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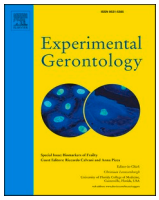

Review

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/m^2) or overweight (BMI >25 kg/m^2). 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 growth 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/m^2 has been associated with near 50 % greater health care expenses owing to the management of obesity-related comorbidities, while a BMI >40 kg/m^2 was associated with 100 % greater healthcare costs (Andreyeva et al., 2004). Another study showed that a BMI >30 kg/m^2 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/m^2, and by about 8 to 10 years for those who maintain a BMI of 40 to 45 kg/m^2 (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 revaluation 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 PREDIMED 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 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 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).

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	• 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.	• 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.	• Carbohydrate: 50–60 % of total energy; total fat: <30 %; protein: 15 %; SFAs <10 %. • Usually, 500–1000 kcals/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	• 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.	• 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.).	• 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

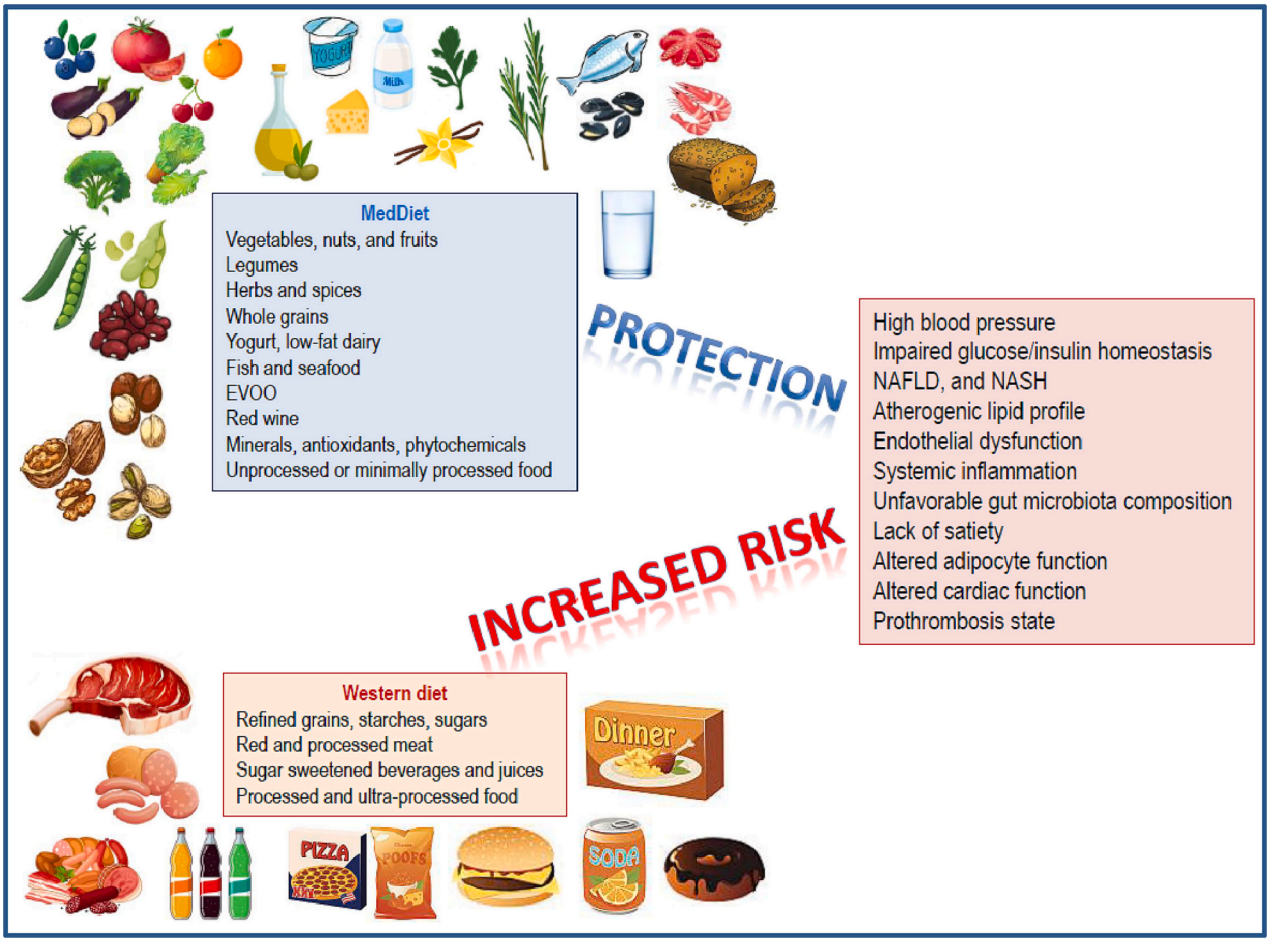

Fig. 1. Different components of Mediterranean and Western diets and their health consequences. EVOO: extravirgin olive oil; NAFLD: non-alcoholic fat liver disease; NASH: non-alcoholic steatohepatitis.

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 (Lotfi 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

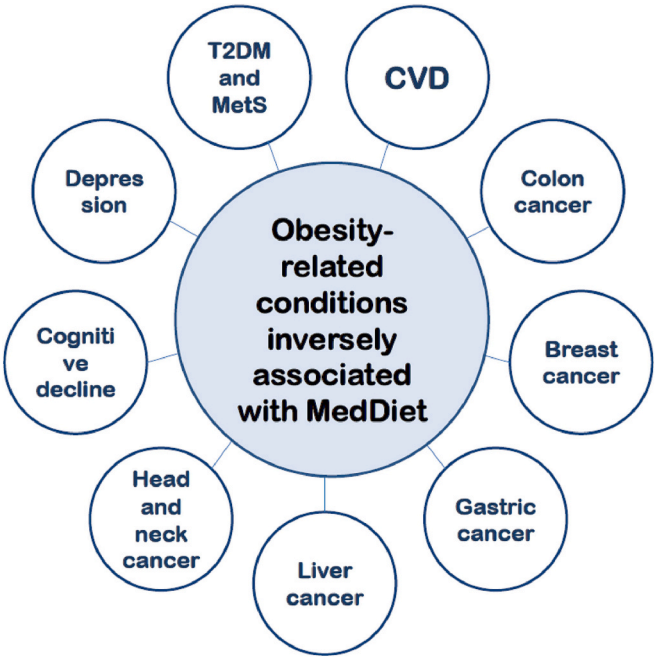

Fig. 2. Non-communicable diseases that have been inversely associated with a higher adherence to the Mediterranean dietary pattern. CVD: cardiovascular disease; MedDiet: Mediterranean diet; MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus.

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; Trichopoulou et al., 2003; Trichopoulou et al., 1995; 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), 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 (Landecho 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 MedDiet that contain anti-inflammatory compounds.

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
• 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

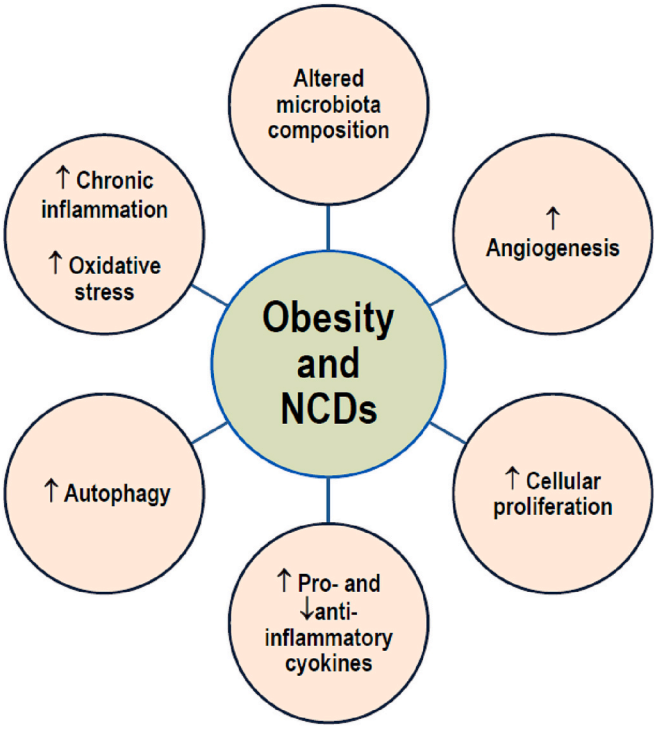

Fig. 3. Some molecular mechanisms associated with reduced inflammation and oxidative stress that may help explain the benefits of Mediterranean dietary pattern on disorders linked to obesity. NCDs: non-communicable diseases.

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

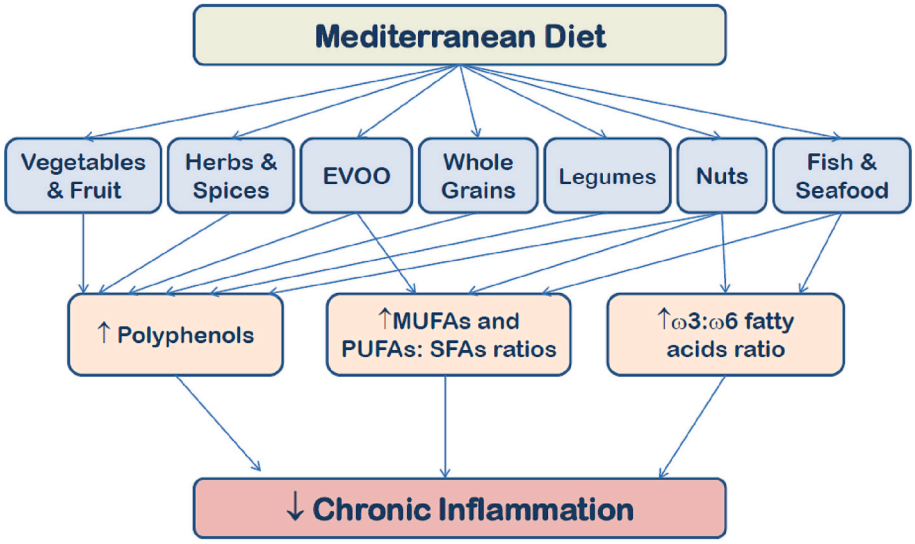

Fig. 4. Food components of the Mediterranean dietary pattern with anti-inflammatory molecules linked to reduced chronic inflammation. EVOO: extravirgin olive oil; MUFAs: monounsaturated fatty acids; PUFAs: polyunsaturated fatty acids; SFAs: saturated fatty acids.

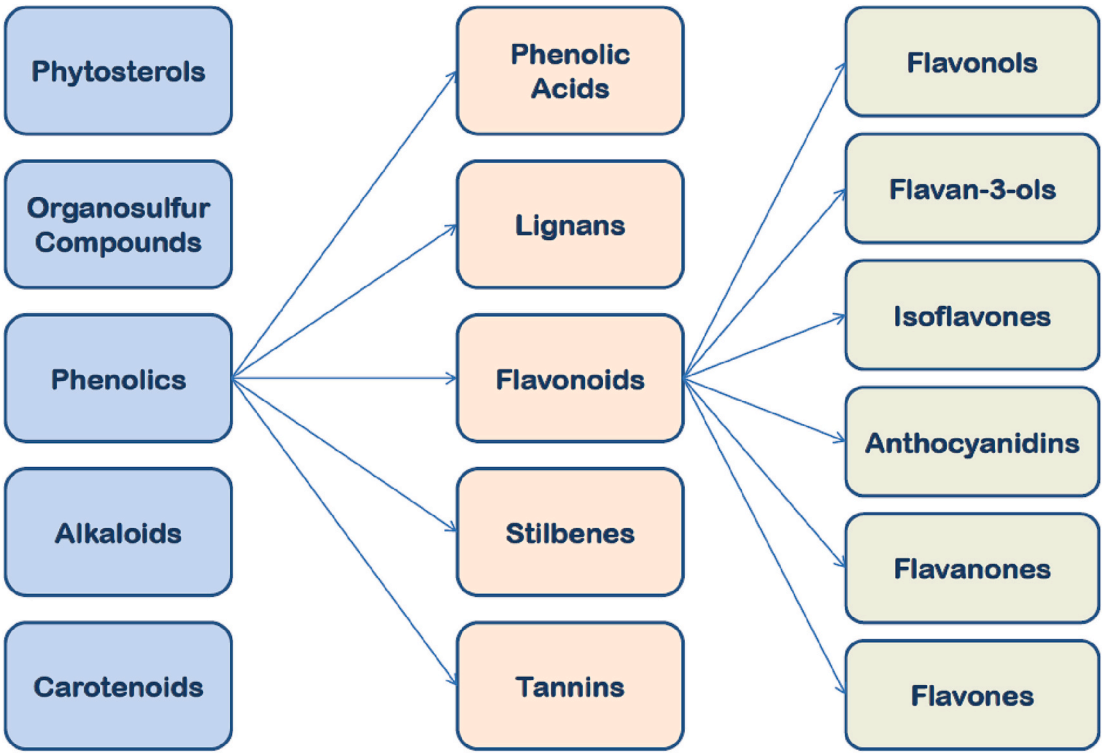

Fig. 5. Phenolic compounds contained in vegetables and fruit, which are some of the main components of the Mediterranean dietary pattern.

(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 (Pagliai 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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Institutional review board statement

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Informed consent statement

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability statement

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References

Ajala, O., English, P., Pinkney, J., 2013. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am. J. Clin. Nutr. 97 (3), 505–516.

Andreyeva, T., Sturm, R., Ringel, J.S., 2004. Moderate and severe obesity have large differences in health care costs. Obes. Res. 12 (12), 1936–1943.

Anstey, K.J., Cherbuin, N., Budge, M., Young, J., 2011. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes. Rev. 12 (5), e426–e437.

Appel, L.J., Van Horn, L., 2013. Did the PREDIMED trial test a Mediterranean diet? N. Engl. J. Med. 368 (14), 1353–1354.

Atzeni, A., Martinez, M.A., Babio, N., Konstanti, P., Tinahones, F.J., Vioque, J., Corella, D., Fito, M., Vidal, J., Moreno-Indias, I., et al., 2022. Association between ultra-processed food consumption and gut microbiota in senior subjects with overweight/obesity and metabolic syndrome. Front. Nutr. 9, 976547.

Augimeri, G., Montalto, F.I., Giordano, C., Barone, I., Lanzino, M., Catalano, S., Ando, S., De Amicis, F., Bonofiglio, D., 2021. Nutraceuticals in the Mediterranean diet: potential avenues for breast cancer treatment. Nutrients 13 (8).

Babio, N., Toledo, E., Estruch, R., Ros, E., Martinez-Gonzalez, M.A., Castaner, O., Bullo, M., Corella, D., Aros, F., Gomez-Gracia, E., et al., 2014. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. CMAJ 186 (17), E649–E657.

Bamia, C., Lagiou, P., Buckland, G., Grioni, S., Agnoli, C., Taylor, A.J., Dahm, C.C., Overvad, K., Olsen, A., Tjonneland, A., et al., 2013. Mediterranean diet and colorectal cancer risk: results from a european cohort. Eur. J. Epidemiol. 28 (4), 317–328.

Banting, W., 1993. Letter on corpulence, addressed to the public. 1869. Obes. Res. 1 (2), 153–163.

Barnard, N.D., Alwarith, J., Rembert, E., Brandon, L., Nguyen, M., Goergen, A., Horne, T., do Nascimento, G.F., Lakkadi, K., Tura, A., 2022. A Mediterranean diet and low-fat vegan diet to improve body weight and cardiometabolic risk factors: a randomized, cross-over trial. J. Am. Nutr. Assoc. 41 (2), 127–139.

Basolo, A., Magno, S., Santini, F., Ceccarini, G., 2022. Ketogenic diet and weight loss: is there an effect on energy expenditure? Nutrients 14 (9).

Bayes, J., Schloss, J., Sibbritt, D., 2022. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND" study): a randomized control trial. Am. J. Clin. Nutr. 116 (2), 572–580.

Beard, J.R., Officer, A., de Carvalho, I.A., Sadana, R., Pot, A.M., Michel, J.P., Lloyd-Sherlock, P., Epping-Jordan, J.E., Peeters, G., Mahanani, W.R., et al., 2016. The world report on ageing and health: a policy framework for healthy ageing. Lancet 387 (10033), 2145–2154.

Beunza, J.J., Toledo, E., Hu, F.B., Bes-Rastrollo, M., Serrano-Martinez, M., Sanchez-Villegas, A., Martinez, J.A., Martinez-Gonzalez, M.A., 2010. Adherence to the Mediterranean diet, long-term weight change, and incident overweight or obesity: the seguimiento Universidad de Navarra (SUN) cohort. Am. J. Clin. Nutr. 92 (6), 1484–1493.

Bonaccio, M., Di Castelnuovo, A., Costanzo, S., Gialluisi, A., Persichillo, M., Cerletti, C., Donati, M.B., de Gaetano, G., Iacoviello, L., 2018. Mediterranean diet and mortality in the elderly: a prospective cohort study and a meta-analysis. Br. J. Nutr. 1–14.

Bonsignore, M.R., 2022. Obesity and obstructive sleep apnea. Handb. Exp. Pharmacol. 274, 181–201.

Boutari, C., Mantzoros, C.S., 2022. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 133, 155217.

Bouzas, C., Bibiloni, M.D.M., Julibert, A., Ruiz-Canela, M., Salas-Salvado, J., Corella, D., Zomeno, M.D., Romaguera, D., Vioque, J., Alonso-Gomez, A.M., et al., 2020. Adherence to the Mediterranean lifestyle and desired body weight loss in a Mediterranean adult population with overweight: a PREDIMED-plus study. Nutrients 12 (7).

Bueno, N.B., de Melo, I.S., de Oliveira, S.L., da Rocha, Ataide T., 2013. Very-low-carbohydrate ketogenic diet v. Low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br. J. Nutr. 110 (7), 1178–1187.

Cao, B., Xu, J., Li, R., Teopiz, K.M., McIntyre, R.S., Chen, H., 2022. Interventions targeting comorbid depression and overweight/obesity: a systematic review. J. Affect. Disord. 314, 222–232.

Carlos, S., De La Fuente-Arrillaga, C., Bes-Rastrollo, M., Razquin, C., Rico-Campa, A., Martinez-Gonzalez, M.A., Ruiz-Canela, M., 2018. Mediterranean diet and health outcomes in the SUN cohort. Nutrients 10 (4).

Chang, V.W., Alley, D.E., Dowd, J.B., 2017. Trends in the relationship between obesity and disability, 1988–2012. Am. J. Epidemiol. 186 (6), 688–695.

Chen, L., Magliano, D.J., Zimmet, P.Z., 2011. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat. Rev. Endocrinol. 8 (4), 228–236.

Cottet, V., Touvier, M., Fournier, A., Touillaud, M.S., Lafay, L., Clavel-Chapelon, F., Boutron-Ruault, M.C., 2009. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. Am. J. Epidemiol. 170 (10), 1257–1267.

Couto, E., Boffetta, P., Lagiou, P., Ferrari, P., Buckland, G., Overvad, K., Dahm, C.C., Tjonneland, A., Olsen, A., Clavel-Chapelon, F., et al., 2011. Mediterranean dietary pattern and cancer risk in the EPIC cohort. Br. J. Cancer 104 (9), 1493–1499.

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., et al., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505 (7484), 559–563.

De Filippis, F., Pellegrini, N., Vannini, L., Jeffery, I.B., La Storia, A., Laghi, L., Serrazanetti, D.I., Di Cagno, R., Ferrocino, I., Lazzi, C., et al., 2016. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut 65 (11), 1812–1821.

Dehghan, M., Mente, A., Zhang, X., Swaminathan, S., Li, W., Mohan, V., Iqbal, R., Kumar, R., Wentzel-Viljoen, E., Rosengren, A., et al., 2017. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 390 (10107), 2050–2062.

Delgado-Lista, J., Alcala-Diaz, J.F., Torres-Pena, J.D., Quintana-Navarro, G.M., Fuentes, F., Garcia-Rios, A., Ortiz-Morales, A.M., Gonzalez-Requero, A.I., Perez-Caballero, A.I., Yubero-Serrano, E.M., et al., 2022. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 399 (10338), 1876–1885.

Dinu, M., Pagliai, G., Casini, A., Sofi, F., 2018. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur. J. Clin. Nutr. 72 (1), 30–43.

Dominguez, L.J., Barbagallo, M., Munoz-Garcia, M., Godos, J., Martinez-Gonzalez, M.A., 2019. Dietary patterns and cognitive decline: key features for prevention. Curr. Pharm. Des. 25 (22), 2428–2442.

Dominguez, L.J., Di Bella, G., Veronese, N., Barbagallo, M., 2021. Impact of Mediterranean diet on chronic non-communicable diseases and longevity. Nutrients 13 (6).

Dominguez, L.J., Veronese, N., Vernuccio, L., Catanese, G., Inzerillo, F., Salemi, G., Barbagallo, M., 2021. Nutrition, physical activity, and other lifestyle factors in the prevention of cognitive decline and dementia. Nutrients 13 (11).

Dominguez, L.J., Veronese, N., Baiamonte, E., Guarrera, M., Parisi, A., Ruffolo, C., Tagliaferri, F., Barbagallo, M., 2022. Healthy aging and dietary patterns. Nutrients 14, 4.

Drewnowski, A., 2018. Nutrient density: addressing the challenge of obesity. Br. J. Nutr. 120 (s1), S8–S14.

Elagizi, A., Kachur, S., Carbone, S., Lavie, C.J., Blair, S.N., 2020. A review of obesity, physical activity, and cardiovascular disease. Curr. Obes. Rep. 9 (4), 571–581.

Esposito, K., Kastorini, C.M., Panagiotakos, D.B., Giugliano, D., 2011. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. Metab. Syndr. Relat. Disord. 9 (1), 1–12.

Esposito, K., Maiorino, M.I., Bellastella, G., Chiodini, P., Panagiotakos, D., Giugliano, D., 2015. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open 5 (8), e008222.

Estruch, R., Ros, E., 2020. The role of the Mediterranean diet on weight loss and obesity-related diseases. Rev. Endocr. Metab. Disord. 21 (3), 315–327.

Estruch, R., Martinez-Gonzalez, M.A., Corella, D., Salas-Salvado, J., Ruiz-Gutierrez, V., Covas, M.I., Fiol, M., Gomez-Gracia, E., Lopez-Sabater, M.C., Vinyoles, E., et al., 2006. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann. Intern. Med. 145 (1), 1–11.

Estruch, R., Ros, E., Salas-Salvado, J., Covas, M.I., Corella, D., Aros, F., Gomez-Gracia, E., Ruiz-Gutierrez, V., Fiol, M., Lapetra, J., et al., 2018. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N. Engl. J. Med. 378 (25), e34.

Estruch, R., Martinez-Gonzalez, M.A., Corella, D., Salas-Salvado, J., Fito, M., Chiva-Blanch, G., Fiol, M., Gomez-Gracia, E., Aros, F., Lapetra, J., et al., 2019. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. Lancet Diabetes Endocrinol. 7 (5), e6–e17.

Fernandez, C.A., Potts, K., Bazzano, L.A., 2022. Effect of ideal protein versus low-fat diet for weight loss: a randomized controlled trial. Obes. Sci. Pract. 8 (3), 299–307.

Fito, M., Guxens, M., Corella, D., Saez, G., Estruch, R., de la Torre, R., Frances, F., Cabezas, C., Lopez-Sabater Mdel, C., Marrugat, J., et al., 2007. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch. Intern. Med. 167 (11), 1195–1203.

Galbete, C., Schwingshackl, L., Schwedhelm, C., Boeing, H., Schulze, M.B., 2018. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: an umbrella review of meta-analyses. Eur. J. Epidemiol. 33 (10), 909–931.

Gan, T., Schaberg, K.B., He, D., Mansour, A., Kapoor, H., Wang, C., Evers, B.M., Bocklage, T.J., 2021. Association between obesity and histological tumor budding in patients with nonmetastatic colon cancer. JAMA Netw. Open 4 (4), e213897.

Garcia-Arellano, A., Martinez-Gonzalez, M.A., Ramallal, R., Salas-Salvado, J., Hebert, J. R., Corella, D., Shivappa, N., Forga, L., Schroder, H., Munoz-Bravo, C., et al., 2019. Dietary inflammatory index and all-cause mortality in large cohorts: the SUN and PREDIMED studies. Clin. Nutr. 38 (3), 1221–1231.

Garcia-Mantrana, I., Selma-Royo, M., Alcantara, C., Collado, M.C., 2018. Shifts on gut microbiota associated to Mediterranean diet adherence and specific dietary intakes on general adult population. Front. Microbiol. 9, 890.

Gardner, C.D., Trepanowski, J.F., Del Gobbo, L.C., Hauser, M.E., Rigdon, J., Ioannidis, J. P.A., Desai, M., King, A.C., 2018. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA 319 (7), 667–679.

Gardner, C.D., Landry, M.J., Perelman, D., Petlura, C., Durand, L.R., Aronica, L., Crimarco, A., Cunanan, K.M., Chang, A., Dant, C.C., et al., 2022. Effect of a ketogenic diet versus Mediterranean diet on glycated hemoglobin in individuals with prediabetes and type 2 diabetes mellitus: the interventional keto-med randomized crossover trial. Am. J. Clin. Nutr. 116 (3), 640–652.

Ge, L., Sadeghirad, B., Ball, G.D.C., da Costa, B.R., Hitchcock, C.L., Svendrovski, A., Kiflen, R., Quadri, K., Kwon, H.Y., Karamouzian, M., et al., 2020. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. BMJ 369, m696.

Gentile, C.L., Weir, T.L., 2018. The gut microbiota at the intersection of diet and human health. Science 362 (6416), 776–780.

Georgoulis, M., Yiannakouris, N., Tenta, R., Fragopoulou, E., Kechribari, I., Lamprou, K., Perraki, E., Vagiakis, E., Kontogianni, M.D., 2021. A weight-loss Mediterranean diet/lifestyle intervention ameliorates inflammation and oxidative stress in patients with obstructive sleep apnea: results of the "MIMOSA" randomized clinical trial. Eur. J. Nutr. 60 (7), 3799–3810.

Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390 (10100), 2017, 1211–1259.

Global, B.M.I.M.C., Di Angelantonio, E., Bhupathiraju, Sh.N., Wormser, D., Gao, P., Kaptoge, S., Berrington de Gonzalez, A., Cairns, B.J., Huxley, R., Jackson, Ch.L., et al., 2016. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 388 (10046), 776–786.

Guasch-Ferre, M., Bullo, M., Martinez-Gonzalez, M.A., Ros, E., Corella, D., Estruch, R., Fito, M., Aros, F., Warnberg, J., Fiol, M., et al., 2013. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med. 11, 164.

Hall, K.D., Chen, K.Y., Guo, J., Lam, Y.Y., Leibel, R.L., Mayer, L.E., Reitman, M.L., Rosenbaum, M., Smith, S.R., Walsh, B.T., et al., 2016. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. Am. J. Clin. Nutr. 104 (2), 324–333.

Hall, K.D., Ayuketah, A., Brychta, R., Cai, H., Cassimatis, T., Chen, K.Y., Chung, S.T., Costa, E., Courville, A., Darcey, V., et al., 2019. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. Cell Metab. 30 (1), 67–77 e63.

Handakas, E., Chang, K., Khandpur, N., Vamos, E.P., Millett, C., Sassi, F., Vineis, P., Robinson, O., 2022. Metabolic profiles of ultra-processed food consumption and their role in obesity risk in british children. Clin. Nutr. 41 (11), 2537–2548.

Hebert, J.R., Shivappa, N., Wirth, M.D., Hussey, J.R., Hurley, T.G., 2019. Perspective: the dietary inflammatory index (DII)-lessons learned, improvements made, and future directions. Adv. Nutr. 10 (2), 185–195.

Hershey, M.S., Sanchez-Villegas, A., Sotos-Prieto, M., Fernandez-Montero, A., Pano, O., Lahortiga-Ramos, F., Martinez-Gonzalez, M.A., Ruiz-Canela, M., 2022. The Mediterranean lifestyle and the risk of depression in middle-aged adults. J. Nutr. 152 (1), 227–234.

Hession, M., Rolland, C., Kulkarni, U., Wise, A., Broom, J., 2009. Systematic review of randomized controlled trials of low-carbohydrate vs. Low-fat/Low-calorie diets in the management of obesity and its comorbidities. Obes. Rev. 10 (1), 36–50.

Hodge, A.M., Bassett, J.K., Dugue, P.A., Shivappa, N., Hebert, J.R., Milne, R.L., English, D.R., Giles, G.G., 2018. Dietary inflammatory index or Mediterranean diet score as risk factors for total and cardiovascular mortality. Nutr. Metab. Cardiovasc. Dis. 28 (5), 461–469.

Hu, T., Mills, K.T., Yao, L., Demanelis, K., Eloustaz, M., Yancy Jr., W.S., Kelly, T.N., He, J., Bazzano, L.A., 2012. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am. J. Epidemiol. 176 (Suppl. 7), S44–S54.

Huo, R., Du, T., Xu, Y., Xu, W., Chen, X., Sun, K., Yu, X., 2015. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. Eur. J. Clin. Nutr. 69 (11), 1200–1208.

Jabbour, J., Rihawi, Y., Khamis, A.M., Ghamlouche, L., Tabban, B., Safadi, G., Hammad, N., Hadla, R., Zeidan, M., Andari, D., et al., 2022. Long term weight loss diets and obesity indices: results of a network meta-analysis. Front. Nutr. 9, 821096.

Jacobs Jr., D.R., Steffen, L.M., 2003. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am. J. Clin. Nutr. 78 (3 Suppl), 508S–513S.

Jacobs, D.R., Tapsell, L.C., 2013. Food synergy: the key to a healthy diet. Proc. Nutr. Soc. 72 (2), 200–206.

Karl, J.P., Armstrong, N.J., Player, R.A., Rood, J.C., Soares, J.W., McClung, H.L., 2022. The fecal metabolome links diet composition, food processing and the gut microbiota to gastrointestinal health in a randomized trial of adults consuming a processed diet. J. Nutr. nxac161 Online ahead of print.

Keys, A., 1995. Mediterranean diet and public health: personal reflections. Am. J. Clin. Nutr. 61 (6 Suppl), 1321S–1323S.

Kjellberg, J., Tange Larsen, A., Ibsen, R., Hojgaard, B., 2017. The socioeconomic burden of obesity. Obes. Facts 10 (5), 493–502.

Knoops, K.T., Groot de, L.C., Fidanza, F., Alberti-Fidanza, A., Kromhout, D., van Staveren, W.A., 2006. Comparison of three different dietary scores in relation to 10-year mortality in elderly european subjects: the HALE project. Eur. J. Clin. Nutr. 60 (6), 746–755.

Knowler, W.C., Barrett-Connor, E., Fowler, S.E., Hamman, R.F., Lachin, J.M., Walker, E. A., Nathan, D.M., 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N. Engl. J. Med. 346 (6), 393–403.

Konieczna, J., Romaguera, D., Pereira, V., Fiol, M., Razquin, C., Estruch, R., Asensio, E. M., Babio, N., Fito, M., Gomez-Gracia, E., et al., 2019. Longitudinal association of changes in diet with changes in body weight and waist circumference in subjects at high cardiovascular risk: the PREDIMED trial. Int. J. Behav. Nutr. Phys. Act. 16 (1), 139.

Kouris-Blazos, A., Gnardellis, C., Wahlqvist, M.L., Trichopoulos, D., Lukito, W., Trichopoulou, A., 1999. Are the advantages of the Mediterranean diet transferable to other populations? A cohort study in Melbourne, Australia. Br. J. Nutr. 82 (1), 57–61.

Kovesdy, C.P., Furth, S.L., Zoccali, C., 2017. Obesity and kidney disease: hidden consequences of the epidemic. Pediatr. Nephrol. 32 (4), 537–545.

Kuang, M., Lu, S., Xie, Q., Peng, N., He, S., Yu, C., Qiu, J., Sheng, G., Zou, Y., 2022. Abdominal obesity phenotypes are associated with the risk of developing non-alcoholic fatty liver disease: insights from the general population. BMC Gastroenterol. 22 (1), 311.

Lai, J.S., Hiles, S., Bisquera, A., Hure, A.J., McEvoy, M., Attia, J., 2014. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am. J. Clin. Nutr. 99 (1), 181–197.

Landecho, M.F., Tuero, C., Valenti, V., Bilbao, I., de la Higuera, M., Fruhbeck, G., 2019. Relevance of leptin and other adipokines in obesity-associated cardiovascular risk. Nutrients 11 (11).

Larsson, S.C., Wolk, A., 2007. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am. J. Clin. Nutr. 86 (3), 556–565.

Lasheras, C., Fernandez, S., Patterson, A.M., 2000. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. Am. J. Clin. Nutr. 71 (4), 987–992.

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., Straif, K., 2016. Body fatness and cancer-viewpoint of the IARC working group. N. Engl. J. Med. 375 (8), 794–798.

Lean, M., 2011. VLED and formula LED in the management of type 2 diabetes: defining the clinical need and research requirements. Clin. Obes. 1 (1), 41–49.

Limongelli, G., Monda, E., D'Aponte, A., Caiazza, M., Rubino, M., Esposito, A., Palmiero, G., Moscarella, E., Messina, G., Calabro, P., et al., 2021. Combined effect of Mediterranean diet and aerobic exercise on weight loss and clinical status in obese symptomatic patients with hypertrophic cardiomyopathy. Heart Fail. Clin. 17 (2), 303–313.

Lin, L., Bai, S., Qin, K., Wong, C.K.H., Wu, T., Chen, D., Lu, C., Chen, W., Guo, V.Y., 2022. Comorbid depression and obesity, and its transition on the risk of functional disability among middle-aged and older chinese: a cohort study. BMC Geriatr. 22 (1), 275.

Link, L.B., Canchola, A.J., Bernstein, L., Clarke, C.A., Stram, D.O., Ursin, G., Horn-Ross, P.L., 2013. Dietary patterns and breast cancer risk in the California teachers study cohort. Am. J. Clin. Nutr. 98 (6), 1524–1532.

Lohmann, A.E., Soldera, S.V., Pimentel, I., Ribnikar, D., Ennis, M., Amir, E., Goodwin, P. J., 2021. Association of Obesity with Breast Cancer Outcome in relation to cancer subtypes: a meta-analysis. J. Natl. Cancer Inst. 113 (11), 1465–1475.

de Lorgeril, M., Renaud, S., Mamelle, N., Salen, P., Martin, J.L., Monjaud, I., Guidollet, J., Touboul, P., Delaye, J., 1994. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 343 (8911), 1454–1459.

Lotfi, K., Saneei, P., Hajhashemy, Z., Esmaillzadeh, A., 2022. Adherence to the Mediterranean diet, five-year weight change, and risk of overweight and obesity: a systematic review and dose-response meta-analysis of prospective cohort studies. Adv. Nutr. 13 (1), 152–166.

Ludwig, D.S., 2016. Lowering the Bar on the low-fat diet. JAMA 316 (20), 2087–2088.

Mancini, J.G., Filion, K.B., Atallah, R., Eisenberg, M.J., 2016. Systematic review of the Mediterranean diet for long-term weight loss. Am. J. Med. 129 (4), 407–415 e404.

Martinez-Gonzalez, M.A., Bes-Rastrollo, M., 2014. Dietary patterns, Mediterranean diet, and cardiovascular disease. Curr. Opin. Lipidol. 25 (1), 20–26.

Martinez-Gonzalez, M.A., de la Fuente-Arrillaga, C., Nunez-Cordoba, J.M., Basterra-Gortari, F.J., Beunza, J.J., Vazquez, Z., Benito, S., Tortosa, A., Bes-Rastrollo, M., 2008. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ 336 (7657), 1348–1351.

Martinez-Gonzalez, M.A., Garcia-Arellano, A., Toledo, E., Salas-Salvado, J., Buil-Cosiales, P., Corella, D., Covas, M.I., Schroder, H., Aros, F., Gomez-Gracia, E., et al., 2012. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS One 7 (8), e43134.

Martinez-Gonzalez, M.A., Salas-Salvado, J., Estruch, R., Corella, D., Fito, M., Ros, E., 2015. Benefits of the Mediterranean diet: insights from the PREDIMED study. Prog. Cardiovasc. Dis. 58 (1), 50–60.

Martinez-Gonzalez, M.A., Gea, A., Ruiz-Canela, M., 2019. The Mediterranean diet and cardiovascular health. Circ. Res. 124 (5), 779–798.

Martinez-Gonzalez, M.A., Buil-Cosiales, P., Corella, D., Bullo, M., Fito, M., Vioque, J., Romaguera, D., Martinez, J.A., Warnberg, J., Lopez-Miranda, J., et al., 2019. Cohort profile: design and methods of the PREDIMED-plus randomized trial. Int. J. Epidemiol. 48 (2), 387–388o.

Mendez, M.A., Popkin, B.M., Jakszyn, P., Berenguer, A., Tormo, M.J., Sanchez, M.J., Quiros, J.R., Pera, G., Navarro, C., Martinez, C., et al., 2006. Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity. J. Nutr. 136 (11), 2934–2938.

Mendonca, R.D., Pimenta, A.M., Gea, A., de la Fuente-Arrillaga, C., Martinez-Gonzalez, M.A., Lopes, A.C., Bes-Rastrollo, M., 2016. Ultraprocessed food consumption and risk of overweight and obesity: the University of Navarra Follow-up (SUN) cohort study. Am. J. Clin. Nutr. 104 (5), 1433–1440.

Mente, A., de Koning, L., Shannon, H.S., Anand, S.S., 2009. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch. Intern. Med. 169 (7), 659–669.

Merra, G., Noce, A., Marrone, G., Cintoni, M., Tarsitano, M.G., Capacci, A., De Lorenzo, A., 2020. Influence of Mediterranean diet on human gut microbiota. Nutrients 13 (1).

Mitrou, P.N., Kipnis, V., Thiebaut, A.C., Reedy, J., Subar, A.F., Wirfalt, E., Flood, A., Mouw, T., Hollenbeck, A.R., Leitzmann, M.F., et al., 2007. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP diet and health study. Arch. Intern. Med. 167 (22), 2461–2468.

Moradi, S., Entezari, M.H., Mohammadi, H., Jayedi, A., Lazaridi, A.V., Kermani, M.A.H., Miraghajani, M., 2023. Ultra-processed food consumption and adult obesity risk: a systematic review and dose-response meta-analysis. Crit. Rev. Food Sci. Nutr. 63 (2), 249–260.

Murtaugh, M.A., Sweeney, C., Giuliano, A.R., Herrick, J.S., Hines, L., Byers, T., Baumgartner, K.B., Slattery, M.L., 2008. Diet patterns and breast cancer risk in hispanic and non-hispanic white women: the four-corners breast cancer study. Am. J. Clin. Nutr. 87 (4), 978–984.

Namkoong, S., Cho, C.S., Semple, I., Lee, J.H., 2018. Autophagy dysregulation and obesity-associated pathologies. Mol. Cells 41 (1), 3–10.
Nguyen, T.V., Arisawa, K., Katsuura-Kamano, S., Ishizu, M., Nagayoshi, M., Okada, R., Hishida, A., Tamura, T., Hara, M., Tanaka, K., et al., 2022. Associations of metabolic syndrome and metabolically unhealthy obesity with cancer mortality: the Japan multi-institutional collaborative cohort (J-MICC) study. PLoS One 17 (7), e0269550.
Noad, R.L., Rooney, C., McCall, D., Young, I.S., McCance, D., McKinley, M.C., Woodside, J.V., McKeown, P.P., 2016. Beneficial effect of a polyphenol-rich diet on cardiovascular risk: a randomised control trial. Heart 102 (17), 1371–1379.
Nordmann, A.J., Nordmann, A., Briel, M., Keller, U., Yancy Jr., W.S., Brehm, B.J., Bucher, H.C., 2006. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch. Intern. Med. 166 (3), 285–293.
Obert, J., Pearlman, M., Obert, L., Chapin, S., 2017. Popular weight loss strategies: a review of four weight loss techniques. Curr. Gastroenterol. Rep. 19 (12), 61.
Osler, M., Schroll, M., 1997. Diet and mortality in a cohort of elderly people in a north european community. Int. J. Epidemiol. 26 (1), 155–159.
Osorio-Conles, O., Olbeyra, R., Moize, V., Ibarzabal, A., Giro, O., Viaplana, J., Jimenez, A., Vidal, J., de Hollanda, A., 2022. Positive effects of a Mediterranean diet supplemented with almonds on female adipose tissue biology in severe obesity. Nutrients 14 (13).
Pagliai, G., Russo, E., Niccolai, E., Dinu, M., Di Pilato, V., Magrini, A., Bartolucci, G., Baldi, S., Menicatti, M., Giusti, B., et al., 2020. Influence of a 3-month low-calorie Mediterranean diet compared to the vegetarian diet on human gut microbiota and SCFA: the CARDIVEG study. Eur. J. Nutr. 59 (5), 2011–2024.
Pastori, D., Carnevale, R., Nocella, C., Novo, M., Santulli, M., Cammisotto, V., Menichelli, D., Pignatelli, P., Violi, F., 2017. Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular events in atrial fibrillation: effect of adherence to Mediterranean diet. J. Am. Heart Assoc. 6 (6).
Pinto, X., Fanlo-Maresma, M., Corbella, E., Corbella, X., Mitjavila, M.T., Moreno, J.J., Casas, R., Estruch, R., Corella, D., Bullo, M., et al., 2019. A Mediterranean diet rich in extra-virgin olive oil is associated with a reduced prevalence of nonalcoholic fatty liver disease in older individuals at high cardiovascular risk. J. Nutr. 149 (11), 1920–1929.
Popkin, B.M., 2006. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. Am. J. Clin. Nutr. 84 (2), 289–298.
Pounis, G., Costanzo, S., Bonaccio, M., Di Castelnuovo, A., de Curtis, A., Ruggiero, E., Persichillo, M., Cerletti, C., Donati, M.B., de Gaetano, G., et al., 2018. Reduced mortality risk by a polyphenol-rich diet: an analysis from the moli-sani study. Nutrition 48, 87–95.
Purcell, S., Hossain, I., Evans, B., Porter, G., Richardson, G., Ellsmere, J., 2022. Morbid obesity and severe knee osteoarthritis: which should be treated First? J. Gastrointest. Surg. 26 (7), 1388–1393.
QuickStats: prevalence of obesity* and severe obesity(dagger) among persons aged 2-19 years - National Health and Nutrition Examination Survey, 1999-2000 through 2017-2018. MMWR Morb. Mortal. Wkly Rep. 69 (13), 2020, 390.
Ramallal, R., Toledo, E., Martinez-Gonzalez, M.A., Hernandez-Hernandez, A., Garcia-Arellano, A., Shivappa, N., Hebert, J.R., Ruiz-Canela, M., 2015. Dietary inflammatory index and incidence of cardiovascular disease in the SUN cohort. PLoS One 10 (9), e0135221.
Razquin, C., Sanchez-Tainta, A., Salas-Salvado, J., Buil-Cosiales, P., Corella, D., Fito, M., Ros, E., Estruch, R., Aros, F., Gomez-Gracia, E., et al., 2017. Dietary energy density and body weight changes after 3 years in the PREDIMED study. Int. J. Food Sci. Nutr. 68 (7), 865–872.
Reynolds, A., Mann, J., Cummings, J., Winter, N., Mete, E., Te Morenga, L., 2019. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 393 (10170), 434–445.
Rinninella, E., Cintoni, M., Raoul, P., Lopetuso, L.R., Scaldaferri, F., Pulcini, G., Miggiano, G.A.D., Gasbarrini, A., Mele, M.C., 2019. Food components and dietary habits: keys for a healthy gut microbiota composition. Nutrients 11 (10).
Romaguera, D., Norat, T., Vergnaud, A.C., Mouw, T., May, A.M., Agudo, A., Buckland, G., Slimani, N., Rinaldi, S., Couto, E., et al., 2010. Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. Am. J. Clin. Nutr. 92 (4), 912–921.
Roncero-Ramos, I., Alcala-Diaz, J.F., Rangel-Zuniga, O.A., Gomez-Delgado, F., Jimenez-Lucena, R., Garcia-Rios, A., Vals-Delgado, C., Romero-Baldonado, C., Luque, R.M., Ordovas, J.M., et al., 2020. Prediabetes diagnosis criteria, type 2 diabetes risk and dietary modulation: the CORDIOPREV study. Clin. Nutr. 39 (2), 492–500.
Roses, C., Cuevas-Sierra, A., Quintana, S., Riezu-Boj, J.I., Martinez, J.A., Milagro, F.I., Barcelo, A., 2021. Gut microbiota bacterial species associated with Mediterranean diet-related food groups in a northern spanish population. Nutrients 13 (2).
Rosi, A., Tesan, M., Cremonini, A., Biasini, B., Bicchieri, L., Cossu, M., Brighenti, F., Dall'Aglio, E., Scazzina, F., 2020. Body weight of individuals with obesity decreases after a 6-month high pasta or low pasta Mediterranean diet weight-loss intervention. Nutr. Metab. Cardiovasc. Dis. 30 (6), 984–995.
Rossi, M., Turati, F., Lagiou, P., Trichopoulos, D., Augustin, L.S., La Vecchia, C., Trichopoulou, A., 2013. Mediterranean diet and glycaemic load in relation to incidence of type 2 diabetes: results from the greek cohort of the population-based european prospective investigation into cancer and nutrition (EPIC). Diabetologia 56 (11), 2405–2413.
Rumbo-Rodriguez, L., Zaragoza-Marti, A., Sanchez-SanSegundo, M., Ferrer-Cascales, R., Laguna-Perez, A., Hurtado-Sanchez, J.A., 2022. Effectiveness of a two-year multicomponent intervention for the treatment of overweight and obesity in older people. Nutrients 14 (22).
Salas-Salvado, J., Bullo, M., Estruch, R., Ros, E., Covas, M.I., Ibarrola-Jurado, N., Corella, D., Aros, F., Gomez-Gracia, E., Ruiz-Gutierrez, V., et al., 2014. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann. Intern. Med. 160 (1), 1–10.
Salas-Salvado, J., Diaz-Lopez, A., Ruiz-Canela, M., Basora, J., Fito, M., Corella, D., Serra-Majem, L., Warnberg, J., Romaguera, D., Estruch, R., et al., 2019. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-plus trial. Diabetes Care 42 (5), 777–788.
Sayon-Orea, C., Razquin, C., Bullo, M., Corella, D., Fito, M., Romaguera, D., Vioque, J., Alonso-Gomez, A.M., Warnberg, J., Martinez, J.A., et al., 2019. Effect of a nutritional and behavioral intervention on energy-reduced Mediterranean diet adherence among patients with metabolic syndrome: interim analysis of the PREDIMED-plus randomized clinical trial. JAMA 322 (15), 1486–1499.
Schwarzfuchs, D., Golan, R., Shai, I., 2012. Four-year follow-up after two-year dietary interventions. N. Engl. J. Med. 367 (14), 1373–1374.
Schwingshackl, L., Missbach, B., Konig, J., Hoffmann, G., 2015. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. Public Health Nutr. 18 (7), 1292–1299.
Schwingshackl, L., Schwedhelm, C., Galbete, C., Hoffmann, G., 2017. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. Nutrients 9 (10).
Schwingshackl, L., Morze, J., Hoffmann, G., 2020. Mediterranean diet and health status: active ingredients and pharmacological mechanisms. Br. J. Pharmacol. 177 (6), 1241–1257.
Shai, I., Schwarzfuchs, D., Henkin, Y., Shahar, D.R., Witkow, S., Greenberg, I., Golan, R., Fraser, D., Bolotin, A., Vardi, H., et al., 2008. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N. Engl. J. Med. 359 (3), 229–241.
Singh, B., Parsaik, A.K., Mielke, M.M., Erwin, P.J., Knopman, D.S., Petersen, R.C., Roberts, R.O., 2014. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J. Alzheimers Dis. 39 (2), 271–282.
Slomski, A., 2022. Obesity is now the top modifiable dementia risk factor in the US. JAMA 328 (1), 10.
Sofi, F., Macchi, C., Abbate, R., Gensini, G.F., Casini, A., 2014. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 17 (12), 2769–2782.
Springmann, M., Godfray, H.C., Rayner, M., Scarborough, P., 2016. Analysis and valuation of the health and climate change cobenefits of dietary change. Proc. Natl. Acad. Sci. U. S. A. 113 (15), 4146–4151.
Steffen, W., Richardson, K., Rockstrom, J., Cornell, S.E., Fetzer, I., Bennett, E.M., Biggs, R., Carpenter, S.R., de Vries, W., de Wit, C.A., et al., 2015. Sustainability. Planetary boundaries: guiding human development on a changing planet. Science 347 (6223), 1259855.
Taftian, M., Beigrezaei, S., Arabi, V., Salehi-Abargouei, A., 2022. The effect of ketogenic diet on weight loss in adult patients with cancer: a systematic review and meta-analysis of controlled clinical trials. Nutr. Cancer 74 (4), 1222–1234.
Tang, A., Ng, C.H., Phang, P.H., Chan, K.E., Chin, Y.H., Fu, C.E., Zeng, R.W., Xiao, J., Hao Tan, D.J., Quek, J., 2022. Comparative burden of metabolic dysfunction in lean NAFLD vs. non-lean NAFLD - a systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. S1542-3565(22)00669-3.
Theel, W., Boxma-de Klerk, B.M., Dirksmeier-Harinck, F., van Rossum, E.F.C., Kanhai, D. A., Apers, J., van Dalen, B.M., de Knegt, R.J., Holleboom, A.G., Tushuizen, M.E., et al., 2022. Evaluation of nonalcoholic fatty liver disease (NAFLD) in severe obesity using noninvasive tests and imaging techniques. Obes. Rev. 23 (8), e13481.
Thorburn, A.N., Macia, L., Mackay, C.R., 2014. Diet, metabolites, and "western-lifestyle" inflammatory diseases. Immunity 40 (6), 833–842.
Tilman, D., Clark, M., 2014. Global diets link environmental sustainability and human health. Nature 515 (7528), 518–522.
Toledo, E., Salas-Salvado, J., Donat-Vargas, C., Buil-Cosiales, P., Estruch, R., Ros, E., Corella, D., Fito, M., Hu, F.B., Aros, F., et al., 2015. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern. Med. 175 (11), 1752–1760.
Tresserra-Rimbau, A., Rimm, E.B., Medina-Remon, A., Martinez-Gonzalez, M.A., Lopez-Sabater, M.C., Covas, M.I., Corella, D., Salas-Salvado, J., Gomez-Gracia, E., Lapetra, J., et al., 2014. Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial. BMC Med. 12, 77.
Trichopoulou, A., Kouris-Blazos, A., Wahlqvist, M.L., Gnardellis, C., Lagiou, P., Polychronopoulos, E., Vassilakou, T., Lipworth, L., Trichopoulos, D., 1995. Diet and overall survival in elderly people. BMJ 311 (7018), 1457–1460.
Trichopoulou, A., Costacou, T., Bamia, C., Trichopoulos, D., 2003. Adherence to a Mediterranean diet and survival in a greek population. N. Engl. J. Med. 348 (26), 2599–2608.
Tuomilehto, J., Lindstrom, J., Eriksson, J.G., Valle, T.T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., et al., 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N. Engl. J. Med. 344 (18), 1343–1350.
Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., de la Torre, R., Martinez-Gonzalez, M.A., Martinez-Lapiscina, E.H., Fito, M., Perez-Heras, A., Salas-Salvado, J., et al., 2015. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern. Med. 175 (7), 1094–1103.
Verma, S., Hussain, M.E., 2017. Obesity and diabetes: an update. Diabetes Metab. Syndr. 11 (1), 73–79.
Vilar-Compte, M., Burrola-Mendez, S., Lozano-Marrufo, A., Ferre-Eguiluz, I., Flores, D., Gaitan-Rossi, P., Teruel, G., Perez-Escamilla, R., 2021. Urban poverty and nutrition challenges associated with accessibility to a healthy diet: a global systematic literature review. Int. J. Equity Health 20 (1), 40.

Whitlock, G., Lewington, S., Sherliker, P., Clarke, R., Emberson, J., Halsey, J., Qizilbash, N., Collins, R., Peto, R., 2009. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 373 (9669), 1083–1096.

Whitmee, S., Haines, A., Beyrer, C., Boltz, F., Capon, A.G., de Souza Dias, B.F., Ezeh, A., Frumkin, H., Gong, P., Head, P., et al., 2015. Safeguarding human health in the anthropocene epoch: report of the Rockefeller Foundation-lancet commission on planetary health. Lancet 386 (10007), 1973–2028.

Willett, W., Rockstrom, J., Loken, B., Springmann, M., Lang, T., Vermeulen, S., Garnett, T., Tilman, D., DeClerck, F., Wood, A., et al., 2019. Food in the anthropocene: the EAT-lancet commission on healthy diets from sustainable food systems. Lancet 393 (10170), 447–492.

Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 387 (10027), 2016, 1513–1530.

Wormser, D., Kaptoge, S., Di Angelantonio, E., Wood, A.M., Pennells, L., Thompson, A., Sarwar, N., Kizer, J.R., Lawlor, D.A., Nordestgaard, B.G., et al., 2011. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 377 (9771), 1085–1095.

Wu, A.H., Yu, M.C., Tseng, C.C., Stanczyk, F.Z., Pike, M.C., 2009. Dietary patterns and breast cancer risk in asian american women. Am. J. Clin. Nutr. 89 (4), 1145–1154.

Yuan, W., Lu, W., Wang, H., Wu, W., Zhou, Q., Chen, Y., Lee, Y.K., Zhao, J., Zhang, H., Chen, W., 2022. A multiphase dietetic protocol incorporating an improved ketogenic diet enhances weight loss and alters the gut microbiome of obese people. Int. J. Food Sci. Nutr. 73 (2), 238–250.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., et al., 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364 (9438), 937–952.

Zeraattalab-Motlagh, S., Jayedi, A., Shab-Bidar, S., 2022. Mediterranean dietary pattern and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective cohort studies. Eur. J. Nutr. 61 (4), 1735–1748.

Intake of total polyphenols and some classes of polyphenols is inversely associated with diabetes in elderly people at high cardiovascular disease risk. J. Nutr. 146 (4), 2015, 767–777.