



Review

Mediterranean diet in the management and prevention of obesity

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ABSTRACT

The current pandemic of obesity represents a major global public health problem, mainly due to its association with chronic non-communicable disabling conditions and with increased mortality. Population aging increases the chances of non-communicable chronic diseases allowing a longer exposure to risk factors for these disabling conditions. Obesity is a major risk factor contributing to pathological aging. Numerous epidemiological studies have shown that the risk of death due to cardiovascular disease and cancer increases progressively as overweight and obesity rise. Nutrition research is now focused on the effects of combinations of foods in dietary patterns instead of those of single nutrients or foods. The dietary model with the largest body of evidence of health benefit is that traditionally followed by inhabitants of some Mediterranean countries. There is evidence confirming the inverse association of adhering to Mediterranean diet with overweight and obesity. Four meta-analyses of randomized controlled trials, including up to 16 trials, have shown a greater reduction of body weight and BMI with MedDiet compared to other diets, while a meta-analysis of 7 prospective cohort studies, found a reduced risk of becoming obese and gaining weight over time associated with a higher adherence to MedDiet. This narrative review examines studies reporting inverse associations of a higher adherence to the MedDiet with overweight/obesity and with age-associated chronic diseases related to obesity.

1. Introduction

Obesity can be currently considered a pandemic. In fact, over two-thirds of adults in Western countries can be classified as obese (body mass index [BMI] >30 kg/m²) or overweight (BMI >25 kg/m²). The prevalence of obesity has increased almost 3-fold worldwide since 1975, mainly due to the dissemination of unhealthy diets and the adoption of sedentary lifestyles (Boutari and Mantzoros, 2022). Obesity pandemic has become one of the most important global public health problems of this millennium. Compelling evidence demonstrates that obesity curtails life expectancy and increases the risk for numerous preventable chronic diseases, including type 2 diabetes mellitus (T2DM) (Chen et al., 2011), hypertension and other cardiovascular diseases (CVDs) (Elagizi et al., 2020; Wormser et al., 2011), non-alcoholic fatty liver disease (NAFLD) (Kuang et al., 2022), various types of cancer (Lauby-Secretan et al., 2016; Nguyen et al., 2022), depression (Cao et al., 2022), sleep apnea (Bonsignore, 2022), and osteoarthritis (Purcell et al., 2022).

In the last 150 years, human life expectancy has increased as never formerly in history. The World Report on Aging and Health published by

the World Health Organization showed that most people worldwide now can expect to live beyond sixty years (Beard et al., 2016). This extraordinary demographic event was initially partly explained by a reduction in infectious diseases. However, reduction in infant mortality from communicable diseases cannot explain completely the increased life expectancy because it continued in populations older than 50 years (Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 2017). As a result of the increased life expectancy, there has been a constant rise in chronic non-communicable diseases (NCDs), including CVDs, T2DM, neurodegenerative diseases such as Alzheimer's and Parkinson's disease, and several types of cancer. The increased prevalence of NCDs is due to the fact that a longer life increases the time of exposure to the risk factors for these chronic pathologies. Obesity is indeed considered a major risk factor for the development of NCDs.

There is evidence supporting that obesity shortens life expectancy and embodies a substantial chronic disease burden (Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 2017; Willett et al., 2019).

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Overweight and obesity are chief risk factors for the causes of preventable death, and it is responsible for the greatest health expenses worldwide (Kjellberg et al., 2017). However, the clinically significant consequences of obesity can be lessened with as little as 5 to 10 % body weight-loss, which is feasible by several strategies (Obert et al., 2017). For the remission of conditions such as sleep apnea and T2DM generally a higher amount of weight-loss of about 15–20 % body weight-loss is needed (Lean, 2011).

One of the most significant modifiable determinants of healthy aging is an adequate nutrition (Dominguez et al., 2022). Nutrition research on health outcomes has shifted in the past decades from being focused exclusively on single nutrients and foods to examine the effects of combinations of nutrients/foods in dietary patterns considering the possible synergistic and/or antagonistic actions of foods and nutrients when consumed simultaneously in a food pattern (Jacobs and Steffen, 2003; Jacobs and Tapsell, 2013). Also because people do not eat foods or nutrients in isolation and do not easily understand messages regarding these single components, which can partly explain the lack of success in following nutritional health recommendations. Thus, various dietary patterns have been identified aiming to test their effectiveness on weight-loss, including low-fat (Knowler et al., 2002; Fernandez et al., 2022), low-carbohydrate (Hu et al., 2012; Shai et al., 2008), Mediterranean (MedDiet) (Estruch and Ros, 2020; Georgoulis et al., 2021; Limongelli et al., 2021; Rosi et al., 2020; Bouzas et al., 2020; Salas-Salvado et al., 2019), and ketogenic diet (Basolo et al., 2022; Yuan et al., 2022; Taftian et al., 2022), among others. The dietary pattern with the greatest body of evidence on the prevention and treatment of NCDs and on the reduction of mortality is that traditionally followed by populations of some Mediterranean countries (Carlos et al., 2018; Dominguez et al., 2021a; Martinez-Gonzalez et al., 2019a; Martinez-Gonzalez et al., 2015). The Seven Countries Study (Keys, 1995) was the first epidemiological investigation reporting the benefits of this traditional dietary model. Afterwards, multiple health benefits have been confirmed by numerous studies (Galbete et al., 2018; Dinu et al., 2018).

This narrative review examines the available evidence reporting associations of adherence to the Mediterranean dietary pattern with overweight/obesity and with age-associated chronic diseases related to obesity.

2. Epidemiological data on obesity

The global production of food and its distribution have changed remarkably during the second part of the last century until today (Popkin, 2006; Whitmee et al., 2015). The increased life expectancy and reduction of hunger to some extent are partly explained by the improvements in food production and crop yields (Steffen et al., 2015). However, these benefits are counterbalanced by the spreading of unhealthy westernized dietary patterns, which are plenty of processed and ultra-processed food, very rich in calories, and with low content of valuable nutrients (Drewnowski, 2018). This type of food is now known as 'low nutrient-dense food'. This trend has also been fueled by the constant increased urbanization and global availability of low nutrient-dense products (Vilar-Compte et al., 2021). This nutrition transition has greatly contributed to the increasing burden of obesity and related NCDs, and it has also backed, at least in part, the ecological crisis that the world is witnessing today (Tilman and Clark, 2014; Springmann et al., 2016).

The prevalence of diseases linked to unhealthy diets rich in low nutrient-dense products are continuously rising, with over two billion adults worldwide being overweight or obese currently (Willett et al., 2019). The global prevalence of diabetes has increased in parallel with the obesity pandemic from 5.0 % in 1980 to 7.9 % in 2014 in women, and from 4.3 % to 9.0 % in men (Worldwide trends in diabetes since, 2016). The prevalence of obesity and overweight increases with age and reaches its maximum between 50 and 65 years with a slight decreasing trend after that age. At all ages the prevalence of obesity and overweight

is greater in women compared to men. From 1980 to 2019 the world age-standardized prevalence of obesity increased from 4.6 % to 14.0 % (Boutari and Mantzoros, 2022). The countries with the highest number of obese citizens are the US (41.9 %) (QuickStats: prevalence of obesity* and severe obesity(dagger) among persons aged 2-19 years - National Health and Nutrition Examination Survey, 2020), Turkey (17.5 %), and Russia (15.9 %), while American and European countries have the highest global obesity prevalence (Boutari and Mantzoros, 2022).

3. Obesity is a pathological condition

A number of epidemiological investigations have confirmed that obesity and overweight are associated with multiple chronic diseases such as CVDs (Elagizi et al., 2020; Wormser et al., 2011), diabetes (Chen et al., 2011; Verma and Hussain, 2017), NAFLD (Kuang et al., 2022; Tang et al., 2022; Theel et al., 2022), several types of cancer (Lauby-Secretan et al., 2016; Nguyen et al., 2022), especially breast (Lohmann et al., 2021) and colon cancer (Larsson and Wolk, 2007; Gan et al., 2021), dementia (Slomski, 2022; Anstey et al., 2011), chronic renal failure (Kovesdy et al., 2017), and musculoskeletal disorders (Purcell et al., 2022), among many other conditions. The worrying consequences of the obesity/overweight pandemic continue to grow and generate ever higher rates not only of morbidity and mortality but also of disability (Lin et al., 2022; Chang et al., 2017), a prominent worsening in quality of life, and excessive and unsustainable costs for health systems worldwide. For example, a BMI between 30 and 40 kg/m² has been associated with near 50 % greater health care expenses owing to the management of obesity-related comorbidities, while a BMI >40 kg/m² was associated with 100 % greater healthcare costs (Andreyeva et al., 2004). Another study showed that a BMI >30 kg/m² was associated with an increase in annual healthcare costs of about 37 % (Kjellberg et al., 2017).

Thus, there is sufficient evidence and general agreement that maintaining an ideal body weight is an optimal and essential measure to elude the above-mentioned NCDs (Whitlock et al., 2009; Global et al., 2016). The evidence that mortality increases linearly as overweight and obesity increase is also prominent (Global et al., 2016). Life expectancy is reduced by nearly 2 to 4 years on average for people who maintain a BMI between 30 and 35 kg/m², and by about 8 to 10 years for those who maintain a BMI of 40 to 45 kg/m² (Whitlock et al., 2009).

4. Efficacy of weight-loss strategies: low-fat, low-carbohydrate, high-protein diets

The most extensively used recommendation to achieve weight loss has been to follow a diet with low content of calories and fat and with relatively high amounts of carbohydrates. Until today nutritional recommendations indicate a reduction in fat intake to <30 % of total daily dietary calories, while restricting the intake of saturated fatty acids (SFAs) to <10 %. It is also recommended to replace SFAs with polyunsaturated fatty acids (PUFAs) or monounsaturated fatty acids (MUFAs). These recommendations are based on the notion that fats have a greater caloric content compared to carbohydrates. This type of recommendations that began in the 80s and 90s of the last century has not resulted in an effective control of the increasing prevalence of overweight and obesity, which has led to discussions about its reevaluation and to proposals recommending restriction of carbohydrates (Ludwig, 2016). The recommendations of following a low-fat diet come from initial hallmark studies such as the Finish Diabetes Prevention Study (Tuomilehto et al., 2001) and the Diabetes Prevention Program (DPP) (Knowler et al., 2002), which reported modest weight-loss with a clear reduction in the incidence of T2DM combining a low-fat diet and a lifestyle intervention.

Although the tendency to recommend low-fat diets is included in most nutritional guidelines, low-carbohydrate diets have a long history. In fact, these diets began to be used as early as the 19th century

(Banting, 1993). There is evidence from several systematic reviews and meta-analyses comparing these two types of diets showing that low-carbohydrate diets induce a larger weight-loss than low-fat diets in the first 6 months, but that the difference disappears at 12 months (Nordmann et al., 2006; Hession et al., 2009; Jabbour et al., 2022). For both diets, a comparatively high drop-out rate has been observed (Hession et al., 2009).

An additional reason to recommend a low-fat diet was that SFAs intake was linked to elevated concentrations of low density lipoprotein (LDL)-cholesterol, which is a recognized risk factor for CVD. Yet, this notion does not take into account that reducing SFAs intake may also reduce high density lipoprotein (HDL)-cholesterol, which protection seems to be a better predictor of cardiovascular risk (Yusuf et al., 2004). Results from the Prospective Urban Rural Epidemiology (PURE) study comprising data from 18 countries in 5 continents showed that a high carbohydrate intake (>60 % of total calorie intake), particularly from refined foods (i.e., white bread and biscuits) was associated with a higher all-cause and CVD mortality (Dehghan et al., 2017). Contrariwise, a higher fat intake was associated with a reduced risk of incident stroke and death. Therefore, according to PURE's study results, it would be advisable to lessen carbohydrates consumption instead of reducing dietary fat, but this is most probably a naive statement. Indeed, what is important is not only the nutritional composition of diets, but its quality, that is, the sources of the different nutrients as well as the replacements made among the different types of food. As a confirmation of this concept, recent analyses of a large series of systematic reviews and meta-analyses found that the quality of carbohydrates, such as the high content of fiber and the consumption of whole grains, was inversely associated with the incidence of various chronic diseases and death, as well as with a lower frequency of risk factors, comprising being overweight (Reynolds et al., 2019).

Low-fat and low-carbohydrate diets have been compared in various meta-analyses reporting equivalent weight-loss effects in the short and medium term (Shai et al., 2008; Nordmann et al., 2006; Gardner et al., 2018). A recent meta-analysis including many popular diets used today showed that most diets induced modest weight-loss and improvements in CVD risk factors at 6 months, but these effects were largely reduced at 12 months (Ge et al., 2020).

The ketogenic diet, an extreme example of low-carbohydrate diet, has recently become very popular. This diet recommends avoiding practically all carbohydrates. A meta-analysis of 13 studies showed that ketogenic diet was associated with a nonsignificant (<1 kg) difference of weight-loss compared with high-carbohydrate, low-fat diets (Bueno et al., 2013). Likewise, another meta-analysis including 32 randomized controlled trials (RCTs) reported that fat loss and energy expenditure were larger for participants on low-fat diets vs. those on ketogenic diets (Hall et al., 2016). A recently published RCT compared two low-carbohydrate diets with 3 key similarities (incorporating nonstarchy vegetables and avoiding added sugars and refined grains) and 3 key differences (incorporating vs. avoiding legumes, fruits, and whole, intact grains) for their effects on glucose control and cardiometabolic risk factors in participants with prediabetes and T2DM. Both diets, well-formulated ketogenic diet (WFKD) and Mediterranean style Diet (MSD) were followed for 12 weeks. Analyses of 33 participants showed that both diets had similar weight loss effects as well as similar improvement in HbA1c after 12 weeks, possibly due to several shared dietary components. The WFKD led to a significantly higher decrease in triglycerides, but also led to higher LDL cholesterol and lower nutrient intakes likely due to avoiding legumes, fruits, and whole, intact grains with a consequent lower intake of fiber compared with the MSD. Twelve-week follow-up data suggest the MSD is more sustainable (Gardner et al., 2022).

With respect to vegan diet, a recent crossover RCT randomly assigned 62 overweight adults to a MedDiet or a vegan diet for 16 weeks each with a 4-week interval between the interventions. The low-fat vegan diet was associated with higher body weight reduction and

improvements in lipid concentrations and insulin sensitivity compared with a MedDiet. Blood pressure decreased on both diets, but the effect was higher for participants on the MedDiet (Barnard et al., 2022).

5. Mediterranean diet

The concept of the MedDiet, as we conceive it today, was first introduced by the Seven Countries Study, conducted by Keys et al. in the 50s of the past century (Keys, 1995). This ecological investigation conducted predominantly in deprived, rural populations from Crete (Greece) and southern Italy, provided the foundations for the hypothesis that diet may have health protective effects. The Seven Countries Study described the usual eating habits of these populations in the post-war period of the World War II when the globalization had not yet arrived. Keys et al. observed with great surprise that population in the Mediterranean countries had an exceptional longevity with some of the lowest rates of coronary heart disease and cancer vs. Western countries. Evidence that followed this initial study came from the Lyon study (de Lorgeril et al., 1994), reporting that in patients with a history of myocardial infarction (secondary prevention) randomized to receive a Mediterranean-style diet compared to a low-fat diet recommended by the American Heart Association there was a startling 73 % reduction in coronary events after 27 months of follow-up. More recently, the PRE-DIMED study (Prevention with MedDiet) involving 7447 participants with high cardiovascular risk showed that those allocated to follow a Mediterranean-style diet supplemented with extra virgin olive oil (EVOO) or nuts vs. a low-fat diet had a 30 % reduction in the incidence of a composite outcome of myocardial infarction, stroke or cardiovascular death after a follow-up of ~5 years (Estruch et al., 2018). The CORONARY Diet Intervention with olive oil and cardiovascular PREVENTION (CORDIPREV) study, compared the effects of Med Diet and low-fat diets in the secondary prevention of CVD. The study included 1002 patients with established coronary heart disease (CHD) (mean age 59.5 ± 8.7 years; 82.5 % were men) who were randomly assigned to receive a MedDiet or a low-fat diet intervention surveyed by dietitians. After a mean follow-up of 7 years, 198 participants had a composite primary outcome (myocardial infarction, revascularization, ischemic stroke, peripheral artery disease, and cardiovascular death) with significantly different risk (crude rate/1000 person-years: 28.1 [95 % CI 27.9–28.3] in the MedDiet group vs. 37.7 [37.5–37.9] in the low-fat group). Multivariable-adjusted hazard risks were significantly lower for the MedDiet group. These effects were evident in men with no difference found in women. This trial confirms that MedDiet was superior to the low-fat diet in secondary prevention of major CV events (Delgado-Lista et al., 2022).

It is noteworthy that the notion of MedDiet proposed by Keys et al. only in the last century represents the eating habits and lifestyle of Mediterranean populations that have been followed in this region for millennia. Archaeological evidence supports that wine, olive oil, bread, and legumes were already used by these populations in ancient times. The components of MedDiet not only include food preferences but also comprise several non-dietary features of lifestyle, together with historical traditions, knowledge, abilities, and practices that have been passed down from generation to generation. Mediterranean countries have peculiar culinary traditions rich in local products, flavors, aromas, colors, and memories, highlighting taste, contact and respect for nature, and giving special value to preparing, sharing and consuming food together with family and friends (Dominguez et al., 2021a).

MedDiet, as conceived and studied today, is mainly based on foods of plant origin. It comprises the consumption of assorted fresh vegetables and fruits; olive oil as main (and almost only) source of dietary fat for seasoning and cooking; regular consumption of nuts and seeds; legumes consumed several times per week; consumption of whole grains daily; fish and seafood consumed 2 to 3 times per week; consumption of dairy especially yogurt; small portion of cheese consumed less frequently; consumption of 2 to 4 eggs per week; and use of herbs and spices in the

preparation of meals to season them. Sweets and red/processed meat are less frequently consumed in this eating model. The main beverage in the traditional MedDiet is water; wine is consumed in small portions always with meals, in people who are used to drink it or who do not have diseases or use medications that interact with alcohol and contraindicate its use (Table 1).

The fat content of the MedDiet is around 35–45 %, even if this may change in the new proposals of the version with restricted energy (Martinez-Gonzalez et al., 2019b). The sources of fat are mainly MUFAs and PUFAs with small amounts of SFAs. Table 2 compares the main features of the MedDiet with low-carbohydrate and low-fat diets.

A key feature of this dietary pattern is that it essentially includes foods of natural origin that are unprocessed or minimally processed, as opposed to the Western diet, which is based on the frequent consumption of processed and ultra-processed foods, as well as sugary drinks, which are full of calories and very poor in nutrients. Fig. 1 compares the components of MedDiet with those of the Western diet.

6. Mediterranean diet and obesity

Multiple studies have confirmed the health benefits of following the MedDiet (Dominguez et al., 2021a). There is also some specific evidence of the effects of MedDiet on weight-loss and on the reduction of central adiposity. Results from the SUN (Seguimiento Universidad de Navarra – Follow-up from the University of Navarra) project among 10,376 participants with a mean follow-up of 5.7 ± 2.2 years showed that participants with the lowest adherence to MedDiet had the highest mean yearly weight-gain; conversely, those with the highest adherence to MedDiet had the lowest mean weight-gain. These results remained significant and comparable when assessing adherence to MedDiet with different a-priori defined scores (Beunza et al., 2010).

Likewise, analyses from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain comprising 17,238 women and 10,589 men not obese at baseline and followed-up for a mean of 3.3 years found that high adherence to the MedDiet was significantly associated with a lower likelihood of becoming obese among overweight participants, for both men and women. MedDiet adherence was not associated with incident overweight among normal-weight participants at baseline (Mendez et al., 2006). Data from the EPIC-Physical Activity, Nutrition, Alcohol

Table 1
Characteristics of the traditional Mediterranean dietary pattern.

- Fresh vegetables and fruits, legumes, nuts, and seeds consumed daily
- Whole grain products (bread, pasta, rice) consumed daily
- Herbs and spices used daily for preparing and seasoning dishes
- Cold pressed extra-virgin olive oil as the main (and almost only) source of fat consumed daily
- Fresh fruit consumed daily as dessert
- Fish and seafood consumed 2 to 3 times weekly
- Dairy products, mainly yogurt (small portions of local cheese less frequently)
- Consumption of 2–4 eggs weekly
- Red and processed meat consumed unfrequently, in moderate portions, preferably as part of stews and other recipes (1–2 times monthly)
- Cakes, sweets, and dairy desserts consumed only occasionally
- Wine consumed in small amounts always with meals (≤ 1 drink/day for women; $1-2$ drinks/day for men)^a
- Drinking water
- Diet composed mainly of foods that have undergone minimal processing, that are fresh and locally produced avoiding processed and ultraprocessed foods
- Tasty cooking
- Moderation in portion size
- Direct connection with nature
- Moderate physical activity every day
- Cooking and consuming meals in the company of others
- Adequate rest^b

^a Respecting community's beliefs and previous habits.

^b Enough night sleeping time and eventually small periods of sleeping time during the day (siesta).

Consumption, Cessation of Smoking, Eating Out of Home, and Obesity (EPIC-PANACEA) project including 373,803 participants from 10 European countries reported that participants with a high MedDiet adherence had a 5-year weight change of -0.16 kg (95 % CI $-0.24, -0.07$ kg) and were 10 % less likely to develop overweight or obesity compared to participants with a low adherence to MedDiet (Romaguera et al., 2010). A meta-analysis of 16 RCTs including 3436 participants found that those following the MedDiet had a significant weight lowering effect and reduced BMI compared to controls. The effect of MedDiet on body weight was larger when combined with energy restriction, increased physical activity, and follow up longer than 6 months. Of note, none of the studies reported significant weight-gain with a MedDiet (Esposito et al., 2011). Another meta-analysis of 9 RCTs among 1178 patients with diabetes showed that MedDiet led to greater reductions in hemoglobin A1c, fasting plasma glucose, fasting insulin, BMI, and body weight vs. control diets. Similarly, total cholesterol and triglyceride concentrations were reduced, and HDL-cholesterol was increased (Huo et al., 2015). A systematic review including 5 RCTs and 998 participants found that MedDiet had similar effects on weight-loss and CVD risk factors than low-fat and low-carbohydrate diets (Mancini et al., 2016). Participants randomized to MedDiet had a body weight-loss ranging from 4 to 10 kg, with no significant difference in LDL-cholesterol levels but with larger improvements in triglycerides, and better glycemic control in diabetics (Mancini et al., 2016). A meta-analysis including 20 RCTs with over 6-month interventions compared low-carbohydrate, vegetarian, vegan, low-glycemic index (GI), high-fiber, MedDiet, and high-protein diets with control diets including low-fat, high-GI, American Diabetes Association, European Association for the Study of Diabetes, and low-protein diets in T2DM patients. The only dietary pattern with significant weight loss was the MedDiet (Ajala et al., 2013).

A recent meta-analysis of cohort studies explored the association of adherence to a MedDiet and the risk of overweight and/or obesity. Seven prospective cohort studies were included of which 6 studies ($n = 244,678$ adult participants) reported the risk of overweight and/or obesity, and 4 cohorts ($n = 436,617$ participants) reported the weight change. Combining 15 effect sizes from 6 cohorts the authors found that greater adherence to the MedDiet was significantly associated with a 9 % decreased risk of incident overweight and/or obesity. Linear dose-response analysis of 6 studies showed a 2 % decreased risk of overweight and/or obesity for one additional MedDiet score point. Each unit increase in the MedDiet score was associated with 0.04 kg less weight gain over 5 years (Lotfi et al., 2022).

A recent intervention study aiming to assess the effectiveness of a two-year intervention based on the MedDiet for the treatment of overweight and obesity in a sample of 51 older people from the Mediterranean city of Alicante (Spain) examined the effects of the intervention on psychological well-being. The experimental group received education sessions, an individualized dietary-nutritional treatment based on a MedDiet, and a physical activity program; the control group received Mediterranean nutritional education in a written format. The MedDiet group showed a significantly greater reduction of body weight, fat mass, BMI, and waist circumference. Regarding psychological well-being, depression levels improved at the end of the intervention (Rumbo-Rodriguez et al., 2022).

Thus, recommending the MedDiet with restriction of energy intake seems an ideal choice in order to loss or maintain an optimal body weight in patients at high cardiovascular risk.

Regarding adiposity, a recent study evaluated the short-term effects of a dietary intervention based on the MedDiet supplemented with almonds (MDSA) on the main features of obesity-associated white adipose tissue (WAT) dysfunction. A total of 38 women with obesity were randomly assigned to a 3-month intervention with MDSA vs. maintenance of their usual diet. Subcutaneous (SAT) and visceral adipose tissue (VAT) biopsies were obtained before and after the dietary intervention. MDSA favored the abundance of small adipocytes in WAT. In SAT, the

Table 2
General features and components of Mediterranean diet compared to low-carbohydrate and low-fat diets.

	Mediterranean diet	Low-carbohydrate diet	Low-fat diet
General features	<ul style="list-style-type: none"> • Rich in MUFAs and PUFAs, low in SFAs. • Consistent evidence showing associations with reduced CHD, improved CV risk factors, and inverse relationships with the incidence of various chronic NCDs and all-cause mortality. • Similar weight-loss compared to low-fat and low-carbohydrate diets. • Long-term adherence more possible due to the fact that it is varied, tasty, and with many flavors. • In non-Mediterranean countries the consumption of olive oil and wine is not usual. 	<ul style="list-style-type: none"> • Unrestricted calorie, protein, and fat intakes. • Limits on carbohydrate intake (e.g., 20–60 g/day). • Concerns over high SFAs intake. However, LCD seems safe and effective up to 12 months. • Risk of nutritional deficiencies (fat soluble vitamins A, D, E, K). Supplementation is necessary. • Limited food choices preclude long-term adherence. • Ketone generation may help reducing appetite. High protein content may have satiating effects. • Suboptimal intake of fiber, vitamins and minerals from lack of consumption of cereals, fruits, and vegetables. • Easy to follow (clear indications of which foods to prefer and which to avoid). • Not having to count calories may be appealing to those who follow it. 	<ul style="list-style-type: none"> • Carbohydrate: 50–60 % of total energy; total fat: <30 %; protein: 15 %; SFAs <10 %. • Usually, 500–1000 kcal/day less than metabolic requirements. • Tailored exchanges are generally proposed. • This diet is usually considered appropriate for achieving and maintaining good health. • Major government and health organizations recommend this type of diet (i.e., AHA, ADA, BHF, Diabetes UK, US Department of Agriculture, Public Health England). • The fact that weight loss is slow can be discouraging to those who follow it.
Foods eaten and avoided	<ul style="list-style-type: none"> • No single MedDiet pattern due to differences among Mediterranean countries but generally recommends plant-based foods including fruit, vegetables, whole grains, legumes, and nuts. • Olive oil is the main source of fat. • Lean fish and seafood are recommended in moderate amounts, while the consumption of red and processed meat is limited. • Small portion of wine with meals, if preferred and not contraindicated. 	<ul style="list-style-type: none"> • Emphasis on eating high protein foods (e.g., meat, fish, poultry, eggs, hard cheese, and nuts). • Preference of low-carbohydrate vegetables (e.g., green salad, asparagus, broccoli, etc.) • Limited consumption of fruits. Best choices could be berries, grapefruit, and melon. • Unrestricted consumption of fats (e.g., butter, oils, mayonnaise, lard, fried food). • Avoiding starchy carbohydrate foods (bread, pasta, rice, oats, potatoes, etc.). • Restricted consumption of dairy products. • Total exclusion of refined carbohydrate (e.g., sweets, biscuits, desserts, chocolate, etc.). 	<ul style="list-style-type: none"> • Foods containing high amounts of SFAs, TFAs, sugars, and salt are limited. • Low-energy dense foods such as starchy carbohydrates (e.g., whole grains), fruits and vegetables are recommended. But in practice it often includes high amounts of low-fat processed foods. • Preference for lean proteins and low-fat dairy products to reduce energy intake. • Limited use of food high in fat and sugar (e.g., potato chips, biscuits, oils, spreads, chocolate, etc.).

ADA: American Diabetes Association; AHA: American Heart Association; BHF: British Heart Foundation; CHD: coronary heart disease; CV: cardiovascular; LCD: low-carbohydrate diet; MUFAs: monounsaturated fatty acids; NCDs: non-communicable diseases; PUFAs: polyunsaturated fatty acids; SFAs: saturated fatty acids; TFAs: trans fatty acids.

expression of angiogenesis genes increased after MDSA intervention. In VAT, the expression of genes implicated in adipogenesis, angiogenesis, autophagy and fatty acid usage was upregulated. In addition, a higher immunofluorescence staining for peroxisome proliferator activated receptors, cluster of differentiation 31+ cells, and M2-like macrophages and increased adrenoceptor beta 1 and uncoupling protein 2 contents were found compared to controls. Changes in WAT correlated with a significant reduction in circulating inflammatory markers and LDL-cholesterol levels. These results support a protective effect of a MedDiet supplemented with almonds on obesity-related WAT dysfunction (Osorio-Conles et al., 2022).

The relatively high content of fat in the MedDiet may someone think that it may favor weight-gain and obesity. Because participants to the PREDIMED study received a significant amount of EVOO and walnuts for free, this concern was raised at the time of the first published results of this trial (Appel and Van Horn, 2013). Nevertheless, long-term analyses of the PREDIMED trial specifically concerning body weight and waist circumference have shown that the adjusted differences after 4.8 years of the intervention were not significant vs. the control low-fat diet group in both arms (i.e., EVOO and nuts) (Estruch et al., 2019). Moreover, results on the incidence of T2DM and metabolic syndrome, which are conditions closely related to weight-gain, are comforting. Among 3541 non-diabetic participants of the PREDIMED trial at baseline, those

in the EVOO-enriched MedDiet had ~40 % lower risk of developing T2DM vs. controls (Salas-Salvado et al., 2014). This benefit was also found in the prevention of the metabolic syndrome. The risk of developing metabolic syndrome during the 5-year follow-up in 1919 participants to the PREDIMED trial who did not have it at baseline was not different for those on the low-fat diet group vs. participants in the MedDiet arms. In addition, among 3392 participants without metabolic syndrome at baseline, those in the MedDiet arms were more likely to have reversal of the syndrome than those on a low-fat diet (Babio et al., 2014). The initial assessment of the entire PREDIMED cohort found a significant inverse relationship of adherence to the MedDiet with indexes of global or abdominal obesity (Martinez-Gonzalez et al., 2012). Other analyses of the PREDIMED trial reported that a higher consumption of EVOO and nuts was associated with a modest weight-loss after a median follow-up of 3 years (Razquin et al., 2017).

Of note, results from the entire PREDIMED trial cohort showed that the consumption of ultra-processed foods, refined carbohydrates (i.e., white bread), potatoes, red meat, and alcohol were significantly associated with greater weight-gain and abdominal circumference, while greater consumption of low-fat dairy and vegetables, including nuts, were associated with less gain in body adiposity (Konieczna et al., 2019). In a sub-study of the PREDIMED trial, the MedDiet supplemented with EVOO was associated with a reduced prevalence of NAFLD, another

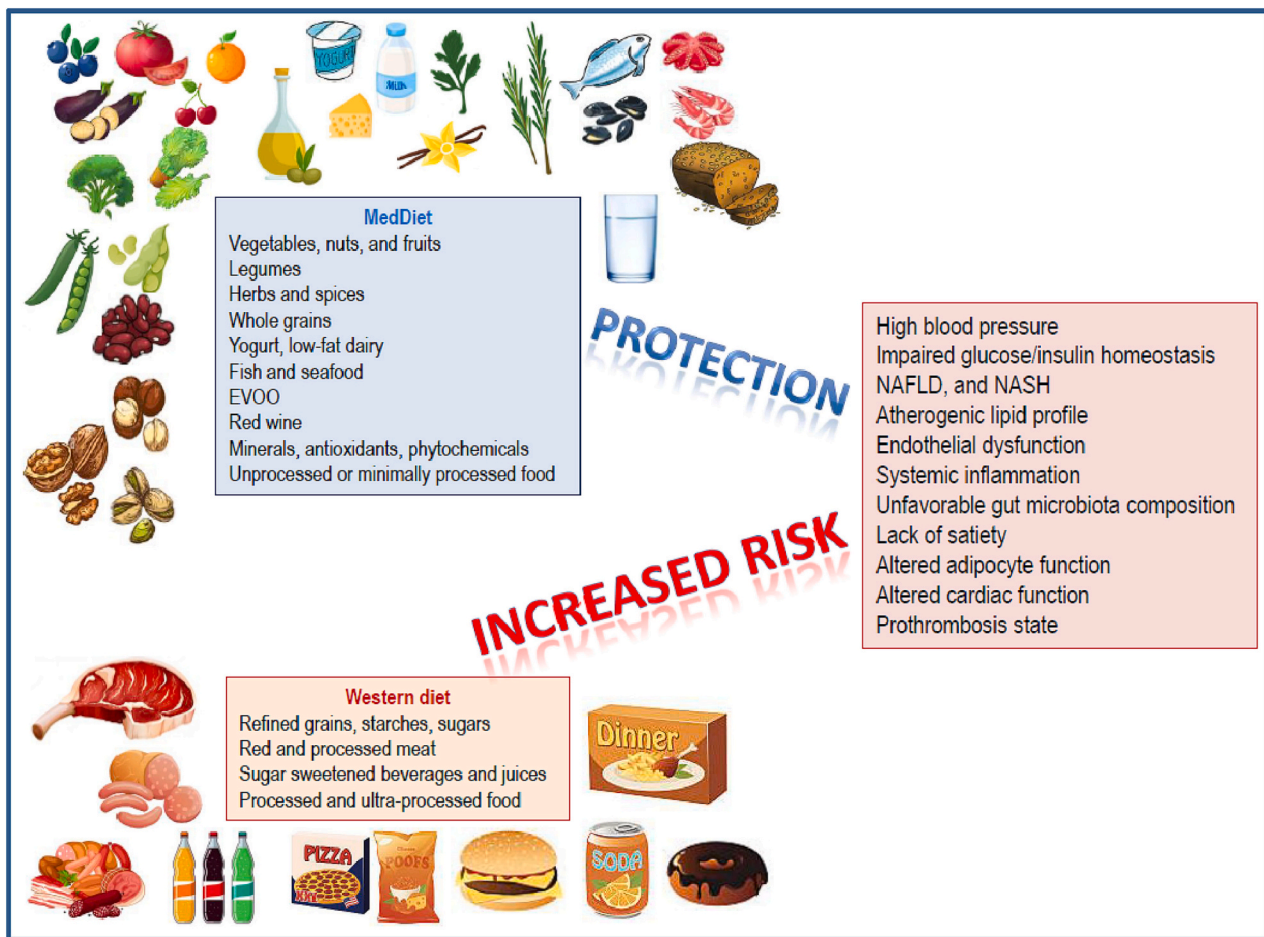


Fig. 1. Different components of Mediterranean and Western diets and their health consequences. EVOO: extravirgin olive oil; NAFLD: non-alcoholic fat liver disease; NASH: non-alcoholic steatohepatitis.

worrying condition closely linked to obesity (Pinto et al., 2019).

The PREDIMED-Plus RCT aimed to go further the original PREDIMED trial by means of assessing whether intentional weight reduction through the promotion of physical activity and an energy-restricted MedDiet resulted in a reduction of incident CVD events beyond what the original PREDIMED had shown. A cohort of 6874 participants overweight or obese and meeting criteria for the metabolic syndrome have been enrolled to date, with a mean age of 65 years, recruited in 23 Spanish centers and randomized into two groups of equal size: an active group receiving recommendations to follow an energy-restricted MedDiet in addition to a structured exercise program vs. a control group where only the MedDiet is suggested. In order to improve adherence to recommendations, EVOO and mixed nuts are supplied free of charge (in smaller amounts than those provided in PREDIMED) to participants in the two supplemented MedDiet arms (Martinez-Gonzalez et al., 2019b).

A pilot preliminary study of the PREDIMED-Plus trial including 626 participants have shown that participants in the intervention group lost an average of 3.2 kg vs. 0.7 kg in the control group after one year; weight-loss >5 % occurred in 33.7 % vs. 11.9 %, respectively. The mean change in abdominal circumference was -3.1 cm (95 % CI -3.8 to -3.5) in the active intervention group vs. 0.7 cm (95 % CI -1.3 to 0.03) in the control group. In addition, cardiovascular risk factors, i.e., fasting blood glucose, HDL-cholesterol, and triglycerides improved in the intervention group (Salas-Salvado et al., 2019). An interim analysis of the full PREDIMED-Plus cohort confirmed that participants in the active intervention had greater increase in adherence to the energy-restricted MedDiet compared to the control group. The difference in total energy intake in the two groups in favor of the intervention group was

translated into a clinically significant weight-loss, decreased BMI, and lower waist circumference in about 40 % of participants from the intervention group vs. 12 to 13 % of the control group. Benefits on cardiovascular risk factors were confirmed as well in this pilot study (Sayon-Orea et al., 2019). Noteworthy, in the two reports of the PREDIMED-Plus trial (Salas-Salvado et al., 2019; Sayon-Orea et al., 2019) the changes in weight and abdominal circumference in favor of the intervention were present already at 6 months and were maintained at 12 months, certainly a record compared to other trials with weight-loss as outcome (Ge et al., 2020). Future results from the PREDIMED-Plus trial are expected in order to test if these modifications can be sustained in the long-term and if they may significantly affect the incidence of CVD. Table 3 shows the summary of results from systematic reviews and meta-analyses of RCTs and cohort studies on the association of MedDiet and obesity. The meta-analyses on RCTs showed a greater reduction of body weight and BMI with MedDiet compared to other diets and the meta-analysis on cohort studies showed a reduced risk of becoming obese and reduced weight gain over time.

It is likely that a varied and palatable diet such as the MedDiet may be more easily followed in the long term, in contrast to a diet with little fat or few carbohydrates that is generally not accepted for long periods of time. This was confirmed by a trial by Schwarzfuch et al., which compared three weight-loss plans: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; or a low carbohydrate diet without calorie restriction in a 2-year workplace intervention. At the end of the trial the healthy dietary changes had long-lasting favorable post-intervention effects, particularly among participants receiving the MedDiet and low-carbohydrate diets (Schwarzfuchs et al., 2012).

Table 3

Summary of results from systematic reviews and meta-analyses of randomized controlled trials and cohort studies on the association of Mediterranean diet and obesity.

Authors/country	Year	n. of trials or prospective cohort studies	n. of participants	Range of age in years	Range of duration of follow-up	Summary of results
Esposito et al. Italy (Esposito et al., 2011)	2011	16 RCTs	3436	30–70	18 days to 5 years	MedDiet group had a significant effect on weight loss (mean difference between MedDiet and control diet, 1.75 kg; 95 % CI, 2.86 to 0.64 kg) and BMI reduction (mean difference, 0.57 kg/m ² ; 95 % CI 0.93 to 0.21 kg/m ²). The effect on body weight was greater in association with energy restriction (mean difference, 3.88 kg, 6.54 to 1.21 kg), increased physical activity (4.01 kg, 5.79 to 2.23 kg), and follow up longer than 6 months (2.69 kg, 3.99 to 1.38 kg). No study reported significant weight gain with a Mediterranean diet.
Ajala et al. UK (Ajala et al., 2013)	2013	4 RCTs of MedDiet (total of 20 RCTs with other diets)	1892	40–75	6 months to 4 years	MedDiet led to significantly greater weight loss [21.84 kg] (P = 0.00001) vs. other diets (low carbohydrate, vegetarian, vegan, low-glycemic index, high fiber, and high protein diets).
Huo et al. China (Huo et al., 2015)	2015	9 RCTs	1178	26–75	4 weeks to 4 years	Compared with control diets, MedDiet led to greater reductions in BMI and body weight, as well as HbA1c, fasting plasma glucose, and fasting insulin. In addition, MedDiet was associated with a decline in systolic and diastolic BP.
Mancini et al. Italy (Mancini et al., 2016)	2016	5 RCTs	998	44–58	12 months to 2 years	MedDiet resulted in greater weight loss than low-fat diet at 12 months (4.1 to 10.1 kg vs. 2.9 to 5.0 kg), but produced similar weight loss as other comparator diets [low-carbohydrate and ADA diet] (4.1 to 10.1 kg vs. 4.7 to 7.7 kg). MedDiet was generally similar to comparator diets at improving other CV risk factor levels, including BP and lipid levels.
Lofti et al. Iran (Lofti et al., 2022)	2022	7 prospective cohort studies	272,222	25–74	5 to 13 years	MedDiet was significantly associated with a 9 % decreased risk of incident overweight and/or obesity (RR: 0.91; 95 % CI: 0.88, 0.94) combining 6 cohorts. Linear dose–response analysis of 6 studies showed a 2 % decreased risk of overweight and/or obesity for one additional unit of MedDiet score (RR: 0.98; 95 % CI: 0.96, 0.99). Each unit increase in the MedDiet score was associated with 0.04 kg less weight gain over 5 years.

ADA: American Diabetes Association; BMI: body mass index; BP: blood pressure; CI: confidence interval; HbA1c: hemoglobin A1c; RCTs: randomized controlled trials; RR: relative risk.

7. Mediterranean diet and other obesity-related chronic diseases

The MedDiet has not only been associated with favorably weight-loss and central adiposity reduction, especially when combined with physical exercise and energy restriction, but it has also been associated with reduced incidence of serious consequences directly related to obesity. This includes T2DM and metabolic syndrome (Salas-Salvado et al., 2014; Sayon-Orea et al., 2019; Martinez-Gonzalez et al., 2008; Rossi et al., 2013; Schwingshackl et al., 2015; Esposito et al., 2015), CVD (Keys, 1995; Dinu et al., 2018; de Lorgeril et al., 1994; Estruch et al., 2018; Delgado-Lista et al., 2022; Sofi et al., 2014; Mente et al., 2009), some types of cancer specifically related to obesity (Schwingshackl et al., 2017; 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; Toledo et al., 2015), cognitive decline (Dominguez et al., 2019; Dominguez et al., 2021b; Singh et al., 2014; Valls-Pedret et al., 2015) for which one of the risk factors is T2DM and having been obese during adult life, and depression (Lai et al., 2014; Hershey et al., 2022; Bayes et al., 2022), which also seems closely related to obesity (Fig. 2). Recently published trials have corroborated the protective effects on CVD. For example, the CORDIPREV study mentioned above, comparing the effects of Med Diet and low-fat diets in the secondary prevention of CVD found a lower risk of a composite CVD outcome for participants in the MedDiet arm vs. participants in the low-fat diet intervention (Delgado-Lista et al., 2022). Conversely, another analysis from the same study aiming to investigate the role of MedDiet and low-fat diet in modulating the risk of T2DM in CHD patients found that the consumption of a low-fat diet was more beneficial than a MedDiet in patients with impaired fasting glucose and impaired glucose tolerance at baseline after a median follow-up of five years (Roncero-Ramos et al., 2020). Nevertheless, a recent meta-analyses on 14 prospective cohort studies (410,303 participants and 41,466 cases) aiming to explore the dose-response relationship between adherence to the MedDiet and the risk of T2DM showed an inverse association in a dose-response manner for

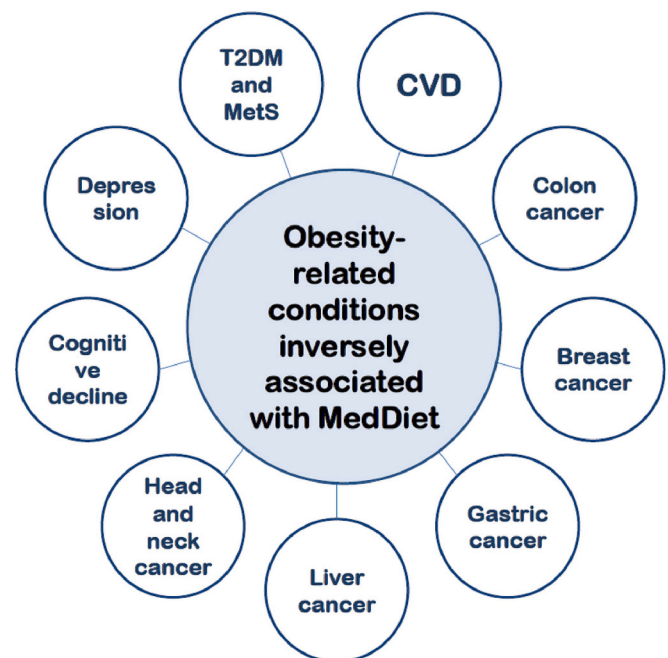


Fig. 2. Non-communicable diseases that have been inversely associated with a higher adherence to the Mediterranean dietary pattern. CVD: cardiovascular disease; MedDiet: Mediterranean diet; MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus.

the highest versus the lowest category of adherence to the MedDiet (RR: 0.79, 95 % CI 0.72, 0.88), and for a 2-point increment in the MedDiet adherence score (RR: 0.86, 95 % CI 0.82, 0.91). The relative risk remained significant after controlling for important confounders and in

almost all subgroups, especially subgroups defined by geographical region (Zeraattalab-Motlagh et al., 2022). This study confirms former results from several observational studies and RCTs on the role of MedDiet in the prevention of T2DM (Schwingshackl et al., 2015) adding the evidence of a dose-response effect and reinforcing that following a MedDiet is an optimal advice for the primary prevention of T2DM.

Similarly, there is cumulative evidence of an inverse relationship between greater adherence to the MedDiet and major CVD risk factors, such as high blood pressure, dyslipidemia, and markers of inflammation (Estruch et al., 2006; Fito et al., 2007; Martinez-Gonzalez and Bes-Rastrollo, 2014). Convincing evidence has been accrued confirming the association of greater adherence to MedDiet and lifestyle with a reduction in total and cause-specific mortality (Keys, 1995; Trichopoulos et al., 2003; Trichopoulos et al., 1995; Osler and Schroll, 1997; Kouris-Blazos et al., 1999; Lasheras et al., 2000; Knuops et al., 2006; Mitrou et al., 2007; Bonaccio et al., 2018), which ultimately means greater longevity. Several clinical mechanisms as well as molecular mediators (Table 4 and Fig. 3) may help to explain the benefits of following the MedDiet on disorders linked to obesity.

8. Molecular mechanisms underlying the beneficial effects of Mediterranean diet on obesity and associated conditions

Even if the mechanisms explaining the beneficial effects of MedDiet are not fully clarified, quite a few molecular and clinical mechanisms have been studied to help explain the favorable actions of this dietary pattern. MedDiet is a combination of biologically active compounds that renders unique this dietary model (Schwingshackl et al., 2020), i.e., an optimal blend of healthy fats, proteins, starches, fiber, vitamins, minerals, and a myriad of bioactive components including polyphenols, terpenes, phytosterols, and other yet unidentified compounds, which may help to explain its various benefits.

Obesity is associated with a state of low-grade chronic inflammation characterized by the release of pro-inflammatory cytokines and adipokines, such as interleukins, tumor necrosis factor-alpha, and leptin, which are produced by white adipose tissue cells and by inflammatory cells infiltrating adipose tissue (Landecheo et al., 2019). Therefore, the potential anti-inflammatory and antioxidant effects of components of the MedDiet may contribute to its effects on obesity and its complications. For example, there is evidence of the associations of health outcomes with the dietary inflammatory index (DII) (Hebert et al., 2019) or with the dietary content of polyphenols. A study by Hodge et al. found that a higher score of MedDiet adherence and lower DII were associated with lower total, CVD and CHD mortality (Hodge et al., 2018), which are conditions associated with obesity. Analyses of data from the SUN project showed that the risk of CV events was doubled for participants in the highest vs. the lowest quartile of the DII (Ramallal et al., 2015). Data from the PREDIMED trial, the SUN cohort and a meta-analysis of 12 prospective studies showed that the highest vs. the lowest quartiles of DII were positively and significantly association with all-cause mortality (Garcia-Arellano et al., 2019). Fig. 4 shows foods that are part of the

Table 4

Mechanisms that may help explain the benefits of Mediterranean diet on disorders linked to obesity.

Beneficial mechanisms of Mediterranean diet in the prevention of obesity-associated disorders
<ul style="list-style-type: none"> • Improvement of insulin resistance • Weight loss • Improvement in lipid profiles • Reduction of endothelial dysfunction • Reduction of oxidative stress • Reduction of chronic low-grade inflammation • Improvement in microbiota composition • Improvement in immune responses • Reduction of prothrombotic mechanisms

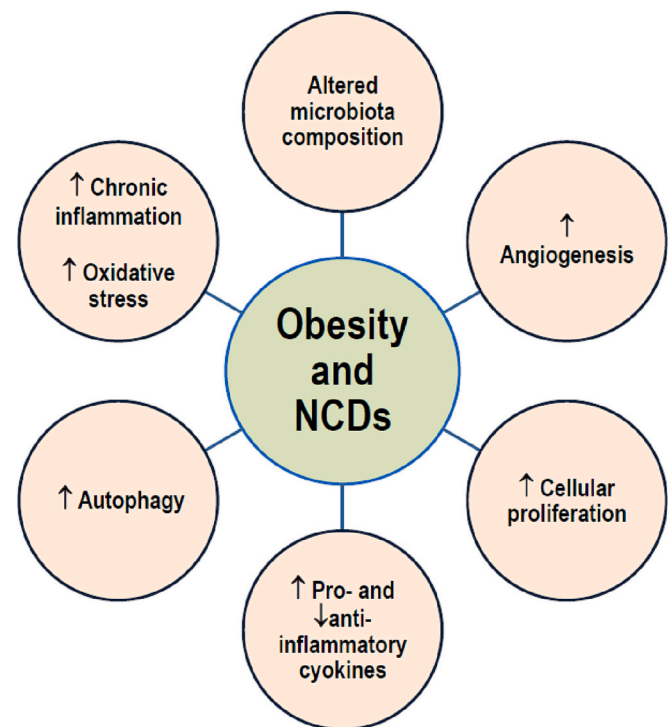


Fig. 3. Some molecular mechanisms associated with reduced inflammation and oxidative stress that may help explain the benefits of Mediterranean dietary pattern on disorders linked to obesity. NCDs: non-communicable diseases.

MedDiet that contain anti-inflammatory compounds.

Autophagy, the natural mechanism of cellular degradation, is crucial to eliminate excessive nutrients, toxic proteins aggregates, damaged organelles and invading microorganisms. Obesity and obesity-associated lipotoxic, proteotoxic and oxidative stress, can frequently interfere with autophagy, which may further aggravate obesity-related metabolic pathologies in multiple organs (Namkoong et al., 2018).

The high content of protective phenolic compounds in the components of MedDiet, especially those present in vegetables and fruit (Fig. 5), may also contribute to explain its multiple benefits. An RCT compared the effects of a high-polyphenol diet (6 portions of fruit and vegetable daily vs. <2 portions) on microvascular function in hypertensive overweight or obese participants. After 8 weeks, endothelial function was better for participants on the high-polyphenol diet (Noad et al., 2016). A high intake of total polyphenols, total flavonoids, and stilbenes was associated with reduced incident diabetes in participants of the PREDIMED trial (J. Nutr., 2015). Pounis et al. reported that those in the highest quintile of polyphenols intake vs. those in the lowest quintile had a lower risk of all-cause mortality risk in the Mediterranean Moli-sani cohort (Pounis et al., 2018). Likewise, in the PREDIMED trial, those who reported a high-polyphenol intake showed a reduced risk of overall mortality vs. those with lower intakes (Tresserra-Rimbau et al., 2014). A systematic review of observational and experimental research found an inverse association of polyphenol consumption contained in the MedDiet and the risk of depression (Bayes et al., 2022), another condition frequently associated with obesity.

As mentioned, several types of cancer, have been specifically related to obesity (Lauby-Secretan et al., 2016; Nguyen et al., 2022; Lohmann et al., 2021; Larsson and Wolk, 2007; Gan et al., 2021). During carcinogenesis, immune and inflammation response produces cytokines and chemokines that enable cancer development, cellular proliferation, angiogenesis and modify tumor microenvironment (Sofi et al., 2014; Augimeri et al., 2021). This may help explain why MedDiet, composed of food with anti-inflammatory properties as well as other anti-cancer effects, has been associated with decreased risk of cancer

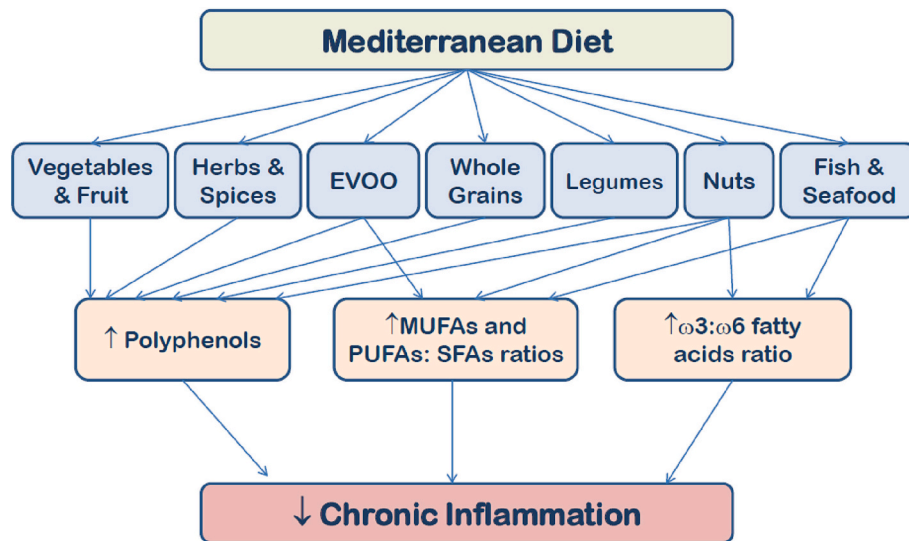


Fig. 4. Food components of the Mediterranean dietary pattern with anti-inflammatory molecules linked to reduced chronic inflammation. EVOO: extravirgin olive oil; MUFAs: monounsaturated fatty acids; PUFAs: polyunsaturated fatty acids; SFAs: saturated fatty acids.

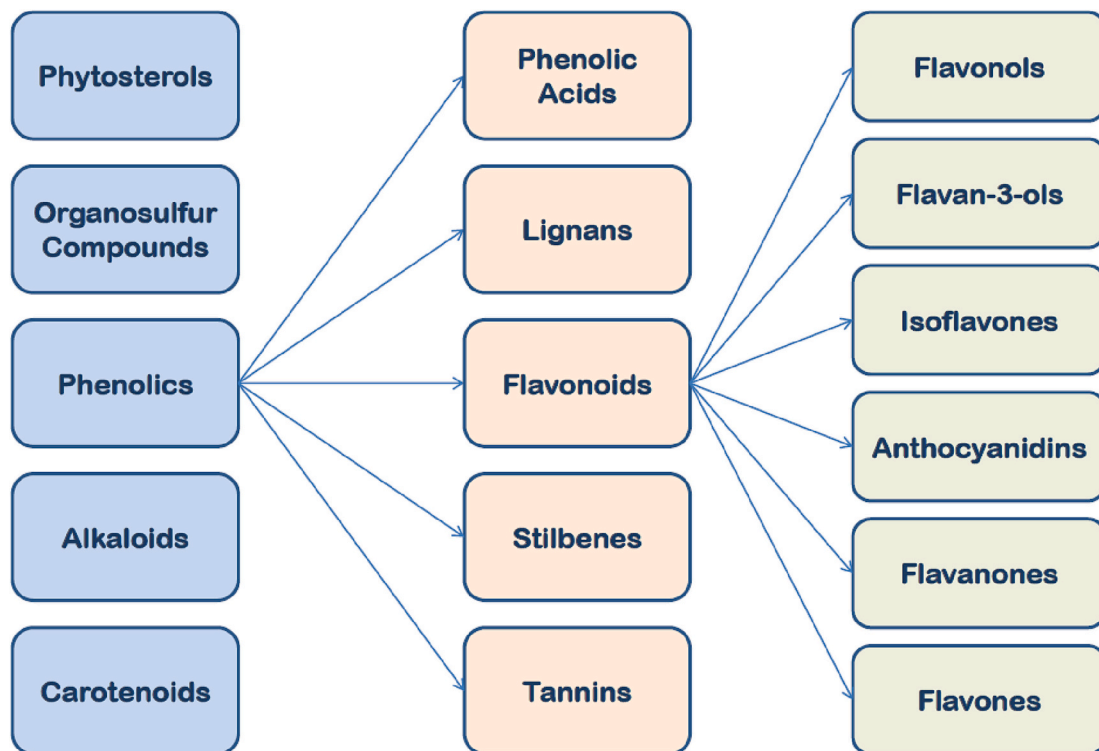


Fig. 5. Phenolic compounds contained in vegetables and fruit, which are some of the main components of the Mediterranean dietary pattern.

(Schwingshackl et al., 2017; Couto et al., 2011; Wu et al., 2009; Murtaugh et al., 2008; Link et al., 2013; Cottet et al., 2009; Bamia et al., 2013; Toledo et al., 2015).

Another key mechanism that can mediate the benefits of MedDiet in obesity and related conditions is the composition of gut microbiota, which appears to play a role in the association of diet and health through metabolites produced by the microbial fermentation of nutrients, particularly the production of short chain fatty acids (SCFAs). Indeed, diet is a major modulator of gut microbiota composition and metabolite production, related to the development of several intestinal and extra-intestinal diseases (Gentile and Weir, 2018; David et al., 2014; Rinninella et al., 2019). Some studies have reported that the MedDiet

produces favorable microbiota composition and SCFAs production (De Filippis et al., 2016; Pastori et al., 2017; Garcia-Mantrana et al., 2018; Merra et al., 2020). Specifically, a higher adherence to the MedDiet was related to an enrichment of Firmicutes and Bacteroidetes and increased fecal SCFAs. Contrariwise, poor adherence to MedDiet was associated with elevated *L-Ruminococcus* and *Streptococcus* bacteria, and higher urinary trimethylamine N-oxide concentrations, a marker of high CVD risk (De Filippis et al., 2016). A study compared the MedDiet with a vegetarian diet in 23 overweight participants showing a significantly higher propionic acid production that was negatively associated with various inflammatory cytokines only in participants following the MedDiet (Pagliari et al., 2020). Analyses from data of the Obekit cohort

found that a higher adherence to MedDiet, as well as a higher consumption of fiber, vegetables, legumes, nuts, and fruit were associated with an increased butyrate-producing taxa (Roses et al., 2021).

A hallmark of MedDiet is its high content of fiber (Schwingshackl et al., 2020; Merra et al., 2020). In fact, the main components of this dietary pattern are fiber-rich, which may help explain its multiple health benefits, including its association with weight loss and with a lower risk of becoming obese. The main sources of dietary fiber, i.e. vegetables, fruit, legumes, whole cereals, and nuts, contain a number of other components with recognized health benefits, such as vitamins, minerals, micronutrients, and phytochemicals with antioxidant and anti-inflammatory actions (Schwingshackl et al., 2020). Therefore, fiber consumption may be considered a marker of a greater inclusion of healthy plant-based foods in a dietary pattern. It has been observed that high dietary fiber intake promotes modifications of gut microbiota in both rodents and humans, with decreased Firmicutes and increased Bacteroidetes, which produces high levels of SCFAs, related with several inflammatory, autoimmune, and allergic diseases (Thorburn et al., 2014).

Perhaps a key mediator to explain the effects of the MedDiet on overweight and obesity is not only given by its components but also by the foods that MedDiet avoids as one of its fundamental characteristics. In fact, a distinctive feature of the Mediterranean dietary pattern is the avoidance of processed and ultraprocessed food consumption, which is typical of westernized diets (Fig. 1). These industrial products are full of calories but poor in nutrients and with very low fiber content, undeniably associated with an increased risk of overweight and obesity (Handakas et al., 2022; Moradi et al., 2023; Mendonca et al., 2016). In fact, not only the food caloric content counts for delineating a healthy diet but also its quality and the preferences and substitutions that are made between the foods that make up the diet.

In a study of 20 young weight-stable adults admitted to a metabolic unit, participants were randomized to receive either ultra-processed or unprocessed diets for 2 weeks immediately followed by the alternate diet for 2 weeks. Meals were equivalent for calorie content, energy density, macronutrients, sugar, sodium, and fiber. Energy intake was significantly greater during the ultra-processed diet (+508 kcal/day), with increased consumption of carbohydrate and fat, but not protein. Weight changes were highly correlated with energy intake, with participants gaining 0.9 kg during the ultra-processed diet and losing 0.9 kg during the unprocessed diet (Hall et al., 2019). Food processing can increase shelf life and palatability, reduce the risk of food-borne pathogens and allow to lower food price. But the downside is that processing also drastically reduces the food content of fiber, polyphenols, minerals, vitamins, and other bioactive compounds. Processing also increases the content of sugar, sodium, and introduces preservatives and additives, trans-fats, and other chemicals, which have been shown to alter microbiota composition (Atzeni et al., 2022; Karl et al., 2022).

Of note, MedDiet beyond the nutritional components also includes many non-dietary lifestyle components, such as regular physical activity, contact with nature, tasty food, and preparing and consuming food in the company of others that can significantly influence weight control and obesity prevention.

9. Challenges and perspectives

There is currently compelling evidence and general agreement that diet has a powerful influence over human health and on numerous diseases. This is particularly true for the pandemic of obesity and T2DM, which are worrisome due to the greater cardiovascular risk they involve, with CVD remaining the first cause of mortality worldwide. There is also accumulated evidence of nutrition research emphasizing priorities to combat these pandemics. The extraordinary impact of health systems and of methods of production, distribution, and consumption of food on the global economy and environmental issues cannot be ignored. Innovative strategies that include interacting multi-sectorial sectors are

needed in order to influence in a relevant way and curve the devastating and unsustainable future consequences of the obesity pandemic. Indeed, overweight and obesity are largely preventable. Supportive environments and communities, including government policies, are crucial in shaping people's choices by making the selection of healthier foods and regular physical activity the ones that are most accessible, available and affordable. Mediterranean lifestyle, which includes nutritional and non-nutritional components, is a paradigm of healthy choices that may help to curve this dreadful future perspective contributing to improve human and planetary health.

10. Conclusions

The obesity pandemic continues to grow worldwide with devastating consequences for people and for health systems, which will not be able to afford the rising costs of obesity-related diseases. There have been controversies raised in the discussion of which of the strategies proposed to control obesity is more effective. Because fats have a higher caloric content compared to carbohydrates, it seems logical to recommend low-fat diets to prevent and treat overweight and obesity as well as their associated health consequences. Yet, this recommendation followed by many nutritional guidelines worldwide has not been effective in counteracting the obesity pandemic that continues to grow. Therefore, the possibility of searching for other strategies not only theoretically more effective, but that are truly applicable and possible to follow by the public should be considered. Diets rich in carbohydrates can also be harmful, especially if they include refined products, sweets and other ultra-processed products instead of vegetables, fruits, and legumes as sources of carbohydrates. The evidence accumulated so far has shown that the effects on weight-loss achieved is similar for low-fat and low-carbohydrate diets in the short-term but that the effects disappear for both in the long-term. The MedDiet is a dietary pattern composed of high-quality foods that has been associated with reduced mortality and lower incidence of several chronic NCDs as well as with similar weight-loss effects as the other approaches. The concern about its moderately high fat content as determinant of eventual weight-gain has been disproved in several studies. Moreover, the PREDIMED and the CORDIPREV trials validated its clear cardiovascular benefit and the absence of weight-gain. Preliminary results from the PREDIMED-plus RCT, still in progress, have shown significant weight control with an energy-restricted MedDiet combined with physical activity. Nevertheless, future analyses of these and other trials are needed to confirm if the effects on weight-loss are lasting and if they are associated with a reduction in CVD.

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Declaration of competing interest

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