QUERI

Benefits and Harms of the Mediterranean Diet Compared to Other Diets

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PREFACE

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The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

A large number of epidemiologic studies have investigated the association between diet and mortality and morbidity. Of particular recent interest is the Mediterranean diet, first described by Ancel Keys over 50 years ago.[1] This diet is characterized by high intake of olive oil, fruits and vegetables, whole grains and cereals, legumes, fish, and nuts; low intake of red meat, dairy products, and sweets; and moderate intake of red wine with meals.[2] Epidemiologic studies have shown that the incidence of cardiovascular disease in populations that consume such diets is lower than in populations that consume a more typical "Western" diet that is rich in red meat, dairy products, processed and artificially sweetened foods, and salt with minimal intake of fruits, vegetables, fish, legumes, and whole grains.[3-5]

Based on these epidemiologic studies, several randomized controlled trials were conducted to test the hypothesis that adopting a Mediterranean diet in adulthood reduces chronic disease burden (*eg*, incidence of and/ or mortality from cardiovascular disease, cancer, type 2 diabetes mellitus [T2DM], hypertension, cognitive impairment, and kidney disease) and/or all-cause mortality (*viz*, PREDIMED, Lyon Heart Study, THIS-DIET).[6-8] These trials included populations from a variety of geographical locations and with a spectrum of demographic and clinical characteristics.

Although several systematic reviews of the relevant observational studies and clinical trials have been published,[9-19] the VA's Evidence-based Synthesis Program, in conjunction with the Office of Quality and Performance and in response to a request from the VA's National Center for Health Promotion and Disease Prevention and Primary Care Services, commissioned the present study to update prior reviews and to specifically assess the implications for the treatment and prevention of common chronic conditions in the Veteran population. We conferred with the topic nominators and Technical Expert Panel (TEP) members and other experts inside and outside the VA to select the parameters of the review, including patient characteristics, interventions, and outcomes (Figure 1, Analytic Framework).

The final Key Questions are:

Key Question 1: Is the Mediterranean diet more effective than other diets in preventing death or the development of type 2 diabetes mellitus, cardiovascular disease, cancer, hypertension, cognitive impairment, or kidney disease?

> **Key Question 1a:** Do the effects vary by gender, age, or BMI?

Key Question 2: Compared to other diets, is the Mediterranean diet associated with fewer adverse outcomes (including death) or less disease progression in people who already have diabetes, cardiovascular disease, cancer, hypertension, cognitive impairment, rheumatoid arthritis, or kidney disease?

> **Key Question 2a:** Do the effects vary by gender, age, or BMI?

Key Question 3: What is the observed adherence to the Mediterranean diet in studies conducted in the United States or Canada?

PICOTS

Population: Adults (age 18 or older), not pregnant or lactating, and not hospitalized or institutionalized. Subgroups of interest: people with type II diabetes, cardiovascular disease, rheumatoid arthritis, cancer, hypertension, cognitive impairment, or kidney disease; different genders, ages, and BMIs.

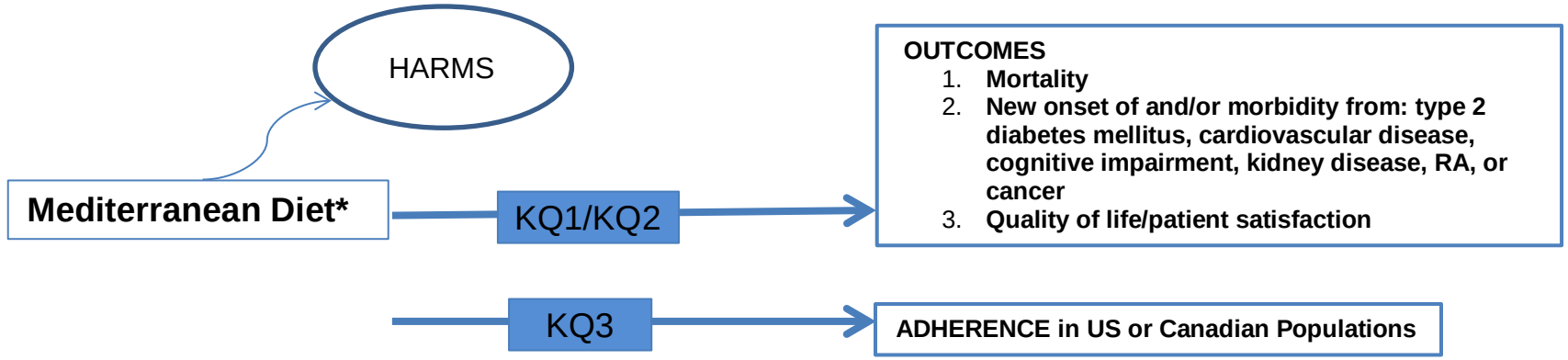
Interventions: A Mediterranean-style diet (*ie*, labelled as a Mediterranean diet or consisting of at least 2 of the following: 1. high monounsaturated:saturated fat ratio (use of olive oil as main cooking ingredient); 2. high consumption of fruits and vegetables; 3. high consumption of legumes; 4. high consumption of grains/cereals; 5. moderate red wine consumption; 6. moderate consumption dairy products; and 7. low consumption of meat and meat products (replaced by increased consumption of fish)

Comparator: Any other type of diet (*eg*, Western, low fat, vegetarian)

Outcomes: *NOTE: Definitions for all outcomes followed definitions used in the included studies.* T2DM, hypertension, and kidney disease were considered present only if the study recorded a clinical diagnosis had been made (*ie*, not just by laboratory values obtained in the study)

KQ1: mortality, quality of life, new onset of T2DM, hypertension, cardiovascular disease (CVD) (myocardial infarction [MI], stroke, or congestive heart failure), kidney disease, cancer, and cognitive impairment (dementia, Alzheimer's disease [AD], or mild cognitive impairment [MCI])

Figure 1. Analytic Framework



PICOTS
Patients: Adults
Intervention**:** Mediterranean diet
Control**:** Other diet (*eg,* Western, vegetarian)
Outcomes: See Above
Timing: at least 1 year follow-up
Setting: Outpatient

***Operational Definition of a Mediterranean Diet:** At least 2 components from this list were required for the Cochrane review (Rees 2014)
1. High monounsaturated:saturated fat ratio (use of olive oil as main cooking ingredient)
2. Moderate red wine consumption.
3. High consumption of legumes.
4. High consumption of grains/cereals.
5. High consumption of fruits/vegetables.
6. Low consumption of meat and meat products and increased consumption of fish.
7. Moderate consumption dairy products

Study Eligibility Criteria (KQ1/KQ2)
English language
≥ 12 months follow-up
For Outcomes 1 and 3
RCTS or systematic reviews of RCTs
≥ 100 participants
For Outcome 2
RCTs for diabetes, CVD, or CKD
Cohort studies for cancer, cognitive impairment and RA

Study Eligibility Criteria (KQ3)
English language
≥ 12 months follow-up
US or Canadian population
RCTs
≥100 participants

KEY QUESTIONS
1. Is the Mediterranean diet more effective than other diets in preventing death or the development of type 2 diabetes mellitus, cardiovascular disease, cancer, hypertension, cognitive impairment, or kidney disease? Do the effects vary by gender, age, or BMI?
2. Compared to other diets, is the Mediterranean diet associated with fewer adverse outcomes (including death) or less disease progression in people who already have diabetes, cardiovascular disease, cancer, hypertension, cognitive impairment, rheumatoid arthritis, or kidney disease? Do the effects vary by gender, age, or BMI?
3. What is the observed adherence to the Mediterranean diet in studies conducted in the United States or Canada?

KQ2:

A. For populations with diabetes, heart disease, kidney disease, and/or hypertension at baseline:
    1. Mortality
    2. Quality of life
    3. Progression of disease, *ie:*
        a. Development of retinopathy, neuropathy, end-stage renal disease, or congestive heart failure
        b. New amputation
        c. New myocardial infarction, stroke, or revascularization procedure
B. For populations with cancer at baseline:
    1. Mortality (all-cause, cancer-specific)
    2. Quality of life
    3. Progression of disease or recurrence
C. For populations with rheumatoid arthritis at baseline:
    1. Pain
    2. Quality of life
    3. Functional status
D. For populations with cognitive impairment at baseline:
    1. Diagnosis of dementia
    2. Quality of life
    3. Functional status

KQ1, KQ2: Any adverse events related to diet in RCTs

KQ3: Adherence measures

Timing: At least one year of follow-up, except for studies of rheumatoid arthritis or cognitive impairment

Setting: Outpatient

Study Type:

KQ1 or KQ2:

Studies of patients with or at risk for cardiovascular disease, hypertension, diabetes, or kidney disease – RCTs of at least 100 people followed for at least one year

Studies of patients with or at risk for cancer – RCTs or cohort studies with at least 100 participants and at least one year follow-up

Studies of patients with or at risk for rheumatoid arthritis or cognitive impairment – randomized controlled trials (RCTs) or cohort studies of any size or follow-up duration

KQ3: RCTs of at least 100 people followed for at least one year

METHODS

TOPIC DEVELOPMENT

This topic was nominated by Linda Kinsinger, MD, MPH, Chief Consultant for Preventive Medicine, National Center for Health Promotion and Disease Prevention; Gordon Schectman, MD, Chief Consultant for Primary Care Services; and Michael Goldstein, MD, Associate Chief Consultant for Preventive Medicine. The evidence review examines the benefits and harms of the Mediterranean diet compared to other diets. Key questions and inclusion criteria were derived with input from the topic nominators and a technical expert panel.

SEARCH STRATEGY

We searched MEDLINE (Ovid), CINAHL, and the Cochrane library for articles published from 1990 through August 2015. Our search was limited to studies of adults published in the English language. The search included the MeSH (Medical Subject Headings) terms fruit; vegetables; nuts; bread; cereals; seeds; fatty acids, monusaturated; seafood; and diet, Mediterranean. To address Key Question 3, an additional search was done in all 3 databases adding the terms adherence and patient compliance. The searches were also repeated with the addition of disease-specific terms to find articles specific to cancer, rheumatoid arthritis, and cognitive impairment. The full search strategies are presented in Appendix A. We also obtained articles by hand-searching the reference lists of systematic reviews and included studies. A separate search was also done in all 3 databases to identify systematic reviews of cohort studies reporting on cardiovascular disease, diabetes, and all-cause mortality.

DEFINITIONS

We included studies with diets that met the criteria defined by a recent Cochrane Review, that is to say, labelled a Mediterranean diet or meeting 2 or more of the following components: 1. high monounsaturated:saturated fat ratio (use of olive oil as main cooking ingredient); 2. high consumption of fruits/vegetables; 3. high consumption of legumes; 4. high consumption of grains/cereals; 5. moderate red wine consumption; 6. moderate consumption of dairy products; and 7. low consumption of meat and meat products (replaced by increased consumption of fish). All included studies met this minimum definition. The names for the diets included terms such as Mediterranean diet, prudent diet, healthy Nordic diet, and healthy pattern.

STUDY SELECTION

Abstracts from MEDLINE (n = 7,672) were reviewed in duplicate independently by investigators and research associates. Abstracts from the CINAHL database (n = 131) and Cochrane Library (n = 1,799) were reviewed by a co-investigator or research associate. Trained researchers identified articles published in peer-reviewed journals related to one of the Key Questions (KQs). For studies addressing KQs 1 and 2 in diseases other than cancer, RA, or cognitive impairment we included RCTs or controlled clinical trials (CCTs) with at least 100 subjects followed for at least one year. For studies of RA and cognitive impairment we included RCTs, CCTs, and cohort studies with any number of participants and no limit on follow-up time. For studies of cancer and for KQ3 we included RCTs and cohort studies with at least 100 participants followed for at least one year. In addition, in order to be included, studies addressing

KQ3 must have taken place in the United States or Canada. For all questions and outcomes, we excluded case series, case reports, qualitative reports, narrative reviews, editorials, or letters. Studies must have also reported one of our outcomes of interest as defined in the Analytic Framework (Figure 1) and PICOTS (above).

All included studies met our definition of a Mediterranean diet. In the randomized trials, the composition of the intervention diets were defined a priori. In the cohort studies, food frequency surveys (either self-administered or administered by research staff) were typically used to categorize subjects' diets based on validated dietary indices. Commonly used indices include the Mediterranean-diet score, the alternate Mediterranean-diet score (aMED), the Healthy Eating Index (HEI), and the Alternate Healthy Eating Index (aHEI). For these indices we generally compared the highest quantile of conformity to a Mediterranean diet to the lowest. We excluded the following:

- Studies that did not involve outpatient adults;
- Studies with diets that were not labelled Mediterranean and did not test or measure a diet that met our criteria for a Mediterranean diet (stated above);
- Studies in women who were pregnant or lactating; and
- For KQ3, studies that were conducted in countries other than the US and Canada.

Full-text reports of studies identified as potentially eligible were obtained for further review using the inclusion and exclusion criteria described above. Each article was independently reviewed by 2 trained researchers. Reasons for excluding a study at full-text review were noted.

DATA ABSTRACTION

Study characteristics (goal of intervention, inclusion/exclusion criteria, diet descriptions, follow-up, and patient characteristics) as well as outcomes (mortality, health-related quality of life, adverse events, satisfaction, new onset of disease, disease progression/recurrence, and adherence) were extracted onto evidence tables by one investigator or research associate and verified by another. The systematic reviews of cohort studies reporting on cardiovascular disease, diabetes, and all-cause mortality were summarized narratively.

RISK OF BIAS ASSESSMENT

We assessed the risk of bias for RCTs using the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome reporting, and selective outcome reporting – a modification of the Cochrane approach to determining risk of bias.[20] For cohort studies risk of bias was determined based on: population (representativeness of sample, uniform application of inclusion/exclusion criteria), outcomes (important outcomes assessed and reported, appropriate length of follow-up), measurement (outcome assessment same for all participants, accurate and reliable tools used), and confounding (appropriate confounding factors included in analysis). Individual studies were rated as low, medium, or high risk of bias. Low risk of bias RCTs had adequate allocation concealment, blinding, and outcome reporting. Low risk of bias cohort studies had appropriate populations, assessed important outcomes with adequate follow-up, used appropriate outcome measurement tools, and adjusted for important potential confounding factors.

DATA SYNTHESIS

Data were summarized by outcome. If applicable, we pooled outcomes data from RCTs and cohort studies separately using Comprehensive Meta Analysis Version 3 (Biostat, Englewood, New Jersey). Most of the studies reported hazard ratios (HR), which we treated as risk ratios (RR). We extracted the HR of the highest conformity to a Mediterranean diet, based on Mediterranean-diet scores, that was compared to the lowest conformity (the reference). Random effects models were used to calculate pooled RRs. If provided, we used the adjusted risk estimates from multivariate models. If HRs or RRs were not reported, we calculated RRs based on the numbers of events and populations reported for each of the diet groups. We measured the magnitude of statistical heterogeneity with the I^2 statistic (75% indicates substantial heterogeneity).[21]

RATING THE BODY OF EVIDENCE

We rated the overall strength of the body of evidence for select outcomes (all-cause mortality [KQ1, KQ2], cancer incidence [KQ1], and cognitive functioning [KQ1]) using the method reported by Owens et al.[22]

PEER REVIEW

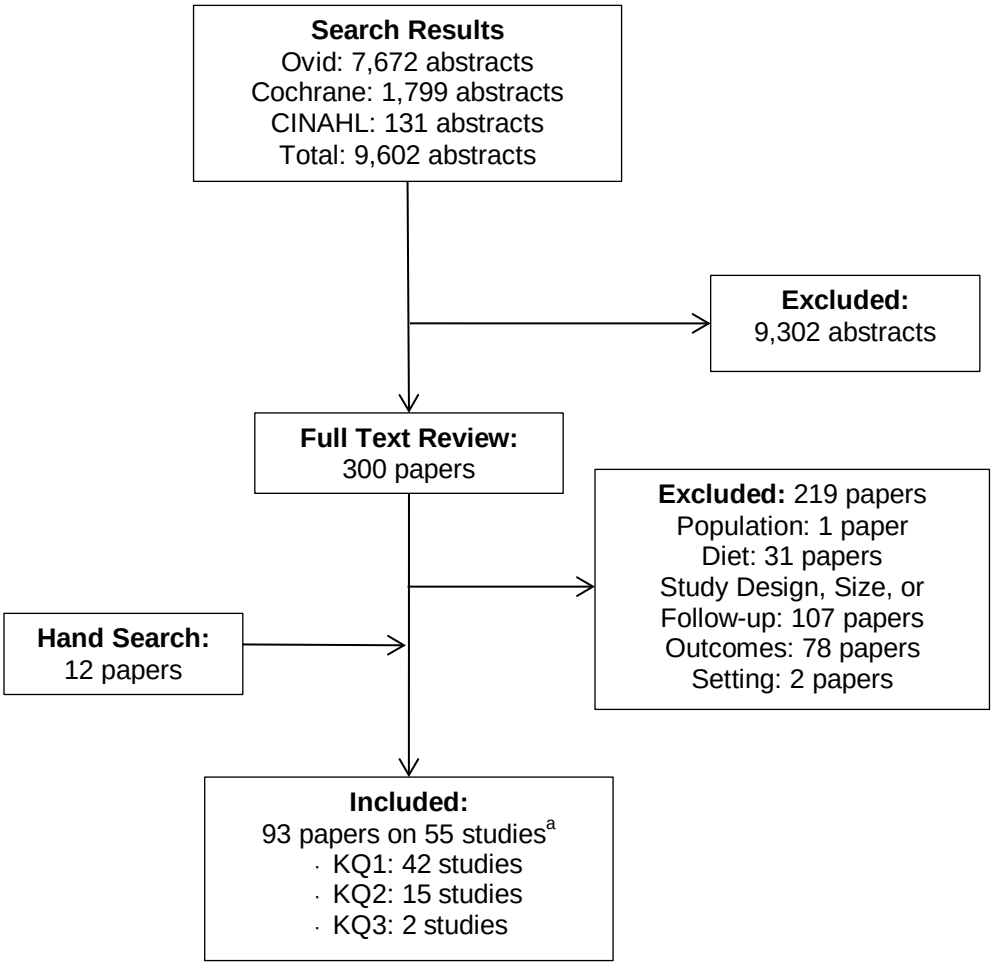
A draft version of this report was reviewed by content experts and clinical leadership. Reviewers' comments and our responses are presented in Appendix B and the report was modified as needed.

RESULTS

LITERATURE FLOW

The overall literature flow is presented below. Literature flows for each of the Key Questions are presented in Appendix D. We reviewed a total of 9,602 abstracts.

Figure 2. Overall Literature Flow (KQ1-3)



[a] Studies may have presented data for more than one KQ.

KEY QUESTION 1: Is the Mediterranean diet more effective than other diets in preventing death or the development of Type II diabetes mellitus, cardiovascular disease, cancer, hypertension, cognitive impairment, or kidney disease?

Overview of Studies (Table 1 and Appendix C, Table 1)

We identified a total of 72 articles reporting results from 42 studies. Three were randomized controlled trials and 39 were cohort studies. The dietary interventions used in the 3 RCTs are detailed in the sections below entitled *all-cause mortality* and *cognitive functioning.* The cohort studies employed a variety of scales to rate each individual's degree of conformity to the Mediterranean diet (see Methods section).

We extracted all-cause mortality (number of studies reporting[k] = 3), cardiovascular outcomes (k = 2), and T2DM (k = 2) only from RCTs. We extracted cancer outcomes from both cohort studies (k = 28) and RCTs (k = 2), cognitive impairment from both cohort studies (k = 13) and RCTs (k = 2), and rheumatoid arthritis from one cohort study. No studies reported new-onset kidney disease or hypertension, or quality of life. Twenty one studies were conducted in North America, 17 in Europe, and 4 in Asia or Australia. The total number of participants was 2,489,225 with a range of sample sizes from 429 to 566,407. The average age of participants was 61 (k = 28) and the mean BMI was 26 (k = 25). For studies using mixed gender cohorts the mean percentage of men was 46% (k = 23).

Outcomes (Appendix C, Tables 1 – 4)

All-Cause Mortality (RCTs only)

All-cause mortality was reported in 3 trials [WHI-DM, PREDIMED, and a smaller study from Hong Kong; total N = 56,711].[7,23,24] PREDIMED was a multicenter trial in Spain that randomized 7,447 people to one of 3 diets: Mediterranean diet supplemented with extra virgin olive oil (EVOO), Mediterranean diet supplemented with mixed nuts, or a control diet. Each of the 2 intervention diets comprised 5 of the 7 components of a Mediterranean diet, including olive oil. The mean age of enrollees was 67 years, 57% were women, 97% were Caucasian, 25% were former and 14% were current smokers, the mean body mass index was 29.8, 82% had hypertension, 50% had diabetes, and 70% had dyslipidemia.[7] Median follow-up was 4.8 years. The primary endpoint was major cardiovascular events (myocardial infarction, stroke, or cardiovascular death).

Table 1. Summary of Included Studies - Key Question 1

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting[a]
Total number of patients evaluated	**2,489,225** (429 to 566,407)	42
Randomized controlled trials, total number of patients	**56,711** (429 to 48,835)	3
Cohort studies, total number of patients	**2,432,514** (723 to 566,407)	39
Age of subjects, years	**61** (36 to 83)	28
Gender, % male patients in mixed gender studies	**46%** (15% to 66%)	23[c]
Mixed gender studies, total number of patients	**1,571,038** (429 to 566,407)	23
Male only studies, total number of patients	**79,265** (1,044 to 47,867)	4
Female only studies, total number of patients	**838,922** (3,220 to 174,638)	15[d]
Body Mass Index	**26** (23 to 30)	25
Location - USA/Canada, total number of patients	**1,487,412** (826 to 494,968)	21[d]
Location - Europe, total number of patients	**956,992** (1,044 to 566,407)	17[b]
Location - Asia/Australia, total number of patients	**44,821** (429 to 42,112)	4[c]

[a] Footnotes indicate RCTs represented in number of studies: [b]PREDIMED,[7,25-28] [c]Kwok 2012,[24] [d]WHI-DM[23,29-32]

The second trial was the WHI-DM, a multi-center trial which randomized 48,835 postmenopausal women to either a usual diet control or a dietary intervention which included goals of total fat intake of <20% of total calories, 5 or more servings per day of fruits and vegetables, and 6 or more servings per day of grains (*ie,* 2 of the 7 components of a Mediterranean diet).[23] Ninety-seven percent of participants had no history of cardiovascular disease at baseline. Participants were followed for an average of 8.1 years. There was no association between diet group and total mortality in either trial.

The third study followed 429 residents of 14 old-age hostels in Hong Kong for 33 months.[24] The intervention group received a diet containing 2 of the 7 Mediterranean diet components: fruit/vegetables and fish. The mortality rate was 13% (27/204) in the group following a Mediterranean diet compared to 11% (25/225) in the control group the statistical significance of this finding was not reported.

Cardiovascular Disease (RCTs only)

Cardiovascular disease outcomes were reported in 2 trials, described above [WHI-DM, PREDIMED, N = 56,282]. The primary endpoint in PREDIMED was major cardiovascular events (myocardial infarction, stroke, or cardiovascular death). Compared to the control diet, both Mediterranean diets were associated with a significant 30% reduction in the primary endpoint (HR 0.70, 95% CI 0.54, 0.92 for EVOO and HR 0.72, 95% CI 0.54, 0.96 for nuts).[7] When the 3 components of this composite endpoint were evaluated individually, only the reduction in stroke risk was significant (HR 0.68, 95% CI 0.49, 0.96).[7] There was no significant

difference between the 2 Mediterranean diets.[7] In WHI-DM, the incidence of all major cardiovascular outcomes reported (including myocardial infarction, CHD death, stroke, revascularization procedures, and various combinations of these outcomes) was similar between the 2 intervention groups.[32]

Type 2 Diabetes Mellitus (RCTs only)

T2DM was reported in 2 trials that included a total of 49,428 people. The PREDIMED study (described above) reported a subgroup analysis based on 3541 participants who did not have T2DM when enrolled in the trial.[26] Compared to the control diet, persons randomized to the Mediterranean diet supplemented with extra virgin olive oil had a significant reduction in risk of developing T2DM over a median 4.1 years of follow-up (HR 0.60, 95% CI 0.43, 0.85).[26] Those randomized to the Mediterranean diet supplemented with nuts had a non-significant reduction in risk of developing T2DM (HR 0.82, 95% CI 0.61, 1.10).

The second trial reporting T2DM as an outcome was the WHI-DM, described above.[30] The incidence of new onset T2DM was similar between the 2 diet groups (HR 0.96, 95% CI 0.90, 1.03).

Cancer (RCTS and cohort studies)

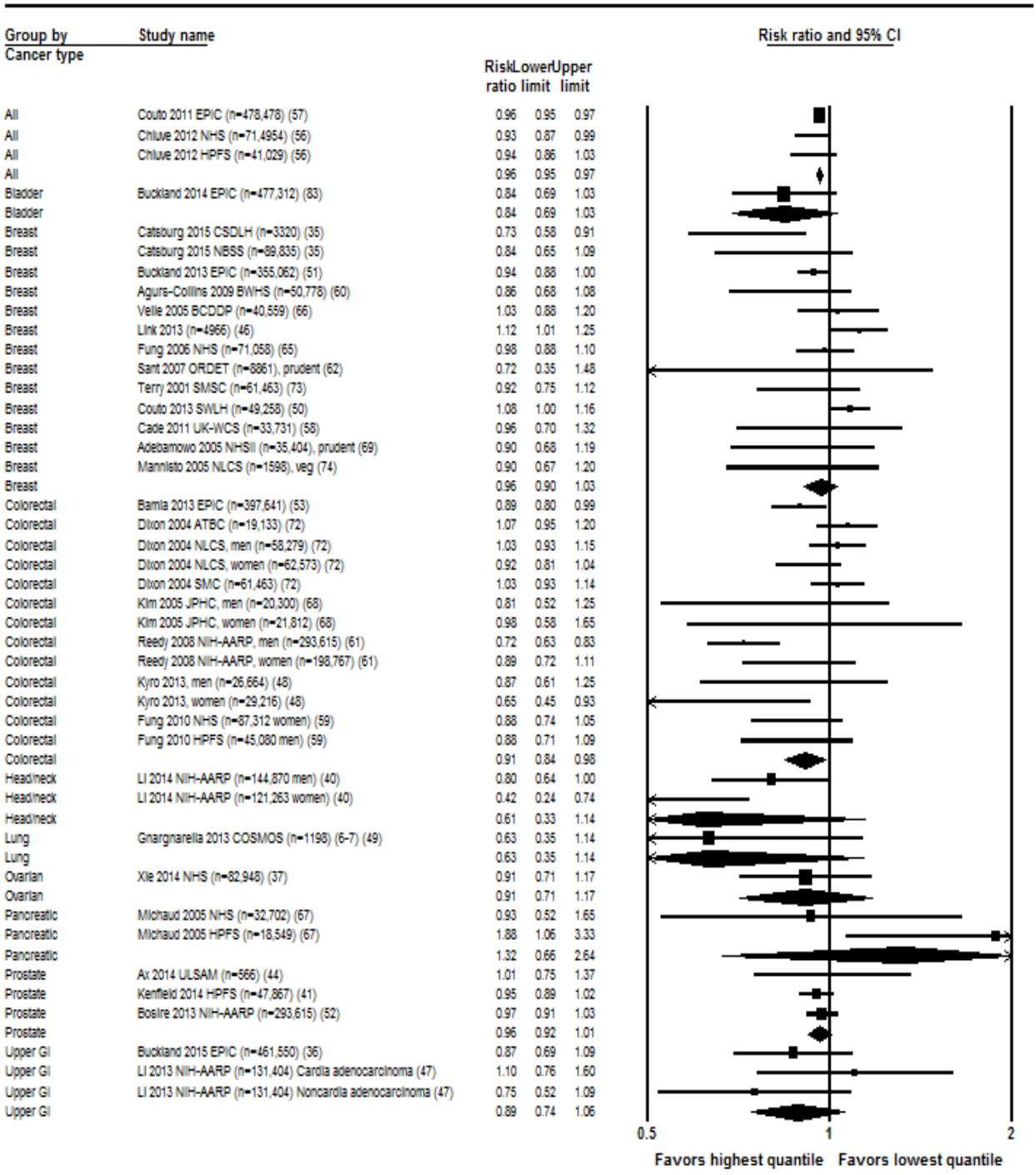
Cancer as an outcome was reported in 30 studies, 2 RCTs (WHI-DM, N = 63,805 and PREDIMED, N = 4,282) and 28 cohort studies, N = 2.5 million.[4,23,27,29,31,33-73]

Total Cancer Incidence

Total cancer incidence was reported in 3 cohort studies and one RCT.[23,56,57] Data from the Nurses' Health Study (NHS, N = 71,495 women) and the Health Professionals Follow-up Study (HPFS, N = 41,029 men), both of which had follow-up times of more than 20 years, were reported in one paper. The multivariate adjusted relative risk of any cancer in the highest compared to the lowest quintile of conformity to the Mediterranean diet was 0.94 (95% CI 0.90, 0.98) for men and women combined.[56] For women, higher diet conformity was associated with decreased risk of all cancer (RR 0.93, 95% CI 0.88, 0.99) but there was no association for men alone (RR 0.94, 95% CI 0.87, 1.03).[56] The third cohort study was conducted in 23 centers in 10 European countries. It enrolled 478,478 men and women and followed them for a median of 8.7 years. Conformity to the Mediterranean diet was assessed using the Mediterranean-diet score, a 9-point score calculated from self- or interviewer-administered food frequency questionnaires.[4] Higher conformity to a Mediterranean diet was associated with a significant reduction in cancer incidence (HR 0.96, 95% CI 0.95, 0.97 for a 2-point increment in the Mediterranean-diet score) (Figure 3).[57] Pooled results from these 3 studies indicated a significantly lower risk of total cancer incidence in people with higher compared to lower conformity to the Mediterranean diet (RR 0.96, 95% CI 0.95, 0.97).

The RCT (WHI-DM, described above) reported similar total cancer incidence in the 2 diet groups (HR 0.97, 95% CI 0.89, 1.05).[23]

Figure 3. Cancer Incidence by Cancer Type, Cohort Studies



I^2 breast = 53%, I^2 colorectal = 60%

Total Cancer Mortality

Total cancer mortality was reported in 13 cohort studies and one RCT.[4,23,33,34,38,39,42,43,45,54,55,63,71] Of the 13 cohort studies, 6 were conducted in Europe and 7 in North America. The studies included a total of 534,058 participants. In the one RCT (WHI-DM, described above) total cancer mortality was similar in the 2 diet groups (HR 0.95, 95% CI 0.90, 1.01) (Figure 4).[23]

Pooled results of the 13 cohort studies are displayed in Figure 4. There was a significant 14% reduction in total cancer mortality in those with the highest level of conformity to the Mediterranean diet compared to those with the lowest level (RR 0.86, 95% CI 0.82, 0.91; I^2 = 77%).

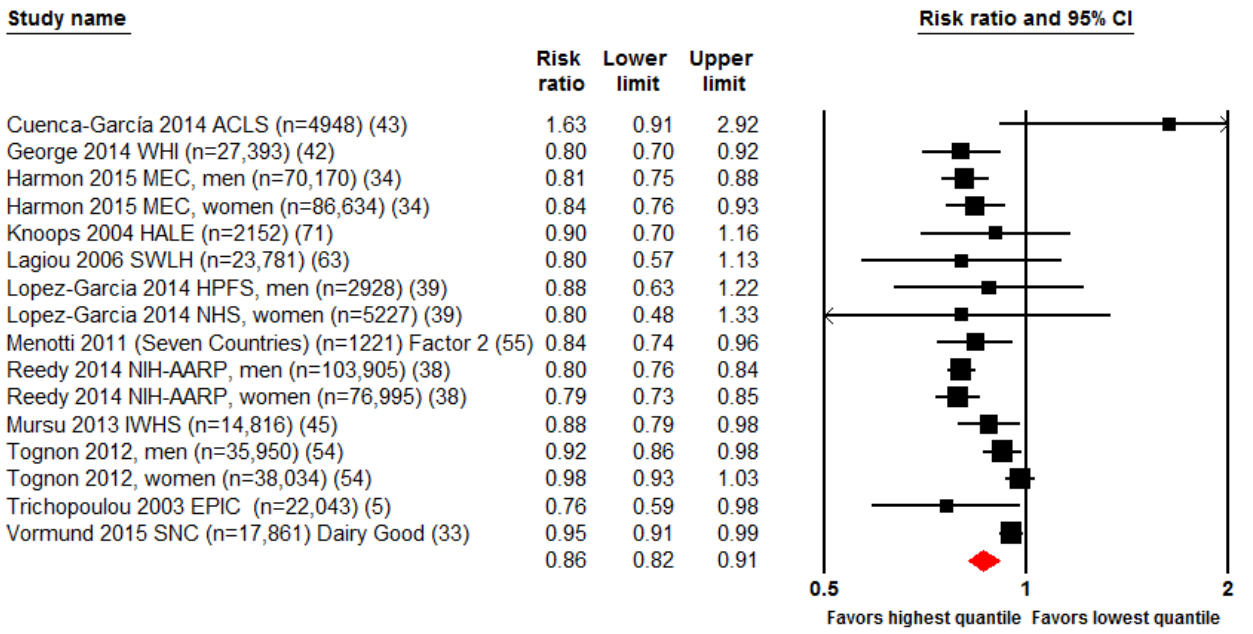
Breast Cancer

Breast cancer incidence was reported in 13 cohort studies and 2 RCTs (WHI-DM and PREDIMED).[27,31,35,46,50,51,58,60,62,65,66,69,73,74] Seven were conducted in the United States, 2 in Canada, and 6 in Europe. The 15 studies included more than 800,000 participants. In WHI-DM (described above), breast cancer incidence was similar between the 2 diet groups (HR 0.91, 95% CI 0.83, 1.01)(Figure 5).[31] In the PREDIMED trial (described above) breast cancer incidence in 4,152 women followed for 4.8 years was significantly lower compared to the control diet in participants assigned the Mediterranean diet with supplemental EVOO (HR 0.32, 95% CI 0.13, 0.79) but not the Mediterranean diet supplemented with nuts.[27]

Pooled results of the 13 cohort studies are displayed in Figure 3. Breast cancer incidence was similar in those who had the highest level of conformity to the Mediterranean diet and those who had the lowest level of conformity (RR 0.96, 95% CI 0.90, 1.03; I^2 = 53%).

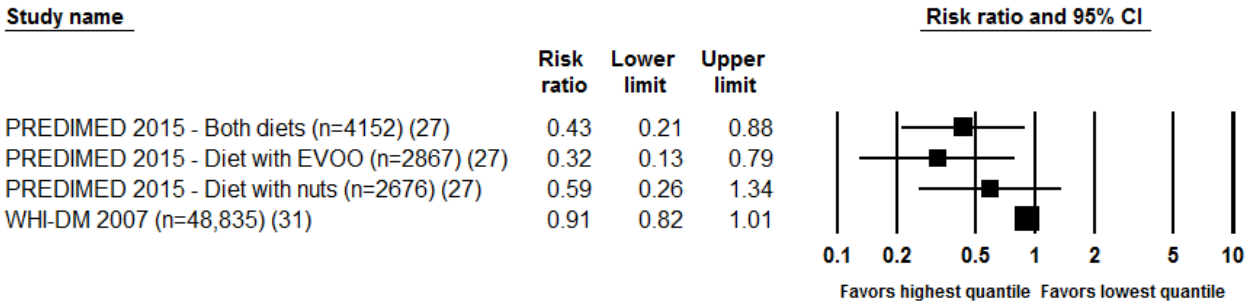
Breast cancer mortality was reported in one study, a prospective population-based cohort study conducted in Sweden (N = 77,151). It reported no association between conformity to a Mediterranean diet and breast cancer mortality (HR 1.12, 95% CI 0.97, 1.29) (Figure 6).[54]

Figure 4. Cancer Mortality, Cohort Studies



I^2 = 77%

Figure 5. Breast Cancer Incidence from PREDIMED and WHI – DM



Colorectal Cancer

Colorectal cancer incidence was reported in 9 cohort studies and one RCT.[23,48,53,59,61,68,72] Of the cohort studies, 5 were conducted in Europe, 3 in the US, and one in Japan. These 9 studies included over 1.3 million participants. In the RCT (WHI-DM, described previously) incidence of colorectal cancer and colorectal cancer mortality were similar between the 2 diet groups (incidence: HR 1.08, 95% CI 0.90, 1.29; mortality: HR 1.26, 95% CI 0.85, 1.85).[23]

Pooled results of the 9 cohort studies are shown in Figure 3. The incidence of colorectal cancer was significantly lower in people with highest conformity to the Mediterranean diet compared to people with the lowest conformity to the Mediterranean diet (RR 0.91, 95% CI 0.84, 0.98; I^2 = 60%).

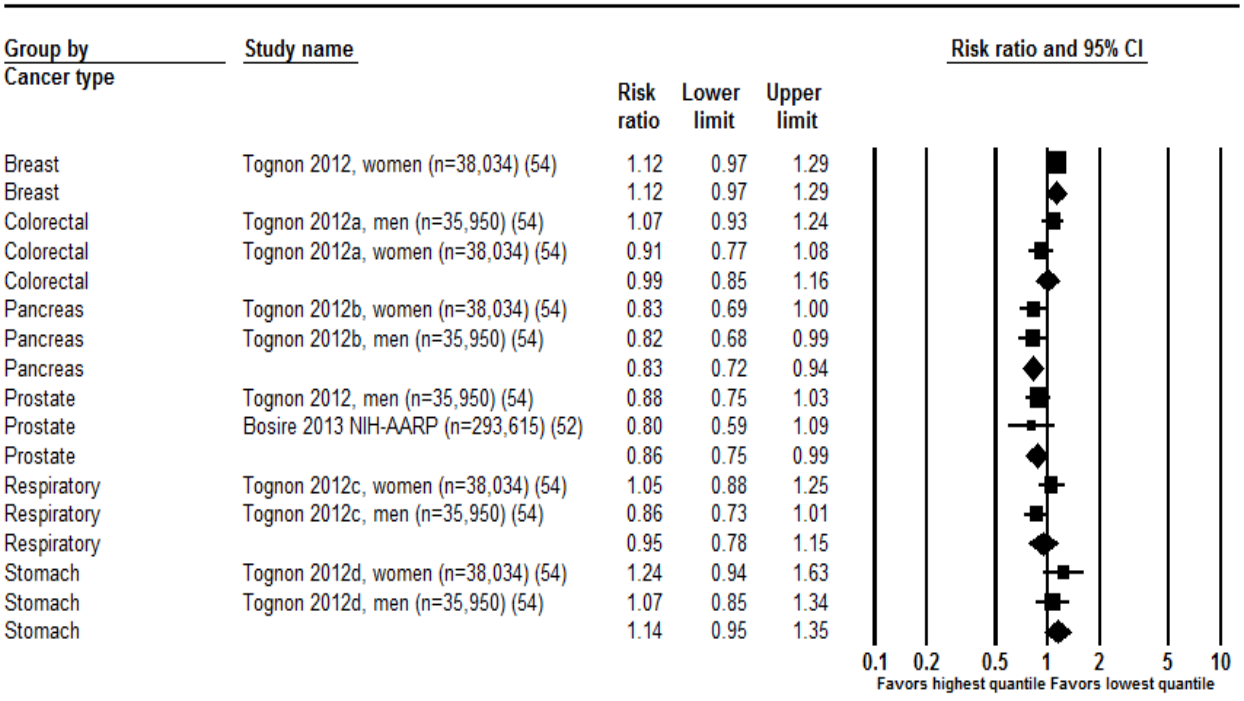
A prospective population-based cohort study conducted in Sweden (N = 77,151), reported no association between conformity to a Mediterranean diet and colorectal cancer mortality for men (HR 1.07, 95% CI 0.93, 1.24) or women (HR 0.91, 95% CI 0.77, 1.08) (Figure 6).[54]

Other Site-specific Cancer (Figure 3)

In cohort studies (Figure 3), the incidence of the following cancers was similar between people with high and low levels of conformity to a Mediterranean diet: ovarian (k = 1), pancreatic (k = 2), head and neck (k = 1), lung (k = 1), bladder (k = 1), prostate (k = 3), and gastric cancer (k = 2).[29,36,37,40,41,44,47,49,52,67,75] In an RCT (WHI-DM, described previously) incidence of ovarian, endometrial, and skin cancers were similar between the 2 diet groups.[29,31]

Two studies reported cancer site-specific mortality (Figure 6). In addition to the findings for breast and colorectal cancer mortality, the prospective population-based cohort study conducted in Sweden (N = 77,151), reported no association between conformity to a Mediterranean diet and stomach, prostate, or respiratory cancer mortality.[54] The authors did find an association between Mediterranean diet score and lower pancreatic cancer mortality but it was only significant in men (HR 0.82, 95% CI 0.68, 0.99).[54] A prospective US population-based cohort study of 293,464 men followed for an average of 8.9 years reported no association between conformity to a Mediterranean diet and incidence of fatal prostate cancer (HR 0.80, 95% CI 0.59, 1.10).[52]

Figure 6. Cancer Mortality by Cancer Type, Cohort Studies



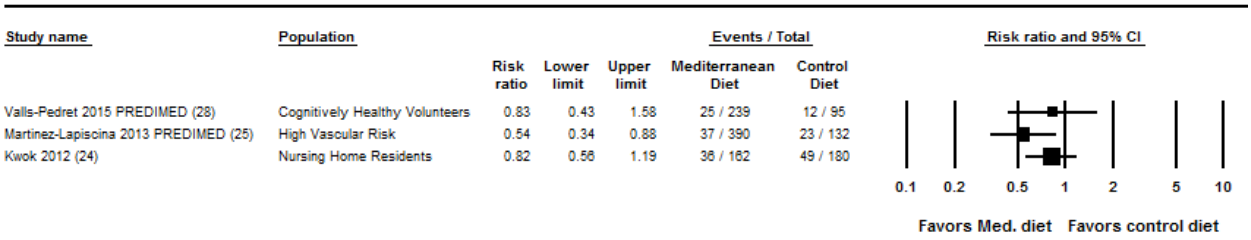
Cognitive Functioning

The effect of a Mediterranean diet on prevention of cognitive decline was reported in 2 RCTs and 14 cohort studies. A RCT conducted in Hong Kong enrolled "old age hostel" residents 75 years of age and older.[24] "Brain preservation" diet meals (fruits, vegetables, fish, reduced salt

intake, and less refined sugar) were provided to the residents in the intervention group. The mean age of the 429 participants was 83 years. At baseline, 59% of the intervention group and 66% of the control group had "questionable dementia" (defined as a Clinical Dementia Rating [CDR] score of 0.5). At 33 months follow-up, data were available for 79% of the intervention group and 80% of the control group. The intervention and control groups were similar in the proportion of patients who were classified as demented (14% intervention, 17% control; RR 0.81, 95% CI 0.49, 1.35) or with cognitive decline (a worsening of the CDR score) (22% intervention, 27% control, RR 0.82, 95% CI 0.56, 1.19) (Figures 7 and 8).[24]

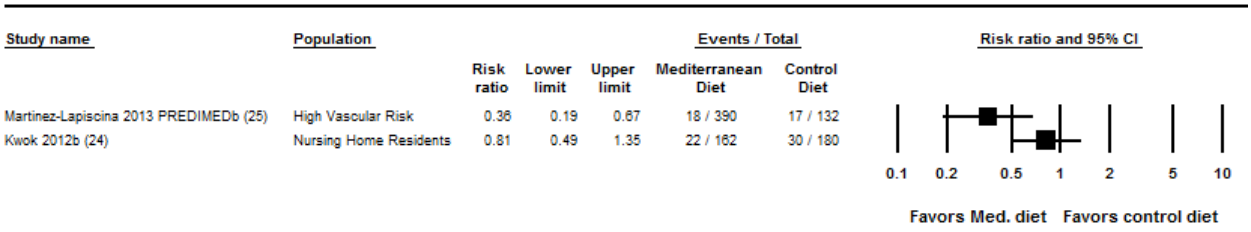
The second RCT was the PREDIMED study. Two of the study sites, Barcelona and Navarra, evaluated the effect of diet on incidence of mild cognitive impairment (MCI) and reported their results independently (Figure 7).[25,28] The Barcelona site, which enrolled 334 people followed for a median of about 4 years, reported similar Mini-Mental State Examination (MMSE) scores and risk of MCI for the intervention and control groups (Figure 7).[28] The Navarra site, which enrolled 522 people followed for a mean of 6.5 years, reported that the risk of MCI was significantly lower in the Mediterranean diet group (RR 0.54, 95% CI 0.34, 0.88) (Figure 7).[25] The Navarra site also reported a significantly lower incidence of dementia in the intervention groups compared to the control group (RR 0.36, 95% CI 0.19, 0.67) (Figure 8).[25]

Figure 7. Mild Cognitive Impairment (PREDIMED) or Cognitive Decline (Kwok)*



*Cognitive decline as defined by an increase in Clinical Dementia Rating Scale score

Figure 8. Dementia



Among the 14 cohort studies, 8 were from the US, 3 from Europe, and 3 from Australia.[76-91] Enrollments ranged from 527 to 16,058 and mean ages at enrollment (reported in 12 of the studies) ranged from 52 to 82. One study used 24-hour dietary records to compute a Mediterranean diet score that ranged from 0 to 9 and a Mediterranean-Style Dietary Pattern score that ranged from 0 to 100%.[80] The remaining studies used food frequency questionnaires to compute a Mediterranean-diet score, most commonly the instrument validated by Trichopoulou (2003), with values ranging from 0 to 9.[4] Follow-up periods ranged from 18 months to 28 years. The single most commonly used cognitive assessment tool was the mini-mental status exam (MMSE), although most studies used a battery of 4 to 18 tests.

Among these 14 cohort studies, only 7 found a significant association between higher conformity to a Mediterranean diet and improved cognitive outcomes (see bulleted list below). Studies presenting data in a way that allowed for determination of risk ratios are presented in Figure 9.

- An Australian study reported a significant correlation between baseline Mediterranean diet score and improvement in MMSE at 18 months, although tests of memory, verbal learning, and verbal fluency did not improve.[78] A study from France reported similar results finding higher diet conformity associated with fewer MMSE errors over a 5-year follow-up but no association with other cognitive tests or incident dementia.[77]

- Two studies from the US reported slower rates of cognitive decline (assessed with a battery of tests) were associated with higher Mediterranean diet conformity over mean follow-up periods of 4 years and 7.6 years.[89,90] Another US study reported a similar outcome for MMSE scores over a mean follow-up of 10.6 years.[91]

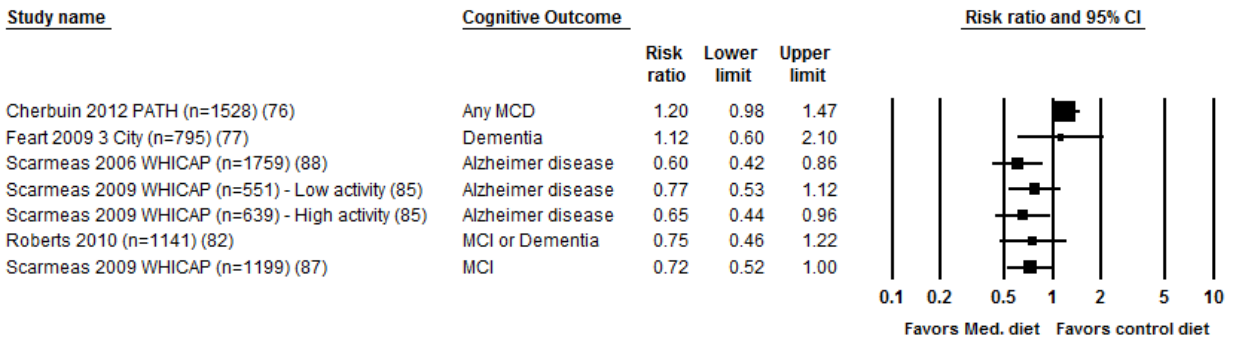
- A US study found a significant association between the highest tertile of Mediterranean-diet score and development of AD over a 4 year (mean) follow-up.[88] The significant association was maintained when the model was adjusted for all vascular variables.[86] In further analyses of the same cohort, a significant association between increased Mediterranean diet conformity and decreased risk of MCI was observed when diet was expressed as a continuous variable but the association was not significant when diet was expressed categorically (tertiles).[87] Another analysis found lower risk of AD in participants with high Mediterranean diet conformity and high levels of physical activity relative to those with low conformity and low activity.[85]

- A study from the US found no association between Mediterranean diet and decline in modified MMSE scores in the overall population although the association was significant in the African-American participants.[92]

- Five studies (2 from the US, and one each from Australia, France, and Greece) reported that diet conformity was not significantly associated with cognitive scores.[79-81,83,84]

- Two studies (one from the US and one from Australia) reported that diet conformity was not significantly associated with development of mild cognitive disorder (any), mild cognitive impairment, or dementia.[76,82]

Figure 9. Cognitive Outcomes for Observational Studies



Rheumatoid Arthritis

Rheumatoid arthritis was an outcome of interest in one paper. They reported results from the NHS and NHS-II, which together included 174,638 female registered nurses followed for over 20 years. Analysis of pooled data found similar risk of developing rheumatoid arthritis in women who scored in the highest and lowest quartiles of the aMED score (HR 0.98, 95% CI 0.80, 1.20).[93]

Diet-related Adverse Events

Participants in the PREDIMED study reported that they experienced no diet-related adverse effects.

KEY QUESTION 1A: DO THE EFFECTS VARY BY GENDER, AGE, OR BMI?

Gender

No RCTs reported outcomes stratified by gender. Seven cohort studies reported all cancer incidence and colorectal, head and neck, and pancreatic cancer incidence. Six cohort studies reported all cancer mortality separately in men and women (Table 2).[33,34,38-40,48,54,56,57,59,61,67,68,72]

Two cohort studies reported cognitive performance by gender (Table 2).[80,90]

Age

The WHI-DM reported risk of composite coronary heart disease and T2DM by age and found no significant interaction between age and risk for either (P = .58 and P = .66, respectively).[30,32]

Two RCTs reported cancer incidence stratified by age groups. The WHI-DM RCT reported total invasive cancer, invasive ovarian cancer, colorectal cancer, non-melanoma skin cancer, and melanoma incidence by diet group for 3 age strata: 50-59 years, 60-69 years, and 70 years and older.[23,29,31] There were no significant interactions between age group and intervention group. The PREDIMED trial reported a post-hoc subgroup analysis of breast cancer incidence in women over and under the age of 67. Breast cancer incidence was significantly reduced in women who were 67 years old or younger (HR 0.16, 95% CI 0.05, 0.50) but not in women over the age of 67 (HR 0.92, 95% CI 0.34, 2.47).[27] However, a test for interaction was not reported.

Two cohort studies reported cancer incidence by age groups and one reported cancer mortality by age (Table 2).[63,72,75]

One cohort study reported cognitive outcomes by age (Table 2).[90]

BMI

The WHI-DM reported risk of composite coronary heart disease and T2DM by BMI and found no significant interaction between BMI and risk for either (P = .07 and P = .74, respectively).[30,32]

Two RCTs reported outcomes by BMI. In WHI-DM there were no differences in incidence of total invasive, invasive ovarian, colorectal, or non-melanoma skin cancers by BMI category.[23,29,31] The PREDIMED trial found significantly reduced breast cancer incidence in women with a BMI less than 30 (HR 0.29, 95% CI 0.11, 0.83) but not in those with a BMI of 30 or greater (HR 0.57, 95% CI 0.22, 1.49). However, a test for interaction was not reported.[27]

Two cohort studies reported cancer incidence by BMI groups (Table 2).[51,60] One cohort study (WHI-OS) reported all cancer mortality in different BMI groups (Table 2).[42]

Summary of Findings for Key Questions 1 and 1A

There is evidence from one RCT that the Mediterranean diet significantly decreases risk of major cardiovascular events, development of T2DM, and incidence of breast cancer.[7,26,27] Cohort studies suggest that the Mediterranean diet may be associated with decreased incidence of, and

mortality from, cancer. The data on cognitive impairment and the available subgroup analyses by age, gender, and BMI are limited and showed mixed results.

Strength of Evidence for Key Questions 1 and 1A

We assessed strength of evidence for all-cause mortality, cancer incidence, and cognitive functioning. The strength of evidence was low for all outcomes evaluated (Table 3).

Table 2. Effect of Greater Diet Conformity on Outcomes by Gender, Age, and BMI in Cohort Studies

Outcomes and Studies	Gender	Age	BMI
NHS/HPFS[56]	Significantly lower in women not men		
EPIC[57]	Significantly lower in women and men		
EPIC[75]		Similar in all age groups	Similar in all BMI groups
SMSC[73]		Similar in all age groups	
BWHS[60]			Significantly lower with BMI < 25 only
NIH-AARP[61]	Significantly lower in men not women		
Kyro 2013[48]	Significantly lower in women not men		
NLCS[72]	Similar in women and men		
JPHC[68]	Similar in women and men		
NHS/HPFS[59]	Similar in women and men		
NIH-AARP[40]	Significantly lower in women not men		
NHS/HPFS[67]	Significantly higher in men not women		
MEC[34]	Significantly lower in women and men		
NHS/HPFS[39]	Similar in women and men		
NIH-AARP[38]	Significantly lower in women and men		
Tognon 2012[54]	Significantly lower in men not women		
SNCG[33]	Significantly lower in men not women		
SWLH[63]		Similar in all age groups	
WHI-OS[42]			Significantly lower with BMI <30 only
MAP[90]	Significantly better in women and men	Significantly better in all age groups	
SU.VI.MAX[80]	Similar in women and men		

Table 3. Strength of Evidence

Outcome	Strength of evidence	Direction	Study design; # studies (N)	Summary/Rationale[a]
Key Question 1: Primary Prevention Studies				
All-cause Mortality	Low	Similar	3 RCTs PREDIMED (7,447) WHI-DM (48,835) Kwok 2012 (429)	Incidence of all-cause mortality was similar between the Mediterranean-like diet and the control diet groups in the 2 larger studies (PREDIMED-combined diets HR 0.89 [95% CI 0.71, 1.12]; WHI HR 0.98 [95% CI 0.91, 1.07]). The trials were not pooled due to large dissimilarity of the study diets. Overall risk of bias is low. Consistency is unknown and there was imprecision (PREDIMED).
All Cancers Incidence	Low	RCT Similar Observational Lowered risk	1 RCT WHI-DM (48,835) 3 Observational (591,002)	In WHI, all cancer incidence was similar between the Mediterranean-like diet and the control diet groups (HR 0.97 [95% CI 0.89, 1.05]). Three large cohort studies reported highest conformity to a Mediterranean diet was associated with a reduction in total cancer incidence compared with lowest conformity (reference group) (pooled HR 0.96 [95% CI 0.95, 0.97]). There is inconsistency between WHI and the cohort studies, and overall risk of bias is medium.
Breast Cancer Incidence	Low	RCT Mixed Observational Similar	2 RCTs WHI-DM (48,835) PREDIMED (4,152) 13 Observational (range 3,320 to 355,062)	In PREDIMED, breast cancer incidence was lower in the combined Mediterranean diet groups compared to control (HR 0.43 [95% CI 0.21, 0.88]). In WHI, breast cancer incidence was similar between the Mediterranean-like diet and the control diet groups (HR 0.91 [95% CI 0.83, 1.01]). The trials were not pooled due to large dissimilarity of the study diets; consistency is unknown. The cohort studies found breast cancer incidence was similar between the highest and lowest conformity groups (RR 0.96 [95% 0.90, 1.03]). Overall risk of bias is medium.
Colorectal Cancer Incidence	Low	RCT Similar Observational Lowered risk	1 RCT WHI-DM (48,835) 9 Observational (range 19,133 to 397,641)	In WHI, colorectal cancer incidence was similar between the Mediterranean-like diet and the control diet groups (RR 1.08 [95% CI 0.90, 1.29]). In the cohort studies, highest conformity to a Mediterranean diet was associated with a reduction in colorectal cancer incidence compared with the lowest conformity (RR 0.91 [95% 0.84, 0.98]) with moderate heterogeneity between studies (I^2 = 60%). There is inconsistency between WHI and the cohort studies, and overall risk of bias is medium.

Outcome	Strength of evidence	Direction	Study design; # studies (N)	Summary/Rationale[a]
Cognitive Functioning	Low	Mixed	2 RCTs PREDIMED (334 and 522) Kwok[24] (429) 14 Observational (range 527 to 16,058)	A sub-study of PREDIMED involving cognitively healthy volunteers (n = 334) reported incidence of MCI was similar between the Mediterranean diet and the control diet groups. A sub-study of PREDIMED of patients with high vascular risk (n = 522) reported risk of MCI and dementia was lower in the Mediterranean diet group compared with the control diet group. An Asian trial of older nursing home residents (n = 429) found the proportions of patients classified as demented or with cognitive decline was similar between the Mediterranean-like diets and the control diet groups. The trials were not pooled due to the large dissimilarity of the study diets and populations, resulting in unknown consistency. Overall risk of bias is moderate. The results from the observational studies were mixed. Three studies analyzing Mediterranean diet as a continuous score reported higher conformity to a Mediterranean diet slowed rates of cognitive decline; 4 did not. Six cohort studies analyzing Mediterranean diet as a categorical variable reported no association with levels of diet conformity and cognitive outcomes; 3 reported mixed results across different subgroups or analyses. Overall risk of bias is medium.
Key Question 2: Secondary Prevention Studies				
All-cause Mortality	Insufficient	Similar	3 RCTs (2,277)	Incidence of all-cause mortality was similar between the Mediterranean-like diets and the control diet groups (RR 0.95 [95% CI 0.53, 1.69]; I^2 = 51%). There is large imprecision and inconsistency, and overall risk of bias is medium.

RCT = randomized controlled trial; PREDIMED = Prevención con Dieta Mediterránea; WHI = Women's Health Initiative; HR = hazard ratio; RR = risk ratio; MCI = mild cognitive impairment

[a] Strength of Evidence Definitions[22]

Precision: Degree of certainty surrounding an effect estimate; in meta-analysis, the confidence interval around the summary effect size

Consistency: Degree to which reported effect sizes appear to have the same direction of effect

Directness: Whether the evidence links the interventions directly to health outcomes

Risk of bias: Degree to which includes studies have a high likelihood of protection against bias; 2 main elements are study design and aggregate quality of the studies

KEY QUESTION 2: Compared to other diets, is the Mediterranean diet associated with fewer adverse outcomes (including death) or less disease progression in people who already have diabetes, cardiovascular disease, cancer, hypertension, cognitive impairment, rheumatoid arthritis, or kidney disease?

Overview of Studies (Table 4 and Appendix C, Table 5)

We identified a total of 19 articles reporting results from 15 studies (Table 4). Eight of the studies were randomized controlled trials and 7 were cohort studies. Six studies were conducted in patients with cancer, 6 in patients with cardiovascular disease, one in patients with cognitive impairment, and 2 in patients with rheumatoid arthritis. Seven of the 15 studies were done in the United States, 5 in Europe, and 3 in Asia. The total number of participants was 19,972 and the mean sample size was 1,331. The mean age of participants was 61.8 years (k = 9 reporting) and the mean BMI was 26.8 (k = 6). Of studies that included both men and women, the mean percentage of men was 64.2% (k = 5). The dietary interventions used in the RCTs are described in Table 5. The cohort studies used a variety of scales to rate each individual's degree of conformity to the Mediterranean diet (see Methods section). No studies reported kidney disease or hypertension.

Table 4. Summary of Included Studies - Key Question 2

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Studies Reporting
Total number of patients evaluated	**19,972** (51 to 4,538)	15
Randomized controlled trials, total number of patients	**5,865** (51 to 3,114)	8
Cohort studies, total number of patients	**14,107** (482 to 4,538)	7
Secondary prevention of cancer, total number of patients	**13,625** (926 to 4,538)	6
Secondary prevention of cardiovascular disease, total number of patients	**5,684** (101 to 3,114)	6
Secondary prevention of cognitive impairment, total number of patients	**482**	1
Secondary prevention of rheumatoid arthritis, total number of patients	**181** (51 to 130)	2
Age of subjects, years	**61.8** (54 to 78)	9
Gender, % male patients in mixed gender studies	**64.2%** (20 to 90)	5
Mixed Gender studies, total number of patients	**4,112** (51 to 1,009)	8
Male only studies, total number of patients	**8,578** (926 to 4,538)	3
Female only studies, total number of patients	**7,282** (130 to 2,619)	4
Body Mass Index	**26.8** (25.4 to 28)	6
Location - USA/Canada, total number of patients	**11,686** (101 to 4,538)	7
Location - Europe, total number of patients	**6,422** (51 to 3,114)	5
Location - Asia/Australia, total number of patients	**1,864** (406 to 1,000)	3

Table 5. Dietary Interventions Used in Trials

RCT Author , Year	Intervention Diet	Control Diet
Burr 2003[94]	3 components (fruits/vegetables, grains/cereals, and low meat/fish)	-Fish -Fruit/vegetables and grains/cereals -'Sensible eating' non-specific advice that did not include the intervention
Lyon Heart Study[6,95-97]	4 components (fat ratio, fruits/vegetables, grains/cereals, and low meat/fish)	Did not receive dietary information from the investigators
Singh 2002[98]	4 components (fat ratio, fruits/vegetables, legumes, and grains/cereals)	National Cholesterol Education Program Step I Prudent Diet (low total and saturated fat, and low cholesterol)
Singh 1992[99]	2 components (fruits/vegetables, low meat/fish)	Prudent diet reflecting the recommendations of the American Heart Association (low meat, eggs, and hydrogenated oil/butter; replaced by meat substitutes and nut oils)
Singh 1991[100]	5 components (fat ratio, fruit/vegetables, legumes, grains/cereals, and low meat/fish)	Usual care
Tuttle 2008[8]	7 components (fat ratio, fruit/vegetables, legumes, grains/cereals, red wine, dairy, and low meat/fish)	Low-fat diet, the American Heart Associate Step II diet (low saturated fat and cholesterol, fruits/vegetables, and grains/cereals)
McKellar 2007[101]	3 components (fat ratio, fruit/vegetables, and legumes)	Received readily available written information on healthy eating
Skoldstam 2003[102]	3 components (fat ratio, fruit/vegetables, and dairy)	Usual diet

Outcomes (Appendix C, Tables 6 – 11)

Cardiovascular Disease and All-cause Mortality

Six RCTs (N = 5,684) reported outcomes in participants with pre-existing cardiovascular disease. The mean sample size was 947. One study was set in the United States, 2 in Europe, and 3 in Asia. The outcomes reported in these studies included all-cause mortality (k = 6), cardiovascular mortality (k = 5), diet-related adverse events (k = 2), new myocardial infarction (k = 5), new stroke (k = 4), new revascularization procedure (k = 3), and development of heart failure (k = 4). Three of the RCTs may contain fraudulent data so we performed our analyses both including and excluding these studies.[98-100,103]

The other 3 RCTs were:

- The Lyon Heart Study which enrolled 605 people after a first myocardial infarction, randomized them to either a 3-component Mediterranean diet group or a no-advice group, and followed them for an average of 2.3 years.[95]

- A Welsh trial which randomized 3,114 men with a history of angina to 4 diet groups (1. oily fish; 2. fruit, oats, and fiber; 3. combination of 1 and 2; and 4. non-specific advice).

Group 3 met our definition of a Mediterranean diet. This trial was interrupted by funding problems. Many of the analyses were performed not by group but by specific dietary components (*eg,* fish advice, fruit advice).[94]

- A trial from Spokane, Washington that enrolled 101 patients within 6 weeks of a first myocardial infarction and randomized them to either a "Mediterranean-style diet" (low fat that emphasized increased consumption of fruits and vegetables, whole grains, cold-water fish, and oils from olives, canola, and soy beans) or a low-fat diet (that emphasized fruits and vegetables and whole grains) and followed them for an average of 4 years.[8]

All-cause Mortality

All 6 of the cardiovascular RCTs reported all-cause mortality. Two of these RCTs reported significantly decreased all-cause mortality in the participants assigned to the Mediterranean compared to the control diet (RR 0.44, 95% CI 0.21, 0.94 and RR 0.55, 95% CI 0.34, 0.75) respectively).[6,97,99] Four studies found similar mortality in the Mediterranean and control diet groups.[8,94,98,100]

Pooled results from the 6 studies showed that all-cause mortality was similar in the Mediterranean diet and the control diet groups (RR 0.85, 95% CI 0.59, 1.21; I^2 = 57%).[6,8,94,97-100] The analysis conducted without the questionable data also showed no evidence of reduction in all-cause mortality (RR 0.95, 95% CI 0.53, 1.69; I^2 = 51%).[6,8,94,97]

Cardiovascular Mortality

Five RCTs reported cardiovascular mortality. Two studies found decreased cardiovascular mortality in participants assigned a Mediterranean diet compared to controls (RR 0.35, 95% CI 0.15, 0.83 and RR 0.58, 95% CI 0.34, 0.83, respectively).[6,97,99] The other 3 studies found that cardiovascular mortality was similar in both diet groups.[8,94,98]

Pooled data from all 5 RCTs show that cardiovascular mortality was similar in groups assigned a Mediterranean and control diet (RR 0.69, 95% CI 0.44, 1.08; I^2 = 67%).[6,8,94,97-99] This result was essentially unchanged when the analysis was conducted without the questionable data (RR 0.68, 95% CI 0.18, 2.47; I^2 = 87%).[6,8,94,97]

Myocardial Infarction

New myocardial infarction was reported as an outcome in 5 RCTs. Two of the 5 studies reported significantly decreased rates of MI in participants assigned to the Mediterranean diet group.[98,99] A third study found similar rates of MI for both groups.[8] The other 2 studies reported fewer MIs in the intervention group than in the control group but the statistical significance of these differences was not reported.[6,100]

We were able to pool data from 4 of the RCTs.[6,8,98,99] The pooled data show that randomization to a Mediterranean diet significantly decreased risk of a new MI (RR 0.56, 95% CI 0.44, 0.72; I^2 = 0%). This finding remained essentially the same when the analysis was conducted without the questionable data (RR 0.32, 95% CI 0.15, 0.67; I^2 = 0%).[6,8]

Stroke

Four RCTs reported new stroke. Two found similar rates in both diet groups.[8,98] The other 2 studies reported fewer strokes in the intervention group than control but did not report the statistical significance.[96,100]

Analysis of the 3 studies that could be pooled shows that participants assigned a Mediterranean diet had similar incidence of new stroke as those assigned a control diet (RR 0.66, 95% CI 0.19, 2.30; $I^2 = 31\%$).[8,96,98] This finding was not qualitatively different when the questionable data were removed (RR 0.76, 95% CI 0.04, 14.51; $I^2 = 61\%$).[8,96]

Other Outcomes

Three RCTs reported incidence of revascularization procedures.[8,95,96,98] The pooled data show similar incidence in the Mediterranean diet and the control diet groups (RR 0.75, 95% CI 0.42, 1.35). This finding was the same when the questionable data were excluded (RR 0.91, 95% CI 0.54, 1.53).[8,95,96]

Four RCTs reported development of heart failure.[6,95,96,98,100] One of the studies, whose data integrity has been questioned, found that participants assigned a Mediterranean diet developed heart failure significantly less often than participants assigned a control diet although the relative risk was not reported.[98] Another study from the same group reported that 2 patients in the Mediterranean diet group and 2 patients in the control diet group developed heart failure.[100] A US study reported no heart failure in either diet group.[8] The Lyon Heart study reported 6 cases of heart failure in the Mediterranean diet group and 11 in the control group.[6,96]

Cancer

Six cohort studies reported outcomes in people with cancer at baseline (N = 13,625). Three of these reported breast cancer outcomes, 2 colon cancer, and 2 prostate cancer.[41,104-110] Five studies were conducted in the United States and one in Europe. The average sample size was 2,271 and the mean age of participants was 64.4 years (k = 3).

Breast Cancer (k = 3)

Both a German study that followed 2,522 post-menopausal breast cancer patients for a median of 5.5 years, and a US study of 1,901 women with early stage breast cancer followed for an average of 3.2 years found similar rates of breast cancer recurrence and mortality across quartiles of conformity to the Mediterranean diet (P for trends >0.05) (Figure 10).[107,109] The NHS, an American study following nurses for more than 6 years, found similar rates of breast cancer mortality across quantiles of an aMED score and, in a sub-study, conformity to a prudent pattern.[105,106]

Colon Cancer (k = 2)

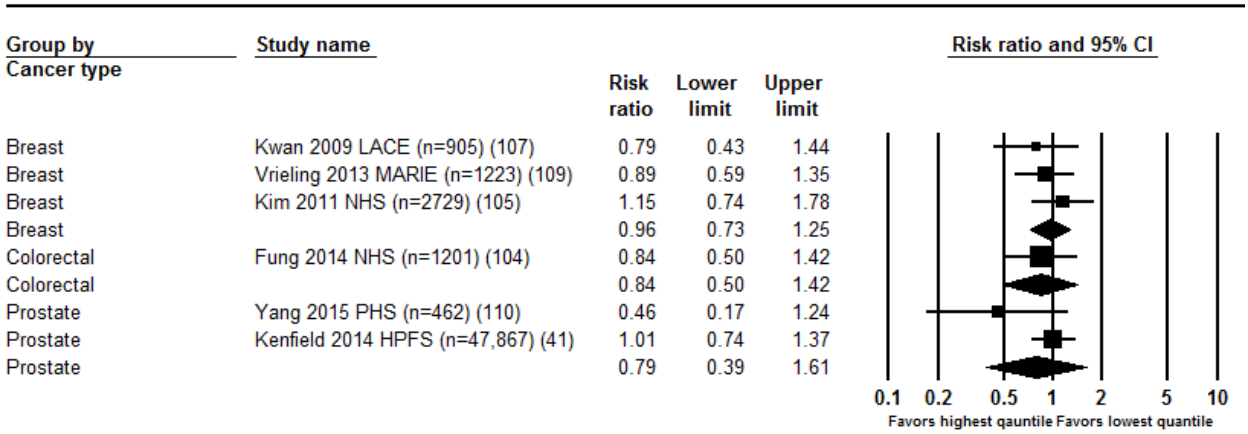
A US study of 1,009 patients with stage III colon cancer followed for an average of 5.3 years found similar rates of colon cancer recurrence across quintiles of conformity to the Mediterranean diet (termed a "prudent" diet) (HR 1.13, 95% CI 0.77, 1.67).[108] A second US study (NHS) of 1,201 women with stage I-III colon cancer followed for a median of 11.2 years

evaluated colon cancer-specific mortality and found no association with aMED score or prudent pattern (Figure 10).[104]

Prostate Cancer (k = 2)

A US study, the Health Professionals Follow-up Study (HPFS), followed 4,538 men with prostate cancer for an average of 9 years and found similar incidence of prostate cancer-specific mortality comparing highest to lowest conformity to a Mediterranean diet (HR 1.01, 95% CI 0.74, 1.37) (Figure 10).[41] Another US study, the Physicians' Health Study (PHS), followed men for 9.9 years and also found similar incidence of prostate cancer specific mortality in participants in the highest and lowest quantiles of a prudent dietary pattern (HR 0.46, 95% CI 0.17, 1.24).[110]

Figure 10. Cancer-specific Mortality by Cancer Type[a]



[a] Sample sizes based on numbers in highest and lowest quantiles (the comparison groups), if provided; otherwise sample size is for entire cohort

Cognitive Impairment

One cohort study of 482 Medicare beneficiaries in New York with mild cognitive impairment reported progression to Alzheimer's Disease.[87] Mean age at enrollment was 78 years and 32% of participants were male. Mean follow-up was 4.3 years. When conformity to a Mediterranean diet was analyzed as a continuous variable, the hazard ratio (per unit of Mediterranean-diet score) for development of AD was not significant (0.89, 95% CI 0.78, 1.02). When conformity to a Mediterranean diet was analyzed by tertiles with the lowest tertile as the reference group, the hazard ratios were significant for both the middle and highest tertiles, indicating that greater conformity to a Mediterranean diet was associated with a lower risk of developing AD. For the highest tertile, the hazard ratio was 0.52 (95% CI 0.30, 0.91).

Rheumatoid Arthritis

One RCT from Sweden and one CCT from the UK enrolled patients with rheumatoid arthritis.[101,102] The RCT included 51 patients with clinically stable disease of at least 2 years duration.[102] Intervention group patients received dietary instructions and some food supplied at no cost. The control group followed a usual diet. After a 3-week outpatient rehabilitation program (meals provided according to group assignment), participants prepared their own meals for the next 9 weeks. Mean age was 58 years, 20% were male, and mean disease duration was

13.6 years (significantly longer in the intervention group: 17 years vs 10 years). There were significant improvements at 12 weeks in the Mediterranean diet group compared to the control group on a global pain score, the 28 joint disease activity score, and the health assessment questionnaire.[102]

The CCT enrolled 130 women age 30 to 70 years from areas of "social deprivation." Participants received either instruction on the Mediterranean diet or readily available information on healthy eating. Mean age of the participants was 54 years; mean disease duration was 9.4 years. At 6 months, mean global pain scores were significantly lower in the Mediterranean diet group compared to the control group. Mean scores on the Health Assessment Questionnaire were significantly better in the Mediterranean diet group at 3 months but not 6 months. Joint disease activity scores were similar in both groups at 3 and 6 months.[101]

Diet-related Adverse Events

Four studies reported adverse events related to the diet. One found no side effects[8] while the other 3 reported minor digestive problems such as diarrhea, dyspepsia, and mild belching in a couple of patients assigned to the intervention diet.[8,95,99,102]

KEY QUESTION 2A: Do the effects vary by gender, age, or BMI?

The reported data did not allow for subgroup analysis by age, gender, or BMI.

Summary of Findings for Key Question 2

Randomization to a Mediterranean diet significantly reduced myocardial infarction but had no significant effects on cardiovascular mortality, stroke, revascularization procedures, or congestive heart failure. There is no evidence that a Mediterranean diet reduces incidence of recurrent breast or colon cancer or mortality associated with breast, colon, or prostate cancer. There is limited, mixed data on the effects of the Mediterranean diet on progression of cognitive impairment and rheumatoid arthritis.

Strength of Evidence for Key Question 2

We assessed strength of evidence for all-cause mortality only and it was rated as insufficient (Table 3).

KEY QUESTION 3: What is the observed adherence to the Mediterranean diet in studies conducted in the United States or Canada?

Two RCTs, conducted in the United States, reported data on adherence (Appendix C, Tables 12 and 13). The WHI-DM, described above in Key Question 1, reported significant changes (all P<0.001) at year 3 in the intervention compared to the control group in consumption of red meat (20% reduction), grains (18% increase), and vegetables and fruit (47% increase).[23]

The second study was a 4-site population-based multicenter trial that enrolled 810 adults with mildly elevated blood pressure.[111] About a third of the participants were African-American and all were recruited from the community. Subjects were randomized to one of 3 groups: general advice on diet, physical activity, and weight loss delivered in 2 30-minute sessions (Group A); behavioral interventions including group and individual counseling sessions designed to encourage weight loss and increase physical activity (Group B); and Group C, which in addition to the Group B interventions received specific advice on increased consumption of fruits and vegetables and low-fat dairy products and reduced consumption of total and saturated fat. At 18 months of follow-up, there was a significant increase of 2.6 (95% CI 2.2, 3.2) servings per day of fruits and vegetables in group C compared to either of the other 2 groups.[111]

SUMMARY AND DISCUSSION

The Mediterranean diet was first described over 50 years ago by Ancel Keys.[1] Interest in this diet has intensified in recent years as many developed and developing countries confront a dramatic increase in obesity and chronic diseases linked to consumption of a typical Western diet rich in red meat, dairy products, processed and artificially sweetened foods, and salt.[112] In contrast, the diet typically consumed in Mediterranean countries in the 1960s emphasized consumption of olive oil, fruits, vegetables, legumes, and whole grains. Many epidemiologic studies, and more recently RCTs, have investigated the effect of this diet on incidence of, and morbidity from, common chronic conditions such as cardiovascular disease, T2DM, and cancer.[3-8] The purpose of this review was to provide an updated summary of the available evidence on the health benefits of the Mediterranean diet.

The Key Questions we addressed were:

Key Question 1: Is the Mediterranean diet more effective than other diets in preventing death or the development of type 2 diabetes mellitus, cardiovascular disease, cancer, hypertension, cognitive impairment, or kidney disease?

Key Question 1a: Do the effects vary by gender, age, or BMI?

Key Question 2: Compared to other diets, is the Mediterranean diet associated with fewer adverse outcomes (including death) or less disease progression in people who already have diabetes, cardiovascular disease, cancer, hypertension, cognitive impairment, rheumatoid arthritis, or kidney disease?

Key Question 2a: Do the effects vary by gender, age, or BMI?

Key Question 3: What is the observed adherence to the Mediterranean diet in studies conducted in the United States or Canada?

OVERVIEW OF METHODS

This systematic review included a total of 55 studies published in English between 1990 and August 2015 that enrolled free-living, non-pregnant, non-lactating adults. We included RCTs that enrolled at least 100 people and followed them for at least a year. For select outcomes (cancer, cognitive impairment, and rheumatoid arthritis) we also included cohort studies.

We included studies whose diets met the criteria used in a recent Cochrane Review[17] (*ie*, labelled a Mediterranean diet or meeting 2 or more of the following components: 1. high monounsaturated:saturated fat ratio (use of olive oil as main cooking ingredient); 2. high consumption of fruits/vegetables; 3. high consumption of legumes; 4. high consumption of grains/cereals; 5. moderate red wine consumption; 6. moderate consumption of dairy products; and 7. low consumption of meat and meat products replaced by increased consumption of fish). All included studies met this minimum definition. The names for the diets included terms such as Mediterranean diet, prudent diet, healthy Nordic diet, and healthy pattern.

SUMMARY OF EVIDENCE BY KEY QUESTION

KQ1: Primary Prevention

We identified 42 studies (3 RCTs and 39 cohort studies) that reported the association between conformity to a Mediterranean diet and the occurrence of outcomes in over 2 million people without a history of the outcome of interest (primary prevention). We found no studies reporting new onset kidney disease or hypertension.

Cardiovascular disease and all-cause mortality (RCTs only). Three trials that included a total of 56,711 people evaluated the effect of the Mediterranean diet on major cardiovascular outcomes (MI, stroke, and CV death) and all-cause mortality.[7,23,24,32] All-cause mortality was similar between diet groups in the 2 trials that reported statistical significance.[7,23]

The PREvencion con DIeta MEDiterranea (PREDIMED) was a Spanish trial of 7,447 people randomized to either a Mediterranean diet with supplemental extra virgin olive oil, a Mediterranean diet supplemented with nuts, or a low-fat control diet. Both of the intervention diets included 5 of the 7 components in our Mediterranean diet definition. After an average follow-up of 4.8 years, both intervention groups had a significant 30% reduction in major cardiovascular events compared to the control group. When the individual components of the composite endpoint were evaluated, only stroke was significantly reduced in the Mediterranean diet group compared to the control group.

The WHI-DM was a US trial of 48,835 women, aged 50-79, assigned either a low-fat diet (which included 2 of the 7 components of the Mediterranean diet) or a usual diet control. After an average follow-up of 8.1 years, there was no significant reduction in major cardiovascular events (either as a composite or individually) in the group assigned to the intervention diet.

Disparate results in these 2 trials may reflect differences in the diets evaluated. In PREDIMED the intervention diet included 5 of the 7 Mediterranean diet components and the control was a low-fat diet. In contrast, in WHI-DM the intervention group received a low-fat diet (which included advice to increase fruit and vegetable and grain intake and thus met our definition of a Mediterranean diet) whereas the control group received general advice only. The fact that the intervention diet in WHI-DM is more similar to the PREDIMED control diet than to the PREDIMED intervention diet may explain why WHI-DM found no benefit and PREDIMED did.

A recent Cochrane review (N = 52,044; k = 11) evaluated the efficacy of a Mediterranean diet for primary prevention of cardiovascular disease.[17] This review included only RCTs of at least 3 months duration with a control group that received either no or only a minimal intervention. RCTs reporting only laboratory endpoints were included. The only study included in both the Cochrane review and the present review was the WHI-DM. Of note, the Cochrane review did not include the PREDIMED study because the comparator intervention did not meet the criterion of "no or minimal" intervention.

We did not include cohort studies in our analysis of total mortality or cardiovascular outcomes. A recent review of prospective cohort studies that included a total of 4.2 million participants without a history of cardiovascular disease reported that a 2-point increase in a Mediterranean diet conformity score was associated with an 8% reduction in all-cause mortality (RR 0.92, 95%

CI 0.87, 0.92) and a 10% decrease in cardiovascular disease incidence and/or mortality (RR 0.90, 95% CI 0.87, 0.92).[18] In addition, a recent meta-analysis that included primary and secondary prevention case-control, cross-sectional, and cohort studies (N = 162,092; k = 9) found that higher conformity to a Mediterranean diet (*ie,* a score of 6 to 9 on the Mediterranean-diet score) was associated with a significant 29% reduction in stroke risk (0.71, 95% CI 0.57, 0.89).[4,16]

Type 2 diabetes mellitus (RCTs only). T2DM was reported in 2 RCTs (N = 49,428), PREDIMED and WHI-DM.[26,30] In WHI-DM there was a similar incidence of T2DM in the intervention and control diet groups.[30] In PREDIMED the incidence of T2DM over 4.1 years of follow-up in people who did not have T2DM at baseline (N = 3,541) was significantly reduced compared to the control diet in the group randomized to the Mediterranean diet supplemented with EVOO (HR 0.60, 95% CI 0.43, 0.85) but not the Mediterranean diet supplemented with nuts (0.82, 95% CI 0.61, 1.10).[26] The disparate findings between WHI-DM and PREDIMED may be related to the differences in these 2 studies' dietary interventions, as discussed above.

A recent systematic review evaluated the association between conformity to the Mediterranean diet and development of T2DM. A pooled analysis of one clinical trial (a single-site report from PREDIMED) and 9 prospective cohort studies (N = 136,846) found a significant association between people with the highest versus lowest conformity to the Mediterranean diet and incidence of T2DM (RR 0.77, 95% CI 0.66, 0.89).[10]

Cancer (RCTs and cohort studies). Two RCTs reported cancer outcomes.[23,27,31] The WHI-DM found no difference in total cancer incidence or mortality. It also reported no difference in colorectal cancer mortality or incidence of breast, colorectal, skin, ovarian, uterine or other cancers between the 2 diet groups. The PREDIMED trial reported a decreased risk of breast cancer in participants assigned the Mediterranean diet supplemented with extra virgin olive oils as compared to the control diet (HR 0.32, 95% CI 0.13, 0.79).

Results of the 28 cohort studies that reported cancer outcomes, comparing highest to lowest Mediterranean diet conformity, are summarized below:

- Total cancer: Significant 4% reduction in incidence (k = 3) and significant 14% reduction in mortality (k = 13)
- Breast cancer: No reduction in breast cancer incidence (k = 13) or mortality (k = 1)
- Colorectal cancer: Significant 9% reduction in incidence (k = 9); no reduction in mortality (k = 1)
- Other cancers:
    - No reduction in ovarian (k = 1), pancreatic (k = 2), head and neck (k = 1), lung (k = 1), bladder (k = 1), gastric (k = 2), or prostate (k = 3), cancer incidence
    - No reduction in pancreatic (k = 1), stomach (k = 1), prostate (k = 2), or respiratory tract (k = 1) cancer mortality

Our findings from the observational data that total cancer incidence and mortality and colorectal cancer incidence were significantly lower in those with the highest conformity to a Mediterranean diet compared to lowest conformity is consistent with findings from a recent systematic review.[18] These findings, however, were not confirmed by the WHI-DM. Although this difference is likely due to the fact that cohort studies are subject to confounding, it is also

possible that a RCT that utilized a more intensive Mediterranean diet intervention than was used in WHI-DM would have corroborated the cohort studies. As noted above, PREDIMED, which did test an intensive Mediterranean diet intervention, reported a significant reduction in breast cancer incidence in the intervention group.

Cognitive impairment. Data from the 2 identified RCTs were mixed.[24,25,28] One site of the PREDIMED trial reported reductions in mild cognitive impairment and dementia in the Mediterranean diet groups compared to control diet while another site reported no associations between diet and cognitive outcomes.[25,28] An RCT in Hong Kong found similar rates of development of dementia after about 3 years of follow-up in 429 participants age $\geq$ 75 who had been randomized to either a diet high in fruits, vegetables, and fish or a control diet.[24] Results from the cohort studies were also mixed although most studies reporting quantiles of Mediterranean-diet score found no association between diet and cognitive impairment.

Rheumatoid arthritis. One cohort study which enrolled 174,638 female registered nurses found similar rates of rheumatoid arthritis in participants with the highest and lowest Mediterranean diet scores (HR 0.98, 95% CI 0.8, 1.2).[93]

Gender, age, or BMI. Several studies reported outcomes stratified by gender, age, or BMI groups. Findings were inconsistent.

KQ2: Secondary Prevention

We identified 15 studies (8 RCTs and 7 cohort studies, N = 19,972) that reported the association between conformity to a Mediterranean diet and the occurrence of outcomes in those with the condition of interest at baseline (secondary prevention). No studies reported kidney disease, hypertension or diabetes. *Of note, there is credible although not definitive evidence that 3 of the RCTs may contain fraudulent data.[98-100,103] Therefore we have not included those data in our summary, below.*

Cardiovascular disease, cardiovascular mortality, and all-cause mortality. Pooled results from 3 RCTs that enrolled people with cardiovascular disease at baseline showed similar all-cause mortality in those assigned the Mediterranean diet compared to those assigned a control diet.[6,8,94,97]

Pooled data from 2 of the 3 RCTs showed that randomization to a Mediterranean diet significantly reduced the risk of myocardial infarction.[6,8] Pooled data showed similar incidence of cardiovascular mortality (k = 2), stroke (k = 2), and revascularization procedures (k = 3) in the 2 diet intervention groups.[6,8,94,96,97]

Of note, all 3 RCTs had substantial limitations. The Lyon Heart Study was the strongest methodologically but it included only 605 people.[6,95-97] The Welsh trial enrolled over 3,000 men but was interrupted by funding problems, leading to convoluted analyses.[94] The Spokane, Washington trial enrolled only 101 patients.[8]

We did not include studies whose only outcome was cardiac risk factors, but other systematic reviews have found that the Mediterranean diet is associated with significant reductions in total

and LDL cholesterol, body weight, blood pressure, fasting plasma glucose, and C-reactive protein.[14,17]

Cancer. In 6 cohort studies that examined outcomes in people with colon cancer (k = 2), breast cancer (k = 3), or prostate cancer (k = 2) there was a similar incidence of cancer recurrence and cancer-specific mortality in those with the highest compared to the lowest conformity to a Mediterranean diet.[41,104-110]

Cognitive impairment. One cohort study in New York that enrolled 482 people with mild cognitive impairment reported similar incidence of progression to Alzheimer's disease in those with higher conformity compared to lower conformity to a Mediterranean diet.[87]

Rheumatoid arthritis. Two small trials of a Mediterranean diet compared to a usual diet (n = 51, 12 week follow-up and n = 130, 26 week follow-up) reported significant improvement in global pain and functional status questionnaire scores. The smaller and shorter trial reported significant improvement in a disease activity score but the larger, longer one did not.[101,102]

KQ3: Adherence

Two RCTs conducted in the United States reported data on adherence.[111,113] Results from these trials show that in the context of a randomized trial with intensive behavioral interventions it is possible to achieve sustained increases in consumption of fruits and vegetables and grains (2 components of the Mediterranean diet). Whether the same results could be achieved in a general population and without a labor-intensive behavioral intervention is not known.

A recent systematic review summarized the effects of interventions to promote a Mediterranean diet or healthy eating pattern in primary health care settings.[12] This review included only RCTs but did not require enrollment of at least 100 subjects or follow-up of at least one year. Fourteen studies were included, only 2 of which studied a Mediterranean diet. Neither of these studies was included in our review as one was conducted in Spain and one in inpatients in the United Kingdom.[114,115] The review concluded that there is moderate evidence that nutritional counselling moderately increases intake of fruits and vegetables and that more intensive interventions with more frequent patient contact are most effective.

APPLICABILITY OF FINDINGS TO THE VA POPULATION

Although the data are limited in that there were few randomized controlled trials and the majority of included studies (whether trials or cohort studies) were not conducted in North American populations, we believe that the available outcome data are applicable to the general VA population.

RESEARCH GAPS/FUTURE RESEARCH

A major gap is the absence of large-scale clinical outcomes trials of a Mediterranean diet in North American populations, both in primary and secondary prevention populations. Such trials are important both to confirm results of the few trials performed abroad and to determine the acceptability of the Mediterranean diet to the American public. In addition, the following areas represent important avenues for future research:

- modeling studies to ascertain if specific components or combination of components of the Mediterranean diet are more protective than others;
- barriers to adoption of a Mediterranean diet in people used to consuming a traditional Western diet and interventions to address those barriers; and
- relative advantages of the Mediterranean diets compared to other healthy diets (*eg*, DASH diet).

STRENGTH OF EVIDENCE

The strength of evidence was low or insufficient for all outcomes evaluated.

CONCLUSIONS

In this systematic review and meta-analysis of 55 published studies we identified a single primary prevention trial which found that consumption of a Mediterranean diet was associated with a significant reduction in major cardiac events, new onset T2DM, and breast cancer incidence. For secondary prevention, data from 2 trials indicate that assignment to a Mediterranean diet reduces incidence of myocardial infarction but not other cardiovascular outcomes. Cohort studies indicate that conformity to a Mediterranean diet pattern is associated with significant reduction in total cancer incidence, total cancer mortality, and colorectal cancer incidence. These associations have not been confirmed in RCTs. Available data on other outcomes, such as cognitive impairment and rheumatoid arthritis, were limited. The available data on dietary adherence suggest that sustained increases in consumption of fruits and vegetables and grains can be achieved with labor intensive behavioral interventions in select populations.

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