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Review

Effects of the Mediterranean diet on longevity and age-related morbid conditions

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ABSTRACT

Objectives: To delineate the influences of the Mediterranean diet (MD) on human mortality and age-related morbid conditions, principally the metabolic syndrome, hypertension, cardiovascular disease, excess body weight, cancer, poor bone mineralization and rheumatoid arthritis, and neurodegenerative disorders.
Method: Citations were selected from a PubMed search according to their clinical and experimental relevance.
Results and conclusions: Individuals who adhere to the principles of the traditional MD tend to have a longer life-span. Both men and women who report eating foods closest to the MD are about 10–20% less likely to die over the course of a study of heart disease, cancer or any other cause. The longevity of Mediterranean people has been related to olive oil, and its several microcomponents of antioxidant potential, present in all MD variants. The prevalence of the metabolic syndrome may be reduced by a MD. The MD is significantly inversely associated with both systolic and diastolic blood pressure. It also has benefits in relation to the prevention of cardiovascular events, reduces the risk of mortality after myocardial infarction, and reduces peripheral arterial disease. The risk of obesity decreases with increasing adherence to the traditional MD. The MD also has a preventive effect on cancer, through its antiproliferative and pro-apoptotic effects, mostly due to the components of virgin olive oil and vegetables. There is some evidence of the benefits of the MD in relation to bone metabolism, rheumatoid arthritis, and neurodegenerative age-related diseases (cognitive deficit, Alzheimer's disease, Parkinson's disease).

Contents

Abbreviations: ATPIII, National Institute of Health Third Adult Treatment Panel; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension (DASH); DHA, docosahexaenoic acid; EPA, eicosapentaenoic; EPIC, European Prospective Investigation into Cancer and Nutrition; HDL-C, high density lipoprotein cholesterol; ICAM-1, intracellular adhesion molecule-1; IL-6, interleukin-6; MD, Mediterranean diet; METS, metabolic syndrome; MUFA, monounsaturated fatty acids; PREDIMED, Prevención con Dieta Mediterránea; PUFA, polyunsaturated fatty acids; RA, rheumatoid arthritis; REM, rapid eye movement; RR, relative risk; SAF, saturated fatty acids; SUN, Seguimiento Universidad de Navarra; VCAM-1, cell adhesion molecule-1; VOO, virgin olive oil; WG, weight gain; WHR, waist-to-hip ratio.

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1. Introduction

During millions of years of evolution, human beings were largely subject to low-fat, high-carbohydrate diets (the foods generally available to our ancestors). The Paleolithic diet was based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts [1,2]. The diet of late archaic hominid populations and their contemporaneous modern humans included marine food supply [3]. Modern civilization was born around the Mediterranean Sea. Ancient Greeks and Romans created a culinary culture that lasted for centuries, into present times [4]. For example, the Ancient Greeks used olives as their main source of fat instead of animal meat; they believed – in contrast to those they deemed barbarians – that animal fat was an unhealthy food. Olive oil was created to help preserve the olives. Barbarians ate more meat and animal products such as milk and cheese because they were nomadic and had less opportunity to grow olive trees or to prepare olive oil. The discovery of America lead to the incorporation of new fruits and vegetables that enriched European gastronomy: tomatoes, corn, potatoes, chocolate, etc. In the 5th century BC Herodotus mentioned a fountain in the land of the Ethiopians, whose healing water was responsible of the exceptional longevity of this people. In Spain, during Moorish rule (from the 8th to the 15th century), stories about the water of eternal life or youth were very popular, and would have been known to the explorers who journeyed to America. Thus, in 1513 the Spanish explorer Juan Ponce de León claimed to have found "restorative waters" in what today is Florida.

Eating is one of life's great pleasures, and there are many time-tested diets that are compatible with good health. In the 1950s, it was reported that people in Crete had long lives because they had much lower rates of stroke, heart disease and certain cancers [5]. Researchers noted that the risk of heart disease was much lower for people throughout the Mediterranean region [6–8], despite the high intake of monounsaturated fatty acids (MUFAs), found in olive oil; and so began research regarding the 'Mediterranean diet' (MD). The World Health Organization sponsored a study regarding the dietary habits of people from seven different countries (Greece, Italy, Yugoslavia, Holland, Finland, the USA and Japan). The research covered a span of 30 years, with the participation of approximately 13,000 subjects aged 40–59. The study found that Cretan men had exceptionally low death rates from heart disease, despite their moderate to high intake of fat [7]. The Cretan diet was similar to other traditional MDs, consisting mostly of olive oil, bread, abundant fruit and vegetables, fish, and a moderate amount of dairy foods and wine. However, one must bear in mind that, when these studies were carried out, the Mediterranean region was an economically depressed area, and most people had a relatively restricted diet, with little meat; moreover, their lifestyle often featured hard physical work, and rates of obesity were very low. Thus, the reported health benefits of the MD may be related more to a physically active lifestyle and other social and cultural issues. Traditional Mediterranean mealtimes were leisurely family affairs, not a fast-food meal at work. The popularity of the MD has grown worldwide during the last 20 years, due to its link with greater longevity and lower rates of cardiovascular disease, cancer and age-associated cognitive decline [9–12]. The MD is a nutritional model based on the traditional diets of some of the countries of the Mediterranean basin, particularly Greece, southern Italy, Portugal, Cyprus, Spain, and Turkey. A recent meta-analysis confirmed the benefits of a MD in individuals aged 65 years and over [13].

Although there is no anti-ageing elixir, a healthy lifestyle may prolong the human life-span. The objective of the present article is to place in perspective the possible benefits of the MD on menopausal women's health, a period of life with high morbidity, and its value in relation to some age-associated conditions.

2. Longevity and mortality

Ageing is the expression of biological changes, and the result of a cumulative and irreversible non-proliferative cell state that leads to senescence. There are many biological explanations of ageing but none is accepted as the sole theory. They have included telomere shortening, damage to the genetic integrity of the body's cells, autoantibody generation, and cumulative oxidative damage [14–16].

A number of studies have examined the association between the MD and longevity. In general, people who adhere to the traditional MD have a longer life-span. Epidemiological studies have reported that the consumption of omega-3 polyunsaturated fatty acids (PUFAs) from both marine and plant sources positively correlates with reduced annual mortality rates from all causes [17] and, above all, from coronary heart disease [18].

In one study conducted in elderly European subjects, a reduced annual mortality risk of 23% was reported from adherence to the MD [19], whereas no statistically significant association was found in another study [20]. In a cohort of elderly Spanish individuals, a diet close to the traditional MD was associated with a significant reduction in overall mortality in subjects aged less than 80 but not in subjects aged 80 or more [21].

The European Prospective Investigation into Cancer and Nutrition (EPIC) Elderly study, which combined the results of nine European countries and assessed diet in terms of its closeness to the MD, on 10-point scale. It found that this score was associated with an increased life-span. For example, a healthy man aged 60 who adheres well to the MD (dietary score of 6–9) can expect to live about 1 year longer than a man of the same age who does not adhere to the diet. However, this association was not significant for 6 of these 9 countries, and the association was absent for the Netherlands, Germany, and Italy [11]. Thus, adherence to a MD is associated with a significantly longer life expectancy, and may be particularly appropriate for elderly people, who are a rapidly increasing group in Europe.

In a more recent analysis of the multicenter EPIC cohort, the association of the prevailing dietary pattern with all-cause mortality was determined in a population of subjects 60 years or older at the time of recruitment [22]. The population included 74,607 subjects without previous coronary heart disease, stroke or cancer.

Participants scored higher for adherence to a 'traditional MD' if they ate more fruits and nuts, grains, beans, fish and vegetables (excluding potatoes), and if they ate less dairy products, meat or saturated fat. Those who drank a moderate amount of alcohol, defined as 5–25 g per day for women and 10–50 g per day for men, also scored higher. An 'alternative MD' was scored similarly, but included only whole (not refined) grains, did not include dairy products, counted fruits and nuts separately, used the same alcohol standard for men and women, and deducted points for meat only if it was red or processed. The association between the MD and decreased mortality seemed strongest among smokers, particularly smokers who were of healthy body weight. Among both smokers and non-smokers, those who were obese did not appear to have their lives lengthened by the MD. People who most closely followed either MD (traditional or alternative) were significantly less likely to die during the first 5 years after the initial surveys. After adjustments for confounding factors, an increased adherence to the plant-based diet was associated with a lower overall mortality, while an increment of one standard deviation in plant-based diet was associated with a statistically significant reduction of 14% of beneficial effects (95% confidence interval 5–23%) in overall mortality. In the Spanish prospective EPIC cohort, over a 6.5-year follow-up, a high intake of fresh fruit, root vegetables, and fruiting vegetables was confirmed as significantly associated with a reduced mortality rate [23]. Among the EPIC cohorts, mortality was also studied in individuals from four Italian regions, who were prospectively followed up for a median of 6.2 years. Four dietary patterns were defined at enrollment and adjusted for potential confounders. The 'olive oil and salad' pattern, which included a high consumption of olive oil, raw vegetables, soups and poultry, was inversely associated with overall mortality in both crude and adjusted models. After adjustment, overall mortality was reduced by approximately 50% in the highest quartile. An association of the 'pasta and meat' pattern with increased overall mortality was also suggested, but only for the highest quartile in a multivariate model [24].

In 1995, the US National Institutes of Health-AARP (formerly known as the American Association of Retired Persons) mailed a questionnaire to 3.5 million AARP members, and 566,000 returned usable answers. The researchers followed up this group for 10 years. People who reported eating foods closest to the MD were about 20% less likely to have died of heart disease, cancer or any other cause; these results were similar in both genders. Mitrou et al. [25] evaluated all-cause mortality in the US NIH-AARP Diet and Health Study (which involved 214,284 men and 166,012 women), using a 9-point score to assess conformity with the MD pattern. The MD was associated with reduced all-cause and cause-specific mortality. In women, significant inverse associations were observed; these decreased risks ranged from 12% for cancer mortality to 20% for all-cause mortality. In a prospective Australian cohort, of whom 24% were Mediterranean-born, the effect of diet was studied by analyzing the principal components of the diet and adjusting for confounding factors [26]. The Mediterranean factor was inversely associated with cardiovascular disease (CVD) and heart-related mortality. The consumption of vegetables and fresh fruit was inversely associated with CVD mortality but only among those without prior cardiac pathology. Therefore, the benefits of MD have been demonstrated beyond the European continent.

A recent meta-analysis that included 12 studies, involving more than 1.5 million individuals whose eating habits and health were tracked for 3–18 years [27], developed an "adherence" score to rate how well people followed the MD. The results demonstrated that a strict MD cuts the risk of all-cause early death by 9%, cardiovascular mortality by 9%, cancer mortality by 6%, and Alzheimer's and Parkinson's disease by 13%.

The longevity of Mediterranean people has been related to olive oil, and its several microcomponents with antioxidant potential, present in all MD variants. However, there are dietary components other than those included in the MD that may also be healthy for women and increase longevity. Thus, a healthy traditional Dutch diet also appears to be beneficial for longevity and feasible for health promotion among older Dutch women. This diet has high intakes of vegetables, fruit, nonalcoholic drinks, dairy products, and potatoes [28].

3. Mediterranean diet and the metabolic syndrome

The metabolic syndrome (METS) has been associated with cardiovascular risk, atherosclerosis, increased risk of type 2 diabetes and cardiovascular mortality [29–31]. The prevalence of the METS increases with age. Some studies have estimated that its prevalence may be as high as 25% of the general population [32–34]. In a 15-year prospective study, it was observed that the METS was significantly more common in women (31.5%) than in men (12.4%) [35], whereas in a cross-sectional study the reverse was found [34]; the latter study found the prevalence of the METS to increase with age, the degree of adiposity and lower social class. In addition, it was associated with an increased risk of cardiovascular events, with a hazard ratio of 1.9 (95% confidence interval, CI, 1.46–2.46), regardless of impaired fasting glucose level or diabetes mellitus [35].

The US National Institute of Health Third Adult Treatment Panel (ATPIII) defined the METS as 3 or more of 5 risk determinants: abdominal obesity (waist circumference >88 cm), increased level of serum triglycerides (≥150 mg/dL), decreased level of high-density lipoprotein cholesterol (HDL-C <50 mg/dL), high fasting glucose level (≥110 mg/dL) and increased blood pressure (≥130/85 mmHg) [36]. An atherogenic diet (i.e., a diet rich in saturated fat and cholesterol) can enhance the risk of cardiovascular disease in individuals with the syndrome, although the atherogenic diet is not listed specifically as an underlying risk factor for the condition. Lifestyle modification and the use of medications to treat the conditions comprising the METS may reduce an individual's chance of developing heart disease or stroke. The prevalence rate of METS may be reduced by nutritional interventions to rates similar to those obtained with drugs such as rosiglitazone and rimonabant. Some cross-sectional studies have suggested that the MD or some of its components may reduce the incidence of the METS [37].

In a cross-sectional study, the relation between the MD and the METS was determined in a representative sample of adults from the Canary Islands (Spain) [33]. In this sample, 24.4% of individuals presented with the METS. Subjects from the third tertile of MD adherence presented a 70% lower prevalence rate of high blood pressure than the first tertile. Fruit consumption had a protective effect on the proportion meeting the criteria for problematic triglyceride levels, while vegetable intake was associated with a higher prevalence of this endpoint. High ratios of intake of monounsaturated fat to saturated fat had a protective effect on insulin resistance. Thus, it seems that some components of the MD may have a preventive effect on insulin resistance. The Spanish SUN (Seguimiento Universidad de Navarra) Study uses methodology similar to that of large American prospective cohorts, in which the recruitment is permanently open [38]. Participants were excluded if at baseline they had implausible values for total energy intake, had a body mass index (BMI) >30 kg/m^2 or reported having other particular risk factors, or met the criteria for the METS. After a 6-year questionnaire follow-up, the results concerning MD adherence were available for 2563 of these participants initially free of the METS and other risk factors. Adherence to the MD was higher among women, older subjects, ex-smokers, and more physically active participants. There was an inverse association between adherence to the MD and the cumulative incidence of the METS.

The different MD components have been studied in relation to the METS in individuals without CVD enrolled in the ATTICA Study, which included a population from the Attica region in Greece [39]. Greater consumption of cereals, fish, legumes, vegetables, and fruits was independently associated with reduced levels of clinical and biological markers linked to the METS, whereas greater consumption of meat and alcohol was associated with an increase in these markers.

A 'diet score' (range 0–55) which reflected the characteristics of the MD was developed to determine the association with cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia and obesity in 150 older people (53 men and 97 women) from various areas of Cyprus [40]. More than 90% of the participants reported consistency in their dietary habits for at least the past three to four decades. Among the women, 18% had diabetes, 58% had hypertension, 68% had hypercholesterolemia, and 52% were obese. After adjustments for confounding factors, a 10-unit increase in the diet score was associated with 21% lower odds of having one additional risk factor in women, compared with 14% lower odds in men. It seems that adherence to a MD is associated with reduced odds of having hypercholesterolemia, hypertension, diabetes and obesity among elderly individuals, especially in women.

To reduce the incidence of the METS, diet strategies have been proposed, including adequate omega-3 fatty acids intake, reduction of saturated and trans-fats, and consumption of fruits and vegetables, nuts, and whole grains and unrefined grains. All these recommendations seek to reduce the vascular inflammation associated with the METS [41]. Fitó et al. [42] reported the results of a Spanish multicenter randomized controlled, parallel-group clinical trial (the Prevención con Dieta Mediterránea [PREDIMED] Study), which included 210 women and 162 men at high cardiovascular risk and aimed to test the efficacy of two traditional MDs plus with either virgin olive oil (VOO) or nuts, in comparison with a low-fat diet, on the primary prevention of coronary heart disease. After 3 months, mean levels of oxidized LDL decreased in the MD plus VOO and MD plus nuts groups, while there was no change in the mean value in subjects who received the low-fat diet. Thus, both types of MD gave significant reductions in cellular lipid levels and LDL oxidation. Some drugs used to treat the METS, like rosiglitazone, produce changes in endothelial function and metabolism similar to those registered in individuals under the MD [43]. In a more recent publication, from the PREDIMED Study, investigators evaluated the effect of a MD supplemented with nuts on METS status [44]. The researchers compared the 1-year effect of two interventions, including MD versus a low-fat diet. Interventions were quarterly regarding the MD plus provision of either 1 L/week of VOO or 30 g/day of mixed nuts, and advice on a low-fat diet (control diet). All diets were *ad libitum*, and there was no increase in physical activity for any of the interventions. The METS diagnostic criteria were those of the National Cholesterol Education Program Adult Treatment Panel III [36]. The prevalence of METS was reduced by 6.7, 13.7 and 2.0% for the MD + VOO, MD + nuts and control groups, respectively. The results indicate that MD + nuts could be an interesting tool in the management of the METS.

The MD also inhibits activation of circulating immune cells [45]. In a controlled study, subjects with diabetes or three or more CVD risk factors were placed in three dietary intervention groups: MD and supplemental VOO, MD with supplemental nuts, and a low-fat diet. After 3 months in both types of MD, monocyte expression of CD49d, CD40, serum interleukin-6 and other adhesion factors significantly decreased, whereas there were no changes or increases after the low-fat diet. It seems that MD with either VOO or nut supplements reduces the intravascular inflammatory condition that potentiates atherogenesis.

Oscillating glucose levels may have more deleterious effects than constant high glicemia on endothelial function and oxidative stress in diabetic patients, which can lead to cardiovascular complications. Adherence to a MD is associated with a reduced risk of diabetes. This protective effect has been related to the high intake of vegetable fat, a low intake of trans fatty acids, abundant VOO and a moderate intake of alcohol. This combination produces a high ratio of MUFAs to SAFs. Thus, individuals who follow a strict MD have a lower risk of diabetes [46]. Among Spanish university graduates without diabetes, participants who adhered closely to a MD pattern had a lower risk of type 2 diabetes after a median follow-up of 4.4 years. The adjusted rate ratios were 0.41 for those with moderate adherence to the MD and 0.17 for those with very high adherence. Therefore, it can be assumed that long-term MD adherence or a healthy lifestyle may multiply the benefits reported in short-term follow-up. However, it is important to bear in mind that this study was in normal-weight young adults and anyone changing their diet to a more Mediterranean-style should be careful not to increase calorie intake by increasing their intake of olive oil. Further, this study did not examine treatment interventions.

4. Hypertension

Nutritional factors and micronutrients have been associated with hypertension. Hypertensive individuals can remarkably reduce their blood pressure through nutritional changes. Increasing the amount of vegetables and fruit and reducing the amount of fat and cholesterol will not only reduce blood pressure but can help with weight loss, which also lowers blood pressure. Thus, fruit and vegetable consumption appears to be inversely related to systolic and diastolic pressure [47]. In young adults, dietary intake over 15 years alters blood pressure. Vegetable intake (whole and refined grains, fruit, vegetables, nuts, or legumes) was inversely related to elevated blood pressure after adjustment for potential confounding factors, whereas meat consumption had adverse effects on blood pressure [48]. Thus, an elevated olive oil consumption and a high fruit and vegetable intake are inversely associated with blood pressure.

The MD, and olive oil in particular, reduced arterial blood pressure in the Greek arm of the EPIC cohort, which used a MD adherence scale [49]. The MD adherence score was significantly inversely associated with both systolic and diastolic blood pressure. Intakes of olive oil, vegetables, and fruit were significantly inversely associated with both systolic and diastolic blood pressure, whereas intake of cereals, meat and meat products, and alcohol, was positively associated with arterial blood pressure. Therefore, both MD pattern and olive oil intake are inversely associated with both systolic and diastolic blood pressure. In the SUN cohort, a MD was not associated with a reduction in blood pressure in young individuals after a median follow-up of 4.2 years, although high adherence to a MD was associated with a reduction in mean levels of both systolic blood pressure and diastolic pressure after 6 years of follow-up [50].

In the Italian EPIC Florence cohort, which included more than 10,000 non-hypertensive women aged 35–64 years who were not receiving any medication for blood pressure, anthropometric indices and blood pressure were related to the types of food ingested. In this particular population, BMI, waist circumference, as well as the consumption of processed meat, potatoes, and wine, were positively associated with blood pressure, whereas a high total consumption of vegetables was inversely associated with systolic and diastolic blood pressure; consumption of olive oil was inversely associated with diastolic pressure, and consumption of leafy vegetables with systolic and diastolic blood pressure. This study confirmed the relevance of anthropometric characteristics and specific foods to blood pressure, and showed that modifiable lifestyle factors may influence blood pressure [51].

Among prehypertensive adults without CVD from the ATTICA cohort, the 5-year incidence of hypertension was 18.7% in men and 24.6% in women [52]. Almost half the participants at the age of 55–65 years had developed hypertension. In addition, greater adherence to MD protects only prehypertensive individuals with abdominal obesity, whereas lower adherence to MD is associated with a trend to develop hypertension. In a more sophisticated study, the combined effect of olive oil and wine on wave reflections and central haemodynamics was studied [53]. Two types of wine (red and white) and two types of olive oil (green and refined, rich and poor in antioxidants, respectively) were used in all four combinations. The results demonstrated that the combination produced beneficial postprandial effects on circulation since central systolic and diastolic pressures were diminished after all combinations of wine and olive oil.

5. Mediterranean diet and cardiovascular risk

Genetic and environmental factors are involved in the genesis of CVD. Thus, genetic polymorphisms have been associated with increased cardiovascular risk [54] but these may be attenuated by appropriate lifestyle and diet. The effect of adherence to the MD on survival among elderly people with previous myocardial infarction (MI) has been studied within the EPIC cohort [55]. Increased adherence to the MD by 2 units on the study scale was associated with an 18% lower overall mortality rate, though with less evidence of the association among northern Europeans.

The effect of the MD has been related to cardiovascular risk factors (diabetes, hypertension, dyslipidemia, or obesity) in asymptomatic Spanish high-risk patients; again, adherence to the MD was rated on a scale (this one of 14 points). The MD was inversely associated with the clustering of hypertension, diabetes, obesity and hypercholesterolemia among this high-risk population [56].

Barzi et al. [57] studied the effect of MD adherence on mortality after a MI in 11,323 Italian individuals who were advised to increase their consumption of fish, fruit, raw and cooked vegetables, and olive oil. When those in the quartile with the worst dietary adherence were compared with those in the best quartile, there was a significant effect on the risk of early death. Tuttle et al. [58] compared the effect of an MD after a first MI with a low-fat diet in a randomized, controlled clinical trial. Both diets were low in saturated fat and cholesterol. After a median follow-up of 48 months, both groups obtained significant benefits when compared with 'usual care' controls without diet intervention, as evaluated by a primary-outcome-free survival index, which included a composite of all-cause and cardiac deaths, MI, hospital admissions for heart failure, unstable angina pectoris, or stroke.

Iqbal et al. [59] assessed the association between dietary patterns and acute MI (AMI) in the case–control INTERHEART cohort, which includes individuals from 52 countries. They compared three types of diet: 'Oriental' (high intake of soy derivatives and sauces), 'Western' (high in fried foods, salty snacks, eggs and low-quality meat), and 'prudent' (with large amounts of fruits and vegetables). The last diet shares some characteristics with the MD. An inverse association was observed between the prudent diet and AMI, with higher levels of fruits and vegetables being protective. The Western diet showed a U-shaped association with AMI, whereas the Oriental diet had no relationship with AMI. It was calculated by a dietary questionnaire that a Western-type diet may increase the risk of AMI by 30% compared with a diet rich in fruit and vegetables.

High adherence to a MD has also been studied in relation to peripheral arterial disease (PAD) in Italian patients with type 2 diabetes and matched with type 2 diabetic control patients without macrovascular complications [60]. Using a semi-quantitative food frequency questionnaire, high adherence to the MD was associated with a significant reduction in the risk of PAD. In addition, diabetes duration, hypertension and butter consumption were also significantly associated with PAD. Thus, MD is helpful for the prevention of PAD in diabetic individuals.

MD supplemented with olive oil or nuts has benefits on cardiovascular risk when compared with a low-fat diet. In the Prevención con Dieta Mediterránea (PREDIMED) study, 772 asymptomatic individuals aged 55–80 years and at high cardiovascular risk were assigned to MD supplemented with either free VOO or free nuts or to a low-fat diet. Both MDs had beneficial effects on cardiovascular risk as measured by metabolic outcomes [61]: they reduced plasma glucose levels, the cholesterol/HDL-C ratio, and systolic blood pressure, although only the MD supplemented with olive oil also reduced levels of C-reactive protein (CRP).

It seems that phytochemical components of the MD diet exert cardioprotective effects through mechanisms that are being progressively elucidated. The components of the MD and circulating markers of inflammation have been evaluated in asymptomatic individuals aged between 55 and 80 years in relation to high cardiovascular risk due to the presence of diabetes or at least three classical cardiovascular risk factors. After adjustment for different confounding factors, a higher consumption of fruits and cereals was associated with lower concentrations of interleukin-6 (IL-6), while subjects with the highest consumption of nuts and VOO showed the lowest concentrations of vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), IL-6 and CRP; however, only for ICAM-1 was this difference statistically significant in the case of nuts and for VCAM-1 in the case of VOO [62]. Thus, some components of MD were associated with lower serum inflammatory marker concentrations, especially those related to endothelial function.

The impact of MD has been also studied in 957 healthy subjects aged 60 years or more from five European countries in the ZINCAGE study. Italians presented the greatest adherence to the MD, Poles the poorest. There were significant effects of the components of the MD on markers of inflammation [63]. Thus, a higher diet score was significantly associated with lower BMI and erythrocyte sedimentation rate and higher HDL-C levels.

Dietary habits are influenced by educational level, as evaluated in the Greek EPIC cohort. Hence, people from the low-education group had a significantly higher prevalence of hypertension, diabetes and dyslipidemias, and were more likely to be sedentary and smokers than were more highly educated individuals [64]. Low-education subjects were more likely to suffer cardiovascular events due to unhealthy lifestyle choices. With higher levels of education, the degree of adherence to the MD increased in subjects aged 35–65 years and this was associated with a lower incidence of cardiovascular events, independent of confounding factors, within a 5-year period [65].

6. Mediterranean diet and body weight

The prevalence of obesity has alarmingly increased in industrialised countries, reaching 30–50% among the general population [66]. This change has been related to social transformation, such as women being incorporated into the workforce, food marketing and an American lifestyle promoted through the mass media [67,68]. Obesity is closely related to inflammation and cardiovascular morbidity. Overweight and obesity are associated with metabolic abnormalities that increase the atherogenic process and cardiovascular risk. The metabolic alterations reported with elevated weight include increases in pro-coagulant proteins (i.e. plasminogen activator inhibitor type-1, tissue factor or factor VII), cytokine secretion, and phagocytic and microbicidal activity, as well as dyslipidemia, hypertension and type 2 diabetes mellitus and cardiovascular disease, which are common features of the METS.

Adherence to the MD was inversely associated with BMI and obesity in a cross-sectional survey carried out in the northeast of Spain. Obesity risk decreased in both men and women with increasing adherence to the traditional MD [69]. In another study, adherence to a MD was assessed through a diet score in Greek individuals who were classified as either overweight (BMI = 25–29.9 kg/m^2) or obese (BMI = 30 kg/m^2 or more). Greater adherence to the MD was modestly associated with a better insulin sensitivity, lower total cholesterol and lower systolic blood pressure, which suggests that MD has some benefit for the cardiovascular system in individuals with elevated body weight [70].

The effect of the MD on body weight is of interest since concerns have been raised that this type of diet may promote weight gain (WG). Mendez et al. [71] studied the Spanish EPIC cohort, which included 17,238 women and 10,589 men, all non-obese and aged 29–65 at baseline. Among initially overweight individuals, 7.9% of women and 6.9% of men became obese, while 13.8% of normal-weight men and 23.0% of normal-weight women became overweight. High MD adherence was associated with a lower likelihood of gaining weight. Thus, MD adherence may actually help to prevent weight gain. In an Italian cohort it was confirmed that adherence to the major characteristics of the MD is unrelated to BMI and waist-to-hip ratio (WHR), confirming previous data from Greece and Spain [72,73]. In addition, a moderately hypoenergetic MD combined with an exercise program during 4 months reduced cardiovascular risk factors in obese women. At 2 and 4 months, weight, BMI, total cholesterol and triglycerides were significantly decreased. Fat free mass, total body water, extracellular water, fasting blood glucose levels and diastolic blood pressure were significantly decreased at 2 months, whereas HDL-cholesterol was significantly increased at 4 months [74].

Over a 10-year follow-up, the effects of fruit and vegetable consumption and other lifestyle factors were studied in relation to WG in healthy subjects aged 15–80 years at baseline [75]. The mean WG over the study period was 3.41 kg. When comparisons were made by quartiles, individuals in the third quartile of fruit intake at baseline had lower risk of WG than those in the lowest quartile. The risk of WG was lowest in subjects of the fourth quartile of vegetable intake, who had an 84% reduced risk of gaining 3.4 kg over 10 years. Therefore, fruit and vegetable content in the MD may reduce long-term risk of subsequent WG and obesity among adults.

A meta-analysis is available regarding MD and body weight, which includes evidence from 21 epidemiological studies (7 cross-sectional, 3 cohorts and 11 intervention studies) [76]. The quality of these studies was varied. Adherence to the MD was associated with a lower prevalence of overweight/obesity or more weight loss in 13 studies, but there was no association in the other eight studies. Differences in diet may have been observed between older and younger individuals with elevated weight. Older patients were more prone to a higher frequency of consumption of fresh fruit and vegetables, and lower daily consumption of sweet high-fat foods. The consumption of moderate amounts of red wine at mealtimes was common in older male patients only. In this population, MD did not protect older obese patients from additional WG [77].

7. Mediterranean diet and cancer

The MD is rich in vegetables, tomato, fruit, fish and olive oil, which all provide important dietary components that may contribute to lower risk of cancer. Lycopene is a major component in tomatoes that has been found to have a potential anticarcinogenic activity [78]. Previous studies also showed that fish consumption correlated with reduced risk of cancer [79]. In addition, VOO has in vitro antiproliferative and pro-apoptotic effects. The most potent olive oil polyphenol is oleuropein aglycone [80]. In vitro studies have demonstrated that VOO phenolic fractions induce anti-cancer effects by suppression of lipogenic specific enzymes, including inhibition of fatty acid synthase, a key enzyme in mammals, involved in the anabolic conversion of dietary carbohydrates to fat [81]. This mechanism of action of olive oil may provide therapeutic moieties for the treatment of human malignancies. A high intake of whole-grain foods also reduced the risk of malignant tumors at all sites except thyroid [82], and the consumption of fruit and vegetables appears to reduce the incidence rate of most malignancies, especially epithelial cancers [83–86].

The effects of some components of the MD on prognosis following treatment for breast cancer have been evaluated. During a 7.3-year follow-up period, survivors of early-stage breast cancer who adopted a diet very high in vegetables, fruit and fiber, and low in fat, did not reduce additional breast cancer events or mortality [87].

Endometrial cancer is associated with elevated body weight, higher total energy intake, more frequent consumption of red meats and fats, and high consumption of sugar, while inversely associated with an elevated intake of fresh vegetables and fruits, whole-grain bread, and pasta intake [88]. Within the EPIC cohort, the risk of developing endometrial cancer was associated with metabolic abnormalities and obesity [89]. The association between diet and risk of endometrial cancer has also been studied in the San Francisco Bay area. Food intake was assessed in terms of its correspondence to a Mediterranean-style diet. Although a mild adherence to the MD was not associated with endometrial cancer risk, high fat consumption, regardless of fruit and vegetable consumption, was associated with an increase in endometrial cancer [90].

Type of food consumption has been associated with rates of epithelial ovarian cancer. Particular nutritional variables have been studied, and inverse associations with cancer risk were found only for MUFAs and crude fiber (independently) [91], while red meat consumption increased ovarian cancer risk and there seemed to be inverse associations for fish consumption and raw and cooked vegetables [92].

The effect of two diets – a MD and the US Food Guide and the Dietary Approaches to Stop Hypertension (DASH) Eating Plan – on the risk of distal colorectal adenoma was evaluated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort. Men and women aged 55–74 were screened for colorectal cancer by sigmoidoscopy at 10 North American centers. The results suggested that both the US dietary recommendations and the MD were associated with a reduced risk of colorectal adenoma [93]. In vitro studies performed with HT-29 human colon cancer cells, an olive skin extract has shown antiproliferative activity by changing membrane permeability and increasing caspase-3-like activity without cytotoxicity [94].

The degree of adherence to the traditional MD was assessed on a 10-point scale (0 minimal; 9 maximal) in 10,582 men and 15,041 women during a median follow-up of 7.9 years. There were 851 incident cancer cases. A two-point increase in the MD adherence scale was associated with a 12% reduction in cancer incidence; this association was stronger among women. The study also found that just consuming more unsaturated fats such as olive oil alone cut the risk by 9% [95]. Among Swedish women, aged 40–49 years at enrollment and followed up for an average of 12 years, a 2-point increase in the MD score, similar to that in the EPIC Greek study, was associated with a borderline significant 16% reduction in overall cancer mortality [96]. Other (observational) studies confirm that high adherence to the MD reduces cancer mortality among men and women [25]. For most digestive tract cancers, the risk decreased as consumption of vegetables and fruit increased. In addition, micronutrients contained in fruit and vegetables (flavones, flavonols and resveratrol) demonstrated an inverse relation to cancer risk, the effect for breast cancer being the most marked. Consumption of olive oil appears to be inversely associated with the incidence of cancers of the colorectum, breast, and respiratory tract [97].

8. Bone metabolism and rheumatoid arthritis

The low incidence of osteoporosis in Mediterranean countries might be explained by diet. There are data showing that, in humans, fruits and grains may protect bone metabolism [98]. Appel et al. [99] reported a reduction of renal calcium loss when the number of fruit and grain servings increased from 3.6 to 9.5. The DASH study showed a significant reduction of bone turnover markers [100].

Epidemiological studies support a positive influence of those diet components on bone mass [101,102], although such studies have scientific limitations since it is very difficult to appraise all aspects of nutrition by questionnaire and there are many environmental confounding factors. Bone protection from phytoestrogens present in legumes – especially in soy – has been observed in the Asiatic population, manifest as a reduction in low-energy fractures [103,104]. Soy is not included in the MD, although it includes other legumes with a high phytoestrogen content, such as lentils, chickpeas, and beans. Other vitamins present in certain fruits and vegetables may also help to maintain bone mass (including vitamin D, vitamin K, vitamin D, folates and β-carotens). Antioxidants have been reported to have positive effects on bone protection [105–111].

The consumption of oily fish is associated with a high intake of omega-3 PUFAs (eicosapentaenoic, EPA, and docosahexaenoic acid, DHA), which are prostaglandin precursors that may be involved in oxidative status. It seems that the ratio of omega-6 to omega-3 in the diet may modify bone formation [112,113]. Oily fish is very rich in vitamins A and D, the effects of which have already been commented in regard to vegetables and fruits. In addition, amelioration of a poor vitamin status has been shown to benefit bone mass [111,114]. On the other hand, experimental evidence shows that olive oil exerts its benefits through vitamin E, oleic acid and polyphenols [115]. In vitro, oleic acid is a potential inhibitor of arachidonic acid, a cytokine RNA messenger involved in bone turnover [115]. In vivo, the only osteoprotector oil component is oleuperin [116].

Bone mass and diet (including adherence to the MD) have been studied in 220 Greek women. Although adherence to the MD had no significant effect on bone mineral density, a pattern of high fish and olive oil intake and low red meat intake was positively associated with bone mineral density at the lumbar spine and total bone mineral content [117].

The evidence for a role of the type of diet on rheumatoid arthritis (RA) is limited to a few observational studies. Consumption of olive oil and consumption of fish – typical components of the MD – were inversely associated with RA among those who followed the dietary recommendations of the Orthodox Church [118]. Thus, an increase in olive oil consumption by two times per week reduced the risk of RA, while yearly adherence to the Orthodox Lent gave a RR of RA of 0.33. Another study has determined the link between olive oil and cooked vegetables in relation to RA. Inverse independent associations were found between increasing consumption of olive oil and cooked vegetables and RA [119]. A 12-week supplementation of fish and olive oil, especially in combination, improved joint pain, handgrip strength and other objective variables among RA patients [120].

9. Central nervous system

Elevated oxidative and nitrosative stress impair neuron integrity and function [121]. Countering this, plant foods rich in antioxidant phenolics have protective effects on central neurons [122–124].

In a case–control study, adherence to the MD, as a predictor of Alzheimer's disease, was evaluated after adjusting the results for age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical co-morbidity index, and BMI [125]. High adherence to the MD was associated with a lower risk of Alzheimer's disease, and this association was not influenced by vascular co-morbidity. The same research group studied the effect of the MD on Alzheimer's disease mortality [126] and showed that this diet may also alter the course of the disease. In particular, high adherence to the MD was inversely associated with the mortality risk.

Cognitive function was evaluated in the prospective EPIC Greek cohort, comprising people aged 60 years or more, residing in Athens and the surrounding Attica region, in relation to dietary and lifestyle variables at enrollment and 6–13 years later. It was found that adherence to the MD, as well as intake of olive oil, MUFA and SFA, was inversely associated with cognitive function, although this was not statistically significant [127]. Burgener et al. [127] reviewed 34 studies of nutritional interventions, including the MD, to prevent and treat Alzheimer's disease. Although the literature supports nutrition for Alzheimer's disease prevention, the evidence is limited.

Nutrients have been studied in association with the risk of Parkinson's disease, but the results have been inconsistent. Dietary patterns were examined in the Health Professionals Follow-Up Study and the Nurses' Health Study in relation to the risk of Parkinson's disease [128]. After 16 years of follow-up, the 'prudent diet' (characterized by high intakes of fruit, vegetables, and fish and a low intake of saturated fat and a moderate intake of alcohol) was inversely associated with that risk, whereas the 'Western diet' was not.

The protective effect of the MD has also been studied in relation to depression. In the prospective SUN cohort, logistic regression analysis was used to assess the association between intake of B-vitamins and omega-3 fatty acids (with the cohort divided by quintile) and the prevalence of depression [129]. Folate intake was inversely associated with depression among men, whereas B12 vitamin intake was inversely associated with depression among women. However, no significant associations were observed for intake of omega-3 fatty acid.

10. Characteristics of the traditional Mediterranean lifestyle

For decades, researchers have been intrigued by the apparent health benefits of the MD. However, it is not really a 'diet' in the way most people would think of. The word 'diet' should not to be confused with a weight-loss program, but rather as individuals' usual food and drink intake. Thus, it is more of a dietary pattern – or, rather, several complementary dietary patterns that have existed around the Mediterranean basin for centuries. In fact, there is no single MD; indeed more than 20 countries have a coastline on the Mediterranean Sea, and more countries are included in what is termed the Mediterranean region. There are many variations to the MD, due to social, political and economic differences between these countries. Further, the concept of the MD is based on dietary habits more typical of the 1960s, and rather different for the most part to present Mediterranean lifestyles.

The MD pattern does, though, typically emphasize fruits, cooked vegetables and legumes, grains (whole, not refined) and, in moder-

Table 1
Components of the Mediterranean diet.

Lifestyle	Regular physical activity is at the base of the pyramid
Food derived from plants	Fruits and vegetables, potatoes, bread and grains, pulses (lentils, chickpeas, lupins), beans, nuts and seeds Common foods: pasta, rice, couscous, and polenta
Minimally processed, seasonally fresh foods	Olives, avocados, grapes, spinach, eggplant, tomatoes, broccoli, peppers, mushrooms, garlic, capers, almonds, walnuts, and peanuts
Olive oil is the principal fat	25–35% of calories, with saturated fat no more than 7–8% of calories
Daily consumption	Of low to moderate amounts of cheese and yogurt
Weekly consumption	Moderate amounts of fish (shellfish, sardines, salmon) Poultry, and from zero to four eggs/week including those used in cooking and baking
Common sweets	Pastries, ice cream and cookies
Meat	Common meats are veal and lamb. Meat is at the top of the Mediterranean diet, recommended to be eaten less frequently than even sweets
Alcohol	Red wine may be consumed in moderation and with meals

ation, wine, nuts, fish and dairy products, particularly yogurt and cheese (Table 1). Further, the consumption of large amounts of olive oil in meals dominates all Mediterranean cuisine. In contrast to the standard American diet, the diet of Mediterranean individuals includes primarily fresh, seasonal vegetables rather than canned or imported products. Since mortality statistics first identified that Mediterranean populations were living longer than other Europeans, scientists have been trying to deduce which components of the MD are responsible for its considerable benefits. Some components are discussed below.

10.1. Olive oil

Wild olives (*Olea europaea*) were collected by Neolithic individuals as early as the 8th millennium BC. Olive oil is pressed from the fruit of the tree, grown widely across the Mediterranean basin. Traditionally, the benefits of MD were linked to its effect on lipoprotein metabolism. Olive oil is rich in several microcomponents that have antioxidant potential as well as its high content in MUFAs [130]. In both animals and humans, the consumption of olive oil can provide heart health benefits such as favorable effects on cholesterol regulation and LDL-cholesterol oxidation, as well as exerting anti-inflammatory, antithrombotic and antihypertensive vasodilatory effects [131–133]. However, there are many other benefits, including on haemostasis: platelet function, thrombogenesis and fibrinolysis [134,135]. A diet enriched in VOO can reduce the sensitivity of platelets to aggregation, decreasing von Willebrand and tromboxane B_2 plasma levels. Moreover, a particular interest has arisen regarding its capacity to decrease fasting factor VII plasma levels and to avoid or modulate its postprandial activation. Also, tissue factor expression in mononuclear cells may be reduced with long-term intake of VOO. Finally, experimental studies have shown that it may also increase fibrinolytic activity, reducing plasma concentration of plasma activator inhibitor type-1. Olive oil's richness in antioxidants may benefit arterial blood pressure, reduce LDL-cholesterol, improve diabetes, and reduce the risk of thrombosis. Some other seed oils – like sunflower, soy, and canola oil – share certain properties; however, olive oil is a natural juice with hundreds of non-fatty microcomponents of biological significance, such as carotenes, phenolics compounds and chlorophyll.

10.2. Fruit and vegetables

A high intake of fresh fruit and vegetables has been shown to protect against both heart disease and cancer, probably due to their antioxidant content. Fruit and vegetable antioxidants, including vitamins and flavonoids, contribute to an anti-inflammatory effect [136–138]. Vegetable fiber intake may also help to prevent inflammation since there is an inverse association between fiber intake and CRP [139,140]. In addition, greater frequency of fruit and vegetable intake is associated with lower CRP and homocysteine concentrations. The Massachusetts Hispanic Elders Study found that with each additional serving of fruit and vegetables, the risk of high CRP and homocysteine levels decreased 21 and 17%, respectively [141].

Tomatoes have come under particular scrutiny because they feature so heavily in Mediterranean food. They contain well-known antioxidants such as vitamin C, carotenoids, flavonoids, and hydroxycinnamic acids. The major benefits of tomato ingestion are, though, related to the antioxidant lycopene [142]. It is a red pigment present in many red fruits and vegetables, although the quantity is higher in cooked tomatoes [78,143], as heat processing increases the availability of lycopene (However, the industrial processing of this fruit into tomato paste involves several treatments that potentially reduce the antioxidant content.). Tomato extract or derivative diet supplements have shown to ameliorate hypertension and cardiovascular disease, to protect the skin against the sun (i.e. ultraviolet rays), to decrease the risk of many chronic diseases including cancer and is antioxidant in many processes [142,144,145]. Dietary consumption of anthocyanins, a class of pigment produced by higher plants like berries and tomatoes, has also been associated with protection against a broad range of human diseases. Transgenic purple tomatoes, enriched with anthocyanins, have been shown to prolong life under experimental conditions [146].

Brassica vegetables, including cabbages, kale, broccoli, Brussels sprouts, and cauliflower, have been shown to have protective effects against cancer, probably due to their relatively high content of glucosinolates, since certain glucosinolates hydrolysis products have shown anticarcinogenic properties [147,148]. In addition, broccoli and cabbage have indole-3-carbinol, which has been found to prevent the progression of different cancers in experimental conditions. This anti-cancer effect could be due to elastase inhibition, since high levels have been linked to poor cancer prognosis, decreased response to chemotherapy, reduced response to endocrine treatment and a reduced survival rate in some human cancers [149].

10.3. Oily fish and polyunsaturated fats

Some researchers believe that the presence of saturated fats in the diet affect memory and possibly increase the risk of developing Alzheimer's disease, while elevated intake of unsaturated fatty acids (MUFA and PUFA) and high levels of antioxidants could act synergistically to improve cognitive performance [150]. Fatty acids comprise about one-fifth of the dry weight of the human brain; 20% of these fatty acids are in the form of omega-3 DHA, which is concentrated in nerve synapses and has anti-inflammatory properties that may be protective against Alzheimer's disease.

Fish, in particular oily fish such as sardines and anchovies, have important health benefits. Oily fish are a source of omega-3 polyunsaturated fats and the complex long-chain derivatives of these fats appear to be particularly beneficial to heart health because of their anti-inflammatory and vasodilatory properties.

The long-chain omega-3 PUFA EPA and DHA are the active constituents of the fish. Low rates of death from coronary heart disease have been reported for populations that consume large amounts of fish, although high intake has been related to high mercury levels [151]. Omega-3 PUFA increases insulin sensitivity and reduces inflammatory markers as well as leukocytes, platelets and vascular endothelial growth factor [152,153].

10.4. Wine in moderation and the French paradox

Throughout the Mediterranean, wine is drunk in moderation and usually taken with meals. For men moderation is two glasses per day, for women one glass per day. Wine, especially red wine, contains a vast array of plant compounds with health-promoting qualities called phytonutrients. Among them, polyphenols, which are powerful antioxidants, protect against LDL oxidation and other pathological sequelae of the oxidative process. Other phytonutrients play a role in the inhibition of platelet aggregation, vasodilation, etc. Polyphenols and vitamin E are antioxidants implicated as possible anti-atherosclerotic agents in the MD. The polyphenol resveratrol, present in grapes, protects vascular walls from oxidation, inflammation, platelet aggregation, and thrombus formation. Resveratrol may act at multiple levels, such as cellular signaling, enzymatic pathways, apoptosis, and gene expression [154–156].

A number of population studies have revealed that people who drink moderate amounts of red wine have less heart disease than non-drinkers. The French paradox is a concept coined by Renaud and de Longeril: it concerns the low incidence of coronary heart disease associated with moderate consumption of red wine (or alcoholic drinks), despite a diet rich in saturated fats [157]. Research suggests that moderate drinkers are less likely to suffer heart attacks than are abstainers or heavy drinkers. Therefore, wine alcohol could be a factor related to the French paradox and as a result it has become widely accepted that a glass or two of red wine per day is good for the heart. However, the validity of this paradox has been questioned. For example, the incidence of heart disease in France may have been underestimated in comparison with that in neighboring Mediterranean countries. In recent years there have been reports concerning the effects of resveratrol and procyanidins as well as other wine components that mimic some of the benefits of caloric restriction, including reduced effects of ageing [158–160].

In a large Italian case–control study, wine drinkers or 'mixed' drinkers (including a large proportion of wine drinkers) did not show any association with indicators of healthy diet [161]. However, in a prospective study, performed among young healthy subjects, the effects of the MD, a high-fat diet and red wine supplementation on haemostatic cardiovascular risk factors and haemostasis variables have been reported. Thus, when both diets were supplemented with red wine (240 mL/day for 30 days), this resulted in a significant decrease of fibrinogen and factor VIIc, and a significant increase in tissue plasminogen activator and plasminogen activator inhibitor 1. No diet or wine effect was detected on CRP or von Willebrand factor. It seems that the MD and moderate short-term consumption of red wine may have complementary, mostly beneficial effects on haemostatic cardiovascular risk factors [162].

Resveratrol also affects several factors involved in tumor promotion and progression, acting on the expression of growth factors and cytokines. Recently, the chemopreventive properties of resveratrol have been associated with the inhibition of NF-kappaB [163].

Olive oil causes postprandial alteration of endothelial function, and red wine may improve it. In healthy subjects, consumption of both red wine and VOO – both rich in antioxidants – improved postprandial flow, and this effect remained for at least 1 h as measured by ultrasound, and was greater than that achieved with white wine and refined olive oil [164].

10.5. Nuts

Nuts are rich in MUFAs and PUFAs, which have been reported to reduce cardiovascular risk, ameliorate lipid profile and triglyceride levels, and decrease inflammatory adhesion molecules in patients with hypercholesterolemia [165–168]. In addition, nuts are rich in arginine, which has a cardioprotective effect by maintaining low CRP levels [169]. In individuals who meet criteria for the METS, a daily 30 g mixed nut supplement for a year reduced the prevalence of the syndrome without changing body weight, and decreased the number of subjects with large waist circumference, high triglycerides or high blood pressure as compared with subjects who did not receive nut supplement [62].

Walnuts are very rich in α-linolenic acid, which exerts a health protective effect on the cardiovascular and other systems. Consumption of four walnuts per day for 3 weeks significantly increases α-linolenic acid and EPA blood levels [170].

10.6. The siesta, sunlight and stress

The *"siesta"* is a traditional afternoon nap or rest after lunch in Spain, Hispanic America and some Mediterranean countries. In Spain, most siestas last less than an hour; the average for daytime napping is some 60 min, whereas in some groups – like students or the unemployed population – the nap time increases to 60–88 min [171]. During the last 25 years, Spanish and much of Hispanic America has adopted Americanized work schedules, with shortened lunchtime and more rigid working hours. Presently, less than 25% of Spaniards still enjoy siestas, just as researchers are beginning to demonstrate the health benefits of an afternoon nap. Thus, in healthy individuals, the siesta is inversely associated with coronary mortality [172]. It seems that a 40-min nap involves more non-REM and restorative sleep, while longer nap periods involved more profound sleep, with both non-REM and REM cycles. The short siesta affords a 34% improvement in performance and 100% increase in alertness. However, daily long siestas were found to have positive associations with the prevalence of several cardiovascular risk factors and measures of subclinical atherosclerosis [173]. The siesta may increase the risk of MI since the post-siesta cardiovascular event profile resembles the period soon after waking up in the morning, when cardiovascular events are prevalent [173,174].

Mediterranean sunlight has a geographic characteristic that is difficult to study in relation to health. Sunlight has been related to levels of serotonin and vitamin D production and a low rate of depression [175–177]. In addition, adequate vitamin D levels are associated with cardiovascular health [178]. A subjective sense of wellbeing, optimism and closeness reduces the rate of many diseases. The traditional Mediterranean lifestyle includes strong family links and street leisure activities (although this has now diminished under the influence of more Western lifestyles, with, for example, shopping more often done in indoor malls rather than outdoor shops and markets). Individuals' happiness depends on the happiness of others with whom they are closely connected [179]. However, during the last decades the Mediterranean lifestyle has changed, and a stressful way of life is nowadays the rule for most people living in developed Mediterranean countries (Spain, Italy, Greece, etc.).

11. Final remarks

Nutrition and lifestyle have driven human evolution [1,2,180–182]. People on a MD had more than a 20% lower chance of dying over a 10-year period than those not on such a diet and that was independent of their age, body weight and gender [19]. It is likely that the MD has some of the nutritional properties of the human Paleolithic diet [1,2,181]. However, there are many factors involved in cardiovascular risk and related conditions, carcinogenesis, bone metabolism and central nervous diseases. The prevalence of these conditions differs with gender and genetic influences. In addition, there are co-morbid conditions in postmenopausal women, aside from dietetic factors, that may explain some gender differences [183,184]. The published evidence indicates that there are heterogeneous degrees of adherence to MD, and this prevents a strict delineation of the influence of gender on the association of MD and various morbid conditions.

Globally, the proportion of people aged over 60 years is growing fast, as a result of both longer life expectancy and declining fertility rates. It is important to maximize the health and functional capacity of older people as well as their independence and quality of life. All industrialised countries face a growing prevalence of chronic age-related conditions. Nutrition and lifestyle may be a way of preventing or at least ameliorating these. In the southern Mediterranean region, cardiovascular disease causes 34–52% of all deaths, and is the major killer among non-communicable diseases [185]. The MD is still the model for southern Mediterranean populations; however, following rapid urbanization, many individuals have changed their lifestyle and food habits. Thus, there has been a fall in the intake of whole-grain foods and a rise in the consumption of meats and animal-derived foods and vegetable oils. Nutritional changes have been accompanied by an increase in daily caloric intake and a reduction in physical activity.

Exactly how the traditional MD may affect life expectancy remains unknown, although it should be the overall dietary pattern – not any particular food – that promotes longevity. Hence, benefits cannot be expected just by adding plenty of olive oil to an unhealthy diet. The combination of healthy weight, varied natural and fresh products, physical activities, a relaxed, well ordered life, and a small dose of sunlight – all together – may reduce cardiovascular events, the METS, insulin resistance, diabetes, cancer and other chronic diseases. There is no Ponce de León's elixir, there is no sort of panacea or a magic diet, although the MD has many ingredients which are a great prophylactic measure, not only for cardiovascular disease but also for other age-related morbid conditions, as discussed. We are what we eat. Nutrition may still improve general health [186], even in the age of genomics.

The most common version of the MD was derived from the studies of Keys et al. [6–9] performed at the University of Minnesota, given its name by the International Conference on the Diets of the Mediterranean in 1993, sponsored by the Harvard School of Public Health, the World Health Organization and the Oldways Preservation and Exchange Trust, and finally promoted by Doctor Willett, from Harvard University. This was the origin of the concept of the "Mediterranean Diet". It is true that the dietary pattern was found in the most deprived areas of Greece, Italy and Spain. The MD implies exercise, activity, healthy nutrition and natural products [116,187–189]. The traditional MD has been portrayed as a pyramid, with daily physical activity at its base. Table 1 includes some of key components of the MD. A healthy diet and being physically active are the most important routes to good health.

Competing interest

None.

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