

# Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake

## A Systematic Review and Meta-analysis

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**Background:** Mediterranean diets may be healthier than typical Western diets.

**Purpose:** To summarize the literature comparing a Mediterranean diet with unrestricted fat intake with other diets regarding their effects on health outcomes in adults.

**Data Sources:** Ovid MEDLINE, CINAHL, and the Cochrane Library from 1990 through April 2016.

**Study Selection:** Controlled trials of 100 or more persons followed for at least 1 year for mortality, cardiovascular, hypertension, diabetes, and adherence outcomes, as well as cohort studies for cancer outcomes.

**Data Extraction:** Data extracted by 1 investigator was verified by another. Two reviewers assessed risk of bias and strength of evidence.

**Data Synthesis:** Two primary prevention trials found no difference in all-cause mortality between diet groups. One large primary prevention trial found that a Mediterranean diet resulted in a lower incidence of major cardiovascular events (hazard ratio [HR], 0.71 [95% CI, 0.56 to 0.90]), breast cancer (HR, 0.43 [CI, 0.21 to 0.88]), and diabetes (HR, 0.70 [CI, 0.54 to 0.92]). Pooled analyses of primary prevention cohort studies showed that compared with the lowest quantile, the highest quantile of adherence to a Mediterranean diet was associated with a reduction in

total cancer mortality (risk ratio [RR], 0.86 [CI, 0.82 to 0.91]; 13 studies) and in the incidence of total (RR, 0.96 [CI, 0.95 to 0.97]; 3 studies) and colorectal (RR, 0.91 [CI, 0.84 to 0.98; 9 studies]) cancer. Of 3 secondary prevention studies reporting cardiovascular outcomes, 1 found a lower risk for recurrent myocardial infarction and cardiovascular death with the Mediterranean diet. There was inconsistent, minimal, or no evidence pertaining to any other outcome, including adherence, hypertension, cognitive function, kidney disease, rheumatoid arthritis, and quality of life.

**Limitations:** Few trials; medium risk-of-bias ratings for many studies; low or insufficient strength of evidence for outcomes; heterogeneous diet definitions and components.

**Conclusion:** Limited evidence suggests that a Mediterranean diet with no restriction on fat intake may reduce the incidence of cardiovascular events, breast cancer, and type 2 diabetes mellitus but may not affect all-cause mortality.

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Chronic diseases, such as diabetes, cardiovascular disease, and cancer, are among the leading causes of morbidity and mortality in the United States and other developed countries. Despite advances in diagnosis and treatment, global deaths due to cardiovascular disease and the prevalence of diabetes increased by more than 40% from 1990 to 2013 (1-3). Typical Western diets, which are high in saturated fats, sugar, and refined grains, are causally associated with development of cardiovascular disease, diabetes, and some types of cancer, including breast and colorectal cancer (4). Although a recent study found that dietary quality in the U.S. population improved between 1999 and 2010, the authors noted that it remains "far from optimal" (5).

The Mediterranean diet has been defined as "primarily a plant-based diet characterized by a high ratio of monounsaturated to saturated fats with total fat accounting for 30-40% of daily energy consumption" (6). Interest in this diet, which was first described more than 60 years ago in the Seven Countries Study (7), resurfaced about a decade ago with the publication of a large prospective cohort study reporting a significant association between adherence to a Mediterranean diet and a reduction in total mortality (8). Since then,

many observational studies and a few clinical trials examining the association between a Mediterranean diet and various clinical outcomes have been published, although the definition of the diet varied among the investigations. The purpose of this systematic review is to summarize the literature on the effect of the Mediterranean diet on health outcomes and to assess whether North American populations are likely to adhere to such a diet.

## METHODS

Our objectives were to determine whether the Mediterranean diet is more effective than any other diet in preventing mortality and new onset of disease in healthy persons (primary prevention) or mortality and disease progression in those who have diabetes, cardiovascular disease, cancer, hypertension, cognitive

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impairment, rheumatoid arthritis, or kidney disease (secondary prevention), as well as to assess the level of adherence to a Mediterranean diet in trials conducted in the United States and Canada. This manuscript is based in part on a Department of Veterans Affairs (VA) Evidence-Based Synthesis Program report prepared for the VA National Center for Health Promotion and Disease Prevention and Primary Care Services, available at [www.hsrd.research.va.gov/publications/esp/](http://www.hsrd.research.va.gov/publications/esp/).

### Definition of a Mediterranean Diet

For clinical trials, we defined a Mediterranean diet as one that placed no restriction on total fat intake and included 2 or more of the following 7 components: a high monounsaturated-to-saturated fat ratio (for example, the use of olive oil as a main cooking ingredient), high fruit and vegetable intake, high consumption of legumes, high grain and cereal intake, moderate red wine consumption, moderate consumption of dairy products, and low consumption of meat and meat products with increased intake of fish (9). This definition of a Mediterranean diet was identical to the one we used for the full VA report except that the latter definition did not require the diet to be unrestricted in total fat intake. Observational studies were included if they assessed the association between 2 or more of these components and any of our outcomes of interest. In these studies, food-frequency surveys (either self-administered or conducted by research staff) typically were used to categorize participants' diets into quantiles of adherence to a Mediterranean diet based on validated dietary indices.

### Data Sources

We searched Ovid MEDLINE, CINAHL, and the Cochrane Library for primary studies and systematic reviews published from 1990 through April 2016. We limited the search to English-language studies in non-pregnant, nonlactating adults and excluded those in hospital patients. Search terms included the Medical Subject Headings for dietary components (such as Fruit, Vegetables, Cereals, Fatty Acids, Monounsaturated, and Seafood), Diet, Mediterranean, and Patient Compliance. We also hand-searched the reference lists of systematic reviews and included studies. The full search strategies are presented in **Table 1** of the **Supplement** (available at [www.annals.org](http://www.annals.org)).

### Study Selection

Two investigators independently evaluated each abstract from MEDLINE to determine whether a full-text review was warranted, 1 investigator reviewed abstracts from the CINAHL database and Cochrane Library, and 2 investigators independently performed a full-text review. For studies of cardiovascular disease, hypertension, total mortality, or diabetes, we included randomized, controlled trials (RCTs) or controlled clinical trials with at least 100 participants followed for at least 1 year. For studies of cancer and health-related quality of life, we included RCTs, controlled clinical trials, and cohort studies with at least 100 participants followed for at least 1 year. For studies of rheumatoid

arthritis and cognitive impairment, we included RCTs, controlled clinical trials, and cohort studies with any number of participants and no minimum follow-up time. Trials could compare a Mediterranean diet with any other type (such as Western or low-fat) and must have reported 1 of our outcomes of interest (mortality, health-related quality of life, diet-related adverse events, participant satisfaction, new onset of disease, or disease progression or recurrence). Our outcomes definition required a clinical diagnosis (such as hypertension or diabetes), not just a test result (such as elevated blood pressure or hemoglobin A<sub>1c</sub>). To assess adherence to a Mediterranean diet in a North American population, we looked at trials conducted in the United States or Canada that enrolled at least 100 participants, followed them for at least 1 year, and reported adherence to an assigned diet as an outcome.

### Data Extraction and Quality Assessment

Study characteristics (goal of intervention, inclusion and exclusion criteria, diet descriptions, follow-up, patient characteristics, and outcomes) were extracted onto evidence tables by 1 investigator or research associate and verified by another. Disagreements were discussed until a consensus was reached.

Risk of bias for trials was based on the following criteria: sequence generation, allocation concealment, blinding, and outcome reporting—a modification of the Cochrane approach to determining risk of bias (10). Risk of bias for cohort studies was based on methods for selecting the population, identifying and measuring outcomes, length of follow-up, and controlling for confounding (11). Confounders of interest included age and cardiac risk factors. Multivariate analysis was considered an appropriate method for controlling for confounding. Individual studies were rated as low, medium, or high risk of bias. Using the method reported by Owens and colleagues (12), we rated the overall strength of the body of evidence for all-cause mortality; all-cancer, breast cancer, and colorectal cancer incidence; and cognitive functioning in primary prevention, and all-cause mortality in secondary prevention.

### Data Synthesis and Analysis

Data were summarized by outcome. We pooled results if the patient populations, dietary measures, and outcomes were comparable. Outcomes data from clinical trials and cohort studies were pooled separately. Most studies reported hazard ratios (HRs), which we treated as risk ratios (RRs). For cohort studies, we extracted the adjusted HR comparing the highest adherence to a Mediterranean diet, based on Mediterranean diet scores, to the lowest adherence (the reference). Data were analyzed in Comprehensive Meta-Analysis version 3 (Biostat) using DerSimonian and Laird random-effects models to calculate pooled RRs (13). We used the adjusted risk estimates, if provided, from multivariate models. If HRs or RRs were not reported, we calculated RRs based on reported data. We measured the magnitude of statistical heterogeneity with the  $I^2$  statistic ( $\geq 75\%$  indicates substantial heterogeneity) (14). We conducted post hoc sensitivity analyses to

examine differences in cancer mortality, total cancer incidence, and colorectal cancer incidence in primary prevention studies, based on a follow-up of 10 years or less, 10 to less than 20 years, and 20 years or longer.

### Role of the Funding Source

The funding source (Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative) assigned the topic and reviewed the key questions but was not involved in data collection, analysis, or manuscript preparation or submission.

## RESULTS

As shown in Figure 1, we identified 10 349 abstracts and performed full-text reviews on 320 articles. Ninety papers representing 56 unique studies met all inclusion criteria. Three of these studies were not included in the analysis (15-17) because of credible evidence that the data may be fraudulent (18). We found no studies reporting new-onset kidney disease, hypertension, diet-related adverse effects, participant satisfaction, or adherence. In general, cohort studies rated as medium risk of bias had 2 or more deficiencies in the population, outcomes, or measurement domains. Characteristics of the included studies are summarized in Table 2 of the Supplement, and more detailed descriptions are given in Tables 2 and 3 of the Supplement.

### Primary Prevention

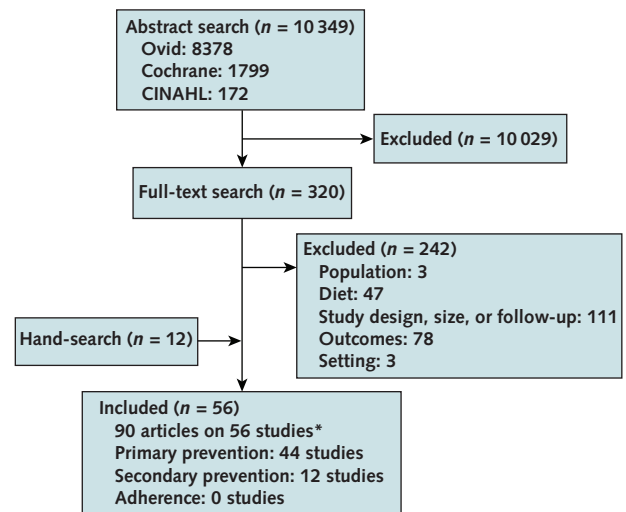
We identified 72 articles (37 low and 35 medium risk of bias) reporting results from 44 studies (2 RCTs and 42 cohort studies) that assessed the association between adherence to a Mediterranean diet and the occurrence of outcomes in persons without a history of the outcome of interest. The strength of evidence for all-cause mortality, all-cancer incidence, breast and colorectal cancer incidence, and cognitive functioning were all rated as low (Table 4 of the Supplement).

### Cardiovascular Disease, All-Cause Mortality, and Diabetes (RCTs Only)

One trial evaluated the effect of the Mediterranean diet on major cardiovascular outcomes (myocardial infarction, stroke, cardiovascular death), diabetes, and all-cause mortality (19, 20), and a second trial reported all-cause mortality (21).

The PREDIMED (Prevención con Dieta Mediterránea) study was a low-risk-of-bias trial that randomly assigned 7447 participants to a Mediterranean diet with supplemental extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a low-fat control diet (19). Both intervention diets included recommendations for 5 of the 7 components that made up our Mediterranean diet definition; grain and dairy products were not specifically recommended. After an average follow-up of 4.8 years, participants in the 2 Mediterranean diet groups combined had a 29% reduction in major cardiovascular events (myocardial infarction, stroke, or cardiovascular death) compared with the

Figure 1. Literature search and selection.



\* Studies may have presented data for both primary and secondary prevention; 3 studies were excluded because of concerns about fraudulent data.

control group (HR, 0.71 [95% CI, 0.56 to 0.90]) (19), but all-cause mortality was the same (4.7%) in both groups (HR, 0.89 [CI, 0.71 to 1.12]) (19). In a medium risk-of-bias substudy of participants who did not have type 2 diabetes at baseline (3541 participants), the incidence of type 2 diabetes was lower in the 2 Mediterranean diet groups combined than in the control group (HR, 0.70 [CI, 0.54 to 0.92]) (20).

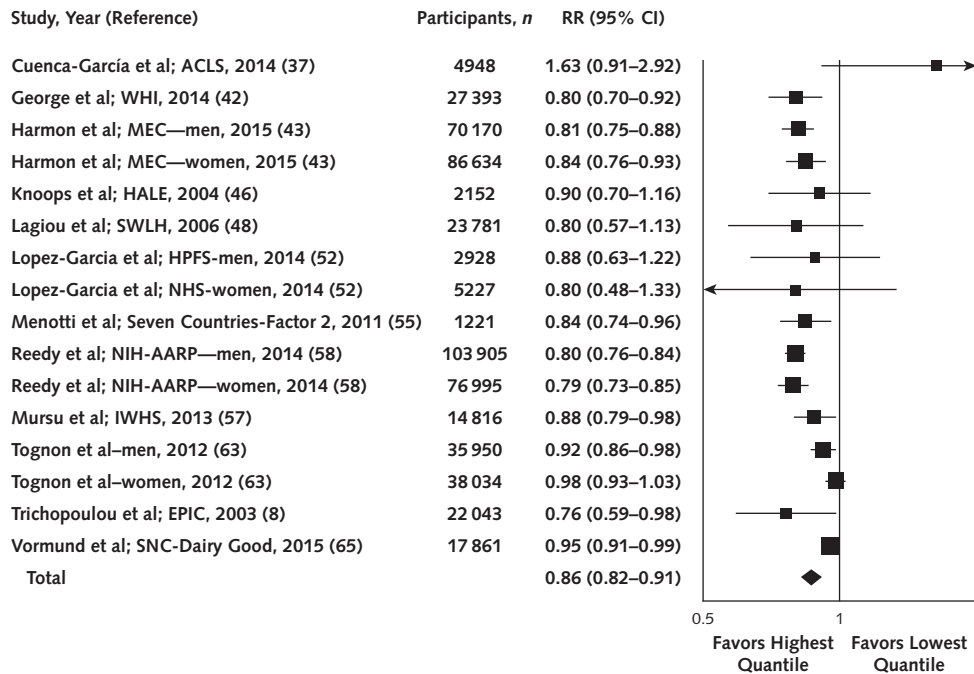
A second, smaller trial (medium risk of bias) randomly assigned 429 residents of 14 geriatric hostels in Hong Kong to a diet containing 2 of the 7 Mediterranean diet components (fruits and vegetables and fish) or to a usual diet and followed them for 33 months (21). Thirteen percent of enrollees in the Mediterranean diet group died, compared with 11% in the control group (RR, 1.19 [CI, 0.72 to 1.98]).

### Cancer

PREDIMED, the only trial reporting cancer outcomes, found a lower risk for breast cancer in the 2 Mediterranean diet groups combined than in the control group (HR, 0.43 [CI, 0.21 to 0.88]) (22).

Twenty-eight cohort studies (half low and half medium risk of bias; 2 262 786 participants) with follow-up periods of 4 to 40 years reported cancer outcomes and compared groups with the highest and lowest Mediterranean diet adherence (8, 23-66). Pooled analyses indicated that compared with the lowest quantile, the group in the highest quantile of adherence to a Mediterranean diet had a 14% reduction in total cancer mortality (RR, 0.86 [CI, 0.82 to 0.91];  $I^2 = 77%$ ; 13 studies) (Figure 2) (8, 37, 42, 43, 46, 48, 52, 55, 57, 58, 63, 65). The direction of effect was consistent in all but 1 study (37); however, a sensitivity analysis removing that study did not change the  $I^2$  value. Pooled analyses (not shown) indicated a 4% reduction in total cancer inci-

**Figure 2.** Primary prevention: cancer mortality, by adherence to Mediterranean diet in cohort studies.



ACLS = Aerobics Center Longitudinal Study; EPIC = European Prospective Investigation Into Cancer and Nutrition; HALE = Healthy Ageing: a Longitudinal Study in Europe; HPFS = Health Professionals Follow-up Study; IWHS = Iowa Women's Health Study; MEC = Multiethnic Cohort Study; NHS = Nurses' Health Study; NIH-AARP = National Institutes of Health-AARP Diet and Health Study; RR = risk ratio; SNC = Swiss National Cohort; SWLH = Swedish Women's Lifestyle and Health; WHI = Women's Health Initiative.

dence (RR, 0.96 [CI, 0.95 to 0.97];  $I^2 = 0\%$ ; 3 studies) (34, 35) and a 9% reduction in colorectal cancer incidence (RR, 0.91 [CI, 0.84 to 0.98];  $I^2 = 63\%$ ; 9 studies) in persons in the highest compared with the lowest quantile of adherence to a Mediterranean diet (27, 38, 40, 45, 47, 59). Sensitivity analyses found no differences in relative risk for total cancer mortality, colorectal cancer incidence, or all-cause cancer incidence when studies were stratified by length of follow-up. Pooled analyses found similar incidences of breast cancer at the highest and lowest levels of Mediterranean diet adherence (RR, 0.96 [CI, 0.90 to 1.03];  $I^2 = 53\%$ ; 13 studies). Two cohort studies (465 106 participants) with a median follow-up of 8.5 and 10.5 years, respectively (25, 53), evaluated the association between Mediterranean diet adherence and lung cancer incidence. Both studies found a lower incidence of lung cancer in persons with the highest adherence than in those with the lowest (HR, 0.20 [CI, 0.04 to 0.90], and 0.85 [CI 0.79 to 0.91], respectively) (25, 53). We found no other associations between Mediterranean diet adherence and site-specific cancer incidence or mortality.

**Cognitive Impairment and Dementia**

Data from 2 RCTs (1 low and 1 medium risk of bias) were mixed (21, 67, 68). One site of the PREDIMED trial (522 participants) reported reductions in the risk for mild cognitive impairment (RR, 0.54 [CI, 0.34 to 0.88]) and dementia (RR, 0.36 [CI, 0.19 to 0.67]) over a 6.5-

year (mean) follow-up in the Mediterranean diet groups compared with the control group, whereas another site (334 participants) reported no association between diet and risk for mild cognitive impairment (RR, 0.83 [CI, 0.43 to 1.58]) over a 4-year (median) follow-up (67, 68). The previously described RCT in Hong Kong reported that dementia developed in 14% of the intervention and 17% of the control group during 33 months of follow-up (RR, 0.81 [CI, 0.49 to 1.35]) (21). Results from the 15 cohort studies (roughly half low and half medium risk of bias; 45 831 participants; mean follow-up, 6 years) also were mixed. Outcomes evaluated ranged from change in cognitive scale scores to clinical diagnosis of Alzheimer disease (69–87).

**Rheumatoid Arthritis**

A cohort study that enrolled 174 638 female registered nurses and had medium risk of bias found similar rates of rheumatoid arthritis over a mean follow-up of more than 20 years in those with the highest and lowest Mediterranean diet scores (HR, 0.98 [CI, 0.8 to 1.2]) (88).

**Health-Related Quality of Life**

One article reported health-related quality of life in 2 cohort studies in older adults living in Spain who were followed for 2 to 4 years (4287 participants). Neither study found an association between Mediterra-



nean diet indices and mental scores on the Short Form-36 Health Survey. Results for the physical Short Form-36 Health Survey score were mixed (89).

### Secondary Prevention

We identified 12 studies (4 RCTs, 1 controlled clinical trial, and 7 cohort studies; 18 209 participants) reported in 17 mostly medium-risk-of-bias articles that investigated the association between a Mediterranean diet and the occurrence of outcomes in those with the condition of interest at baseline (secondary prevention) (44, 82, 90-104).

### Cardiovascular Disease, Cardiovascular Mortality, and All-Cause Mortality (RCTs Only)

Three RCTs were conducted in patients with cardiovascular disease. The Heart Institute of Spokane Diet Intervention and Evaluation Trial, rated as medium risk of bias, enrolled only 202 patients and found no outcome differences between the 2 diet groups (102). The Lyon Heart Study (605 participants; low risk of bias) reported that random assignment to a Mediterranean diet reduced the risk for a new myocardial infarction (RR, 0.32 [CI, 0.15 to 0.70]) and cardiovascular death (RR, 0.32 [CI, 0.13 to 0.78]) (91-94). A study from Wales, a medium-risk-of-bias trial enrolling 3114 men, was interrupted by funding problems, leading to uncertainty regarding the integrity of outcomes reporting and analysis (90). It found no differences between diet groups in either myocardial infarction or cardiovascular mortality. Neither the Lyon trial nor the Welsh trial found any differences between diet groups in stroke incidence or all-cause mortality. Overall, the strength of evidence for all-cause mortality was rated as insufficient (Table 4 of the Supplement).

### Cancer

Cohort studies examining outcomes in persons with colon cancer (2 studies, 1 low and 1 medium risk of bias; 2210 participants), breast cancer (3 studies, low to medium risk of bias; 7152 participants), or prostate cancer (2 studies, both medium risk of bias; 5464 participants) revealed a similar incidence of cancer recurrence and cancer-specific mortality in those in the highest and those in the lowest quantile of adherence to a Mediterranean diet (40, 95-98, 100, 103, 104). Average follow-up in these studies ranged from 5.3 to 11.2 years and did not vary by cancer type.

### Cognitive Impairment

One cohort study in New York with low risk of bias that enrolled 482 persons with mild cognitive impairment reported a similar incidence of progression to Alzheimer disease during a mean follow-up of 51.6 months between those with higher and those with lower adherence to a Mediterranean diet (82).

### Rheumatoid Arthritis

Two small trials comparing a Mediterranean diet with a usual diet in persons with rheumatoid arthritis reported mixed results. A 12-week low risk-of-bias RCT in 51 participants found improvement in disease activity and pain scores in the Mediterranean diet group, but no difference in health-related quality of life (101). A 6-month controlled clinical trial (130 participants) with medium risk of bias reported no differences between the diet groups in global pain or disease activity scores (99).

## DISCUSSION

We conducted this systematic review to evaluate the health benefits of a Mediterranean diet. Our primary conclusion is that there is limited evidence from randomized trials that a Mediterranean diet with no restriction on fat intake may be associated with a reduced incidence of cardiovascular events, breast cancer, and type 2 diabetes mellitus but does not affect all-cause mortality. The observational data reveal that total cancer incidence and mortality and colorectal and lung cancer incidence were lower in persons with the highest adherence to the Mediterranean diet compared with those with the lowest but show no association between Mediterranean diet adherence and breast cancer risk. Inconsistent, minimal, or no evidence exists for all other outcomes, including hypertension, kidney disease, rheumatoid arthritis, cognitive impairment, and quality of life.

Our results generally are consistent with those of other recent systematic reviews (105-107), although those that included studies with less rigorous designs tended to report more significant associations. For example, contrary to our findings, recent reviews that included case-control or cross-sectional studies reported that Mediterranean diet adherence was inversely associated with the development of cognitive decline and of several site-specific cancers, including gastric, pancreatic, and prostate (108, 109).

Our results, however, differ from a Cochrane review (52 044 participants; 11 studies) evaluating the efficacy of a Mediterranean diet for primary prevention of cardiovascular disease (9). That study's definition of a Mediterranean diet did not include the no restriction of total fat intake, but otherwise was identical to ours; it also required the control diet to be "minimal intervention." As a result of these differences in inclusion criteria, there was no overlap between studies in the Cochrane review and those included here. In particular, PREDIMED was not included in the Cochrane review because the comparator intervention (a low-fat diet) did not meet its control diet criterion. On the other hand, the Cochrane review included the WHI-DM (Women's Health Initiative-Dietary Modification) study (110, 111) because its intervention diet included increased consumption of fruits, vegetables, and grains, but we did not include it here because it was a low-fat diet. We believe that our operational definition of a Mediterranean diet (low-fat diets excluded), which re-

sulted in exclusion of WHI-DM and inclusion of PRE-DIMED, more accurately reflects the current conceptualization of a Mediterranean diet. The lack of a clearly articulated and widely accepted definition of a Mediterranean diet is an ongoing problem that must be resolved for this field to move forward (6).

Several studies postulated possible mechanisms by which a Mediterranean diet might positively affect clinical outcomes, including reductions in total and low-density lipoprotein cholesterol, body weight, blood pressure, fasting plasma glucose, and C-reactive protein (9). Some evidence also exists that the high concentration of antioxidant and anti-inflammatory molecules in the diet may be beneficial (112, 113). Recently, greater adherence to the Mediterranean diet in a subgroup of women enrolled in the Nurses' Health Study was associated with longer telomeres, the repetitive DNA sequences at the ends of chromosomes that are linked to greater life expectancy (114).

We found no studies meeting our inclusion criteria for the dietary adherence outcome. A recent systematic review summarized the effects of interventions to promote a Mediterranean diet or healthy eating pattern in primary health care settings (115). Fourteen RCTs were included, only 2 of which studied a Mediterranean diet. Neither of these studies was included in our review because 1 was conducted in Spain and 1 in hospitalized patients in the United Kingdom (116, 117). The review concluded that there is some evidence that nutritional counseling moderately increases intake of fruits and vegetables and that intensive interventions with more frequent patient contact are most effective. A Cochrane review noted that many interventions (including contracts, feedback, and telephone follow-up) enhance dietary adherence in various circumstances but that no single intervention or group of interventions is clearly better than others (118). The U.S. Preventive Services Task Force found adequate evidence that intensive behavioral counseling interventions promoting a weight loss diet resulted in favorable changes in such intermediate outcomes as body weight, blood pressure, lipid and glucose levels, and physical activity (119).

In January 2016, the U.S. Department of Health and Human Services and Department of Agriculture released new dietary guidelines (120) that continue to emphasize the importance of limiting fat intake, despite evidence from such trials as PREDIMED that a Mediterranean diet in which total fat comprises 40% of energy intake results in fewer cardiovascular events than a low-fat diet (19). Experts have expressed disappointment with these guidelines, commenting that an opportunity was missed to focus the public's attention on the dangers of refined grain products and added sugar, which likely are the major culprits behind the U.S. obesity epidemic (121, 122).

We acknowledge several limitations. First, we included only English-language publications, although we are unaware of any major clinical outcomes trials reported in another language that would have altered our findings. Second, we used DerSimonian and Laird random-effects models, which may produce estimates

with erroneously high precision if the number of studies meta-analyzed is small or if the estimates vary widely among the studies (123). Third, the possibility of selective reporting and publication bias may have affected our findings. Finally, and most importantly, the available primary literature included only a few RCTs, and about half of the cohort studies were medium risk of bias because of unclear descriptions of the population and sampling, follow-up, and outcomes assessment. For the selected outcomes evaluated, the strength of evidence was low or insufficient.

In conclusion, evidence from a few RCTs suggests that a Mediterranean diet with no restriction on fat intake may be associated with reduced incidence of cardiovascular events, breast cancer, and type 2 diabetes mellitus compared with any other diet, but does not affect all-cause mortality. Future investigation should include randomized trials in U.S. populations to assess adherence, efficacy, and effect on a wider range of clinical outcomes; modeling studies to determine whether specific Mediterranean diet components or combinations of components are more protective than others; and randomized trials to assess the relative effectiveness of the Mediterranean diet compared with other healthy diets, such as the DASH (Dietary Approaches to Stop Hypertension) or prudent diet.

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**Reproducible Research Statement:** *Study protocol:* Registered in PROSPERO (CRD42015020262) at [www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/). *Statistical code:* See Methods. *Data set:* Not available.

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