Mediterranean Dietary Patterns and Cardiovascular Health

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## Keywords

Mediterranean diet, cardiovascular disease, prevention, health

## Abstract

The Mediterranean dietary pattern has been linked with reduced cardiovascular disease incidence and mortality. Components of the Mediterranean diet associated with better cardiovascular health include low consumption of meat and meat products, moderate consumption of ethanol (mostly from wine), and high consumption of vegetables, fruits, nuts, legumes, fish, and olive oil. Increasing evidence indicates that the synergy among these components results in beneficial changes in intermediate pathways of cardiometabolic risk, such as lipids, insulin sensitivity, oxidative stress, inflammation, and vasoreactivity. As a result, consumption of a Mediterranean dietary pattern favorably affects numerous cardiovascular disease risk factors, such as dyslipidemia, hypertension, metabolic syndrome, and diabetes. Moreover, strong evidence links this dietary pattern with reduced cardiovascular disease incidence, reoccurrence, and mortality. This review evaluates the current evidence behind the cardioprotective effects of a Mediterranean dietary pattern.

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## INTRODUCTION

Nutritional factors play a role in both the promotion of health and the development of disease. The Mediterranean dietary pattern, which represents the eating habits of populations bordering the Mediterranean Sea in the 1960s, has long been reported to be a favorable approach to preventing cardiovascular disease and preserving good health (136). In the 1960s, the Seven Countries study demonstrated a relationship between saturated fat intake, fasting blood cholesterol concentrations, and coronary heart disease mortality in various populations and suggested a protective effect of traditional Mediterranean dietary patterns (54). The more recent World Health Organization (WHO)-sponsored Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) program (122) collected data on cardiovascular-related mortality from 21 countries from the 1970s to 1990s. An analysis of preliminary data found a north-south gradient in cardiovascular disease-related mortality, with more deaths occurring in the northern and fewer deaths in the southern, or Mediterranean, areas (122). More recently, several studies have

established a beneficial role for the main components of the Mediterranean diet on cardiovascular disease risk factors (7, 16, 28, 33, 56).

Adherence to a Mediterranean dietary pattern is associated with reductions in serum lipids, blood pressure, insulin resistance, arterial stiffness, and oxidative stress in addition to improvements in subclinical atherosclerosis and cardiovascular disease risk. In patients with cardiovascular disease or diabetes, adherence to a Mediterranean dietary pattern reduces the incidence of recurrent myocardial infarction and cerebrovascular events. Importantly, people who adhere to a Mediterranean diet are less likely to suffer sudden cardiac death and age-related cognitive decline. Herein, we review components of the Mediterranean dietary pattern and its effect on cardiovascular disease risk factors and cardiovascular health.

## MEDITERRANEAN DIET OVERVIEW

The traditional Mediterranean diet was based on food patterns typical of Crete, Greece, and southern Italy in the early 1960s. Variations exist but have been less well described in other parts of Italy, France, Lebanon, Morocco, Spain, Portugal, Turkey, and elsewhere in the Mediterranean region (54). The selection of this specific time and geography is based on two lines of evidence (135):

1. Data on food availability and dietary intake in the Mediterranean region describe dietary patterns with many common characteristics.
2. Dietary patterns sharing these common characteristics have been associated with low rates of chronic disease and high adult life expectancy in epidemiological studies conducted throughout the world.

This diet was low in saturated fat ( $\leq 7\%$  to  $8\%$  of energy), with total fat ranging from  $25\%$  to  $35\%$  of energy from one area to another. Early data also indicated that work in the field (by men) or kitchen (by women) resulted in a lifestyle that included regular physical activity and was associated with far less obesity than was observed in the United States at the time (54).

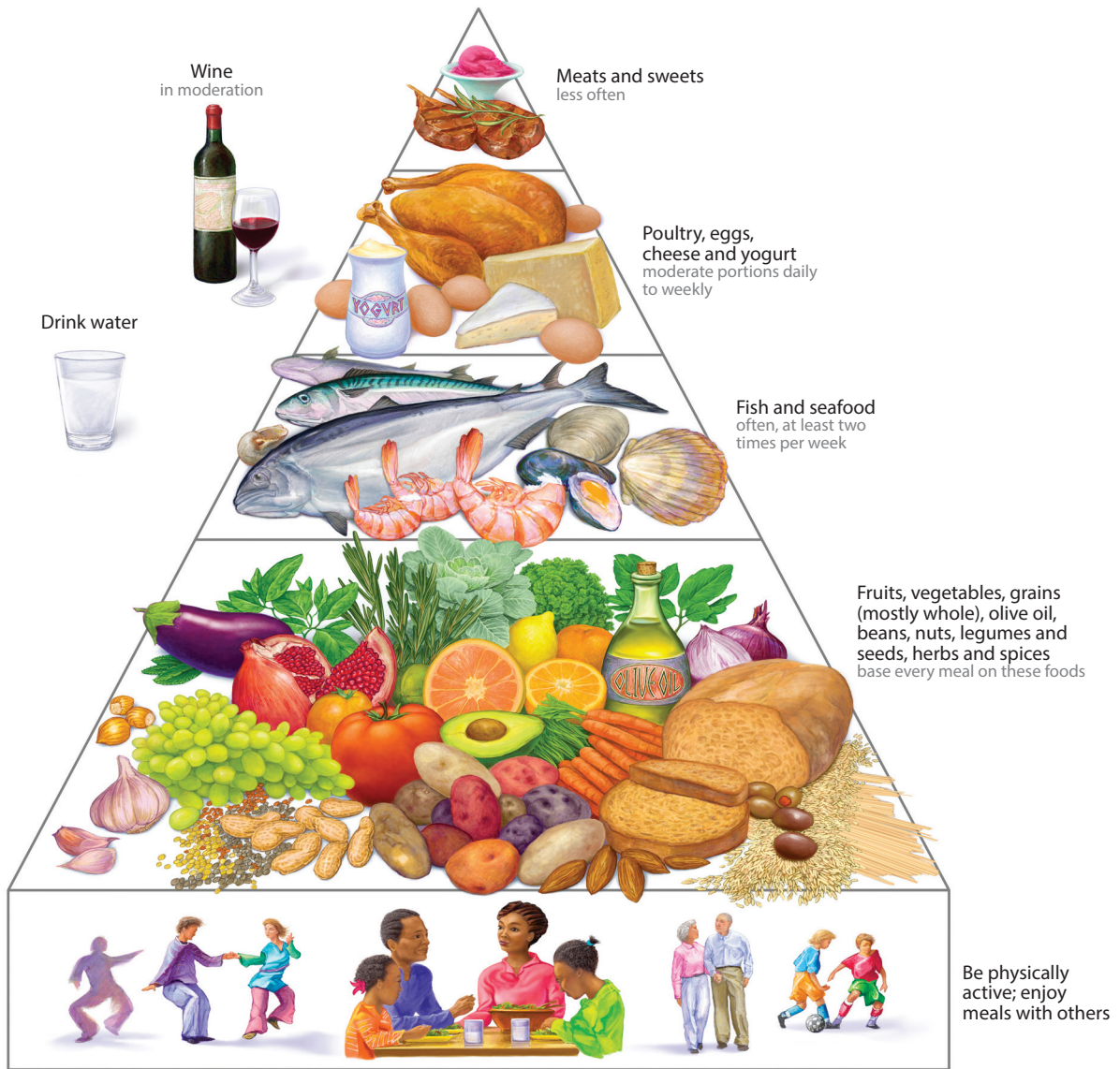
In January 1993, international experts on diet, nutrition, and health convened to review research on the composition and health implications of Mediterranean dietary patterns during the past half-century. The International Conference on the Diets of the Mediterranean was the first in a series jointly organized by Oldways Preservation & Exchange Trust and the World Health Organization (WHO)/Food and Agriculture Organization Collaborating Center in Nutritional Epidemiology at Harvard School of Public Health to describe and evaluate the public health implications of traditional diets (136). Subsequent conferences were organized in 1998, 2000, and 2003. This collaboration led to the development of numerous food guide pyramids reflecting the diversity of worldwide dietary traditions associated with good health. The most recent Mediterranean diet pyramid is summarized in **Figure 1**.

## COMPONENTS OF THE MEDITERRANEAN DIETARY PATTERN

The Mediterranean dietary pattern has several distinct characteristics that collectively create a diet that is ample in fruits, vegetables, complex carbohydrates, and monounsaturated fat, and low in animal fat and simple sugars. The principles that apply to a Mediterranean dietary pattern are summarized in **Table 1**, and their health benefits are discussed in detail in the following section.

### Plant-Based Foods

The foundation of the Mediterranean dietary pattern is the consumption of a wide variety of minimally processed whole grains, fruits, vegetables, legumes, and nuts. Plant-based diets provide a



**Figure 1**

Mediterranean diet food pyramid. The Mediterranean diet pyramid is designed to convey a general sense of the relative proportions and frequency of servings of foods and food groups that contribute to this dietary pattern. Figure © 2009 Oldways Preservation & Exchange Trust; [www.oldwayspt.org](http://www.oldwayspt.org).

natural source of fiber, essential vitamins, and minerals, all of which promote healthy development. Plant-based foods are naturally rich in antioxidants and low in saturated fats (25, 121). A plant-based diet is associated with higher fasting plasma ascorbic acid concentrations and antioxidant status in addition to lower cholesterol, improved glycemic control, and lower blood pressure in adults (6, 68, 104).

**Table 1** Dietary and lifestyle components of the traditional Mediterranean diet

| Dietary components   |   |
|----------------------|---|
| 1.                   | High consumption of food from plant sources, including grains, vegetables, fruits, nuts, and seeds                            |
| 2.                   | Emphasis on a variety of minimally processed and seasonally fresh, locally grown foods  |
| 3.                   | Olive oil as the principal dietary fat used for cooking, baking, and flavoring  |
| 4.                   | Total fat ranging from 25% to 35% of energy, with saturated fat accounting for $\leq 7\%$ to 8% of energy                     |
| 5.                   | Daily consumption of low to moderate amounts of dairy products, mainly cheese and yogurt                                      |
| 6.                   | Twice-weekly consumption of low to moderate amounts of fish and poultry; up to seven eggs per week                            |
| 7.                   | Fresh fruit as the typical dessert, with sweets containing concentrated sugars or honey consumed only a few times per week    |
| 8.                   | Consumption of red meat only a few times per month  |
| 9.                   | Moderate consumption of wine, normally with meals. Approximately 1–2 glasses per day for men and 1 glass for women (optional) |
| 10.                  | Use of herbs and spices to flavor food instead of salt or fat   |
| Lifestyle components |   |
| 1.                   | Regular daily physical activity   |
| 2.                   | Meals in the company of friends and family  |

### Nuts

Nuts are energy-dense foods that are rich in total fat and unsaturated fatty acids. Nearly one-half of the total fat in nuts is made up of unsaturated fat, which includes monounsaturated fatty acids (oleic acid), polyunsaturated fatty acids (linoleic acid and  $\alpha$ -linoleic acid), and omega-3 fatty acids (101). In addition, nuts are rich sources of proteins such as L-arginine, an amino acid precursor of nitric oxide (an endogenous vasodilator) (44). Nuts are high in dietary fiber (99), folic acid, antioxidant vitamins (tocopherols and phenolic compounds) (8), and salutary minerals (calcium, magnesium, and potassium) (111). Frequent nut consumption is associated with decreased inflammatory markers (48), increased resistance to cholesterol oxidation (31), and more favorable cholesterol profiles [decreased low-density lipoprotein cholesterol (LDL-C) and increased high-density lipoprotein cholesterol (HDL-C)] (64). Finally, several large epidemiologic studies have consistently associated frequent nut consumption with a reduced incidence of coronary heart disease (53, 64). Of note, processing can remove antioxidants and macronutrients; thus, the health benefits of nuts are greatest when consuming whole, unpeeled, and unsalted products (8).

### Olive Oil

Olive oil was the Mediterranean region's principal source of fat and was primarily used in place of the animal fats that are typical of northern European diets. Olive oil is composed of a glycerol fraction (90–99%) and a nonglycerol or unsaponifiable fraction (0.4–5%). Oleic acid, a monounsaturated fatty acid, represents 60–80% of the fatty acids present in olive oil (2). Oleic acid represents 15% of total daily energy consumption in traditional Mediterranean diets (136). Consumption of monounsaturated fatty acids has been shown to reduce plasma levels of LDL-C, increase HDL-C, and protect against lipid peroxidation (91). In comparison, the consumption of saturated fatty acids increases both LDL-C and HDL-C, while polyunsaturated fatty acids reduce both LDL-C and HDL-C (20). In addition, the unsaponifiable fraction of olive oil is rich in tocopherols, aromatic hydrocarbon compounds, and sterols (128). These polyphenol compounds can reduce lipid oxidation and increase the availability of circulating antioxidants (128). Normal metabolic processes result in the formation of reactive oxygen species that can oxidize and damage

cellular macromolecules, which accelerates atherosclerosis (89). Oleuropein and its byproduct, hydroxytyrosol, are the main polyphenols found in olive oil and have been shown to reduce lipid peroxidation, inhibit platelet aggregation, reduce proinflammatory molecule formation, and increase nitric oxide production (47, 73, 83, 103).

## Dairy Products

Mediterranean dietary patterns typically include small amounts of dairy products from a variety of animals including goats, sheep, cows, and camels (59). Due to the lack of refrigeration, milk in the Mediterranean region was frequently preserved and consumed as yogurt or cheese in low to moderate amounts. Dairy is an essential source of dietary calcium. When combined with caloric restriction, increased calcium and dairy intake may augment weight loss, specifically fat loss from the abdominal region (144). This is important, as abdominal obesity is the most prevalent manifestation of the metabolic syndrome and is a marker of dysfunctional adipose tissue and insulin resistance (19). The advent of low- and nonfat dairy products allowed for increased consumption of dairy without concomitant increases in caloric intake and weight gain. In a subgroup analysis of 2,290 patients, including 1,845 with hypertension, participating in the Prevención con Dieta Mediterránea [Prevention with Mediterranean Diet (PREDIMED)] study, the consumption of low-fat dairy was associated with reduced systolic and diastolic blood pressures [−4.2 (95% CI: −6.9, −1.4) and −3.2 (95% CI: −3.2, −0.4) mmHg, respectively] and cardiovascular events in patients adhering to a Mediterranean-style diet (125). Dairy products are rich in calcium and magnesium, which have been associated with lower blood pressure (130). Finally, dietary calcium may suppress 1,25-dihydroxyvitamin-D concentrations, thereby decreasing vascular smooth muscle cell intracellular calcium and leading to reductions in blood pressure (143) and vascular calcification (132).

## Animal Protein

Traditional Mediterranean diets included foods from animals in limited amounts (59) in comparison with the high intake of meats, dairy, and processed grains that is typical of Western diets. Meat contains no fiber and few antioxidant nutrients; its energy displaces that from plant foods, which contain an abundance of essential nutrients (10). The consumption of processed red meat has been linked to increased risk of hypertension, metabolic syndrome, type 2 diabetes, cardiovascular disease, and heart failure (5, 49, 79). This may be attributable to the high levels of sodium, nitrite, and nitrates in processed meats (55). Nitrites and nitrates are frequently used as preservatives, and higher blood nitrite concentrations have been associated with endothelial dysfunction and insulin resistance in adults (55, 82). In addition, the consumption of unprocessed red meat has been linked with an increased risk for type 2 diabetes, metabolic syndrome, and cardiovascular disease (5, 79). This is attributed, in part, to the higher saturated fat and cholesterol content of meat (43). In a large prospective cohort study, Pan et al. (79) observed 37,698 men from the Health Professional Follow-Up Study (1986–2008) and 83,644 women from the Nurses' Health Study (1980–2008) who were free of cardiovascular disease at baseline. They found that substitutions of one serving per day of other foods (including fish, poultry, nuts, legumes, low-fat dairy, and whole grains) for one serving per day of red meat were associated with a 7% to 19% lower mortality risk (79).

Fish are an abundant source of polyunsaturated fatty acids (especially omega-3), minerals (calcium, iron, selenium, and zinc), and vitamins (A, B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, E, and D) (112). The health benefits of fish are largely attributed to their high omega-3 polyunsaturated fatty acid content. Deep saltwater fish, such as mackerel and salmon, are generally fattier and contain higher amounts of omega-3



fatty acids (23). Omega-3 fatty acids have antithrombotic, anti-inflammatory, hypolipidemic properties and promote nitric oxide-induced endothelial relaxation (58). Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of cardiovascular disease (15, 42). In addition, evidence from prospective secondary prevention studies suggests that omega-3 fatty acid supplementation ranging from 0.5 to 1.8 g/day (either as fatty fish or fish oil supplements) significantly reduces subsequent cardiac and all-cause mortality (45, 115). Of note, some species of fish may contain significant levels of methylmercury, polychlorinated biphenyls, dioxins, and other environmental pollutants. These substances bioconcentrate in the aquatic food chain and are highest in older, larger, predatory fish (58). The benefits and risks of eating fish vary depending on a person's stage in life, and consumption of a wide variety of species is the best approach to both minimizing mercury exposure and increasing omega-3 fatty acid intake.

## Wine

In the context of the Mediterranean dietary pyramid, moderate wine consumption is defined as one to two glasses per day for men or one glass per day for women. An inverse association between moderate alcohol consumption and cardiovascular disease has been consistently reported in populations from the United States, Europe, and Asia (9, 46, 92, 96). The consumption of moderate amounts of alcohol is associated with a 20% to 40% risk reduction in cardiovascular disease and stroke even after controlling for other cardiovascular disease risk factors (75, 92, 98). In the Health Professionals Follow-Up Study, Rimm et al. (95) reported a 36% reduction in cardiovascular disease risk in men consuming 0.5 to 2.5 drinks per day compared with abstainers after adjusting for fat, cholesterol, and fiber. The cardioprotective effect of moderate alcohol consumption was sustained during long-term follow-up and resulted in a cardiovascular risk reduction of 26% to 42% (78). Similarly, in the Nurses' Health Study consumption of 0.5 to 1.5 drinks per day was associated with a 40% risk reduction in cardiovascular disease and ischemic stroke (119).

Moderate alcohol consumption reduces coronary risk in multiple ways, including increasing levels of HDL-C, decreasing levels of LDL-C (36), and reducing platelet aggregation (93) and systolic and diastolic blood pressures (140). It is estimated that 18% of the reduction in CVD risk is attributable to decreases in LDL-C and 45% to increases in HDL-C (61). Alcohol is a natural anticoagulant, and consumption decreases fibrinogen while increasing both fibrinolytic and antithrombin activity (21). In the Caerphilly Prospective Heart Disease Study, alcohol consumption was associated with reduced platelet aggregation, with a greater reduction in smokers as well as subjects with a high intake of saturated fatty acids and low intake of polyunsaturated fatty acids (93). In addition to the protective effects of alcohol, wine also contains several phenols and flavonoids that act as natural antioxidants. Resveratrol, a phenolic compound found in the skin of grapes and in red wine, can inhibit LDL-C oxidation, suppress platelet aggregation, and reduce myocardial damage during ischemia-reperfusion (139). Thus, the cardioprotective effects of moderate alcohol consumption are further augmented by the antioxidant properties of wine. From a public health perspective, wine should be avoided whenever consumption would put an individual or others at risk, such as during pregnancy or before driving, or in individuals with a history of addiction or substance abuse. Wine is considered an optional part of the Mediterranean dietary pattern, and its consumption should be based on individual circumstances.

## Herbs and Spices

The updated 2008 Mediterranean Diet Pyramid (**Figure 1**) includes the addition of herbs and spices. The use of herbs and spices enhances the flavor and palatability of food, reducing the

need to add salt or fat when cooking. In addition, herbs are a natural source of phytochemicals, including flavonoids and polyphenols. These compounds are potent antioxidants and can inhibit lipid peroxidation as well as suppress cholesterol synthesis (12).

### **Physical Activity and Lifestyle**

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure (123). The Mediterranean population in the early 1960s was highly active, and groups observed in Greece were leaner than their European counterparts (54). Numerous prospective epidemiological studies have consistently demonstrated an inverse relationship between physical activity and cardiovascular events, with a graded relationship of decreasing cardiovascular event rates with increasing levels of physical activity (86). Physical activity both prevents and helps reduce many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance, glucose intolerance, elevated triglyceride concentrations, and obesity (30, 63, 124). Physical activity is also an important adjunct to diet for achieving and maintaining weight loss (137).

Importantly, certain lifestyle factors may facilitate healthy behaviors and reduce cardiovascular risk, such as (*a*) the social support and sense of community that accompany sharing food with family and friends, (*b*) lengthy meals that provide relaxation and relief from daily stress, and (*c*) delicious meals that stimulate enjoyment of healthy diets. Although the majority of research on shared meals is in adolescents, there is consistent evidence that the frequency of communal meals is positively associated with intakes of fruits, vegetables, grains, and calcium-rich foods, and negatively associated with soft drink consumption (120). A summary of dietary and lifestyle components of the traditional Mediterranean diet can be found in **Table 1**.

## **MEDITERRANEAN DIETARY PATTERN AND CARDIOVASCULAR DISEASE RISK FACTORS**

Since the landmark Seven Countries study (54), several studies in different populations have established a beneficial role for the main components of the Mediterranean dietary pattern on the development of cardiovascular disease risk factors and incidence. However, research interest in this field has been focused on estimating adherence to the dietary pattern as a whole rather than analyzing individual components in relation to the health status of the population. This is because analyses of single nutrients ignore important synergistic interactions between components of a diet, and more importantly, because people do not eat isolated nutrients (117). A diet rich in fruits, vegetables, legumes, and nuts, with olive oil as the principal source of added fat, moderate consumption of red wine and dairy, and low consumptions of red meat has been associated with significant reductions in serum lipids, fasting blood glucose, blood pressure, insulin resistance, arterial stiffness, and oxidative stress. These findings are discussed in detail in the following section.

### **Lipoproteins and Cholesterol**

The majority of saturated fats in the Mediterranean dietary pattern are derived from olive oil. Oleic acid, a monounsaturated fatty acid, represents 60% to 80% of the fatty acids present in olive oil. Increased consumption of monounsaturated fatty acids not only reduces lipoprotein levels but also decreases the susceptibility of LDL-C to oxidation (91). The Indo-Mediterranean Diet Heart Study was a randomized, single-blind trial involving 1,000 patients with angina pectoris, myocardial infarction, or surrogate risk factors for cardiovascular disease (114). Subjects were



randomized to consume a diet rich in whole grains, fruits, vegetables, walnuts, and almonds or the Step 1 National Cholesterol Education Program (NCEP) diet (57). After two years, both groups had significant reductions in total cholesterol, LDL-C, and triglycerides ( $p < 0.001$  for all); however, reductions were greater in the Mediterranean diet group. In addition, HDL-C rose in the Mediterranean diet group but fell in the Step 1 diet group ( $+0.03$  versus  $-0.03$  mmol/L,  $p = 0.029$ ) (114). The largest study to evaluate the health effects of the Mediterranean diet to date has been the multicenter PREDIMED study, which randomized 7,447 subjects at high risk for cardiovascular disease to receive a low-fat diet or a Mediterranean diet supplemented with extra virgin olive oil (1 liter per week) or nuts (30 g per day) (100). In a short-term substudy of 772 patients, Estruch et al. (28) found that compared to a low-fat diet, adherence to either Mediterranean diet resulted in greater reductions in cholesterol:HDL-C ratio. Similarly, the Mediterranean Diet, Cardiovascular Risks, and Gene Polymorphisms (Medi-RIVAGE) study examined the effects of a Mediterranean-style or low-fat diet on risk factors in 212 volunteers with moderate risk for cardiovascular disease (131). After three months of dietary intervention, changes in body mass index (BMI), cholesterol, and insulin sensitivity were measured, and significant reductions were found in total and triacylglycerol-rich lipoprotein cholesterol, triacylglycerols, and apolipoprotein B (apoB) levels with a Mediterranean-style diet.

Apolipoprotein B is a major component of LDL-C and other non-HDL particles, including very-low-density lipoprotein cholesterol (VLDL-C) (141). There are two types of apoB: apoB<sub>48</sub> and apoB<sub>100</sub>. ApoB<sub>48</sub> is produced in the intestine and an essential component of lipoproteins derived from exogenous dietary sources (chylomicrons) (141). ApoB<sub>100</sub> is synthesized by the liver and serves as a ligand for the LDL receptor-mediated uptake of LDL particles by the liver and extrahepatic tissues (141). Higher levels of plasma apoB<sub>100</sub> can convey increased coronary disease risk, even when LDL-C is normal, in patients receiving statin therapy (60, 113). Richard et al. (94) investigated the effects of a Mediterranean dietary pattern with and without weight loss on apoB<sub>100</sub> metabolism in men with metabolic syndrome. Nineteen men ages 24 to 62 years were initially given an isoenergetic control diet for five weeks, followed by an isoenergetic Mediterranean dietary pattern for an additional five weeks. Compared to the control diet, the Mediterranean diet reduced LDL-apoB<sub>100</sub> pool size ( $-14.2\%$ ,  $p < 0.01$ ) and increased LDL-C particle size ( $p < 0.01$ ) but had no effect on VLDL-apoB<sub>100</sub> pool size or triglyceride concentrations. Consumption of a Mediterranean dietary pattern increased LDL-C catabolism even in the absence of weight loss (94).

## Metabolic Syndrome

In 2004, the NCEP's Adult Treatment Panel III (ATP III) report identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease. The metabolic syndrome represents a complex interaction between genetic, metabolic, and environmental factors that leads to a proinflammatory/prothrombotic milieu within the body. It is clinically diagnosed when three of the five following criteria are present: abdominal obesity, depressed HDL-C, elevated triglycerides, elevated blood pressure, and elevated fasting glucose (**Table 2**) (38). The first prospective cohort study to evaluate the effect of the Mediterranean dietary pattern on metabolic syndrome was the Seguimiento Universidad de Navarra (SUN) study (126). The SUN study followed 2,563 participants free of metabolic syndrome or risk factors for six years and monitored their adherence to a Mediterranean-style diet. Participants with higher baseline adherence to a Mediterranean-style diet exhibited lower levels of all metabolic syndrome risk factors except fasting glucose (126). Furthermore, compared to participants with the lowest adherence to the Mediterranean dietary pattern, participants with the highest adherence had the lowest incidence of metabolic syndrome,

**Table 2 ATP III clinical identification of the metabolic syndrome**

| Risk factor                                     | Defining level     |
|---|--------------------|
| Abdominal obesity, given as waist circumference |                    |
| Men   | > 102 cm (> 40 in) |
| Women   | > 88 cm (35 in)    |
| Triglycerides                                   | ≥ 150 mg/dl        |
| High-density lipoprotein cholesterol            |                    |
| Men   | < 40 mg/dl         |
| Women   | < 50 mg/dl         |
| Blood pressure                                  | ≥ 130/≥ 85 mm Hg   |
| Fasting glucose                                 | ≥ 110 mg/dl        |

even after adjusting for age, sex, physical activity, smoking, and total energy intake (multivariate-adjusted OR = 0.20 (95% CI: 0.06, 0.56) (126).

These results were replicated by Babio et al. (4) in a cross-sectional study conducted in 808 cardiovascular high-risk participants of the Reus PREDIMED center. After adjusting for age, sex, total energy intake, smoking status, and physical activity, participants with the greatest adherence to the Mediterranean diet had the lowest odds ratio of having metabolic syndrome (OR = 0.44, 95% CI: 0.27, 0.70) compared to those in the lowest quartile (4). In a focused analysis on metabolic syndrome in the previously described PREDIMED study, 1,224 participants at high risk for cardiovascular disease were recruited. At baseline, 61.4% of patients met criteria for metabolic syndrome (107). After one year, the prevalence of metabolic syndrome was reduced by 6.7% in the Mediterranean diet + olive oil group, 13.7% in the Mediterranean diet + nuts group, and 2.0% in the low-fat diet (control) group. After adjustment for sex, age, baseline obesity status, and weight changes, the odds ratios for reversion of metabolic syndrome were 1.3 (95% CI: 0.8, 2.1) for the Mediterranean diet + nuts group and 1.7 (95% CI: 1.1, 2.6) for the Mediterranean diet + nuts group compared with the control diet group (107).

The effect of the Mediterranean dietary pattern on metabolic syndrome was evaluated in a recent meta-analysis of 50 studies including 534,906 individuals (51). The combined effect of prospective studies and clinical trials demonstrated that adherence to the Mediterranean dietary pattern was associated with a reduced risk of metabolic syndrome (log hazard ratio: -0.69, 95% CI: -1.24, -1.16). Furthermore, the Mediterranean dietary pattern had a beneficial effect on individual components of metabolic syndrome, including waist circumference (-0.42 cm, 95% CI: -0.082, -0.02), HDL-C (1.17 mg/dl, 95% CI: 0.38, 1.96), triglycerides (-6.14 mg/dl, 95% CI: -10.35, -1.93), systolic (-2.35 mm Hg, 95% CI: -3.51, -1.18) and diastolic blood pressure (-1.58 mm Hg, 95% CI: -2.02, -1.13), and glucose (-3.89 mg/dl, 95% CI: -5.84, -1.95) (51). The authors concluded that adoption of a Mediterranean-style diet was important for the primary and secondary prevention of metabolic syndrome and its individual components (51).

## Diabetes and Insulin Resistance

Diabetes mellitus is an increasingly important global public health problem that threatens to reach pandemic levels by 2030 (41). Diet is an important risk factor for diabetes, and dietary interventions are successful in preventing type 2 diabetes and improving glycemic control (80). Several characteristics of the Mediterranean diet can protect against diabetes, including a high intake of fiber and vegetable fat, a low intake of *trans*-fatty acids, and a moderate intake of alcohol (108, 110). Furthermore, diets rich in monounsaturated fatty acids improved glycemic control in

people with diabetes, suggesting that a high intake improves insulin sensitivity (97). In a prospective cohort study, Martínez-González et al. (69) followed 13,380 Spanish university graduates without diabetes at baseline for a median of 4.4 years. After four years, participants who adhered closely to a Mediterranean diet had a lower risk of diabetes. The adjusted incidence rate ratios for diabetes were 0.41 (95% CI: 0.19, 0.87) for those with moderate adherence and 0.17 (95% CI: 0.04, 0.75) for those with the highest adherence compared with low-adherence controls. A two-point increase in the Mediterranean diet score was associated with a 35% relative reduction in the risk of diabetes (95% CI: 0.44, 0.95) (69).

The Reus PREDIMED study randomized 418 nondiabetic subjects ages 55 to 80 years to receive either one of two Mediterranean diets (supplemented with nuts or olive oil) or a low-fat control diet (106). Diets were ad libitum, and no advice on physical activity was given. After a median follow-up of four years, diabetes incidence was 10.1% (95% CI: 5.1, 15.1), 11.0% (95% CI: 5.9, 16.1), and 17.9% (95% CI: 11.4, 24.4) in the group receiving the Mediterranean diet supplemented with olive oil, the group receiving the Mediterranean diet supplemented with nuts, and the control group, respectively (106). Multivariable adjusted hazard ratios of diabetes were 0.49 (95% CI: 0.25, 0.97) and 0.48 (95% CI: 0.24, 0.96) in the groups receiving the Mediterranean diet supplemented with olive oil and nuts compared to the control group. When the two Mediterranean diet groups were pooled and compared with the control group, diabetes incidence was reduced by 52% (95% CI: 27, 86) even in the absence of significant changes in body weight or physical activity, although differences barely reached statistical significance (106). Similar results were found in the analysis of the Greek cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study (102). From a total of 22,295 participants, actively followed for a median of 11 years, 2,330 cases of incident type 2 diabetes were reported (102). As seen with previous studies, there was an inverse association between Mediterranean diet score and diabetes risk (HR 0.88, 95% CI: 0.78, 0.99). Adherence to a Mediterranean dietary pattern with a low glycemic load provided a significant 20% protection from new-onset diabetes (102).

## Endothelial Function

The vascular endothelium plays a key role in the regulation of vascular tone, platelet activity, leukocyte adhesion, and thrombosis. It is intimately involved in the development of atherosclerosis as well (18, 39). Diets rich in saturated fatty acids have been shown to induce temporary endothelial dysfunction in addition to traditional cardiovascular risk factors, inflammation, and oxidative stress (1, 13). In contrast, the Mediterranean dietary pattern, with its high monounsaturated fat content, has been shown to have favorable effects on endothelial function.

Fuentes et al. (32) studied the effects of either a low-fat or Mediterranean diet on endothelial function in 22 hypercholesterolemic men consuming a high saturated fat diet. Flow-mediated vasodilation of the brachial artery, a measure of endothelial nitric oxide, was significantly higher after the Mediterranean diet intervention (13.5% versus 9.9%,  $p = 0.027$ ) but was unchanged after the low-fat diet intervention. The Mediterranean diet also improved endothelial function in obese patients supervised for strict adherence compared to those who received only regular dietary counseling (90). The underlying mechanism of the effect of the Mediterranean diet on endothelial function may in part be due to its favorable effects on improving the redox balance with increased nitric oxide bioavailability and antioxidant properties (26, 50). In a larger single-blind trial, Esposito et al. (27) randomized 181 patients with metabolic syndrome to either a Mediterranean-style diet or a low-fat prudent diet. After two years, subjects consuming the Mediterranean dietary pattern had an improved endothelial function score (1.9,  $p < 0.001$ ) compared to the score of the control group, which remained unchanged (0.2,  $p = 0.33$ ).

## Oxidative Stress

Increased oxidative stress has been linked to both impaired endothelial function and increased LDL oxidation leading to atherosclerosis (11, 40). The Mediterranean dietary pattern is rich in natural antioxidants and is associated with reduced levels of systemic biomarkers of oxidative stress. In a substudy of PREDIMED, Mitjavila et al. (74) randomized 110 women with metabolic syndrome to receive either a Mediterranean diet supplemented with nuts or olive oil or a low-fat diet and measured urinary levels of two oxidative stress markers, F2-isoprostane (F2-IP) and the DNA damage base 8-oxo-7, 8-dihydro-2-deoxyguanosine (8-oxo-dG). After one year, urinary excretion of F2-IP was significantly lower in those who consumed a Mediterranean diet supplemented with virgin olive oil compared to the other two groups. Urinary levels of 8-oxo-dG were lower in both Mediterranean diet groups as compared to the low-fat group (74). This study was the first randomized trial to show that adoption of a Mediterranean dietary pattern can reduce markers of systemic oxidative stress.

Olive oil is a natural source of antioxidant phenolic compounds and has been shown to reduce oxidative DNA damage. Machowetz et al. (67) randomized 182 healthy men to consume olive oil with a low, medium, or high phenolic content in a crossover fashion. Compared to baseline, consumption of olive oil resulted in a 13% reduction in urinary 8-oxo-deoxyguanosine, a DNA oxidation metabolite (67). The Mediterranean dietary pattern has also been shown to improve redox balance by its favorable effects on plasma aminothiols. In a twin study, Dai et al. (14) found that each unit increment in the Mediterranean diet score was associated with a 7% increase in the ratio between glutathione and oxidized glutathione, with higher ratios indicating lower oxidative stress burden. Finally, adherence to a Mediterranean dietary pattern was associated with improved total antioxidant capacity in a large Greek registry of patients without underlying cardiovascular disease. A diet score examining an overall compliance with the Mediterranean dietary pattern was directly correlated with total antioxidant capacity.

## Hypertension

The Mediterranean dietary pattern can reduce blood pressure and thus the complications of long-term hypertension. In a subgroup analysis of the ATTICA study, 2,282 patients over the age of 18 were randomly sampled from the Attica province of Greece (85). Participants were classified as hypertensive if they were taking antihypertensive medication or had an average blood pressure >140/90 mm Hg measured three times five minutes apart. Adherence to a Mediterranean-style diet was determined using a food frequency questionnaire. After adjusting for confounding variables, participants consuming a Mediterranean dietary pattern were 26% less likely to be hypertensive (85). Additionally, among those patients who were treated for hypertension, control of blood pressure was better in those adopting the Mediterranean diet. These effects could not be attributed to any individual component of the diet but rather to adoption of the diet as a whole (85).

The EPIC study prospectively followed 20,000 Greek patients ages 20 to 86 for five years via questionnaires regarding diet and exercise and found that the consumption of a Mediterranean-style diet had an inverse relationship with both systolic and diastolic blood pressures (87). Similarly, the Spanish SUN study was a prospective cohort study of 9,408 men and women followed for the development of hypertension for a median of 4.2 years (77). Although the consumption of a Mediterranean-style diet was not associated with the development of hypertension, it was associated with reduced changes in mean levels of systolic blood pressure [high adherence:  $-3.1$  mm Hg (95% CI:  $-5.4, -0.8$ )] and diastolic blood pressure [high adherence:  $-1.9$  mm Hg, 95% CI:  $-3.6, -0.1$ ]] after six years of follow-up, indicating that consumption of a Mediterranean dietary pattern

could prevent age-related changes in blood pressure (77). In a substudy of the PREDIMED trial, Domenech et al. (22) evaluated the effects of a Mediterranean diet supplemented with nuts or olive oil on 24-hour ambulatory blood pressures. At one year, patients receiving the Mediterranean diet supplemented with nuts or olive oil had a decrease in their mean systolic blood pressure [−2.6 mm Hg (95% CI: −4.3, −0.9) and −2.3 mm Hg (95% CI: −4.0, −0.05), respectively] and diastolic blood pressure [−1.2 mm Hg (95% CI: −2.2, −0.2) and −1.2 mm Hg (95% CI: −2.2, −0.2), respectively] compared to controls, who had an increase in systolic and diastolic blood pressures (22).

## Arterial Stiffness

Aging is associated with structural and functional changes of the vessel wall, which result in decreased vascular dispensability and elevated arterial stiffness (3). As a result of increased arterial stiffness, systolic blood pressure rises, causing a rise in left ventricular workload and subsequent cardiac hypertrophy (3). Arterial stiffness can be evaluated by measuring pulse wave velocity between two sites in the arterial tree, with a higher pulse wave velocity indicating stiffer arteries. Alternatively, the relative change in lumen diameter during the cardiac cycle adjusted for the driving pulse pressure provides a measure of arterial distensibility. Numerous studies have shown that aortic pulse wave velocity and carotid distensibility are predictors of cardiovascular events and mortality (62, 72). In a randomized cross-over study, Papamichael et al. (81) used applanation tonometry and aortic pulse wave analysis to measure arterial wave reflections one, two, and three hours postprandially in 15 healthy subjects and 15 matched controls. Subjects were fed four standard meals, on different days, containing 50 g of olive oil and 250 ml of wine. Compared to controls, all supplemented meals led to reductions in central augmentation index, systolic blood pressure, and diastolic blood pressure (81). In the Amsterdam Growth and Health Longitudinal Study, which followed 373 adolescents from a mean age of 13 years to age 36, individuals with stiffer carotid arteries had lower Mediterranean diet scores and were less likely to have adhered to this dietary pattern during the preceding 24 years compared to those with less stiff arteries (129). This study provides evidence that early adherence to a Mediterranean-style diet may prevent the development of arterial stiffness in adulthood (129).

## MEDITERRANEAN DIETARY PATTERN AND CARDIOVASCULAR DISEASE INCIDENCE AND MORTALITY

The Mediterranean dietary pattern, through its salutary effects on cardiovascular disease risk factors, has been associated with reduced cardiovascular disease incidence and mortality. The beneficial effects of the Mediterranean dietary pattern on subclinical cardiovascular disease, primary and secondary prevention, atrial fibrillation, and microvascular cerebrovascular disease and accident are reviewed in the following sections.

### Subclinical Cardiovascular Disease

Atherosclerosis involving the large arteries is a surrogate for underlying coronary artery disease and a strong predictor of future cardiovascular events (66). The easy accessibility of the carotid artery and growing availability of ultrasonography make carotid intima-media thickness (IMT) a reasonable target for evaluation. In the Northern Manhattan study, 1,374 relatively healthy subjects were evaluated for carotid artery disease using B-mode ultrasonography (35). Moderate and strict adherence to a Mediterranean dietary pattern was inversely associated with carotid IMT

after adjusting for covariates (35). Similarly, in a substudy of the PREDIMED study, 164 patients underwent ultrasonography of their carotid arteries at baseline and after dietary intervention for a mean of 2.4 years (105). At two years, mean carotid IMT progressed in the control diet group (0.052 mm, 95% CI: -0.01, 0.12), whereas it regressed in the Mediterranean diet + nuts group (-0.084 mm, 95% CI: -0.16, -0.01) and remained unchanged in the Mediterranean diet + olive oil group (-0.003 mm, 95% CI: -0.07, 0.07) (105). These findings were repeated separately in the PREDIMED-Navarra study, which randomized 187 patients and followed carotid IMT for one year (76). Among subjects with carotid IMT  $\geq 0.9$  mm, one-year IMT changes versus control demonstrated significant differences of -0.08 mm (95% CI: -0.15, -0.01) for the Mediterranean diet + olive oil group and -0.07 mm (95% CI: -0.14, -0.01) for the Mediterranean diet + nuts group (76). No significant differences were observed in patients with carotid IMT  $< 0.9$  mm.

### Primary Prevention of Cardiovascular Disease

Adherence to a Mediterranean dietary pattern not only improves cardiometabolic profiles but also leads to a reduction in overall cardiovascular mortality. In an analysis of 15,152 patients from 52 countries, the INTERHEART study found that  $>90\%$  of the risk for myocardial infarction was due to modifiable risk factors such as smoking, hypertension, diabetes, hyperlipidemia, abdominal obesity; psychosocial factors; decreased physical activity; and low consumption of fruits, vegetables, and alcohol (142). Importantly, daily consumption of fruits and vegetables was associated with reduced risk of myocardial infarction (OR = 0.70, population-attributable risk 13.7% for lack of daily consumption) (142). In addition, there is evidence from longitudinal population studies that adherence to a Mediterranean diet also favorably affects long-term cardiovascular outcomes. A meta-analysis by Sofi et al. (117) evaluated the association between consumption of a Mediterranean dietary pattern and health outcomes in 12 prospective studies with a total of 1,574,299 subjects and found that adoption of a Mediterranean dietary pattern was associated with a 9.0% reduction in overall mortality and mortality from cardiovascular disease (relative risk 0.91, 95% CI: 0.87, 0.95). These findings are supported by the PREDIMED primary prevention trial, which demonstrated that consumption of a Mediterranean diet supplemented with either nuts or olive oil decreased rates of myocardial infarction, stroke, and cardiovascular death (29). The trial was prematurely discontinued by the data safety and monitoring board after a median follow-up of 4.8 years given the multivariable-adjusted hazard ratios were 0.70 (95% CI: 0.54, 0.92) and 0.72 (95% CI: 0.54, 0.96) for the Mediterranean diet supplemented with olive oil or nuts, respectively (29).

### Secondary Prevention of Cardiovascular Disease

Evidence-based preventive strategies geared toward improving long-term cardiovascular outcomes are an integral component of secondary prevention. Among individuals with pre-existing cardiovascular disease, adoption of a Mediterranean dietary pattern has been shown to slow progression of disease and decrease the occurrence of future cardiovascular events (73). Dehghan and colleagues followed 31,546 subjects  $\geq 55$  years of age with preexisting cardiovascular disease or diabetes with end-organ damage receiving optimal medical therapy for a median of 56 months (17, 114). Dietary habits were assessed using either the modified Alternative Healthy Eating Index or the Diet Risk Score. A higher score on either index was consistent with a Mediterranean dietary pattern. At 56 months, patients who scored in the healthiest quintile of either dietary index had a significantly lower risk of cardiovascular events (HR = 0.78, 95% CI: 0.71, 0.87) (17). The risk



reductions for CV death, myocardial infarction, congestive heart failure, and stroke were 35%, 14%, 28%, and 19%, respectively (17).

One of the earliest randomized trials studying the effect of the Mediterranean dietary pattern in patients after myocardial infarction was the Lyon Diet Heart Study (16). De Lorgeril et al. randomized 423 patients to follow either a Mediterranean diet or a heart-prudent diet as recommended by their physicians. After a mean follow-up of 46 months, those adhering to a Mediterranean dietary pattern were less likely to suffer from cardiac death and nonfatal myocardial infarction (primary outcome) and unstable angina, stroke, heart failure, and pulmonary or peripheral embolism (secondary outcome). Adjusted risk ratios were 0.23 (95% CI: 0.11, 0.48) and 0.30 (95% CI: 0.18, 0.51), respectively (16). Patients adhering to a Mediterranean dietary pattern were >70% less likely to suffer from recurrent cardiovascular events. The cardioprotective effects of following a Mediterranean dietary pattern were evident as early as five months and increased over five years (16). The benefits of the Mediterranean dietary patterns in the secondary prevention of cardiovascular disease have been demonstrated in multiple populations. The Indo-Mediterranean Diet Heart Study randomized 1,000 Southeast Asians with either risk factors for cardiovascular disease or preexisting cardiovascular disease to either a Mediterranean dietary pattern supplemented with nuts or the NCEP Step 1 prudent diet (114). After two years, patients adhering to a Mediterranean dietary pattern were less likely to suffer from either myocardial infarction or sudden cardiac death compared to those on the NCEP diet (HR = 0.48, 95% CI: 0.33, 0.71) (114).

## Atrial Fibrillation

Atrial fibrillation, the most common arrhythmia found in clinical practice, with an estimated lifetime risk of 25% (65), results in an age-dependent increase in the risk of cerebrovascular incident; the population-attributable risk increases steadily from 6.7% between ages 50 and 59 years to 36.2% between ages 80 and 89 years (138). Increasing longevity and improved survival after myocardial infarction has resulted in a steady increase in the prevalence of atrial fibrillation and its associated comorbidities (84). In spite of advances in the understanding of the pathophysiological mechanisms that cause atrial fibrillation, preventive strategies are limited. In a substudy of the PREDIMED trial, 6,705 participants without atrial fibrillation at randomization were followed for a median of 4.7 years (70). Compared to controls, adherence to a Mediterranean diet supplemented with olive oil significantly reduced the risk of atrial fibrillation (HR = 0.62; 95% CI: 0.45, 0.85). No significant effect was found for the Mediterranean diet supplemented with nuts (HR = 0.89; 95% CI: 0.65, 1.20).

## Microvascular Cerebrovascular Disease and Accident

The effects of the Mediterranean diet have been studied in areas of cognition and cerebrovascular disease. Consumption of a Mediterranean diet is associated with lower white matter hyperintensity volume on magnetic resonance imaging, a marker of small vessel damage in the brain (34). Prospective studies have provided evidence for a favorable relationship of a Mediterranean-type diet with slower cognitive decline, reduced risk of progression from mild cognitive impairment to Alzheimer's disease, and reduced risk for cerebrovascular accident. In a substudy of the PREDIMED trial, the PREDIMED-Navarra trial assessed global cognitive performance in 522 participants at high vascular risk randomized to either a low-fat or Mediterranean-style diet supplemented with either nuts or olive oil (71). The Mini-Mental State Examination (MMSE) and Clock-Drawing Test (CDT) were used to assess cognitive performance after 6.5 years of

nutritional intervention. Participants consuming a Mediterranean-style diet supplemented with either nuts or olive oil had higher mean MMSE and CDT scores compared to controls, even after adjustment for cerebrovascular disease and dementia risk factors (adjusted differences: 0.62, 95% CI: 0.18, 1.05 for MMSE and 0.51, 95% CI: 0.20, 0.82 for CDT) (71). These results were supported by the Cache County Study on Memory, Health, and Aging, which followed 3,831 subjects with the MMSE over 11 years (133).

The Mediterranean dietary pattern has also been found to reduce the risk of cerebrovascular incidents. Scarmeas et al. (109) demonstrated the microvascular benefits of the Mediterranean dietary pattern in a study of 707 patients >65 years of age followed for an average of 5.8 years. Higher adherence to a Mediterranean dietary pattern was associated with a 36% risk reduction of cerebrovascular infarction on magnetic resonance imaging (OR = 0.64, 95% CI: 0.42, 0.97) (109). In a case-control study of 500 patients, Kastorini et al. (52) found that each 1/55-unit increase in the Mediterranean diet score was associated with a 17% risk reduction (95% CI: 0.72, 0.96) in ischemic stroke in nonhypercholesterolemic patients, and a 10% risk reduction (95% CI: 0.81, 0.99) in hypercholesterolemic patients. Similar results have been reported by the Nurses' Health Study, which followed 74,886 women ages 38 to 63 years without a history of cardiovascular disease for 20 years (33). Compared to women in lowest quintile, women in the highest quintile of Mediterranean diet score were 13% less likely to suffer from stroke (RR = 0.87, 95% CI: 0.73, 1.02; *p* for trend = 0.03) (33). Finally, in a meta-analysis of 170,383 patients, Psaltopoulou et al. (88) examined the association between adherence to a Mediterranean dietary pattern and risk of cognitive impairment and stroke. High adherence to a Mediterranean dietary pattern was consistently associated with reduced risk for cognitive impairment (RR = 0.60, 95% CI: 0.43, 0.89) and stroke (RR = 0.71, 95% CI: 0.57, 0.89). Moderate adherence was similarly associated with reduced risk for cognitive impairment, with a marginal trend for stroke reduction (88).

## **Mortality**

Adherence to the Mediterranean dietary pattern has also been associated with decreased all-cause mortality. In a large prospective study, Trichopoulou et al. (127) followed 22,043 Greeks, 20 to 86 years of age, who were free from preexisting diagnoses of coronary heart disease, diabetes mellitus, or cancer over a median of 44 months. Adherence to a Mediterranean dietary pattern was assessed by a 10-point scale, with higher scores indicating greater adherence (127). Greater adherence to a Mediterranean dietary pattern was associated with a reduction in total mortality (adjusted HR = 0.75, 95% CI: 0.64, 0.87) and death due to coronary artery disease (adjusted HR = 0.67, 95% CI: 0.47, 0.94) (127). Similarly, the Healthy Ageing: A Longitudinal Study in Europe (HALE) project evaluated the effects of dietary patterns on all-cause mortality in 2,339 Europeans, ages 70 to 90 years, over 10 years (56). Adherence to a Mediterranean dietary pattern was associated with a lower risk of all-cause mortality (HR = 0.77, 95% CI: 0.68, 0.88) even when adjusting for age, sex, level of education, BMI, and other cardiovascular disease risk factors (56). Furthermore, among elderly individuals, adherence to a Mediterranean dietary pattern in combination with moderate alcohol consumption and at least 30 minutes of daily physical activity was associated with a 60% risk reduction in all-cause mortality (56). Finally, Bertoia et al. (7) studied the association between the Mediterranean dietary pattern and sudden cardiac death in 93,122 postmenopausal women who were enrolled in the Women's Health Initiative study and followed for 10.5 years. A higher Mediterranean diet score was associated with a lower risk of sudden cardiac death (HR = 0.64, 95% CI: 0.43, 0.94) even after adjustment for age, total energy, race,

income, smoking, and physical activity. The protective effect of the Mediterranean dietary pattern remained unchanged even after adjustment for potential mediators such as coronary artery disease, congestive heart failure, diabetes, BMI, and hypertension (7). In a large meta-analysis of 18 cohort studies with 2,190,627 subjects followed from 4 to 20 years, consumption of a Mediterranean diet was associated with a significant reduction in overall mortality ( $RR = 0.92$ , 95% CI: 0.90, 0.94) and cardiovascular mortality ( $RR = 0.90$ , 95% CI: 0.87, 0.93) (116).

## CONCLUSION

Mortality from cardiovascular diseases in the United States has been declining since the 1970s. Lifestyle modifications are responsible for almost half of this decline, which indicates that dietary interventions can be successful in reducing cardiovascular disease morbidity and mortality (37). The Mediterranean dietary pattern, representing the diet typically consumed among the populations bordering the Mediterranean Sea in the 1960s, has been widely reported to be a model of healthy eating for its salutary contribution to cardiovascular health. Components of the Mediterranean dietary pattern associated with better cardiovascular health include moderate consumption of ethanol (mostly from wine); low consumption of meat and meat products; and high consumption of vegetables, fruits, nuts, legumes, fish, and olive oil. The health benefits of the Mediterranean diet cannot be attributed to a single component but rather are the result of the synergistic relationships among multiple components of this dietary pattern. Consumption of a Mediterranean diet favorably affects numerous cardiovascular disease risk factors, such as dyslipidemia, hypertension, metabolic syndrome, and diabetes. Moreover, it has been proven to reduce cardiovascular disease incidence, reoccurrence, and mortality. Importantly, the 2013 American College of Cardiology/American Heart Association guideline on lifestyle management to reduce cardiovascular risk also recommends a diet strategy that closely resembles a Mediterranean dietary pattern (24). The benefits of the Mediterranean diet suggest that widespread adoption of this dietary strategy could have significant public health implications.

### SUMMARY POINTS

1. The Mediterranean diet is not a specific diet, but rather a dietary pattern followed by inhabitants of areas surrounding the Mediterranean Sea in the 1960s.
2. Principles of this dietary pattern include eating an abundance of whole grains, fruits, vegetables, legumes, and nuts; using olive oil as the principal source of added fat; consuming low to moderate amounts of low-fat dairy daily; consuming a low amount of red meat; consuming a moderate amount of fish and eggs; consuming a moderate amount of wine; and using herbs and spices to flavor food.
3. Adoption of a Mediterranean dietary pattern is associated with significant reductions in serum lipids, fasting blood glucose, blood pressure, insulin resistance, arterial stiffness, and oxidative stress.
4. The Mediterranean dietary pattern is a useful tool in the primary and secondary prevention of cardiovascular disease, and its adoption has significant public health implications.

## FUTURE ISSUES

Robust evidence supports the adoption of a Mediterranean dietary pattern for the maintenance of health and prevention of cardiovascular disease. However, there is a paucity of research on the effect of this dietary pattern on the development and control of other chronic conditions, such as cancer, arthritis, and autoimmune disorders. More research is needed to determine if the salutary effects of the Mediterranean dietary pattern can be extended to other diseases. In addition, although the popularity of the Mediterranean dietary pattern has grown among health professionals and major scientific panels (24, 134), there has been a progressive shift to a non-Mediterranean dietary pattern, even in countries bordering the Mediterranean Sea (118). Going forward, researchers must partner with public health officials to encourage industries to produce healthier food options and to encourage the public to adopt dietary patterns with known health benefits.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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