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The Mediterranean diet and health: a comprehensive overview

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Abstract. The Mediterranean diet (MedDiet), one of the most studied and well-known dietary patterns worldwide, has been associated with a wide range of benefits for health. In the present narrative review, we aimed to provide a comprehensive overview of the current knowledge on the relation of the MedDiet to important health outcomes, considering both observational and intervention studies with both risk factors and clinical diseases as outcomes. In addition, we considered the clinical and public health impacts of the MedDiet on both human and planetary health. Earlier research confirmed by recent studies has provided strong evidence for the benefits of the MedDiet on cardiovascular health, including reduction in the incidence of cardiovascular outcomes as well as risk factors including obesity, hypertension, metabolic syndrome, and dyslipidaemia. There is also evidence that MedDiet is associated with lower rates of incident diabetes, and better glycaemic control in diabetic patients compared to control diets. In prospective studies, adherence to the MedDiet reduced mortality, especially cardiovascular mortality, hence increased longevity. In addition, it has been associated with less age-related cognitive dysfunction and lower incidence of neurodegenerative disorders, particularly Alzheimer's disease. Furthermore, the relatively low environmental impacts (water, nitrogen and carbon footprint) of the MedDiet is an additional positive aspect of the Mediterranean dietary model. It is likely that the combination of a healthy diet with social behaviours and the way of life of Mediterranean regions makes the MedDiet a sustainable lifestyle model that could likely be followed in other regions with country-specific and culturally appropriate variations.

Keywords: cancer, cardiovascular disease, chronic diseases, health, mediterranean diet, neurodegenerative diseases.

Introduction: The Mediterranean diet concept and definition

The Mediterranean diet (MedDiet), the term that was coined by Ancel keys back in 1960 [1], is one of the most studied and well-known dietary patterns worldwide. The origins of the traditional MedDiet pattern are found in civilizations surrounding the Mediterranean Sea, so that this pattern has been closely associated with the social behaviours and lifestyles of that region. The MedDiet has been recognized by UNESCO as an intangible cultural heritage that is deeply rooted into its geographical origin and whose agricultural and dietary practices have a responsible interaction with the environment.

Descriptions of the traditional MedDiet have reflected food patterns typical of Crete, much of the rest of Greece and southern Italy in the early 1960s [2]. Variations of the MedDiet exist but have been less well described in other parts of Italy, France, Lebanon, Morocco, Portugal, Spain, Tunisia, Turkey and elsewhere in the Mediterranean region. The MedDiet is most closely tied to traditional areas of olive cultivation in the Mediterranean region and has historically been associated with low rates of chronic diseases and high adult life expectancy [2], even though shifts in diets and lifestyles over recent decades have blurred these relationships. The traditional MedDiet is characterized by a high intake of plant foods (fruits, vegetables, breads and other cereals (traditionally minimally refined), potatoes, beans, nuts and seeds); minimally processed, seasonally fresh and locally grown foods; fresh fruits as typical dessert, with sweets containing sugars or honey a few times

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per week; a high intake of olive oil (especially virgin and extra-virgin olive oil) used as the principal source of fat; a moderate intake of dairy products (mostly as cheese and yoghurt); zero to four eggs a week; fish and poultry consumed in low to moderate amounts; red meat consumed in low amounts; and wine in moderation, consumed with meals. The relatively high intake of nuts, olive oil and moderate intake of wine, particularly red wine during meals, makes the MedDiet unique and different from the other healthy diet patterns, but it can be considered a primarily plant-based diet [2] (Fig. 1). Individual foods and components of the MedDiet (e.g. extra-virgin olive oil and nuts) have well-documented health benefits [3,4], but in recent years special attention has been given to the overall combination of foods, expressed as a dietary pattern, that may be most strongly related to health due to the additive or synergistic effects of the components. Variations of Mediterranean dietary patterns have existed around the Mediterranean region with plant foods at the centre of the plate and olive oil as the primary fat being constant components. For example, couscous, vegetables and legumes have been important in North Africa; and pasta, polenta, rice or potatoes along with vegetables and legumes have been prominent in southern Europe, among others [2]. In some cultures, alcoholic beverages would not be included. A key issue is whether the benefits of the MedDiet pattern can be generalized to populations outside the Mediterranean region. In these populations, the consumption of olive oil has usually been low, so this part of the definition has usually been broadened to include other largely unsaturated plant oils, and the diets have often called 'Mediterranean-type' dietary patterns.

The first scientific evidence indicating the health benefits of the MedDiet came from the seminal report, led by Keys and colleagues, called the Seven Countries Study [1]. These investigators documented incidence and mortality due to cardiovascular disease (CVD) among men using standardized criteria in 14 areas of seven different countries from the Mediterranean region. Dietary data were collected on a subset of these participants. Large differences in rates of CVD were found, and the ecological correlations based on the 14 data points suggested that saturated fat, but not other types of fat, was strongly associated with risk of CVD [1]. However, because of the design of this ecological study, these observations were potentially confounded by many other dietary, lifestyle and environmental variables, and more detailed research was needed. Over the years, many important intervention trials and prospective cohort studies have been conducted to evaluate the effects of MedDiet on numerous health outcomes, as summarized in several systematic reviews and meta-analysis [5-7]. The most consistent and robust evidence for the health benefits of the MedDiet has been observed for cardiovascular risk factors and CVD incidence [5,8], but a large body of the literature also demonstrated potential benefits of MedDiet for a wide range of other health outcomes, including type 2 diabetes (T2D), metabolic syndrome (MetS), obesity, cancer, cognitive decline and CVD mortality, among others.

In the present review, we aim to provide a comprehensive overview of the current knowledge on the relation of the MedDiet to important health outcomes, considering both observational and intervention studies with both risk factors and clinical diseases as outcomes. In addition, we consider the clinical and public health impacts of the MedDiet on both human and planetary health.

Evidence on Mediterranean diet in observational studies

The associations between the adherence to the MedDiet and health have been examined in many case–control and prospective cohort studies. Due to the potential bias in case–control studies and the availability of large prospective cohort studies on this topic, we will be focusing mainly on the latter in this review.

Most of the observational studies calculated MedDiet scores by using *a priori* dietary patterns. One of the most commonly employed scores was proposed by Trichopoulou et al (1995) known as the Mediterranean Diet Score (MDS), which included nine components. One point was assigned for intakes of 'healthy foods' above the sex-specific median (vegetables, fruits/nuts, legumes, fish/seafood, cereals and monounsaturated to saturated lipid ratio), and one point was assigned for intakes below median for meat and dairy products; for alcoholic beverages, 1 point was assigned for moderate intake [9]. Another frequently used dietary pattern to assess adherence is the alternate Mediterranean diet (aMED) [10]. This pattern also includes 9 food groups and classifies participants according to their intake (above or below the cohort-specific median levels), but in this case, a broader definition of fat quality was used.

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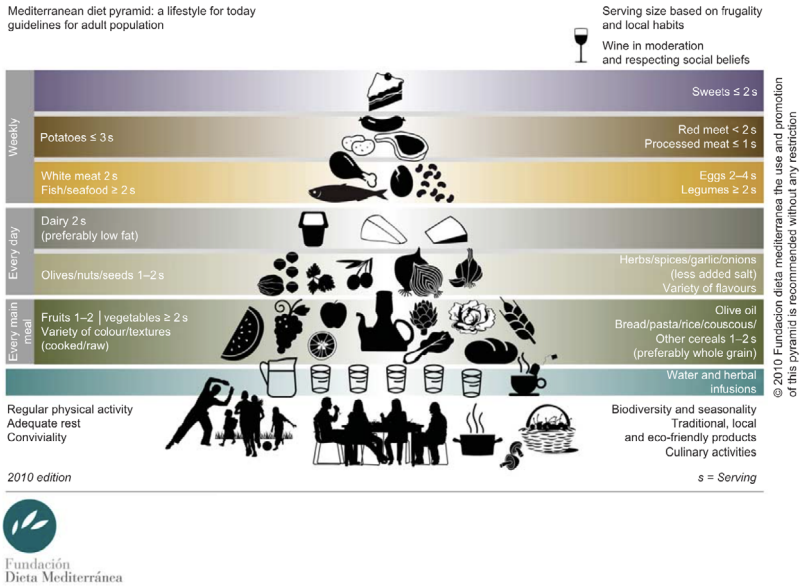

Fig. 1 *The Mediterranean diet pyramid.*

Numerous dietary indices estimating the adherence to the MedDiet have been constructed and applied in different populations.

Evidence on Mediterranean diet in intervention studies

Randomized controlled clinical trials (RCTs) are often considered the gold standard for determining causation between an exposure and outcome. In principle, it would be desirable, as for new drugs and medical devices, to use RCTs to evaluate the effects of diet on health. However, it is often not feasible to use RCT designs for many nutrients and foods. For cardiovascular events and cancer in particular, the intervention would need to last for several years, even decades for some outcomes, and a large sample size is required to have sufficient statistical power [11]. Another potential challenge is the difficulty of maintaining a high adherence to diets for long periods of time. RCTs designed to study the effects of diet on surrogate disease markers or intermediate risk factors require shorter intervention periods and can also provide important evidence on diet and health. The well-conducted prospective observational studies enrolling a large numbers of individuals and with long periods of follow-up can address many questions about diet and health that would be difficult or impossible to study in RCTs, and can be used as a basis for dietary guidelines and policy [12]. Conclusions of causality based on observational studies can be particularly strong when findings are consistent with short-term randomized interventions with intermediate outcomes, such as blood pressure or LDL cholesterol levels for coronary heart disease, or serum oestradiol levels for postmenopausal breast cancer.

Several intervention trials investigating the effects of MedDiet on health have been conducted, providing a strong body of evidence for the health benefits of MedDiet. The published trials covered a wide range of health outcomes and several meta-analyses of RCT have been published. Below, we describe the evidence for MedDiet on several health outcomes from observational and intervention studies.

The Mediterranean diet and health: evidence from observational and intervention studies

Cardiovascular diseases

Observational studies

The MedDiet has consistently been associated with lower incidence of CVD outcomes among and within populations. Apparently, the first reference to the health-promoting properties of the MedDiet was the landmark Seven Countries Study by Ancel Keys

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et al. [1] that focused on cardiovascular risk factors and both incidence and mortality due to CVD. Since then, several prospective cohort studies on the topic have been published. One of the largest studies was a prospective cohort study including 74,886 women from the Nurses' Health Study (NHS) who were followed up to 20 years. This study found that a greater adherence to the MedDiet, as reflected by a higher aMED score, was associated with a 29% (RR: 0.71; 95% CI, 0.62–0.82) lower risk of CHD incidence and a 13% (RR: 0.87; 95% CI, 0.73–1.02) lower risk of stroke in women [10]. Subsequent results from the same group, adding a cohort of male health professionals (Health Professional Follow-up Study, HPFS), showed that an increase in the aMED score from baseline to the first 4 years of follow-up was associated with 9% (95% CI, 3–14%) lower CVD risk during the next 20 years, suggesting that improving adherence to the diet quality scores over time is associated with significantly lower CVD risk in both the short and the long term [13]. Similar results have been observed in European populations, and in the EPIC-Spain cohort study, adherence to the MedDiet was associated with a 27% (RR: 0.73; 95% CI, 0.57–0.94) lower risk of CHD [14]. EPIC also showed that a 2-point increase in a MedDiet score was associated with a 25% lower risk of all-cause mortality in a Greek population [15] and 8% lower risk of all-cause mortality in elderly participants from nine European countries [16].

In a meta-analysis of observational studies, published in 2019, the pooled RR for CHD/myocardial infarction for the highest versus the lowest category of the MDS was 0.70 (95% CI 0.62–0.80), based on 11 cohort studies. The inverse associations were consistent in stratified analysis by study design, endpoint, sex, geographic area and the score used. The pooled RR for the six studies that considered unspecified stroke was 0.73 (95% CI 0.59–0.91) for the highest versus the lowest category of the MDS. However, no associations were identified for haemorrhagic stroke [17]. Recently, another systematic review and meta-analysis, including 38 cohorts, showed inverse associations with CVD mortality (RR: 0.79; 95% CI: 0.77–0.82), CHD incidence (RR: 0.73; 95% CI: 0.62–0.86), CHD mortality (RR: 0.83; 95% CI: 0.75–0.92), stroke incidence (RR: 0.80; 95% CI: 0.71–0.90), stroke mortality (RR: 0.87; 95% CI: 0.80–0.96) and MI incidence (RR: 0.73; 95% CI: 0.61–0.88), when comparing the highest versus the lowest categories of MedDiet adherence [8].

Intervention studies on cardiovascular risk factors

Many RCTs have been conducted evaluating the effects of MedDiet on intermediate CVD outcomes, including blood lipids, blood pressure, inflammatory biomarkers, and subclinical markers of atherosclerosis and endothelial function, as well as body weight.

In a 2019 meta-analysis, when compared with no or minimal intervention, the MedDiet slightly reduced total cholesterol (−0.16 mmol/L, 95% CI −0.32 to 0.00, 5 RCTs) and little or no effect was seen on LDL and HDL cholesterol, and triglycerides. However, when MedDiet interventions were compared with other dietary interventions for primary prevention, a small reduction in LDL cholesterol (−0.15 mmol/L, 95% CI −0.27 to −0.02, 7 RCTs) and triglycerides (−0.09 mmol/L, 95% CI −0.16 to −0.01, 7 RCTs) was seen with little effect on total or HDL cholesterol [18]. Results from subsamples of the well-known PREDIMED trial (PREvención con DIEeta MEDiterránea), described below in more detail and not included in the meta-analysis above, showed benefits of a MedDiet on apolipoproteins B, A-1 and their ratio, and also on LDL atherogenicity and beneficial changes on LDL size; HDL function was also improved [19,20]. Benefits of MedDiet on blood lipids are consistent with the broader literature showing the benefits of monounsaturated and polyunsaturated fatty acids on blood lipids [21,22] and also a meta-analysis on red meat RCT, showing that substituting red meat with high-quality plant protein sources, but not with fish or low-quality carbohydrates, leads to more favourable changes in blood lipids and lipoproteins [23]. Moreover, results from an umbrella review of meta-analyses suggested that subjects allocated to a MedDiet, as compared with subjects in the control diet, had better anthropometric, metabolic, and inflammatory risk parameters. Specifically, they found suggestive evidence supporting greater effectiveness of the MedDiet in reducing body weight, BMI and waist circumference, lowering total cholesterol, increasing HDL-cholesterol and reducing inflammatory parameters such as CRP and IL-6 when compared with control diets [5].

Regarding blood pressure, a meta-analysis including six trials (and more than 7,000 individuals), found that adopting a MedDiet pattern for at least 1 year reduced both systolic and diastolic blood pressure levels. The effect was higher for systolic blood pressure (−1.44 mm Hg) but also consistent

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for diastolic blood pressure (−0.70 mm Hg). The authors were cautious in interpreting these data because only six trials were eligible for inclusion [24]. These results were consistent with another meta-analysis of RCTs of several types of healthy diets, where MedDiet reduced systolic blood pressure by 3.02 mm Hg and diastolic blood pressure by 1.99 mmm Hg, 3 RCTs were included [25]. In a RCT conducted in Australia including 166 subjects older than 64 years, which was not included in the meta-analyses above, blood pressure was reduced in the MedDiet group at 3 and 6 months of follow-up. In addition, endothelial function (assessed by flow-mediated dilatation, FMD) also improved in the MedDiet group compared to the control group. Specifically, at 6 months, the percentage of flow mediated dilation (FMD) was higher by 1.3% (95% CI: 0.2%–2.4%; $p = 0.026$) in the MedDiet group [26].

In the MÉDITA study, a two-arm, single-centre randomized trial, 215 men and women with newly diagnosed T2D were randomized to a MedDiet or a low-fat diet, with a total follow-up of 8.1 years. Over this period, the Mediterranean diet dampened the inflammatory milieu of T2D [27]. Also, the MedDiet led to more favourable changes in glycaemic control and coronary risk factors and delayed the need for antihyperglycaemic drug therapy [28]. In addition, the MedDiet significantly delayed deterioration erectile function in men and female sexual function in women [29]. In another report by the same group, women with metabolic syndrome assigned to the MedDiet intervention group improved female sexual function index, while the index remained stable in the control group. In addition, CRP levels were also reduced in the intervention group [30].

Intervention studies on cardiovascular disease outcomes

The Lyon Diet Heart Study has been a benchmark for many studies on the MedDiet conducted thereafter. This was a secondary prevention RCT that evaluated the effect of a Mediterranean-type diet high in alpha-linolenic acid on the risk of a second myocardial infarction or death after 46 months of follow-up [31]. Individuals randomized to the MedDiet group experienced a 47% reduced risk of myocardial infarction and cardiovascular death, as compared to the control group [31]. In another secondary prevention trial, the GISSI-Prevenzione, patients who had suffered from a myocardial infarction and who were advised to have high intake of fish, fruits, olive oil, raw and cooked vegetables, had 49% reduced risk of death in comparison with those who were not advised so [32].

The landmark PREDIMED trial is the largest intervention study designed to evaluate the effects of the MedDiet on primary cardiovascular prevention among persons at high risk of CVD. A total of 7,447 participants were randomized to either a MedDiet supplemented with extra-virgin olive oil, a MedDiet supplemented with nuts or a control diet (advice to reduce all types of fat) [33]. Compared to the control group, the MedDiet intervention supplemented with extra-virgin olive oil reduced risk of the primary end-point (a composite of myocardial infarction, stroke and cardiovascular death, cases = 288) by 30% (RR: 0.70; 95% CI, 0.54–0.92) and the MedDiet supplemented with nuts reduced the risk by 28% (RR: 0.72; 95%, 0.54–0.96) after a median of 4.8 years of follow-up [33]. The planned duration was 6 years, but the trial was prematurely stopped for ethical reasons when an interim analysis at 4.8-year provided sufficient evidence of benefit for the two MedDiets [34].

A recent meta-analysis including three RCTs with a total of over 9,000 participants (including the PREDIMED trial) further confirmed these associations, showing that total CVD incidence was reduced by 38% after adhering to a MedDiet pattern compared to control groups (RR: 0.62; 95% CI, 0.50–0.78, $n = 2$) and total myocardial infarction (MI) incidence was reduced by 35% (RR: 0.65; 95% CI: 0.49–0.88, $n = 2$) [8].

In summary, the current evidence based on effects on intermediate-risk factors, long-term cohort studies, and randomized trials strongly indicates that adherence to a MedDiet reduces the risk of several cardiovascular outcomes. These findings are consistent across different populations including those outside the Mediterranean region. The benefits of MedDiet on CVD incidence can be explained at least in part by favourable effects on known risk factors such as diabetes and the metabolic syndrome (described below), and dyslipidaemia, hypertension, and endothelial function.

Diabetes

Observational studies

Evidence from prospective studies concluded that MedDiet adherence is inversely associated with the

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risk of diabetes [35]. In a meta-analysis of eight prospective studies, 5 in Southern Europe and 3 in non-Mediterranean populations, risk of T2D was 13% lower among those following a MedDiet (RR for highest vs lowest quantiles: 0.87; 95% CI: 0.82–0.93). In a subsequent report of the ATTICA study including 3,042 participants, not included in the previous meta-analysis, medium and high compared with low adherence to the MedDiet were associated with lower 10-year incidence of diabetes diagnosis, by 49% in men and 69% in women [36].

Intervention studies

The inverse association in observational cohort studies was confirmed in the PREDIMED trial, in which a Mediterranean diet (diet advice either supplemented with olive oil or nuts) resulted in a 30% risk reduction compared with the control group [37]. In a meta-analyses including 5 RCTs, the MedDiet provided better glycaemic control among patients with type 2 diabetes and prediabetes compared with control diets, including lower fat diets [38].

In summary, there is strong evidence from observational studies, RCTs among patients with type 2 diabetes and one RCT on the incidence of T2D, showing that MedDiet could reduce the risk of type 2 diabetes.

Metabolic syndrome

Observational studies

Metabolic syndrome (MetS) is a cluster of risk factors for CVD and T2D, including increased blood pressure, dyslipidaemia (increased triglycerides and lowered HDL-cholesterol), increased fasting glucose and central obesity. Several observational studies, including cross-sectional and longitudinal studies, have evaluated the associations between MedDiet and MetS. In a meta-analysis of observational studies, including eight cross-sectional and four prospective studies with 33,847 individuals and 6,342 cases of MetS, lower risks of 19% (risk ratio (RR) = 0.81; 95% CI: 0.71–0.92) were observed with greater adherence to MedDiet [39]. Regarding individual components of the MetS, inverse associations were significant for waist circumference, blood pressure and low HDL-C levels.

Intervention studies

Two RCTs specifically evaluated the effect of MedDiet on MetS remission. The first one conducted by Esposito et al. showed that at 2 years of follow-up, 40 patients in the intervention group had features of the metabolic syndrome, compared with 78 patients in the control group (P<.001) [40]. The second one was conducted in a subset of the PREDIMED trial and included 5801 participants. Both the MedDiet + extra-virgin olive oil and the MedDiet + nuts groups showed a greater remission of the MetS compared with the control group with (control vs. olive oil HR = 1.35; 95% CI: 1.15–1.58 and control vs nuts HR = 1.28; 95% CI: 1.08–1.51), but not with risk of metabolic syndrome onset [41]. In a meta-analysis of these two RCTs, participants with MetS allocated to a MedDiet, as compared with those following a control diet, had a 49% (95% CI 14%–96%) greater probability of remission from MetS during a follow-up of 2–5 years [38].

In sum, observational studies have shown that MedDiet could be beneficial for MetS development, and RCTs confirmed the remission of MetS on those participants allocated to MedDiet interventions.

Overweight and obesity

Observational studies

MedDiet is often perceived by the general population as likely to increase body weight because of the relatively high percentage of energy from total fat, being about 40% in the traditional diet of Greece. Consequently, some dietitians and physicians are reluctant to recommend it to obese individuals. However, evidence from observational studies has suggested that MedDiet is not associated with weight gain or increased waist circumference. In a report from the EPIC study including 373,803 men and women for a median of five years, individuals with high adherence to MedDiet lost 0.16 kg (95% CI: −0.24, −0.07 kg) and were 10% less likely to become overweight or obese than those participants with a low adherence [42]. Results from the CARDIA study also showed reductions in waist circumference among participants following a MedDiet [43].

Intervention studies

There is compelling evidence that a low-fat diet has little benefit for CVD risk and weight control, whether energy restricted or not; this was shown in two large, long-term intervention trials evaluating low-fat diets for CVD prevention [44,45]. Importantly, in a meta-analysis of RCTs comparing the long-term effect (≥1 year) of low-fat and higher-

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fat dietary interventions on weight loss, low-fat interventions did not lead to greater weight loss compared with higher-fat weight loss interventions; in studies with equal intensity of intervention, the weight loss was slightly greater with higher fat diets [46]. A systematic review including five RCTs ($n = 998$) showed that the MedDiet resulted in greater weight loss than the low-fat diet at ≥12 months (range of mean values: −4.1 to −10.1 kg vs 2.9 to −5.0 kg), but produced similar weight loss as other comparator diets (range of mean values: −4.1 to −10.1 kg vs −4.7 to −7.7 kg), including a low-carbohydrate diet and the American Heart Association Diet [47]. Similar findings have been reported in a recent meta-analysis including 18 RCTs examining MedDiet against control diets for outcomes of abdominal obesity; greater reductions in waist circumference and visceral fat with the MedDiet compared with control diets occurred mostly when diets were energy-restricted [48]. Thus, evidence suggests that reducing energy rather than the changing the macronutrient composition of the diet is most important for weight loss, and that the MedDiet does not have a deleterious effect on weight control. Indeed, an ancillary analysis in the PREDIMED study showed that adjusted differences in 4.8-year changes in body weight in the MedDiet with olive oil and nuts groups were −0.41 (95% CI, −0.83, 0.01) and −0.02 (95% CI, −0.45, 0.42) kg, compared to the control group. Respective differences for the changes in waist circumference were −0.47 (CI, −1.11, 0.18) and −0.92 (CI, −1.60, −0.24) cm [49]. Thus, a long-term intervention with an unrestricted-calorie, high-fat, high vegetable fat MedDiet was associated with little changes in body weight and less gain in central adiposity [50].

In other RCTs, the MedDiet has also been effective for weight control compared to other dietary interventions. The DIRECT RCT included about 300 moderately obese subjects followed for 2 years and was aimed at comparing the effectiveness for weight loss and safety of a MedDiet, restricted-calorie diet to two control groups: low carbohydrate and low fat. After two years, the mean weight loss was 4.6Kg and greater among those assigned to the MedDiet. Among those with diabetes, changes in fasting glucose and insulin were also better in the MedDiet group [51]. At 6 years after the study initiation, and 4 years without an intervention, weight loss was sustained in the MedDiet group. For the entire 6-year period, the total weight loss was 0.6 kg in the low-fat group, 3.1 kg in the MedDiet group and 1.7 kg in the low carbohydrate group ($p = 0.01$ for all comparisons) [52]. In an earlier 18-month RCT that included 101 overweight men and women, a moderate-fat diet based on the MedDiet and a low-fat diet were compared. The weight loss was superior in the moderate-fat MedDiet group (4.1 kg) compared to 2.9kg in the low-fat group [53].

In summary, suggestive evidence with moderate effects from observational and intervention studies has shown that MedDiet is not associated with obesity and does not increase weight gain. Benefits on weight loss are stronger with energy-restricted MedDiet interventions.

Cancer

Observational studies

Many observational studies have evaluated the associations between the adherence to MedDiet and risk of overall cancer incidence, risk of different cancer subtypes, cancer mortality and risk of recurrence in cancer survivors.

A comprehensive meta-analysis, including 117 studies with a total population of 3,202,496 participants, has recently been published [54] (see Fig. 2). In observational studies, higher adherence to the MedDiet was inversely associated with cancers of the breast (RR: 0.94, 95% CI 0.90–0.97; N studies = 23), colorectal (RR: 0.83, 95% CI 0.76–0.90; N studies = 17), head and neck (RR: 0.56, 95% CI 0.44–0.72; N studies = 9), respiratory tract (RR: 0.84, 95% CI 0.76–0.94; N studies = 5), gastric (RR: 0.70, 95% CI 0.61–0.80; N studies = 7), bladder (RR: 0.87, 95% CI 0.76–0.98; N studies = 4) and liver (RR: 0.64, 95% CI 0.54–0.75; N studies = 4). In addition, the highest adherence to MedDiet was inversely associated with overall cancer mortality (RR: 0.87, 95% CI 0.82–0.92; N studies = 18) and all-cause mortality among cancer survivors (RR: 0.75, 95% CI 0.66–0.86; N studies = 8). There was no evidence of associations with overall prostate cancer (RR = 0.98; 95% CI: 0.93–1.04, N studies = 11).

Another meta-analysis including five large cohorts focused on the risk of postmenopausal breast cancer classified by oestrogen/progesterone receptor (ER/PR) subtypes [55]. A statistically significant inverse association was found between MedDiet adherence and risk of ER negative (ER-) breast cancer, with a HR of 0.60 (95% CI: 0.39–

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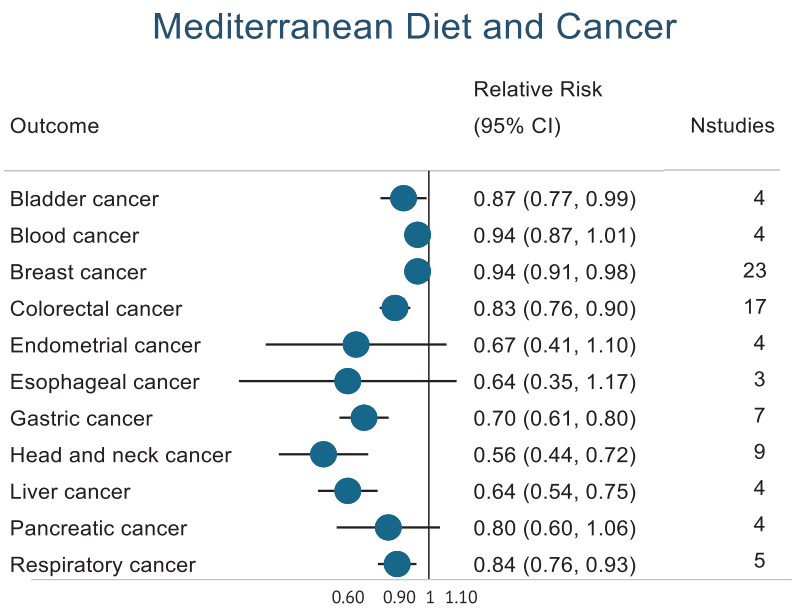

Fig. 2 *Summary of meta-analysis of observational studies on Mediterranean diet and cancer. Estimates were obtained from Morze et al 2020. The figure shows relative risks (closed blue circles), and horizontal bars represent the 95% confidence intervals for highest versus lowest categories of adherence to Mediterranean diet.*

0.93) for high- versus low-diet adherence (*P* for trend = 0.032). MedDiet adherence non-significantly associated with ER positive (ER+) or total breast cancer risk. These findings support an inverse association between MedDiet adherence and oestrogen receptor-negative breast cancer.

Intervention studies

The evidence on RCTs for MedDiet and cancer is limited and inconclusive. In the Lyon Heart Study, a 61% reduction in cancer incidence after four years of follow-up was found, but the analysis was based only on 24 incident cases [56]. In the PREDIMED, the impact on malignancies focused on breast cancer, which was diagnosed in 35 of the 4,152 participating women over the 4.2 years of follow-up. Women in the MedDiet + extra-virgin olive oil arm exhibited significant protection (HR = 0.32; 95% CI: 0.13–0.79), and a protective trend was found for those in the MedDiet+nuts arm [57]. A recent meta-analysis on MedDiet and cancer identified only one RCT evaluating cancer mortality and another RCT evaluating breast cancer risk. There was no evidence from RCTs for cancer mortality, but MedDiet was associated with a low incidence of breast cancer [54].

In brief, current results provide suggestive evidence that greater adherence to the MedDiet is inversely associated with cancer mortality in the general population, and with all-cause mortality among cancer survivors, as well as lower risks of colorectal, head and neck, respiratory, gastric, liver, bladder and oestrogen receptor-negative breast cancers. Evidence from RCTs is limited.

Cognitive function

Observational studies

Several published meta-analyses indicate that higher adherence to the MedDiet is associated with better global cognition and episodic memory [58], lower risks of cognitive impairment [59,60] and neurodegenerative diseases [59,61]. Figure 3 shows prospective studies analysing the association between adherence to the MedDiet and cognitive decline, dementia and Alzheimer's disease (Adapted from: [6]). A recent meta-analysis has identified 31 longitudinal studies of the MedDiet in relation to cognitive decline, dementia or Alzheimer's disease [61]. Higher adherence to the MedDiet was associated with less cognitive decline after 4 to 26 y of follow-up. Another meta-analysis

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including 9 cohort studies involving 34,168 participants found that compared with the lowest category of adherence, the highest MedDiet scores were associated with lower risk of developing cognitive disorders; the pooled RR (95% CI) was 0.79 (0.70–0.90) [62]. One of the larger and most recent studies was conducted in 27,842 men health professionals and showed that in a multivariate model, compared with men having a MedDiet score in the lowest quintile, those in the highest quintile had a 36% lower odds of a poor self-reported subjective cognitive function (SCF) score (odds ratio 0.64, 95% CI 0.55–0.75; P, trend <0.001) and a 24% lower odds of a moderate SCF score (OR 0.76, 95% CI 0.70–0.83; P, trend<0.001) [63]. Another dietary pattern, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), that overlaps broadly with the MedDiet, but that but singled out specific foods thought to be neuroprotective like green leafy vegetables and berries, was strongly associated with delay of cognitive decline [64].

Intervention studies

The evidence for cognition outcomes on MedDiet from RCTs is scarce. In a systematic review that included 6 RCTs, authors found that the MedDiet was the most widely researched dietary pattern and provided the strongest evidence against cognitive decline in older adults [65]. As an example, in a subset of 522 participant from the PREDIMED study, participants in the MedDiet+extra-virgin olive oil and MedDiet+nuts group had better cognition assessed by Mini-Mental State Examination (MMSE) and Clock Drawing Test after 6.5 years of follow-up, as well as lower incidence of mild cognitive impairment and dementia, compared to a control diet [66]. In another report of the PREDIMED, those in the MedDiet+extra-virgin olive oil scored significantly better than controls on the Rey Auditory Verbal Learning Test (RAVLT) and Colour Trail Test part 2. The MedDiet+nuts group had significantly improved memory composite, while MedDiet+extra-virgin olive oil group had significantly better performance of the frontal and global cognition composites than control group [67].

Because much of dementia is due to vascular disease, the strong evidence that the adherence to the MedDiet can reduce risk cardiovascular disease provides additional support for a reduction in dementia. Whether this dietary pattern also reduces the underlying pathology of Alzheimer's disease will require further study. In brief, highly suggestive evidence for the benefits of MedDiet on cognitive function and neurodegenerative diseases has been found from observational studies and a few RCTs.

Longevity and total mortality

Observational studies

In several prospective studies, better adherence to the MedDiet has been associated with greater longevity or lower risk of all-cause mortality. One of the first studies was conducted in three Greek villages and included data from 182 elderly residents; one-unit increase in a MedDiet score was associated with a significant 17% reduction in the risk of death. This study provided the first direct evidence that MedDiet could increase life expectancy, at least among older people [9]. These findings were even replicated in a cohort of a northern European elderly population, where one-unit increase in the MedDiet score was associated with 21% lower risk of overall mortality [68]. Likewise, consistent results were shown in a Spanish study [69] of 161 non-smoking men and women aged 65 years. A one-unit increase in the eight-unit Mediterranean diet score was again associated with a significant 31% lower mortality among elderly subjects. These findings suggest that adherence to a traditional Mediterranean diet is associated with greater longevity. Evidence from a meta-analysis of observational studies published in 2019, which included twenty nine prospective studies with 1,676,901 participants, found a reduction of 10% in all-cause mortality (RR = 0.90; 95% CI: 0.89–0.91) for every 2-point increase in adherence to the MedDiet. Subgroup analyses showed that a significant inverse association was stronger in participants who lived in the Mediterranean region compared with non-Mediterranean areas (HRs: 0.82 compared with 0.92, respectively). Moreover, a nonlinear dose–response meta-analysis indicated that the risk of all-cause mortality linearly decreased with the increase in adherence to a MedDiet [70].

Telomere length has become a generally accepted biomarker of the ageing process, with shorter length reflecting cumulative cell damage through stress and inflammation. Among 4676 healthy middle-aged women, those who more closely followed the MedDiet had longer telomere length [71]. In a recent meta-analysis that included 8 original cross-sectional studies and 13,733 participants

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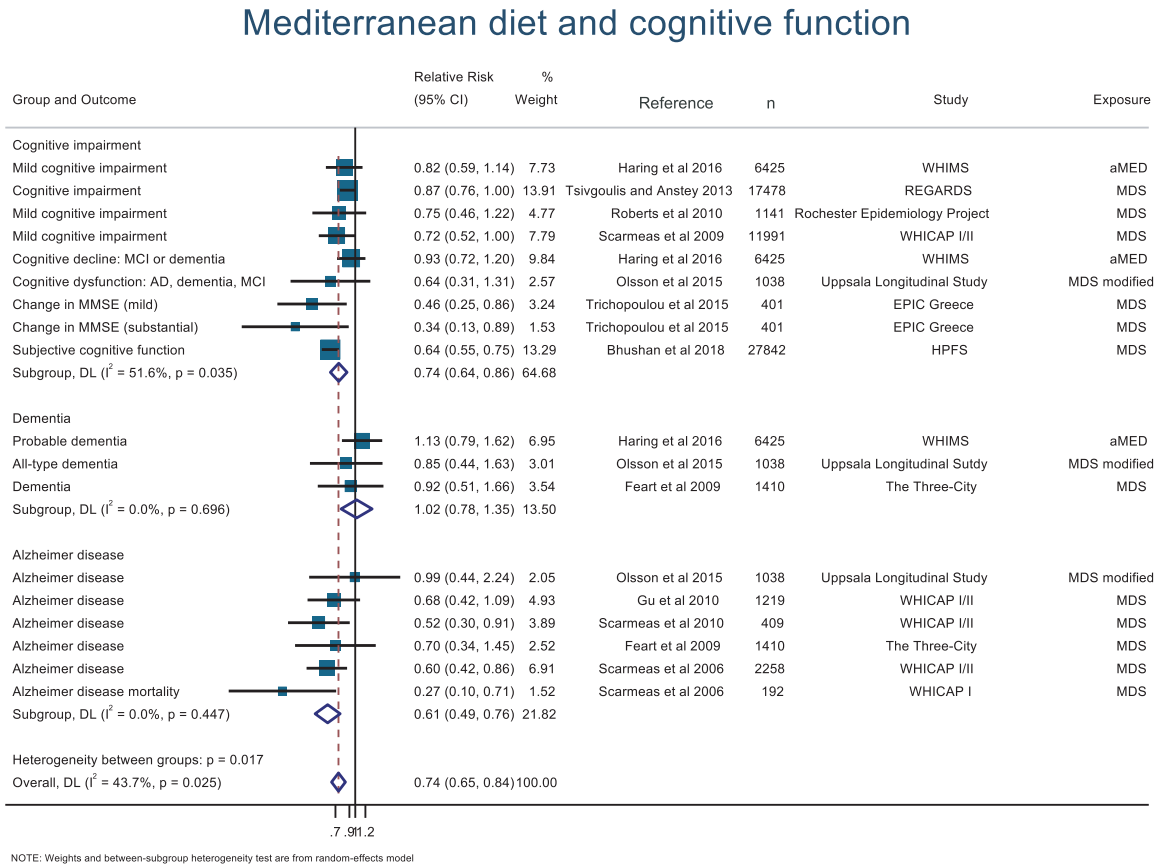

Fig. 3 *Prospective studies on the association between adherence to the Mediterranean diet and cognitive decline, dementia and Alzheimer disease. Estimates obtained and adapted from Serra-Majem et al. Mol Aspects Med. 2019. The figure shows relative risks (closed blue circles), and horizontal bars represent 95% confidence intervals for highest versus lowest categories of adherence to Mediterranean diet. Blue diamonds are the summary meta-analysis obtained from forest plots and random-effects meta-analysis of studies evaluating adherence to Mediterranean diet and cognitive decline, dementia and Alzheimer disease. Abbreviations: MCI, mild cognitive impairment; AD, dementia; MMSE, Mini-Mental State Examination; aMED, alternative Mediterranean diet score; MDS, Mediterranean diet score.*

from 5 countries, a positive association between adherence to the MedDiet and telomere length was observed [72]. These data provide evidence that the MedDiet is capable of slowing the biological processes related to ageing.

Intervention studies

While an inverse association between adherence to MedDiet and lower risk of all-cause mortality in observational studies has been demonstrated, findings from intervention studies have been inconsistent. In the PREDIMED trial, where total mortality was considered a secondary outcome, MedDiet interventions had a null effect on all-cause mortality (RR = 1.01; 95% CI: 0.81–1.25) [33], and the trial was stopped for ethical reasons because of the benefit for the primary endpoint. Results from the Lyon Heart Study showed that MedDiet interventions could reduce the risk of total mortality, but the number of cases was low [73]. In a published a meta-analysis including 5 RCTs, no evidence for benefits of MedDiet on overall mortality was observed [74]. However, they included a secondary prevention trial providing dietary advice (consumption of two portions of oily fish twice a week and increase intake of fruits, vegetables and oats), which cannot be considered a MedDiet *per se* [75], and RCTs including HIV-infected patients with a

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very small sample (4 cases/ 48 participants) and a very imprecise confidence interval (RR = 0.31; 95% CI: 0.03–2.74), and thus, the results from the latter may not be reliable [76].

At this time, while inverse associations between MedDiet adherence and overall mortality have been demonstrated in observational studies, the effects of MedDiet on total mortality in RCTs seem null. However, there is limited evidence to support these conclusions. It is possible that the insufficient duration of the RCTs and, thus, the small number of cases may have derived inconsistent results. Sufficiently powered randomized trials addressing this outcome would probably be considered unethical because such a trial would be stopped when reductions in a major outcome such as incidence of cardiovascular disease became clear.

Summary of evidence for health

Earlier research confirmed by recent studies has provided strong evidence for the benefits of the MedDiet on cardiovascular health, including reduction in the incidence of cardiovascular outcomes as well as risk factors including obesity, hypertension, metabolic syndrome and dyslipidaemia. There is also evidence that MedDiet is associated with lower rates of incident diabetes, and better glycaemic control in diabetic patients compared to control diets. In prospective studies, adherence to the MedDiet reduced mortality, especially cardiovascular mortality, hence increased longevity. In addition, it has been associated with less age-related cognitive dysfunction and lower incidence of neurodegenerative disorders, particularly Alzheimer's disease. The effects of the MedDiet in clinical trials are summarized in Fig. 4; benefits have been seen for a wide range of health outcomes including CVD mortality, CHD and stroke incidence, type 2 diabetes, metabolic syndrome and breast cancer.

In Table 1, we provide an overall summary for the evidence of the MedDiet on health outcomes in observational and intervention studies. The rationale to grade the certainty of the evidence were as follows: O (No evidence) – no evidence; 1 (Weak) – Null or ambiguous findings; 2 (Suggestive) – one or two supporting studies without clear refutation; 3 (Highly Suggestive) – 3 or more largely consistent prospective studies or meta-analysis without clear refutation; 4 (Convincing) – combination of multiple well-designed cohort studies plus randomized intervention studies with intermediate endpoints or consistent randomized trials with substantial number of endpoints and no clear refutation. An expanded table with references and estimates can be found in Table S1. In brief, convincing evidence has been found for cardiovascular disease, diabetes and metabolic syndrome; the evidence for total and breast cancer and cognitive function is highly suggestive; and, suggestive for total mortality, overweight and obesity, and specific cancers.

Our conclusions are consistent with those of a recent umbrella review of 13 meta-analysis of observational studies and 16 meta-analysis of RCTs that included 37 different health outcomes and a total population of over 12,800,000 persons. It was concluded that there is robust evidence from observational studies that greater adherence to the MedDiet is associated with lower risk of CVD, CHD, myocardial infarction, diabetes, overall cancer incidence and neurodegenerative diseases [5]. For most of the site-specific cancers, as well as for inflammatory and metabolic parameters, the evidence was interpreted as only suggestive and weak, and further research is needed for these outcomes. Furthermore, meta-analyses of RCTs demonstrated that subjects allocated to a MedDiet, as compared with subjects following control diet, had better metabolic and inflammatory risk parameters and lower risk of cardiovascular outcomes [5].

The Mediterranean Diet from an environmental perspective

The relatively low environmental impacts (water, nitrogen and carbon footprint) of the MedDiet is an additional positive aspect of the Mediterranean dietary model. The MedDiet has been proposed as a *'gold standard'* diet not only because of its major health and nutrition benefits, but also its lower environmental impact and richness in biodiversity, its high sociocultural food value and its positive local economic returns [77]. From an environmental and economic perspective, in Mediterranean regions the production of typical foods comprising the core of the MedDiet (i.e. nuts, olive oil, fruits and vegetables, grains and legumes, traditionally with some animals such as sheep grazing among tree crops) has existed for thousands of years, providing direct evidence of sustainability. This production system contributed to rural social structures and economies and the preservation of biodiversity [77]. These food systems limited the environmental impacts of exporting/importing foods from other regions.

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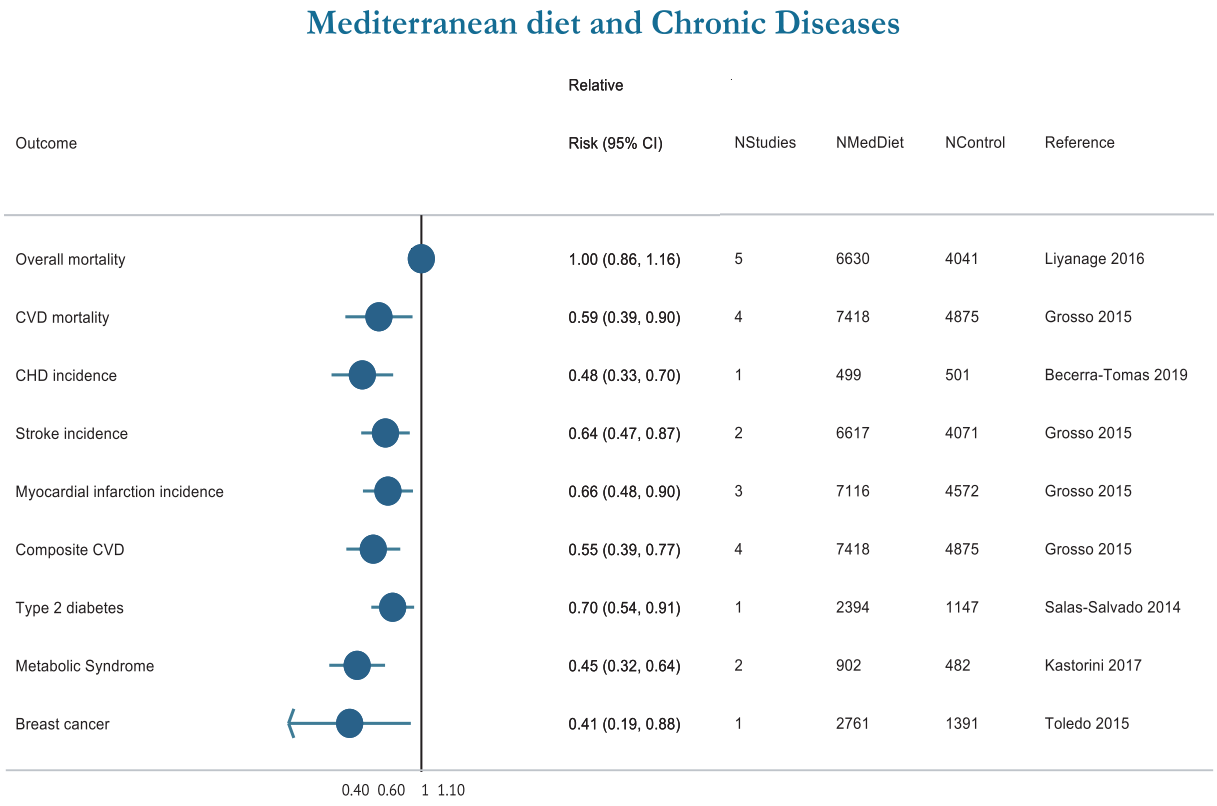

Fig. 4 *Summary of Meta-Analyses of Randomized Controlled Trials on Mediterranean Diet and Chronic Diseases. The figure shows relative risks (closed blue circles), and horizontal bars represent 95% confidence intervals for Mediterranean diet intervention versus control groups.*

Agriculture is one of the main contributors to the emission of greenhouse gases (GHGs) CH4 and N2O, and other parts of the food system such as fertilizer production, cultivation and transportation promote CO2 emissions through the use of fossil fuels. Food production is responsible for up to 30% of global GHGs emissions and 70% of freshwater use [78,79]. However, food items vary substantially in their environmental footprints [6,77,79]. Animal-based foods are by far the most land- and energy-intensive compared with plant origin and ruminants are uniquely high in production of CH4 and N20. Plant foods such as vegetables, cereals and legumes, nuts and olives have the lowest GHG emissions even where processing and substantial transportation are involved. Because the MedDiet is mainly a plant-based diet with low consumption of animal products, it has a smaller water footprint and lower greenhouse gas emissions compared with other dietary patterns [77]. The MedDiet encourages the use of a wide range of crops for cereals, fruits and vegetables, not only cultivated products but also wild species, thus sustaining them together with local and traditional knowledge about their use. Also, animal food production uses grazing or foraging grass among tree crops rather than producing grains mainly to feed animals. The seasonal consumption of fresh and local products, biodiversity, variety of foods (especially fruits and vegetables of different colours), traditional culinary activities, conviviality and frugality represents the cornerstone of conserving the Mediterranean diet heritage.

The EAT-Lancet Commission was charged with developing diets for the global population by 2050 that are both healthy and environmentally sustainable [79]. Beginning with a review of available

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Table 1 *Summary of the evidence of Mediterranean diet and Health Outcomes*

Health outcome	Summary of cohort studies	Summary of intervention studies	Strength of the evidence
Cardiovascular disease	Inverse associations with CHD, CVD incidence and mortality. Weak evidence for stroke.	Reduction in risk factors: blood lipids, blood pressure and inflammatory biomarkers. Reduction in CHD, stroke, CVD incidence and mortality in large RCTs.	4 (Convincing)
Total mortality	Reduction in overall mortality.	Null evidence but limited data.	2 (Suggestive)
Diabetes	Lower risk of T2D incidence.	Meta-analysis showed better glycaemic control in T2D patients. RCTs for metabolic syndrome are supportive. In PREDIMED, lower incidence of T2D.	4 (Convincing)
Metabolic syndrome	Lower risk of developing MetS.	Greater probability of MetS remission with MedDiet.	4 (Convincing)
Overweight and obesity	MedDiet not associated with weight gain or increased waist circumference.	MedDiet greater weight loss than low fat diet at >12 months. Improved abdominal obesity, waist circumference and visceral fat than controls.	2 (Strongly suggestive, moderate effect)
Cancer	Inverse association with cancer incidence and mortality. Lower risks of colorectal, head and neck, respiratory, gastric, liver, bladder and breast cancer.	Lower risk of cancer incidence in the Lyon Heart Study and lower risk of breast cancer in the PREDIMED.	3 (Highly suggestive) for total cancer and breast cancer 2 (Suggestive) for other specific cancers
Cognitive function	Lower risk cognitive impairment and Alzheimer's disease.	Beneficial for cognitive decline.	3 (Highly suggestive)

Strength of the evidence: O (No evidence) – no evidence; 1 (Weak) – Null or ambiguous findings; 2 (Suggestive) – one or two supporting studies without clear refutation; 3 (Highly Suggestive) – 3 or more largely consistent prospective studies or meta-analysis without clear refutation; 4 (Convincing) – Combination of multiple well-designed cohort studies plus randomized intervention studies with intermediate endpoints OR consistent randomized trials with substantial number of endpoints and no clear refutation.
CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MedDiet, Mediterranean diet; MetS, metabolic syndrome. Expanded table with references and estimates can be found in the appendix; RR, relative risk; T2D, type 2 diabetes.

evidence on specific food groups and health, the Commission arrived at a healthy reference diet with target numbers and ranges for each food group. Notably, although the review process began with the evaluation of each element of the diet individually, the targets that emerged were very similar to the traditional MedDiet, thus complementing and supporting the literature that has evolved based on the overall Mediterranean pattern. For example, the Greek men in Crete in the mid-20th century had an average intake of red meat and poultry combined of about 35 g/day, and the EAT-Lancet target number was just over 40 grams per day. By evaluating the components independently, the EAT-Lancet approach allows great flexibility in terms of varieties of foods,

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agricultural systems, cultural traditions and individual dietary preferences. These elements can be combined in various types of omnivore, vegetarian and vegan diets, including as an example the MedDiet, as well as other healthful plant-based diets. The Commission noted that the best studied example is the traditional MedDiet, which provided important evidence for feasibility of the healthy reference dietary targets.

After developing the dietary targets for specific food groups, the EAT-Lancet Commission used the published literature on life cycle analysis (which assesses the environmental impacts of each food group) to determine whether the dietary targets could be produced for what will be almost 10 billion people in 2050 while remaining within sustainable limits for greenhouse gas production and other environmental variables. For greenhouse gas emissions, this healthy dietary pattern was probably feasible, but if dairy foods were increased much beyond one serving per day or red meat much beyond about 1 serving per week, remaining within sustainable limits would not be feasible. Along these lines, another study evaluating the health and environmental impacts of food, key food groups of the MedDiet were associated with lower environmental impact and better health outcomes [80]. Of the foods associated with improved health (wholegrain cereals, fruits, vegetables, legumes, nuts, olive oil and fish), all except fish have among the lowest environmental impacts, and fish has markedly lower impacts than red and processed meats. Foods associated with the largest negative environmental impacts—unprocessed and processed red meat—are consistently associated with the largest increases in disease risk [80,81]. Another study conducted in a Spanish population showed that the MedDiet may be the healthiest option, with relatively low environmental footprints. However, its monetary costs were the highest. The plant-based diet was the eco-friendliest pattern, relatively healthy and affordable. The Western dietary pattern was the least recommended pattern according to health criteria and ecosystems consequences, but it was the most affordable food pattern [82]. In addition, a meta-analysis including 8 studies on dietary patterns have shown consistent evidence indicating that a dietary pattern higher in plant-based foods (e.g. vegetables, fruits, legumes, seeds, nuts, whole grains) and lower in animal-based foods (especially red meat), as well as lower in total energy, is both healthier and associated with a lesser impact on the environment [83]. Recommended diets included vegetarian (with variations) diets, dietary guidelines-related diets, Mediterranean-style diets and the Dietary Approaches to Stop Hypertension (DASH) diet [83]. These analyses support the potential of the MedDiet for being environmentally sustainable, but changes in production methods, for example those that are dependent on fossil fuels, can negate this sustainability.

In summary, it is likely that the combination of a healthy diet with social behaviours and the way of life of Mediterranean regions makes the MedDiet a sustainable lifestyle model that could likely be followed in other regions with country-specific and culturally appropriate variations.

Discussion

Clinical and public health implications

There is strong and consistent evidence, showing that certain dietary patterns, such as the MedDiet, play a pivotal role in the prevention of chronic diseases. Therefore, promoting a healthy diet should be a cornerstone of public health initiatives.

As described above, evidence from observational and intervention studies showed that MedDiet is beneficial for the prevention of several chronic diseases including cardiovascular outcomes, cancer and neurodegenerative diseases, among others. Of note, the relative importance of each food composing the MedDiet is likely to differ by the outcome. For example, fruits and vegetables may have a stronger impact on cognitive function than other food groups, while nuts may have a stronger impact on cardiovascular risk factors and CVD incidence and mortality. Olive oil intake has been associated with lower risk of CHD and total CVD, especially when substituting other fats such as margarine, butter, mayonnaise and dairy fat. However, no associations with CVD were observed in a large cohort study when olive oil substituted other healthy plant-based oils, suggesting that plant-based oils may also be a good alternative to more saturated animal fats [84].

In the last years, globalization, industrialization, a rapid increase in fast-food restaurants and advances in food industry have transformed the traditional MedDiet of most Mediterranean regions into a more global and 'Western' or industrial dietary patterns [85]. The intake of fresh fruit and vegetables, nuts, legumes, whole-grain and fish

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has been replaced by processed energy-dense food, rich in refined carbohydrates, sugar and sugar-sweetened beverages, and animal or partially hydrogenates fats [86]. These diet changes combined with a more sedentary lifestyle, both at work and in leisure-time activities, are major contributors to the increase in obesity and CVD epidemic of the last decades. Therefore, the scientific studies documenting the benefits of MedDiet and its components are essential to guide populations policies and individual decisions towards a more plant-based diet that is both healthy for human populations and sustainable for our planet. Although the studies based on Mediterranean populations have found a higher and more consistent effect than those studies carried out in non-Mediterranean countries [70,87], current research has pointed out that non-Mediterranean regions could adopt a Mediterranean-type dietary pattern, or other healthy plant-based diets, which may have health benefits similar to those reported in the Mediterranean regions.

Public health policies and appropriate nutritional recommendations to promote MedDiet or other healthy plant-based diets along with a healthy lifestyle at different levels (schools, universities, primary care centers, hospitals, etc.) should be a cornerstone for the prevention of chronic disease at a national and international level. Importantly, despite the high-quality evidence emphasizing the health benefits of the MedDiet, there are several barriers that often prevent the adherence to such pattern, including lack of time, lack of culinary skills, availability and economic limitations. Thus, promoting the adoption of the MedDiet and adapting its characteristics to food availability and to country-specific and culturally appropriate variations is key.

Because food systems are a major driver of poor health and environmental degradation, global efforts are urgently needed to collectively transform diets and food production. Therefore, knowledge on the health and environmental benefits of the MedDiet should be translated not only as recommendations that target individuals and their families but also as economic and other policies that facilitate access to these foods.

Overall Summary

Collectively, evidence from long-term observational studies and randomized trials of cardiovascular risk factors and disease outcomes strongly and robustly supports many health benefits of the MedDiet including reductions of CVD incidence and mortality, type 2 diabetes and metabolic syndrome, incidence of some cancers and cognitive function. To date, the evidence on other outcomes, including incidence of specific cancers, is promising, and further long-term epidemiologic studies and possibly well-conducted RCTs on these outcomes are warranted. Strongly suggestive evidence indicates that the MedDiet does not increase adiposity or obesity, and it may reduce these outcomes compared to some dietary patterns. Although the MedDiet was initially studied in countries around the Mediterranean Sea, the benefits of this overall dietary pattern have been found to be generalizable to many other Western countries, including the United States, Australia, the United Kingdom and Nordic countries, among others. Additional research on the specific components of the MedDiet can be useful to optimize the amounts and content, for example the specific types of fruits and vegetables. Furthermore, most of the research on MedDiet has been conducted in Mediterranean or other Western countries, so further research on Mediterranean-type diets in other populations and geographical regions is desirable. Moreover, MedDiet can be considered not only a healthy diet but also part of a sustainable lifestyle and food system model that can be adapted to country-specific agricultural resources and cultures.

Conflicts of interest

The authors report no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of the evidence of Mediterranean diet and Health Outcomes.

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