

Mediterranean Diet and Longevity

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Introduction

In the past 150 years, a demographic revolution has taken place as never in history. At the end of the 19th century, life expectancy in Europe, one of the world regions with the largest aging population, was about 35 years, similar to people living in Ancient Rome when it was around 30 years according to historic sources. (Harman, 2001) Today, many people from Japan and most European nations live beyond 80 years. The recently published World Report on Aging and Health of the World Health Organization, states that now most people worldwide can expect to live beyond 60 years (Beard et al., 2016).

A key determinant among the multiple factors that may have contributed to this extraordinary demographic event has been the decline in mortality from infectious diseases. However, increased life expectancy did not rely only on child mortality decline, because mortality patterns also changed in old age with increasing life expectancy after the age of 50 years (Beard et al., 2016). Decreasing rates of infectious diseases have been accompanied by an expansion in diseases more frequently seen in old age, such as cardiovascular disease (CVD), cancer, and neurodegenerative diseases. This apparent puzzle between lengthening the average duration of life and increasing degenerative diseases is not surprising, because if the organism lives longer, risk factors have more time to provoke diseases, such as CVD and cancer, not only in industrialized nations but also in developing and underdeveloped countries.

Thus, mortality attributable to chronic diseases, so called noncommunicable diseases (NCDs), has grown steadily and continues to grow throughout the world. Not only mortality but also morbidity, disability and deterioration of the quality of life are growing in association with the development of these frequent diseases (Harman, 2001). The NCDs are more frequently seen in old age, hence, relentless aging of the world population in the last 150 years, is one of the cardinal factors to explain the explosion of NCDs that we are witnessing. The consequences for health, health systems, their workforce, and budgets are profound (Beard et al., 2016). The achievements of medicine might aim not only at the extension of life but also at ensuring an old age as free as possible of morbidity and disability.

A key contributor of this alarming scenario has been identified in the unfavorable changes in lifestyle of entire populations, which involve a greater incidence of risk factors, associated with the increased life expectancy. This allows a greater number of people to be in age groups vulnerable to cardiovascular events, type 2 diabetes (T2D), cancer, and neurodegenerative diseases. The sedentary lifestyle, the lack of exercise, the unbalanced diet, overeating and cigarette smoking will be the true architects of the increased incidence of obesity, diabetes, dyslipidemia and hypertension, all powerful risk factors for CVD and some types of cancer.

A large body of research data has consistently shown that certain dietary patterns, such as the traditional eating habits and lifestyle unique to the Mediterranean basin (Mediterranean diet, MeDiet), may play a fundamental role in the prevention and treatment of chronic diseases and improved longevity. MeDiet has been included in the 2015–20 Dietary Guidelines for Americans as a healthy dietary pattern (Tagtow et al., 2016). This dietary prototype has been linked to greater nutrient adequacy in both observational and intervention studies, helping to address under-consumption of calcium, potassium, magnesium, and fiber, nutrients that have been identified as of public health concern. MeDiet, as a dietary pattern focused on the consumption of plant-based food, but that admits low amounts of animal food, and favoring local and seasonal food production, emerges as an eating model that

could address both environmental and health concerns. The traditional MeDiet must be understood as not only a cluster of foods, but also as a cultural model that involves the way food is produced, selected, processed, and distributed, as well as other elements of lifestyle. These features have led to the inscription of MeDiet on the list of intangible cultural heritage of humanity by UNESCO in 2010 (Dermeni and Berry, 2015).

Regrettably, current diets in the Mediterranean countries are moving away from the traditional MeDiet regarding the amounts and proportions of food groups. This is due to the widespread diffusion of westernization and globalization of food production and consumption, related to the homogenization of eating behavior in the modern area.

The aim of this chapter is to review the trajectories of MeDiet from its origins in the 1950s until today; and to emphasize the different approaches and evidence that have come to light in the last six decades regarding the link between the adherence to this healthy dietary pattern and longevity with decreased mortality and morbidity derived from chronic diseases associated with aging.

History and Definition of the Mediterranean Dietary Pattern

The ecological evidence of results from the Seven Countries Study beginning in the 1950s, before globalization made its influence on lifestyle, including diet, first introduced the concept of MeDiet, as conceived today in nutritional research (Keys, 1995). Southern European participants from olive-tree growing areas of the Mediterranean basin showed life expectancies, which were among the highest in the world, while incident coronary heart disease (CHD), cancer, and other chronic diseases were among the lowest. Rather than a specific dietary pattern, a collection of eating habits traditionally followed by these populations first defined the traditional MeDiet, which are rooted ever since prehistory and history, in the same places where they are found in modern times. The study of this persistence has fascinated historians, physicians, scholars of food and agro-pastoral activities, of the migrations of large and small populations, and of the wars consequent to them.

Through the history of humanity, societies have learned to develop a multitude of different ways of combining the foods available in that particular geographical area. The traditional eating patterns are the result of this long and jagged path. Some types of traditional eating patterns, such as the Mediterranean or the Japanese, have shown an association with a lower frequency of CVD, cancer, and neurodegenerative diseases. The term Mediterranean diet, together with the nutritional value, is permeated with a deep symbolic meaning, a unique way of being in this region, cradle of the oldest civilizations, scene of the bloodiest wars, and point of departure of the three monotheistic religions that have marked the face of History. It is clear that the mechanism by which traditional eating models were developed did not occur only in the Mediterranean basin. Nevertheless, only in this area there are sufficient historical, literary, and traditional testimonies to allow verification of hypotheses, comprising archeological vestiges, such as food remains, especially in the tombs, artifacts used for eating, ceramics, objects for cooking, and vessels for food transportation. In addition, there are papyri, terracotta tablets, parchments, wall inscriptions, and literary sources of classical authors, from Homer onwards (Fig. 1).

To describe the main characteristics of what is today called Mediterranean dietary pattern, even if generic, we may say that this nutritional model, that has remained constant over time and space, is mainly, but not exclusively, plant-based. It comprises an abundant consumption of seasonal and colorful vegetables, poorly tampered with by culinary interventions, fresh fruit of the season consumed at the end of every meal, nuts and seeds (as snacks and as part of recipes), legumes several times per week, unprocessed cereals every day, high consumption of olive oil as the main source of fat (for cooking and added raw for seasoning), moderate amount of fish (in the past it has been a function of sea distance but it has been generally at a moderate consumption 2–3 times/week), herbs and spices to season recipes, dairy products (milk, yogurt, cheese) allowed daily in limited quantities, eggs (3–4/week), sweets made with sugar or honey, but only a few times a week, red meat and meat products with extreme moderation, drinking plenty of water, as opposed to wine, which is consumed in moderation with meals always respecting beliefs of each community (Dermeni and Berry, 2015). A distinctive feature of MeDiet is the use of unprocessed nutrient-dense foods, in stark contrast to “empty calories” of westernized diets rich in processed food that are full of calories but poor in nutrients, undeniably associated with an increased risk of overweight and obesity (Fig. 2). Together with dietary choices, the MeDiet is part of lifestyle, and comprises historical knowledge, practices, skills, and traditions, transmitted from generation to generation, ranging from the landscape to the table, and providing a sense of belonging and continuity to the community. Mediterranean tradition offers a cuisine rich in colors, aromas, and memories, emphasizing the flavors and the harmony with nature, as well as the importance of cooking and eating together with family and friends. Crucial bases of the traditional MeDiet have been climate, flora and hardship. The role played by physical activity, in the more general context of the relationship between the MeDiet and lifestyle, is fundamental (Table 1 and Fig. 3).

It is interesting to recall the origin of the concept of MeDiet that today has become so common. In 1948, the Greek government, worried about the need to improve the economic, social and health conditions of the population in the postwar period, invited the Rockefeller Foundation to undertake an epidemiological study on the eating habits of the islanders of Crete, where traditions had remained intact throughout the centuries. American epidemiologists, led by Leland G. Allbaugh, interviewed a sample of the population, chosen at random, obtaining information on various parameters related to lifestyle. Concerning nutrition, plant foods constituted over 60% of the total daily caloric intake, well above the 37% documented in that period in the United States. The surprising observation was that the Cretans consumed a daily amount of fat similar to that of American citizens, about 107 g



Fig. 1 Traditional olive oil jars and press from 20th century BC (*left*) and ancient Minoan frescoes with wine drinking vessels from 15th century BC (*wright*) in the Knossos palace (*Crete*).

Mediterranean diet

Western diet

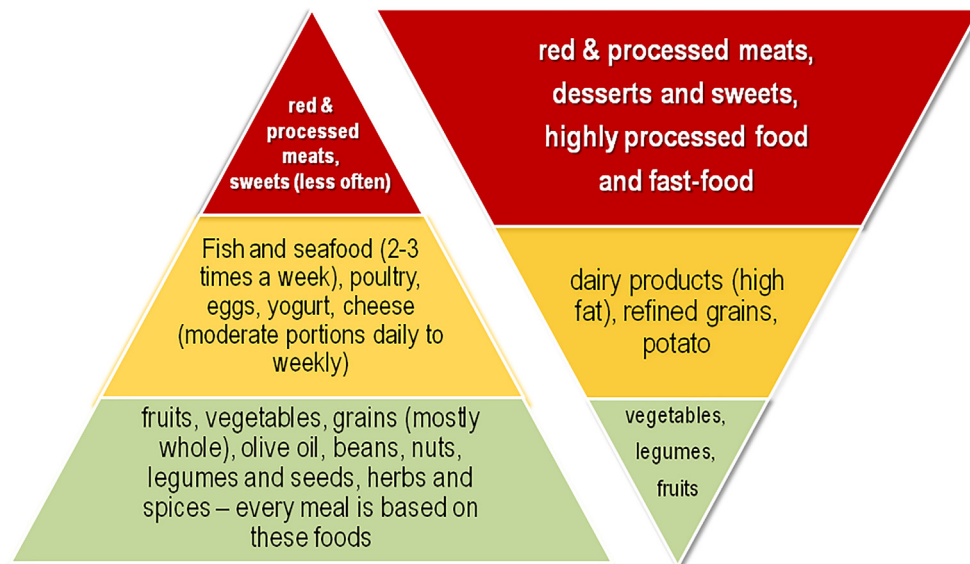
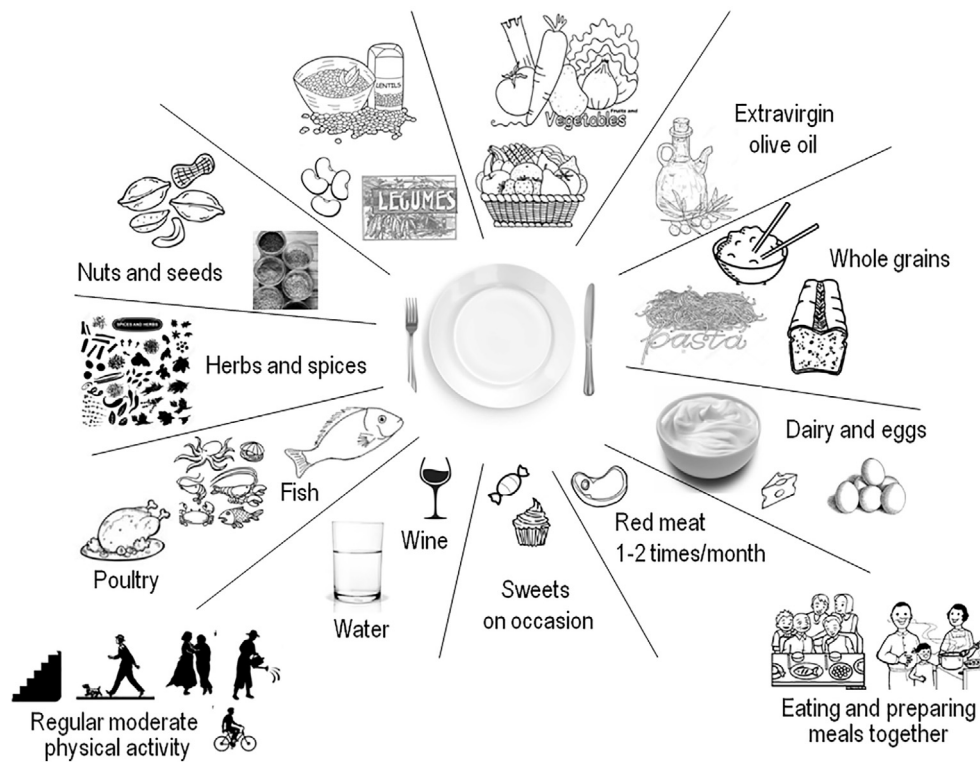


Fig. 2 Food pyramids of Mediterranean and Western diet. As illustrated by the pyramids, the basis of the Mediterranean diet (*in green*) is minimally represented in the Western diet, while the consumption of red and processed meats, sweets, industrial- and fast-food (*in red*) constitute the majority of consumption in the Western diet, while is minimally represented in the Mediterranean diet. High-fat dairy products, refined grains, and potato (*yellow*) are also frequently consumed in the Western diet, as opposed to the Mediterranean diet where other healthy foods are consumed instead.

Table 1 Dietary characteristics of the traditional Mediterranean dietary pattern and lifestyle*Mediterranean dietary pattern*

- A variety of fresh fruits and vegetables; legumes, nuts, seeds every day.
- Bread and other grain products (pasta, rice), mostly whole.
- Herbs and spices to season food.
- Cold pressed extra-virgin olive oil as the main source of fat.
- Fresh fruit everyday as dessert; sweets, cakes and dairy desserts only on occasion.
- Frequent consumption of fish and seafood (2–3 times/week).
- Dairy products on a daily basis, mainly yogurt (less often small portions of local cheese).
- Eggs (high quality proteins) 2–4 per week.
- Red and processed meat consumed unfrequently, in moderate portions, if possible as a part of stews and other recipes (1–2 every month).
- Drinking plenty of water.
- Wine in moderation with meals (≤ 1 drink/day for women and 1–2 drinks/day for men), (respecting beliefs of each community and former habits).
- Foods that have undergone minimal processing, that are fresh and locally produced.
- Direct connection with nature.
- Tasty cooking.
- Moderation in portion size.
- Moderate physical active every day is just as important as eating well.
- Meals and cooking in the company of others.
- Adequate rest (enough night sleeping time and eventually for small periods of time during the day [siesta]).

**Fig. 3** Nutritional and lifestyle components of the Mediterranean dietary pattern, which has been associated with improved longevity and reduced incident age-related chronic diseases.

a day, but with differences as regards the quality of fat consumed: mainly olive oil in the Cretans and saturated fatty acids (SFA) of animal origin in Americans.

The eating habits of the Cretans, as observed in the 1950s and 1960s, resulted in an excellent health standard, better than what could be expected from a population not yet influenced by the “advances” of Western societies and exposed, as then believed, to the harmful effects of poor food, social and public hygiene. The model of the MeDiet was born from these considerations, which led to the execution of the Seven Countries Study by Keys (1995) and the creation of the term. Curiously, at the time of the study, Cretan peasants complained to the interviewers of their meat-poor diet, still unaware at that time that one of the reasons for their excellent health was the low consumption of meat combined with the hard work of the fields. Indeed, the notion that food in excess is poorly

suited to a healthy life has been common knowledge even in times of shortage when fatness was pursued and considered the best expression of health. Nonetheless, in those years, people would not easily believe a physician who would recommend the benefits of a frugal diet, made of foods considered “poor” and of low intake of meat, fats and sugars, combined with continuous physical activity, which at that time was considered degrading. The knowledge of “good food to eat” and to grow has often been accompanied by limited availability and misery for so much of the population. Next to what was to be defined in the future the healthiest diet in the world, has been the availability of food at the limit of survival, where parsimonious eating and using what nature offered was not only a choice of life but also a necessity. However, it is also true that ancient Greeks, for social and political reasons, did not like to binge, which was stigmatized, both on a moral and on a physical level. They believed that what makes men is the measure, the rule, while appetites were considered typical of brutes and beasts. As a matter of fact, Plato considered gluttony, or the folly of the belly, a crime against the Republic.

In summary, MeDiet means moderate consumption of dietary healthy choices, but in the context of ancient habits deeply rooted in the cultural and historical features of those peoples of rural societies who have benefited, without being aware, for centuries. This diet is not only health promoting, confirmed by compelling evidence, but also delicious, which can help a greater number of people to follow it more easily.

Assessment of Mediterranean Diet Adherence

The evidence put forward by the Seven Countries Study was largely an ecological observation. Lately, an operational definition was necessary in order to perform and make comparisons among different epidemiological studies in diverse populations to assess the health effects of conformity with the MeDiet. Trichopoulou et al. proposed the most commonly used operational definition of adherence to the traditional MeDiet through a simple score in 1995 (Trichopoulou et al., 1995), that was afterwards updated (Trichopoulou et al., 2003). In brief, this score assigns one point for each one of six beneficial components that are consumed (vegetables, fruits and nuts, legumes, cereal, fish, ratio of monounsaturated fatty acids [MUFA] to SFA) with the use of the sex-specific median as the cut-off. For components assumed to be detrimental (meats, and dairy products, which are rarely low-fat in Mediterranean countries), the consumption of an amount lower than the sex-specific median for that population is considered as one point added to the score, while a higher amount has a value equal to zero. For alcohol, one point is added to the score for men who consume 10–50 g/day and to women who consume 5–25 g/day. Thus, the total score ranges from 0 (minimal adherence to MeDiet) to 9 (maximal adherence) (Trichopoulou et al., 2003). Because this score is based on sample medians, it is highly dependent on the specific characteristics of the sample. This may entail a limitation for the comparison of diverse samples and the transferability of results among different populations. An alternative score (Mediterranean Diet Adherence Screener [MEDAS]) has been validated using absolute/normative cut-off points for the consumption of specific food groups (predefined servings/day or servings/week) and was effectively used in the PREDIMED (Prevención con Dieta Mediterránea) intervention trial (Estruch et al., 2018). Both, MEDAS and the 9-point MeDiet score similarly predicted macronutrient distribution and disease incidence or mortality (diabetes incidence, CVD or all-cause mortality) (Dominguez et al., 2013). Table 2 shows the points considered by MeDiet score and by MEDAS. There are, however, some disparities in the definition of MeDiet, and several other scores have been proposed. The

Table 2 Two Mediterranean dietary pattern scores of adherence

MEDAS ^a (0–14 points) (Estruch et al., 2018; Dominguez et al., 2013)	Mediterranean diet score (0–9 points) (Trichopoulou et al., 2003)
1. Olive oil as main culinary fat	1. Vegetables ^b
2. ≥ 4 tablespoons/day olive oil	2. Fruits and nuts ^b
3. ≥ 2 servings/day vegetables	3. Legumes ^b
4. ≥ 3 servings/day fruits	4. Fish ^b
5. ≥ 3 servings/week legumes	5. Cereals ^b
6. ≥ 3 servings/week fish	6. MUFA/SFA ratio ^b
7. ≥ 3 servings/week nuts	7. Meat/meat products ^c
8. ≥ 2 servings/week olive oil sauce with tomato, garlic, and onion (“sofrito”)	8. Dairy products ^c
9. Preference for poultry > red meats	9. Alcohol: 5–25 g/day (women) 10–50 g/day (men)
10. < 1/day red/processed meats	
11. < 1/day butter/margarine/cream	
12. < 1/day carbonated/sugared sodas	
13. < 2/week commercial bakery, cakes, biscuits, or pastries	
14. ≥ 7 glasses/week of wine	

^aMEDAS means Mediterranean Diet Adherence Screener.

^bOne point if the consumption was at or above the sex-specific median.

^cOne point if the consumption was below the sex-specific median.

disparities may be due to multiple reasons, which are not completely clear. The definition of MeDiet varies with geography, historical time and the nationality of the authors. It is possible that the dissimilarities of dietary patterns and lifestyle of diverse Mediterranean countries can explain these variations, keeping in mind that there are also several characteristics that are common to all of them, and that there is robust and compelling evidence of its benefits. The MeDiet has gone from being an empirical description of traditional eating behaviors of Mediterranean populations to health scientific evidence.

Aging—Mediterranean Diet Effects on Longevity and Incident NCDs

Facing the relentless increase of older adults worldwide with the foreseeable consequence that health systems can become unsustainable if aging is accompanied with multimorbidity and disability in a number of elders, there is growing awareness of the unquestionable need of planning approaches for implementing primary and secondary prevention of NCDs. Indeed, hypertension, CHD, cerebrovascular disease, diabetes, arthritis, and cancer currently account for a major segment of health care expenditures (Beard et al., 2016).

Accumulated knowledge in nutritional research suggests a reduction in total and cause-specific mortality with increasing adherence to MeDiet pattern (Keys, 1995; Trichopoulou et al., 1995, 2003; Osler and Schroll, 1997; Kouris-Blazos et al., 1999; Lasheras et al., 2000; Knoops et al., 2006; Mitrou et al., 2007; Bonaccio et al., 2018). There is also evidence that the incidence or risk of major chronic diseases in older adults, such as CVD (Keys, 1995; Estruch et al., 2018; de Lorgeril et al., 1994; Sofi et al., 2014; Mente et al., 2009; Martinez-Gonzalez and Bes-Rastrollo, 2014; Dinu et al., 2018) obesity, metabolic syndrome and diabetes (Beunza et al., 2010; Mendez et al., 2006; Romaguera et al., 2010; Esposito et al., 2011; Mancini et al., 2016; Martinez-Gonzalez et al., 2008; Rossi et al., 2013; Salas-Salvado et al., 2014; Schwingshackl et al., 2015) some types of cancer, (Schwingshackl and Hoffmann, 2015; Guasch-Ferre et al., 2013; Couto et al., 2011; Wu et al., 2009; Murtaugh et al., 2008; Link et al., 2013; Cottet et al., 2009; Bamia et al., 2013) cognitive impairment (Dominguez and Barbagallo, 2016; Singh et al., 2014; Valls-Pedret et al., 2015) and unipolar depression (Lai et al., 2014) can be reduced and even prevented with healthy lifelong dietary habits in agreement with the MeDiet model. There is as well evidence for reduction of major cardiovascular risk factors, including hypertension, dyslipidemia, and inflammatory markers (Estruch et al., 2006; Fito et al., 2007).

The beneficial effects of such a dietary pattern appear to depend on the interactive and synergistic combinations of foods and nutrients rather than to the action of isolated nutrients themselves. Nutritional factors can have a major impact on the health and functional status of older adults, and besides a lifetime approach with preventive measures against the development of NCDs, it is of highest relevance to identify risk factors for malnutrition that often occur in old age.

Mortality

Adherence to MeDiet has been associated with prolonged survival in several populations. After the former ecological evidence from the Seven Countries Study (Keys, 1995), the first cohort longitudinal studies designed with mortality as outcome included small number of participants from Greece (Trichopoulou et al., 1995), Denmark (Osler and Schroll, 1997), Australia (Kouris-Blazos et al., 1999), and Spain (Lasheras et al., 2000).

In 1995, a first study collected data from 182 older adults living in Greek villages (Trichopoulou et al., 1995) assessing diet with a validated, extensive, semi-quantitative questionnaire on food intake (FFQ). A one-unit increase in the score of adherence to MeDiet was significantly associated with a 17% reduction in overall mortality. The study carried out in Denmark (Osler and Schroll, 1997) to test this dietary pattern in a non-Mediterranean population, enrolled 202 older adults, men and women, born between 1914 and 1918, followed for 6 years. Using the same MeDiet score as in the Greek study, this study in a Danish population showed similar results: a one-unit increase in the diet score was associated with a significant 21% reduction in mortality. A third study was undertaken in Melbourne, Australia (Kouris-Blazos et al., 1999) among Anglo-Celts and Greek Australians older adults, aiming to examine whether the benefits observed in Greece and Denmark could be transferable to populations with quite different dietary habits. The study involved 141 Anglo-Celts and 189 Greek Australians, men and women, aged over 70 years. Again the results were similar, with a one-unit increase in the diet score corresponding to a 17% significant reduction in overall mortality. Mortality reduction as the conformity with MeDiet score increased was similarly evident among Anglo-Celts as among Greek Australians. A fourth study was conducted in Spain (Lasheras et al., 2000) among 161 institutionalized nonsmokers older adults of both genders followed for 9 years. Interestingly, in this vulnerable population, mortality reduction associated with one-unit increase in adherence to the MeDiet score was even higher (31%), perhaps because the risk of death was also higher in this population. Nevertheless, the effect was evident only for persons aged < 80 years.

A seminal study published in 2003 (Trichopoulou et al., 2003) included a population of 22,043 Greek adults from the general population evaluated at baseline with a validated FFQ and followed for 44 months. Participants with a higher degree of adherence to the MeDiet presented a significant reduction in total mortality with every two-point increment in the adherence score corresponding to a 25% reduction in total mortality, after adjustment for confounders. Mortality linked to CHD was reduced by 33% and cancer-related mortality was reduced by 24% for each two-point increment in MeDiet score.

The Healthy Aging a Longitudinal Study in Europe (HALE) (Knoops et al., 2006) a multinational European study involving 3496 participants aged 70–90 years from 10 European countries showed that participants who followed a MeDiet had over 50%

reduction in mortality from any cause, and from CV- and cancer-related causes. A large study conducted in the United States (Mitrou et al., 2007) confirmed the association between adherence to MeDiet and incident mortality, using the 9-point score to assess conformity with MeDiet. The study included 214,284 men and 166,012 women in the National Institutes of Health-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. Adherence to MeDiet was associated with reduced all-cause and cause-specific mortality. In men, all-cause, CVD, and cancer mortality were reduced by 21%, 22%, and 17%, respectively; while in women, decreased risks ranged from 12% for cancer mortality to 20% for all-cause mortality. The results remained unchanged when analyses were restricted to never smokers. A Swedish study assessing 1037 older adults (540 females) showed that diet macronutrient composition was not associated with mortality, while a modified MeDiet score showed a significant inverse association with a 7% reduction in all-cause mortality. In a recent meta-analysis (Bonaccio et al., 2018) of seven prospective studies with a total of 11,738 participants and 3874 deaths, one-point increment in MeDiet score was associated with 5% lower risk of all-cause incident mortality.

In summary, the results from numerous studies in diverse populations provide strong evidence for a beneficial effect of higher conformity with MeDiet on the risk of death from all causes, as well as deaths due to CVD and cancer, suggesting the appropriateness of adopting or preserving this dietary pattern to maximize the likelihood of survival.

Cardiovascular Disease

The leading cause of death in Western countries remains CVD, which has several modifiable risk factors; including smoking, low physical activity, unhealthy diet, and obesity. The promotion and maintenance of CV health through lifestyle modifications represents a public health priority. One of the main outcomes of the Seven Countries Study was CHD (Keys, 1995). In this ecological study, the population from Crete had near 30-fold lower rates of CHD compared to persons living in Finland, even if both had a similar fat intake (36%–39% of total energy intake). However, SFA intake contributed near 24% of energy intake in Finland, while it was only about 8% in Crete. A role for MUFA contained in extra virgin olive oil (EVOO) and n-3 PUFA derived from fish and nuts as protective for CVD outcomes is now recognized and could have contributed to the reduced incidence of CV events in the Cretan population. At that time, the low content of SFA in MeDiet was thought to explain the lower incidence of CHD through the reduction of blood cholesterol, but later research revealed that MeDiet is not merely a cholesterol-lowering diet, but has numerous additional health beneficial actions, as shown below.

The Lyon Diet Heart Study (de Lorgeril et al., 1994) was the first randomized trial (RCT) showing a robust cardiovascular protection with a dietary pattern intervention. This secondary prevention trial included 605 patients with a previous myocardial infarction randomly allocated to a MeDiet model vs. a control low-fat diet according to the guidelines of the American Heart Association. The intervention group received advice to increase consumption of vegetables, fruits, and fish but to reduce red meats consumption. Additionally, they were asked to replace butter and cream with a linolenic acid-rich margarine. The results were quite impressive with a 73% relative reduction in the rate of recurrent CHD events after 27 months of follow-up. The use of fat different from EVOO may have opened the road to modifications of the original definition of MeDiet.

Estimates of n-3 PUFA consumption in the United States in 2005–06 indicate that this nutrient contributed approximately 0.05% of energy intake (Blasbalg et al., 2011) while the baseline consumption of n-3 PUFA in the PREDIMED trial was over six times higher (0.32%). (Estruch et al., 2018) Thus, there are important differences between the MeDiet and the USA diet not only in the quantity and source of MUFA, but also in the quantity of n-3 PUFA.

The PREDIMED intervention trial (Estruch et al., 2018) reported that MeDiet, with relatively high fat intake (35%–40% of total energy intake), supplemented with EVOO or nuts reduced the incidence of major cardiovascular events by about 30% among persons at high cardiovascular risk over 4.8 years of follow-up vs. a control group advised to follow a low-fat diet. The score of adherence to MeDiet increased in the two intervention groups of the trial and remained unchanged in the low-fat group. The trial was stopped early for meeting benefit requirements.

A number of observational studies and meta-analyses have reported the association of a higher adherence to MeDiet with a lower incident CVD (Sofi et al., 2014; Mente et al., 2009; Martinez-Gonzalez and Bes-Rastrollo, 2014; Dinu et al., 2018). Two meta-analyses reported each a summary estimate across studies as a 10% reduction in the risk of CVD (fatal or nonfatal incident clinical CVD event) for every 2-point increment in MeDiet adherence score (Sofi et al., 2014; Martinez-Gonzalez and Bes-Rastrollo, 2014). According to a recent umbrella meta-analysis (Dinu et al., 2018), there is robust evidence of an association between adherence to MeDiet and a reduced risk of overall mortality, CVD, CHD, myocardial infarction, and diabetes.

Regarding CV risk factors, in a short-term sub-study of the PREDIMED trial (Estruch et al., 2006) there was a significant reduction of plasma glucose levels, systolic blood pressure, and lipid profiles in participants following MeDiet supplemented with olive oil or nuts compared with low-fat diet. Higher adherence to MeDiet showed improvements in inflammatory markers compared with a typical carbohydrate- and SFA-rich diet (Fito et al., 2007). Results on plasma lipid profiles are variable among different studies, in part due to substantial differences in dietary interventions conducted among free-living middle aged or older adults with or without CVD or at high risk for CVD.

One of the characteristics of MeDiet pattern is a light or moderate alcohol consumption (≤ 1 drink/day for women and 1–2 drinks/day for men), which has been associated with a lower risk for all-cause mortality, CHD, T2D, heart failure, and stroke (O'Keefe et al., 2018). Conversely, heavy drinking (> 4 drinks/day) is associated with an increased risk for death and CVD. Excessive alcohol consumption is one of the leading causes of premature deaths worldwide. Therefore, it is not recommended that anyone

begin drinking or drink more frequently searching for the potential health benefits, because moderate alcohol intake is also associated with increased risk of violence, drowning, and injuries from falls and motor vehicle crashes, as well as increased risk of breast cancer in women.

Altogether the evidence available so far suggests a beneficial effect of MeDiet on the primary and secondary prevention of CVD, but further large interventional studies are needed to confirm these findings.

Obesity, Metabolic Syndrome, Type 2 Diabetes

Among the likely factors contributing to the beneficial effects of MeDiet, reduction in body weight and adiposity, mainly at abdominal level, may play an important role. Analyses of a prospective cohort study in Spain, the “Seguimiento Universidad de Navarra” (SUN) longitudinal project (Beunza et al., 2010), showed that participants with the highest adherence to MeDiet had lower average yearly weight gain, when compared to those with the lowest adherence. In the PREDIMED trial (Estruch et al., 2018), 90% of participants were overweight or obese at baseline, and no significant changes in body weight and adiposity occurred within or between groups from baseline to 3 months after, even if MeDiet score significantly changed in the two intervention groups in this period. During the trial, even participants who did not lose weight had the same reduction in CV events.

Results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort study (Mendez et al., 2006) reported that participants within the highest tertile of adherence to MeDiet had reduced incidence of obesity during follow-up; high MeDiet adherence was not associated with incident overweight in participants who had normal weight at baseline. The EPIC-PANACEA study (Romaguera et al., 2010) examined the association between adherence to MeDiet, weight change, and incident overweight or obesity. Participants with high MeDiet adherence gained less weight in 5 years than did participants with low adherence and had 10% lower odds of becoming overweight or obese. The low meat content of MeDiet appeared to account for most of the effects against weight gain in this study. A recent analysis of data from EPIC-Italy (Agnoli et al., 2018) showed that increasing MeDiet index (indicating adherence) was associated with reduced risk of becoming overweight/obese after 5-year follow-up, and with lower risk of abdominal obesity.

A meta-analysis on the association of MeDiet adherence and body weight included 16 RCTs from the USA, Italy, Spain, France, Israel, Greece, Germany, and the Netherlands with a total of 3436 participants (Esposito et al., 2011). Using a random effects model, participants in the MeDiet group had significant weight loss and reduction in BMI compared to those in the control arm. The effect of MeDiet on body weight was greater in association with energy restriction, increased physical activity, and follow-up longer than 6 months. Across all 16 studies, the MeDiet did not cause weight gain.

Even if the definition of metabolic syndrome has been extensively debated in recent years, it is unquestionable that the simultaneous presence of various CV risk factors (i.e., visceral obesity, dyslipidemia, hyperglycemia, and hypertension) increases the risk of CV events and mortality, as well as the genesis of T2D. Hence, interventions reducing metabolic syndrome risk factors may be part of a global strategy to improve population health. In this framework, MeDiet is a potential intervention against metabolic negative health outcomes. In both, observational and intervention studies, adherence to MeDiet was associated with improvements in several cardio-metabolic risk factors (Sofi et al., 2014; Mancini et al., 2016).

As regards diabetes, because MeDiet relies mainly on EVOO, fruits, vegetables, whole grains, and fish, it resembles a dietary pattern with high nutrient density able to lessen the development of NCDs during aging, including T2D. Observational and intervention studies have examined the effects of MeDiet on incident T2D (Martinez-Gonzalez et al., 2008; Rossi et al., 2013; Salas-Salvado et al., 2014; Schwingshackl et al., 2015). A study conducted in Spain with the SUN cohort ($n = 13,380$) (Martinez-Gonzalez et al., 2008) found an inverse association between MeDiet score and the risk of incident T2D. Overall, a two-point increase in MeDiet score was associated with a 35% reduction in T2D risk. Analyses from data of the EPIC-Greece cohort ($n = 22,295$), assessing the relationship between MeDiet adherence and T2D (Rossi et al., 2013), also reported a favorable significant reduced risk. A subgroup analysis of PREDIMED intervention trial (Salas-Salvado et al., 2014) ($n = 3541$) confirmed that a MeDiet enriched with EVOO but without energy restrictions reduced T2D risk among persons with high cardiovascular risk. In a meta-analysis including 122,810 participants from nine studies, higher adherence to MeDiet was significantly associated with a lower risk of incident T2D (Schwingshackl et al., 2015). This association was more evident in studies with a longer follow-up, suggesting that a longer adherence to this dietary pattern is beneficial in the prevention of diabetes.

In summary, the available evidence suggests that adherence to a traditional MeDiet may help prevent weight gain, abdominal obesity, and incident T2D.

Cancer

It is currently accepted that several types of cancer are preventable, and the role of dietary determinants on this prevention seems to be crucial. A recent meta-analysis (Schwingshackl and Hoffmann, 2015) including over 1.7 million participants reported that higher adherence to MeDiet was associated with a significant lower risk of all-cause mortality, several gastrointestinal cancers (including pancreas and liver), breast, prostate, head and neck, and respiratory cancer. These results, derived from observational studies, were confirmed by analyses from the PREDIMED trial (Guasch-Ferre et al., 2013) in which the highest category of nut consumption, a typical component of MeDiet, was associated with a 40% risk reduction in cancer mortality compared with the lowest category.

Also the EPIC study (Couto et al., 2011) has provided data on the MeDiet benefits against the occurrence of cancer. The evidence of potential protection appears stronger for gastric, colorectal, and breast cancer, especially when alcohol is excluded from the definition.

In a case-control study with 2396 Asian-American women aged 25–74 years (Wu et al., 2009) MeDiet was associated with a 35% lower risk for breast cancer. The Four Corners study (Murtaugh et al., 2008) also reported a reduced risk for breast cancer in both, Hispanic and non-Hispanic white women, who adopted MeDiet. In support of a protective association between adherence to MeDiet and incident breast cancer are large prospective studies including 91,779 American women (Link et al., 2013) and 65,374 French women (Cottet et al., 2009). The protective effects of the MeDiet against breast cancer have been related to reduced circulating estrogens, and increased intake of carotenoids that are known to lower oxidative stress. This protective association was greatest in women diagnosed with estrogen receptor-negative and progesterone receptor-negative breast cancer.

There is evidence indicating an inverse association between dietary patterns that are higher in vegetables, fruits, legumes, whole grains, lean meats/seafood, low-fat dairy, and moderate in alcohol; as well as low in red and/or processed meats, saturated fat, and sodas/sweets with the risk of colorectal cancer. Conversely, diets that are higher in red/processed meats, French fries/potatoes, and sources of sugars (i.e., sodas, sweets, and dessert foods) are associated with a greater colorectal cancer risk. Secondary analyses of the Italian cohort from EPIC study (Bamia et al., 2013) (42,275 participants, aged 25–70 years) with no cancer history concluded that higher adherence to MeDiet was associated with an 8%–11% reduction in colorectal cancer risk in men and women. The protective effects were mainly for distal colon and rectal cancer vs. proximal colon cancer. Higher fiber intake (~30 g/day) has been associated with reduced risk of developing colon adenomas and insulin resistance. In MeDiet, fiber is derived mostly from unrefined cereals, fruits, vegetables, and legumes, and stimulates colonic fermentation through higher production of short-chain fatty acids (SCFA) acetate, butyrate, and propionate.

Altogether, these findings suggest that MeDiet may be effective in reducing several types of cancer and overall cancer-related mortality, but more research is needed regarding the most effective single foods/nutrients.

Cognitive Decline, Dementia, and Depression

Age-related diseases affecting the brain and neuromuscular system include Alzheimer's disease (AD) and different forms of dementia ranging from mild cognitive decline to vascular dementia. The global epidemic of dementia affects more than 47 million people worldwide, with cases set to almost triple by 2050. AD accounts for near 70% of all cases of dementia in older adults. Aging of the population is the chief driver of the projected increases. It has been estimated that near 30% of AD cases may be due to potential modifiable factors. These include diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity, low educational attainment, and/or physical inactivity (Beard et al., 2016). Recently, a comprehensive review examined the potential role for specific nutrients and dietary patterns on brain health and dementia prevention (Dominguez and Barbagallo, 2016). Various dietary components and supplements with potential antioxidant, anti-inflammatory, and vasodilating actions have been studied regarding their possible effects on cognitive decline. This includes vitamins (e.g., beta-carotene, folic acid, vitamins C, E, D, B6, and B12), minerals (e.g., zinc and magnesium), omega-3 fatty acids, and other supplements (e.g., curcuminoids, ginkgo biloba, acetyl-L-carnitine, phytoestrogens, tea and (–)-epigallocatechin-3-gallate, resveratrol, garlic, and caffeine). The overall results from small and large-scale trials on these compounds with heterogeneous design (i.e., exposure time, adjustment for potential confounders, age) reported negative or mixed effects, which do not support a clear role for most of these compounds in the prevention of cognitive decline. Instead of single components (nutrients or foods), a healthy cardiovascular-protective dietary pattern combining diverse healthy foods, such as MeDiet, has moderately convincing evidence of being also protective for the development of cognitive decline, and AD. Because of the possible additive and synergistic actions of the different healthy foods/nutrients that characterize a diet, it is plausible that complex dietary patterns may be more robustly related to dementia than individual nutritional factors. MeDiet is rich in foods with anti-inflammatory, antioxidant, and potentially neuroprotective properties, which may be considered as an optimal nutritional option for the preservation of brain health.

A systematic review and meta-analysis of longitudinal cohort studies examining the MeDiet effects on cognition outcomes (Singh et al., 2014) found that higher adherence to this healthy eating pattern was associated with significantly reduced incident AD and cognitive decline. In this meta-analysis, including cohorts from New York, the United States, France, and Australia, participants within the highest tertile of adherence to MeDiet had 33% less risk of cognitive decline or AD when compared to those in the lowest tertile of adherence. Even if data derived from interventional studies are still limited, results from PREDIMED are encouraging. Sub-analyses of the PREDIMED trial (Valls-Pedret et al., 2015) reported that the dietary interventions with MeDiet supplemented with either EVOO or nuts were associated with improved cognitive function when compared to a low-fat diet. The MeDiet encompasses lifestyle and cultural features such as social engagement, culinary activities, physical activity, and adequate rest besides the nutritional components. These lifestyle factors have shown to positively influence the delay of cognitive decline, not only attributable to diet. Thus, future studies should consider all MeDiet lifestyle factors into their design. Although there is some evidence that adherence to MeDiet is associated with a reduced risk of AD, there are also inconsistent findings, mostly because of considerable heterogeneity among studies regarding populations and methods used to assess diet and cognition. Further confirmation in prospective cohort studies and RCTs with longer follow-up, including populations from different ethnicities and different dietary habits is still needed.

Even if there is limited evidence regarding possible benefit of adherence to MeDiet on incident depression, some encouraging results have been reported. A systematic review and meta-analysis (Lai et al., 2014) including 21 studies suggested that high intakes of fruit, vegetables, fish, and whole grains, hallmarks of MeDiet, may be associated with a reduced risk of depression. Nevertheless, further high-quality RCTs and longitudinal cohort studies are warranted in order to validate this finding.

Bone Health

Although the available evidence is limited, recent literature has suggested that MeDiet, together with other healthy dietary patterns, may be associated with a decreased risk of hip fractures. A large observational study combining data from two cohorts from Sweden (Byberg et al., 2016), with a total of 71,333 participants (mean age of 60 years), reported that one-unit increase in a modified MeDiet score was associated with a 6% lower hip fracture rate, after adjustment for confounders. Participants in the highest quintile of adherence to MeDiet had a 22% lower adjusted risk of hip fracture when compared with the lowest quintile, without differences for men and women.

Fermented milk products, such as yogurt, are usual components of the traditional Greek MeDiet, whose consumption is lately increasing in other countries. This type of foods may be ideal for people at high risk of fragility fractures, because they are not only rich in proteins and calcium but also in pro- and pre-biotics, which have been reported as beneficial in the prevention of fractures. Prebiotics are nondigestible fiber compounds that stimulate the growth and activity of microbiota (probiotics) that colonize the large bowel and act as a substrate for their reproduction. A Swedish cohort study (Michaelsson et al., 2018) including 61,240 women, born between 1914 and 1948, assessed with an FFQ in 1987–90 and with a mean follow-up of 22 years, found that a high consumption of the combination of fruits and vegetables (over 5 servings/day) with fermented milk (yogurt or soured milk) (over 2 servings/day) was associated with the lowest rates of hip fracture (–19% vs. low consumption of both fruit/vegetables and fermented milk). In the same study, a high intake of milk (over 3 glasses/day) with a concomitant low intake of fruits and vegetables (<2 servings/day) resulted in 2.5 higher adjusted risk of hip fractures vs. a low intake of milk (<1 glass/day) with a high intake of fruits and vegetables (over 5 servings/day). This is in agreement with the contemporary concept of the benefits of food combinations rather than considering foods or nutrients in isolation. The best example of this paradigm is indeed the Mediterranean dietary pattern.

Frailty

The term frailty has been recognized for over 30 years, indicating a state of extreme vulnerability to endogenous and exogenous stressors exposing the person to high-risk of negative health-related outcomes, which is more frequent in old age, usually caused by the interaction of the physiological age-related decline with chronic diseases/conditions. Research data have shown that the frailty phenotype is predictive of falls, worsening mobility, hospitalization, and death (Beard et al., 2016). The MeDiet is mostly known for its cardiovascular and metabolic preventive and therapeutic properties, but now there is some evidence suggesting that MeDiet may also be of value to prevent and treat frailty in older adults.

A recent meta-analysis (Kojima et al., 2018) including four studies ($n = 5879$ participants aged 60–82 years) followed for a mean of 3.9 years showed that participants with the highest scores of adherence to MeDiet had a 56% reduced risk of becoming frail as compared to those with the lowest scores. This promising results point to the need of future studies to continue exploring whether adherence to MeDiet can reduce this important outcome.

Sustainability

The MeDiet, apart from its positive effects traditionally and historically recognized (i.e., mortality, CVD, diabetes, cancer), has numerous other health benefits that are currently fields of research, as discussed above. Moreover, the concept of MeDiet has evolved in the past decades from being a healthy dietary pattern to be a sustainable dietary pattern, in which nutrition, food, gastronomy, physical activity, social engagement, agriculture, cultures, traditions, environment, and sustainability interplay into a paradigm of an environmentally friendly way of eating and of living.

Notwithstanding its growing popularity worldwide, adherence to MeDiet is decreasing, even in Mediterranean countries (Dernini and Berry, 2015), for multiple reasons related to Western economy, such as urbanization, technology, tourism, as well as the globalization of food production and consumption. The cultural paradigm of healthy eating which is MeDiet has serious threats, including: a) the dissemination of fast-food consumption based on meats, refined cereals, potatoes, ice cream, sweets, and sugar-sweetened drinks; b) the economic crisis, which forces the most disadvantaged populations to consume low-cost industrial food, full of empty calories and poor in nutrients; c) the promotion of high-protein low-carbohydrate diets, used for the loss or maintenance of weight, with a large impact on health. These events pose substantial perils to the preservation and transmission of the MeDiet heritage for future generations. Hence, it is necessary that governments and the society commit to take proper measures to preserve this treasured knowledge based on traditional and cultural foundations, leading the communities towards food diversity and sustainable diets that provide short and long-term health and environmental benefits.

Table 3 Bioactive phytochemicals in fruits and vegetables

<i>Phytochemicals</i>				
<i>Phytosterols</i>	<i>Organosulfur compounds</i>	<i>Carotenoids</i>	<i>Alkaloids</i>	<i>Phenolics</i>
<ul style="list-style-type: none"> • Sitosterol • Campesterol • Stigmasterol • Sitostanol • Campestanol 	<ul style="list-style-type: none"> • Alliin • γ-Glutamyl-5-allyl-L-cysteine • Glucosinolates and derivatives 	<ul style="list-style-type: none"> • α-Carotene • β-Carotene • β-Cryptoxanthin • Lutein • Zeaxanthin • Lycopene 	<ul style="list-style-type: none"> • Caffeine • Trigonelline 	<ul style="list-style-type: none"> • Flavonoids • Phenolic acids • Lignans • Stilbenes • Coumarins • Tannins

Source: Linus Paulin Institute at <https://lpi.oregonstate.edu/mic>

Table 4 Phenolics in fruits and vegetables

<i>Phenolics</i>				
<i>Flavonoids</i>	<i>Phenolic acids</i>	<i>Lignans</i>	<i>Stilbenes</i>	<i>Tannins</i>
<ul style="list-style-type: none"> • Flavonols • Flavan-3-ols • Isoflavones • Anthocyanidins • Flavanones • Flavones 	<ul style="list-style-type: none"> • Hydroxycinnamic acid derivatives <ul style="list-style-type: none"> - Caffeic acid - Ferulic acid - Curcumin 	<ul style="list-style-type: none"> • Cinnamic acid 	<ul style="list-style-type: none"> • Resveratrol 	<ul style="list-style-type: none"> • Proanthocyanidins

Source: Linus Paulin Institute at <https://lpi.oregonstate.edu/mic>

Molecular and Metabolic Mechanisms

The precise mechanisms by which adherence to MeDiet exerts such a constellation of favorable effects is not yet completely known. Nevertheless, a recent review (Tosti et al., 2018) suggests that the most plausible favorable actions induced by this dietary pattern, based on accruing evidence, are:

- lipid-lowering effect;
- protection against oxidative stress, inflammation, and platelet aggregation;
- modification of hormones and growth factors involved in the pathogenesis of cancer;
- inhibition of nutrient sensing pathways by specific amino acid restriction;
- gut microbiota-mediated production of metabolites (i.e., SCFAs acetate, butyrate, and propionate) influencing metabolic health.

Indeed, MeDiet has an arrangement of biologically active food components that makes this diet unique. An appropriate combination of healthy sources of fats, proteins, starches, vitamins, minerals, fiber, as well as active compounds comprising phytosterols, terpenes, flavonoids, other polyphenols, and further still unidentified compounds, may help explain the numerous benefits of this dietary pattern. All together are likely to act synergistically through several biological mechanisms to reduce the risk of NCDs and thus influence individual mortality and morbidity (Tables 3–5 and Fig. 4).

Conclusions

Among various eating models, the Mediterranean dietary pattern meets several fundamental criteria for a high-quality healthy diet. From its origins when Ancel Keys began his studies up to the present moment, compelling evidence accumulated over the years

Table 5 Flavonoids in fruits and vegetables

<i>Flavonoids</i>					
<i>Flavonols</i>	<i>Flavan-3-ols</i>	<i>Isoflavones</i>	<i>Anthocyanidins</i>	<i>Flavanones</i>	<i>Flavones</i>
<ul style="list-style-type: none"> • Quercetin • Kaempferol • Myricetin 	<ul style="list-style-type: none"> • Catechin • Epicatechin • Epigallocatechin • Epigallocatechin gallate • Epicatechin gallate 	<ul style="list-style-type: none"> • Genistein • Daidzein • Biochanin A 	<ul style="list-style-type: none"> • Cyanidin • Delphinidin • Malvidin • Pelargonidin 	<ul style="list-style-type: none"> • Hesperetin • Naringenin • Eriodictyol 	<ul style="list-style-type: none"> • Apigenin • Luteolin • Baicalein

Source: Linus Paulin Institute at <https://lpi.oregonstate.edu/mic>

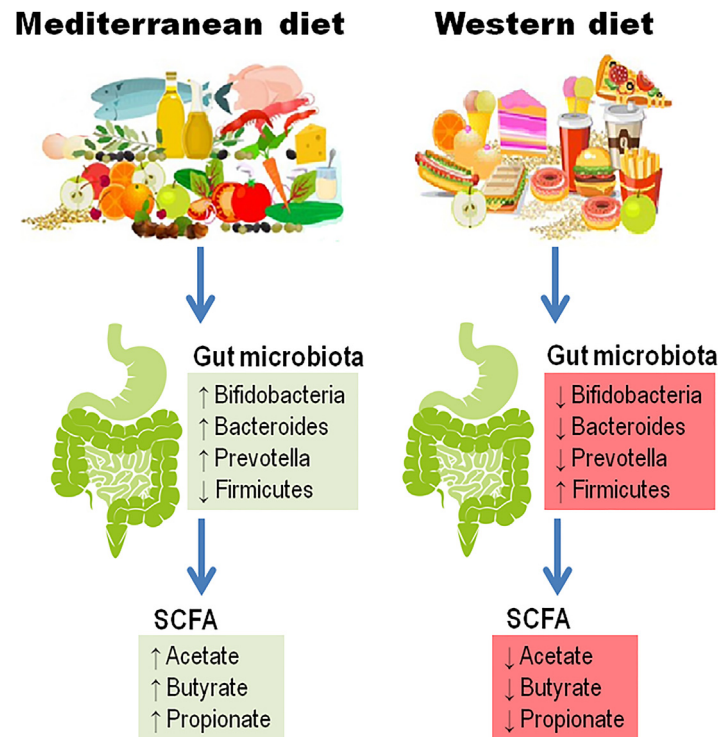


Fig. 4 The Mediterranean diet and the Western diet produce modifications in the gut microbiota composition with subsequent changes in short chain fatty acid (SCFA) production.

indicates that the traditional MeDiet may play a prominent beneficial role for health and longevity. No other food pattern is backed by such consistent observational, prospective, and trial-based evidence supporting the reduction of mortality and of various age-related NCDs. Conversely, suboptimal diet quality is now the leading modifiable cause of death and disability in the world.

The role of MeDiet in the prevention and treatment of CVD is well established. There are also a number of studies confirming the benefits of adherence to MeDiet on metabolic diseases and some types of cancer. Even if the evidence is still limited, available data indicate that MeDiet may have a role in the prevention of neurodegenerative diseases, depression, hip fractures, and frailty. Nevertheless, further confirmation in prospective studies and RCTs with longer follow-up, involving different ethnicities with diverse dietary habits is warranted. The field of nutritional research is beginning to underscore the importance of studying dietary patterns rather than individual foods or nutrients in order to catch the possible additive and synergistic effects of nutrient/food combinations and replacements. As such, dietary patterns with both beneficial and harmful components may result in an overall null effect. In this context, MeDiet is not only an ideal combination of favorable nutritional components, but also an eating model that has been historically and culturally accompanied by other healthy components of lifestyle, such as physical exercise, social engagement, flavorful eating, and adequate rest, honoring the traditions and culture handed down from generation to generation for centuries. In addition, studies that evaluate the environmental impacts related to food patterns repeatedly conclude that a shift towards diets less-based on animal sources and full of vegetable-based foods, such as MeDiet, exert caring actions with the environment, are ecologically correct, therefore, more sustainable.

Regrettably, countries in the Mediterranean basin are abandoning this priceless legacy. For example, in Crete, the Mediterranean island where the first studies were conducted with historically low rates of NCDs, the population is increasingly consuming less fruit and olive oil and more meats compared with earlier generations, with consequent increases in obesity and metabolic diseases.

Policymakers and the general public should initiate global and sustained actions to protect this intangible heritage of traditional knowledge and health of the Mediterranean lifestyle and promote its dissemination worldwide adapting it to the lifestyle and eating patterns of each region, and considering a lifelong and personalized approach. Strong intrinsic Western socio-cultural values, traditions and norms may be challenging barriers to overcome in order to implement MeDiet globally.

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Further Reading

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