QUERI

Benefits and Harms of the Mediterranean Diet Compared to Other Diets

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

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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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. 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. 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.

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, diabetes, hypertension, cognitive impairment, and kidney disease) and/or all-cause mortality (*viz*, PREDIMED, Lyon Heart Study, THIS-DIET). 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, 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. With input from topic nominators and a Technical Expert Panel (TEP) we developed the following Key Questions:

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?

METHODS

Definition of a Mediterranean Diet

We included studies whose diets met the criteria used in 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.

Data Sources and Searches

We searched MEDLINE (Ovid), CINAHL, and the Cochrane library for articles published from 1990 through August 2015. Our search was limited to studies in adult humans published in the English language. An additional search was done in all 3 databases to address Key Question 3 in which the terms adherence and patient compliance were added. Supplemental searches were also done to find articles specific to cancer, rheumatoid arthritis (RA), and cognitive impairment. We also obtained articles by hand-searching the reference lists of systematic reviews and included studies.

Study Selection

For studies addressing Key Questions 1 and 2 in diseases other than cancer, RA, or cognitive impairment and Key Question 3, we included randomized controlled trials (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 minimum follow-up time. For studies of cancer we included RCTs and cohort studies with at least 100 participants followed for at least one year. Studies must have also reported one of our outcomes of interest, which, for Key Questions 1 and 2 included: mortality, quality of life, new onset or progression of disease, and functional status.

We excluded the following:

- Studies that did not involve outpatient adults;
- Studies in which the intervention diet was either not labeled a Mediterranean diet or did not fit our criteria for a Mediterranean diet;
- Studies in women who were pregnant or lactating; and
- For Key Question 3, studies that were conducted in countries other than the US and Canada.

Data Abstraction and Risk of Bias Assessment

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, diet-related 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.

We assessed the risk of bias for trials based on the following criteria: sequence generation, allocation concealment, risk of bias from confounding (for non-randomized studies), blinding, incomplete outcome reporting, and selective outcome reporting – a modification of the Cochrane approach to determining risk of bias. For cohort studies risk of bias was determined based on: population, outcomes, measurement, and confounding. Individual studies were rated as low, medium, or high risk of bias.

Data Synthesis and Analysis

Data were summarized by outcome. If applicable, we pooled outcomes data from RCTs and cohort studies separately. Most of the studies reported hazard ratios (HR), which we treated as relative risks (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 risk ratios (RR). 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).

RESULTS

Results of Literature Search

Our initial literature search identified 78 papers reporting on 46 studies. An updated search yielded another 15 papers, bringing the totals to 93 papers reporting on 55 studies published between 1990 and August 2015.

Summary of Results for Key Questions

Key Question 1: 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, all-cause mortality, and diabetes (RCTs only). Two trials that included a total of 56,282 people evaluated the effect of the Mediterranean diet on major cardiovascular (CV) outcomes (myocardial infarction [MI], stroke, CV death) and diabetes. Three RCTs (n = 56,711) reported all-cause mortality.

PREvención con DIeta MEDiterránea (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 groups assigned a Mediterranean diet had a significant 29% reduction in major cardiovascular events compared to the control group (HR 0.71, 95% CI 0.56, 0.90). All-cause mortality did not differ between the diet groups. The incidence of type 2 diabetes mellitus (T2DM) 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 extra virgin olive oil (HR 0.60, 95% CI 0.43, 0.85) but not in the group randomized to the Mediterranean diet supplemented with nuts (HR 0.82, 95% CI 0.61, 1.10).

The Women's Health Initiative – Dietary Modification (WHI-DM) was a US trial of 48,835 women, aged 50-79, assigned to 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), all-cause mortality, or incidence of T2DM 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.

The third RCT reporting mortality followed 429 residents of 14 old-age hostels in Hong Kong for 33 months. 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 intervention group compared to 11% (25/225) in the control group.

Cancer (RCTs and cohort studies). Two RCTs reported cancer outcomes. The WHI-DM found no difference in total cancer or colorectal cancer incidence or mortality. It also reported no difference in colorectal cancer mortality or the incidence of invasive 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

Cognitive impairment (RCTs and cohort studies). Data from the 2 identified RCTs were mixed. One site of the PREDIMED trial reported reductions in mild cognitive impairment (MCI) and dementia in the Mediterranean diet groups compared to control diet while another site reported no associations between diet and cognitive outcomes. An RCT in Hong Kong found similar rates of development of dementia after about 3 years of follow-up in 429 participants age ≥ 75 who

had been randomized to either a diet high in fruits, vegetables, and fish or a control diet. 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 (Cohort study). 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 0.80, 1.20).

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). Of note, there is credible although not definitive evidence that 3 of the RCTs may contain fraudulent data. Therefore we have not included those data in our summary, below.

Cardiovascular disease, cardiovascular mortality, and all-cause mortality. Three trials were conducted in patients with cardiovascular disease. When pooled, 2 of these trials showed that randomization to a Mediterranean diet significantly reduced the risk of a new MI (RR 0.32, 95% CI 0.15, 0.67; $I^2 = 0$). Pooled data showed similar incidence of cardiovascular mortality (k = 3), stroke (k = 2), and all-cause mortality (k = 3) in the 2 diet intervention groups.

All 3 RCTs had substantial limitations. The Lyon Heart Study was the strongest methodologically but it included only 605 people. The Welsh trial enrolled over 3,000 men but was interrupted by funding problems, leading to convoluted analyses. The Spokane Washington trial enrolled only 101 patients.

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.

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.

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, shorter trial reported significant improvement in a disease activity score but the larger, longer one did not.

KQ3 Adherence

Two RCTs conducted in the United States reported data on adherence (N = 49,373). 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/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.

Strength of Evidence

As can be seen in the Executive Summary Table, the strength of evidence was low or insufficient for all outcomes evaluated.

DISCUSSION

Cardiovascular Disease and Type II Diabetes

Primary Prevention

PREDIMED is the only large randomized controlled trial that tested the effects of an intensive Mediterranean diet (5 of 7 components) on clinical outcomes. Compared to a low-fat control diet, either the Mediterranean diet supplemented with extra virgin olive oil or the Mediterranean diet supplemented with nuts was associated with a significant 30% reduction in major cardiovascular events, the primary endpoint. This trial also reported significant reductions in incident diabetes but only in the group randomized to the diet supplemented with extra virgin olive oil.

A second primary prevention trial, the WHI-DM, found no difference in incidence of major cardiovascular events or diabetes between its 2 diet groups. Although this study met our definition of a Mediterranean diet, it only included 2 of 7 Mediterranean diet components (fruits/vegetables and grains) and its primary goal was to lower total fat intake. The reviewers of this report did not consider this intervention a true Mediterranean diet, nor would many other experts. Indeed, the intervention diet in WHI is more similar to the PREDIMED control diet than to the PREDIMED intervention diet.

Secondary Prevention

Data from 3 RCTs indicates that a Mediterranean diet is associated with a significant reduction in new myocardial infarction but no reduction in cardiovascular mortality, stroke, or other cardiovascular events. *(Three additional secondary prevention trials were identified but are not included in this summary because of credible evidence that they may contain fraudulent data.)*

Cancer

Primary Prevention

PREDIMED documented a significant reduction in breast cancer incidence in women randomized to the Mediterranean diet supplemented with extra virgin olive oil. No other RCT reported reduction in any cancer outcomes. Pooled results of cohort studies showed a significant reduction in total cancer incidence, total cancer mortality, and colorectal cancer incidence but not in breast cancer incidence.

Secondary Prevention

We found no evidence that a Mediterranean diet reduces breast, prostate, or colon cancer recurrence or mortality.

Other Outcomes

There are limited, mixed data on the effects of the Mediterranean diet on primary or secondary prevention of cognitive impairment or rheumatoid arthritis.

Adherence

The available data on dietary adherence suggest that sustained increases in consumption of fruits/vegetables and grains can be achieved, but only with labor-intensive behavioral interventions in select populations.

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.
- Relative advantages of the Mediterranean diets compared to other healthy diets (*eg*, DASH diet).

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.

Executive Summary Table. 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) 12 Observational (range 1,598 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.
Cognitive Functioning	Low	Mixed	2 RCTs PREDIMED (334 and 522) Kwok (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.

Outcome	Strength of evidence	Direction	Study design; # studies (N)	Summary/Rationale[a]
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 (Owens 2010):

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

ABBREVIATIONS TABLE

Abbreviation	Definition
AD	Alzheimer's Disease
BMI	Body Mass Index
CCT	Controlled Clinical Trial
CI	Confidence Interval
HR	Hazard Ratio
MCI	Mild Cognitive Impairment
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RR	Relative Risk
T2DM	Type 2 Diabetes Mellitus

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.

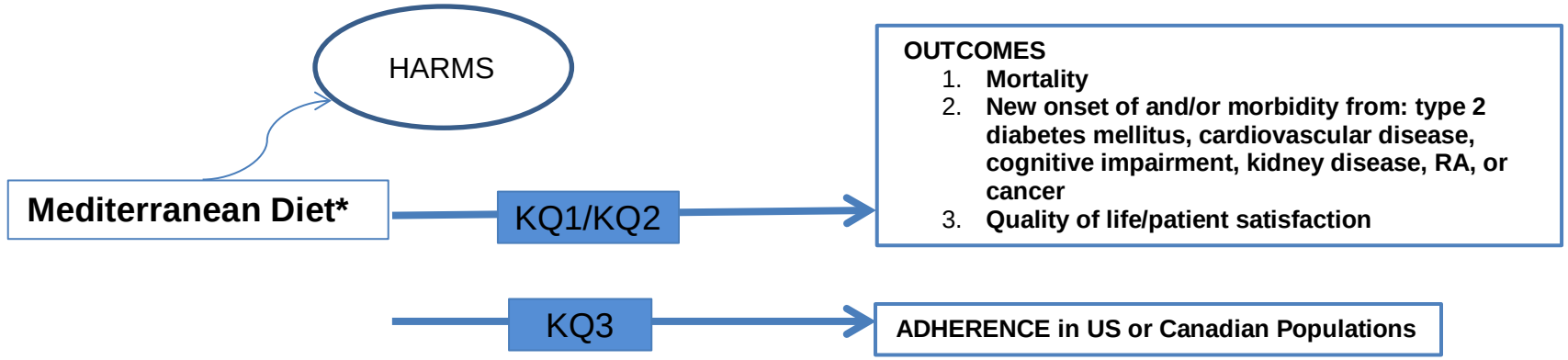
Interventions: A Mediterranean-style diet (*ie*, labelled as a Mediterranean diet or consisting of at least 2 of the following: 1. high monounsaturated:saturated fat ratio (use of olive oil as main cooking ingredient); 2. high consumption of fruits and vegetables; 3. high consumption of legumes; 4. high 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

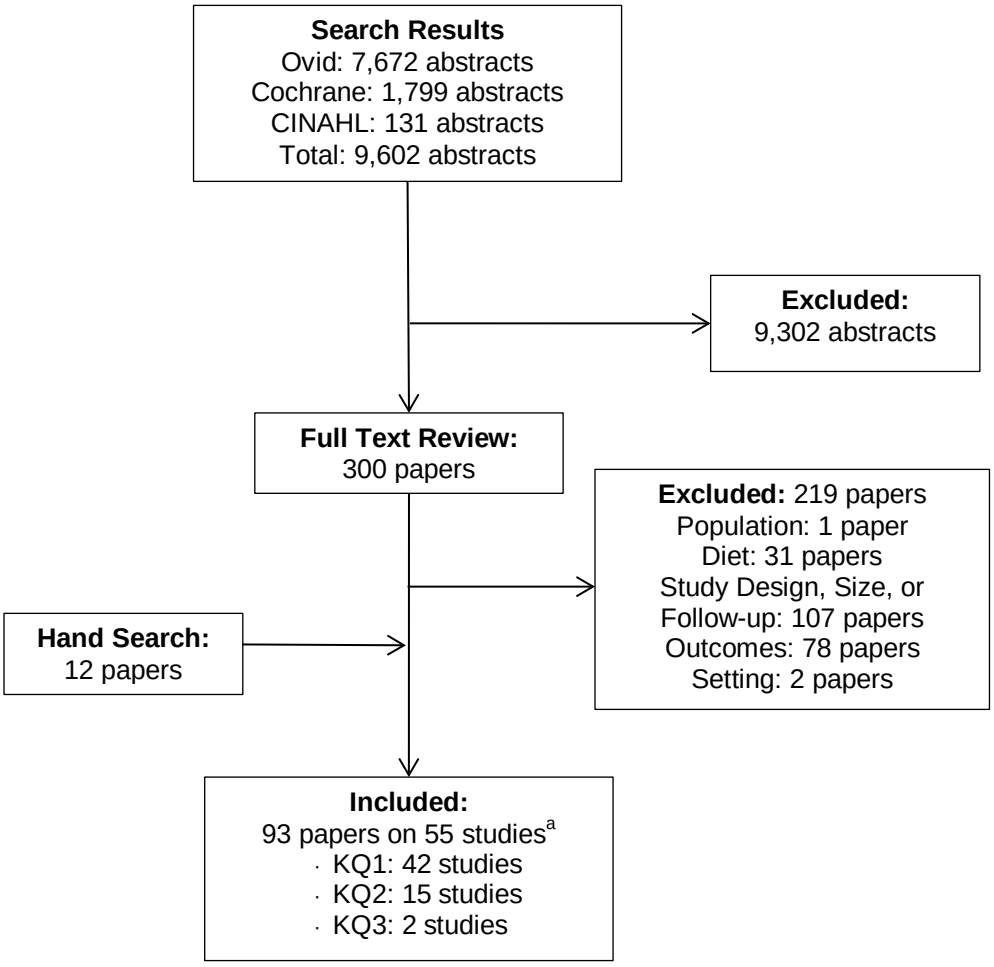
A draft version of this report was reviewed by content experts and clinical leadership. Reviewers' comments and our responses are presented in Appendix B and the report was modified as needed.

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)

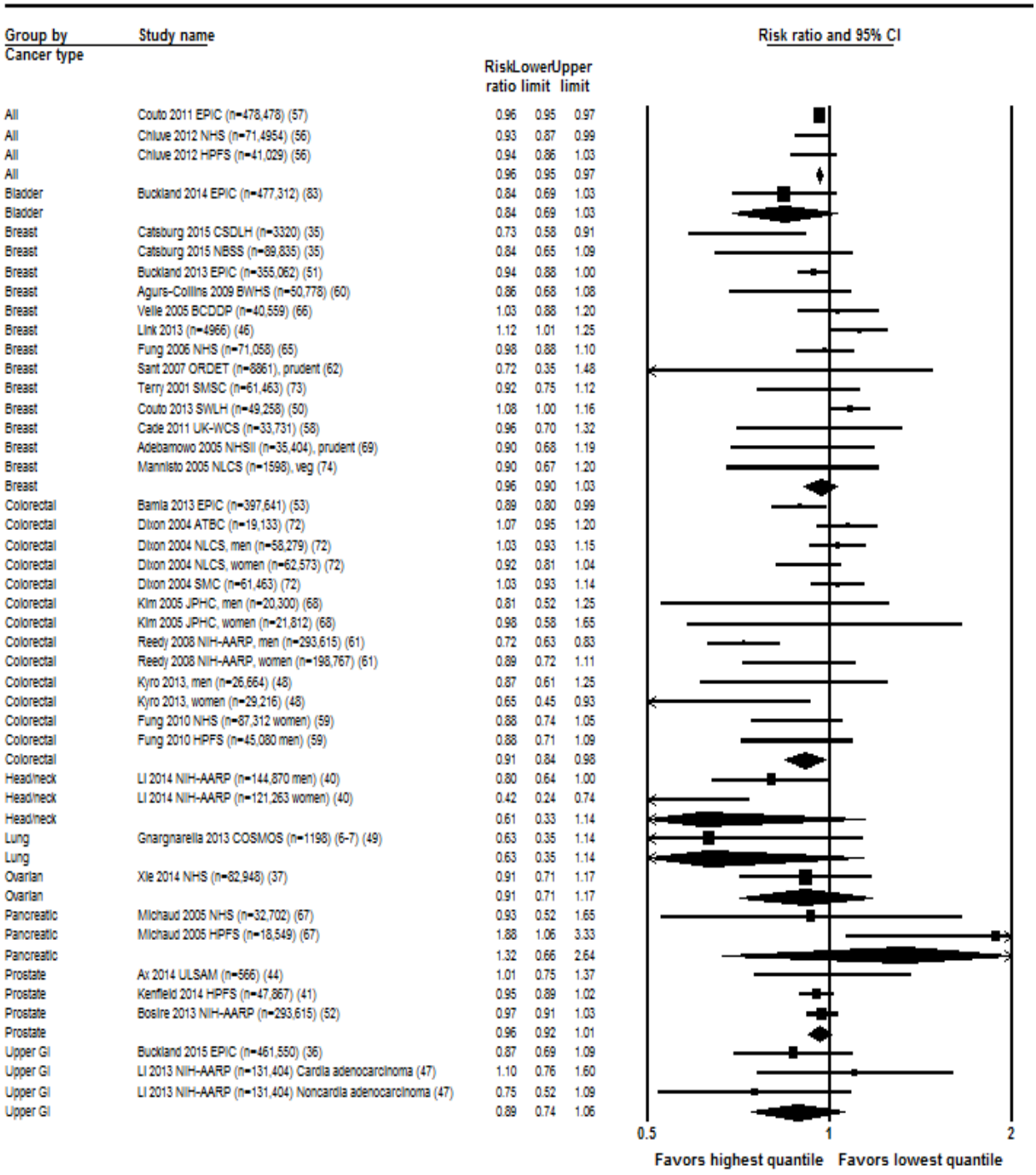
Cancer as an outcome was reported in 30 studies, 2 RCTs (WHI-DM, N = 63,805 and PREDIMED, N = 4,282) and 28 cohort studies, N = 2.5 million.[4,23,27,29,31,33-73]

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%).

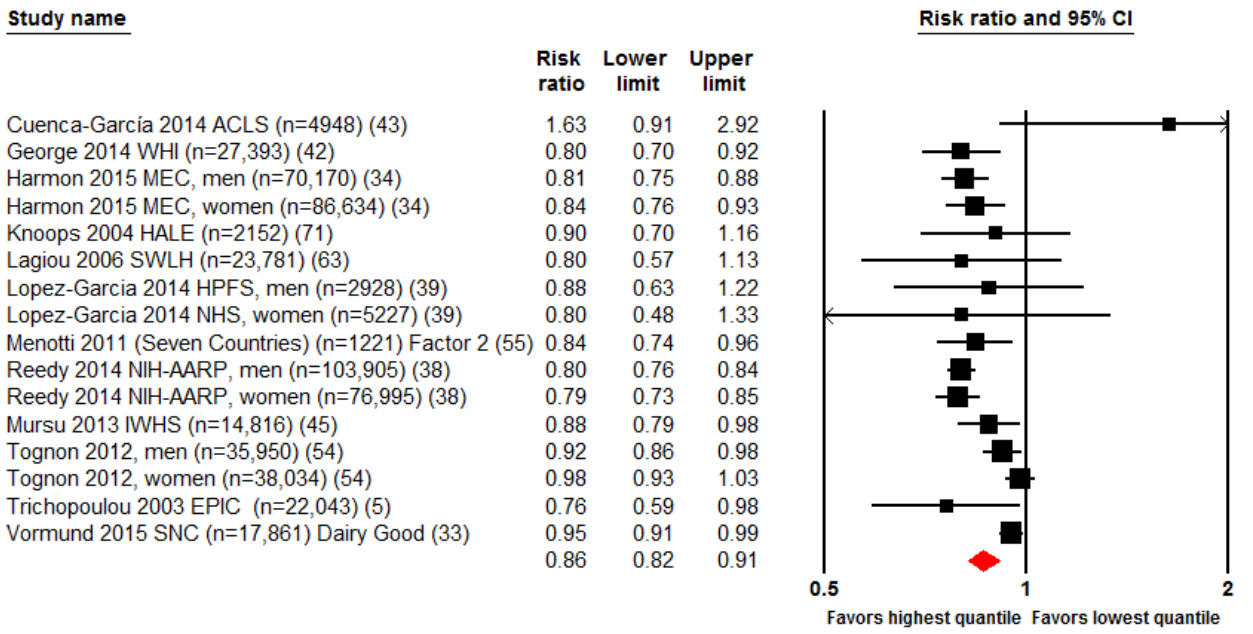
Breast Cancer

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%).

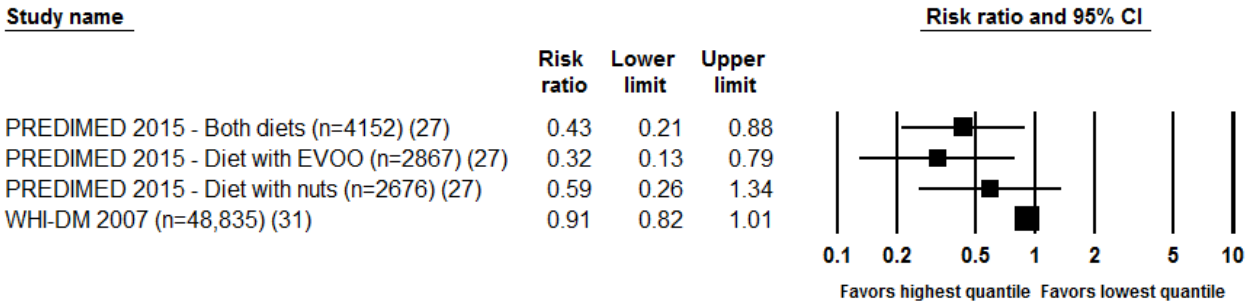
Breast cancer mortality was reported in one study, a prospective population-based cohort study conducted in Sweden (N = 77,151). It reported no association between conformity to a Mediterranean diet and breast cancer mortality (HR 1.12, 95% CI 0.97, 1.29) (Figure 6).[54]

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%).

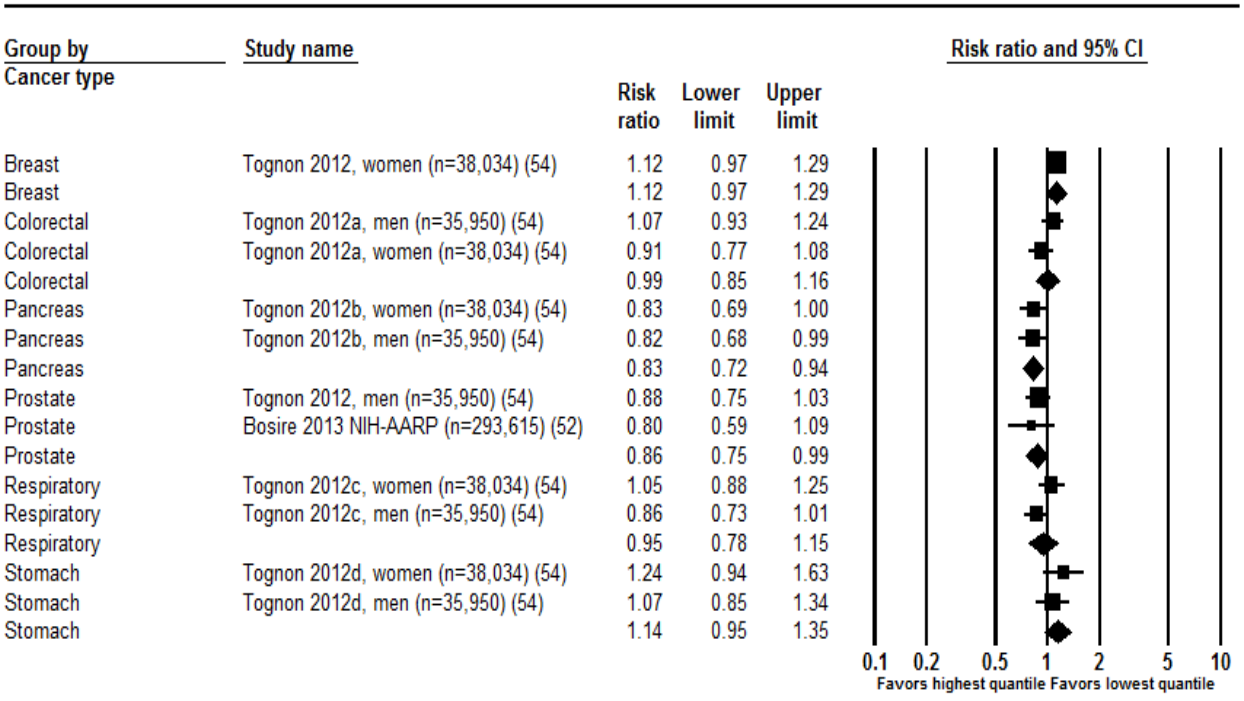
A prospective population-based cohort study conducted in Sweden (N = 77,151), reported no association between conformity to a Mediterranean diet and colorectal cancer mortality for men (HR 1.07, 95% CI 0.93, 1.24) or women (HR 0.91, 95% CI 0.77, 1.08) (Figure 6).[54]

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



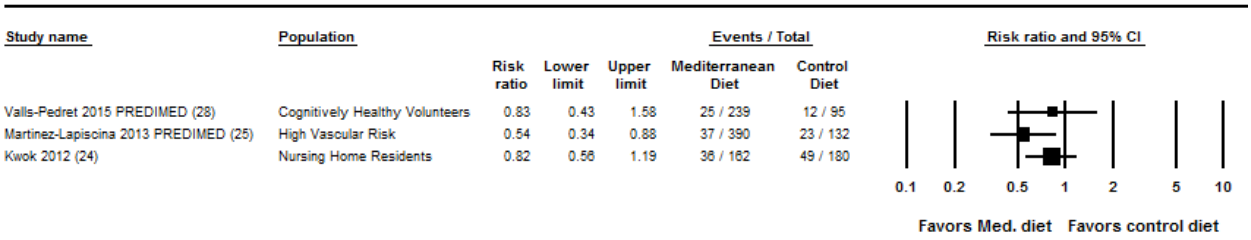
Cognitive Functioning

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]

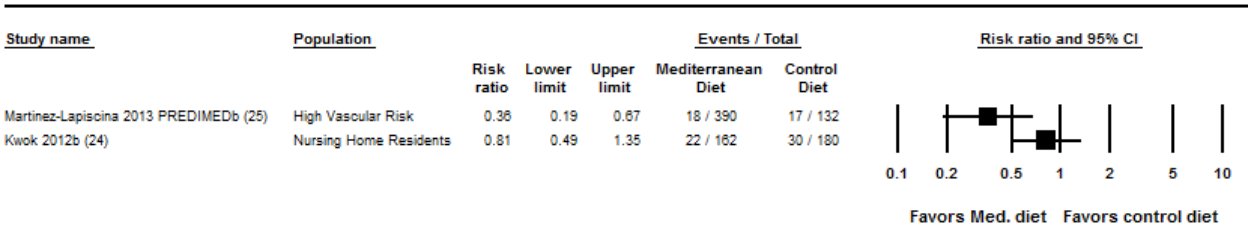
The second RCT was the PREDIMED study. Two of the study sites, Barcelona and Navarra, evaluated the effect of diet on incidence of mild cognitive impairment (MCI) and reported their results independently (Figure 7).[25,28] The Barcelona site, which enrolled 334 people followed for a median of about 4 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]

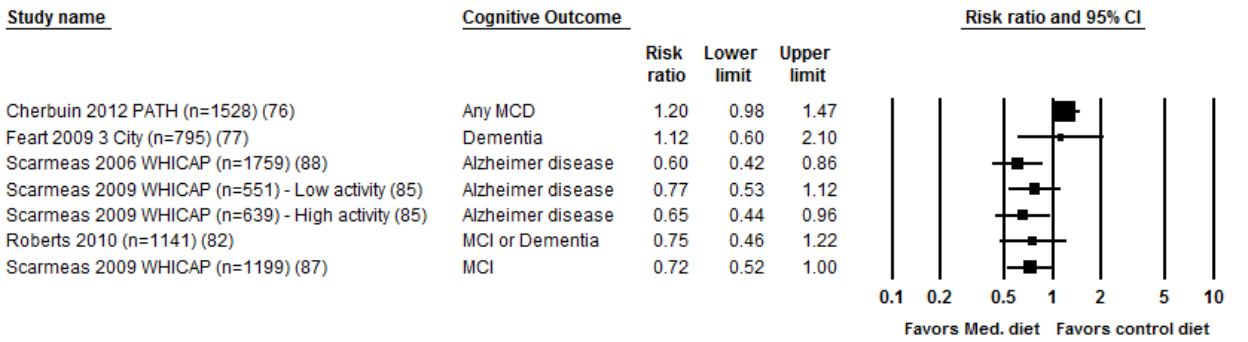
- A US study found a significant association between the highest tertile of Mediterranean-diet score and development of AD over a 4 year (mean) follow-up.[88] The significant association was maintained when the model was adjusted for all vascular variables.[86] In further analyses of the same cohort, 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)

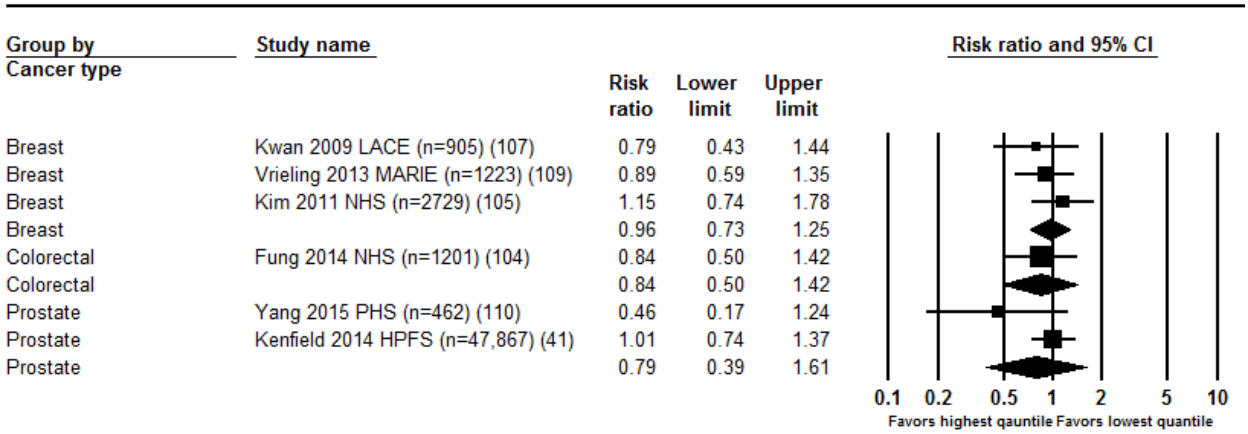
A US study of 1,009 patients with stage III colon cancer followed for an average of 5.3 years found similar rates of colon cancer recurrence across quintiles of conformity to the Mediterranean diet (termed a "prudent" diet) (HR 1.13, 95% CI 0.77, 1.67).[108] A second US study (NHS) of 1,201 women with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

MEDLINE (OVID)

Key Questions 1 and 2 Randomized Controlled Trials

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/
4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.
9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.
21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.
30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/

40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.
49. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/
53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. 52 or 53 or 54 or 55 or 56
58. 37 or 51 or 57
59. randomized controlled trial.pt.
60. controlled clinical trial.pt.
61. randomized.ab.
62. placebo.ab.
63. clinical trials as topic.sh.
64. randomly.ab.
65. trial.ti.
66. 59 or 60 or 61 or 62 or 63 or 64 or 65
67. 58 and 66
68. exp animal/ not humans.sh.
69. 67 not 68
70. limit 69 to (english language and yr = "1990 -Current")
71. limit 70 to "all child (0 to 18 years)"
72. limit 71 to "all adult (19 plus years)"
73. 71 not 72
74. 70 not 73

Key Questions 1 and 2 Cancer

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/
4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.

9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.
21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.
30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/
40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.
49. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/

53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. 52 or 53 or 54 or 55 or 56
58. 37 or 51 or 57
59. exp animal/ not humans.sh.
60. 58 not 59
61. limit 60 to (english language and yr = "1990 -Current")
62. limit 61 to "all child (0 to 18 years)"
63. limit 62 to "all adult (19 plus years)"
64. 62 not 63
65. 61 not 64
66. cancer.mp. or Neoplasms/
67. 65 and 66

Key Questions 1 and 2 Rheumatoid Arthritis

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/
4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.
9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.
21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.

30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/
40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.
49. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/
53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. 52 or 53 or 54 or 55 or 56
58. 37 or 51 or 57
59. exp animal/ not humans.sh.
60. 58 not 59
61. limit 60 to (english language and yr = "1990 -Current")
62. limit 61 to "all child (0 to 18 years)"
63. limit 62 to "all adult (19 plus years)"
64. 62 not 63
65. 61 not 64
66. Arthritis, Rheumatoid/ or Arthritis/
67. 65 and 66

Key Questions 1 and 2 Cognitive Function

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/

4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.
9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.
21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.
30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/
40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.

49. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/
53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. 52 or 53 or 54 or 55 or 56
58. 37 or 51 or 57
59. exp animal/ not humans.sh.
60. 58 not 59
61. limit 60 to (english language and yr = "1990 -Current")
62. limit 61 to "all child (0 to 18 years)"
63. limit 62 to "all adult (19 plus years)"
64. 62 not 63
65. 61 not 64
66. Mild Cognitive Impairment/
67. Delirium, Dementia, Amnestic, Cognitive Disorders/ or Dementia/ or Dementia, Multi-Infarct/
68. Dementia/ or Alzheimer Disease/
69. 66 or 67 or 68
70. 65 and 69

Key Question 3

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/
4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.
9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.

21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.
30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/
40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.
49. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/
53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. 52 or 53 or 54 or 55 or 56
58. 37 or 51 or 57
59. exp animal/ not humans.sh.
60. 58 not 59
61. limit 60 to (english language and yr = "1990 -Current")
62. limit 61 to "all child (0 to 18 years)"
63. limit 62 to "all adult (19 plus years)"
64. 62 not 63

65. 61 not 64
66. adherence.mp.
67. 65 and 66
68. Patient Compliance/
69. 66 or 68
70. 65 and 69

COCHRANE

Key Questions 1 and 2 Randomized Controlled Trials

1. fruit or vegetable or legume or nut? or bread or cereal or grain or (olive next oil) or (monounsaturated next fat) or (mono unsaturated next fat) or fish
2. (fruit or vegetable or nuts or bread or cereals or fatty acids, monounsaturated or seafood):kw
3. ((high or more or increase or elevat or much or rais) near (intake or consumption or consume or eat or amount))
4. (#1 or #2) and #3
5. red next meat or red next wine
6. MeSH descriptor: [Dairy Products] explode all trees
7. ((low or little or medium or moderate or less or decrease or reduc or restrict) near (intake or consumption or consume or eat or amount))
8. (#5 or #6) and #7
9. mediterranean near diet
10. MeSH descriptor: [Diet, Mediterranean] explode all trees
11. #4 or #8 or #10 (Publication year from 1990 to 2015)

Key Questions 1 and 2 Cancer

1. fruit or vegetable or legume or nut? or bread or cereal or grain or (olive next oil) or (monounsaturated next fat) or (mono unsaturated next fat) or fish
2. (fruit or vegetable or nuts or bread or cereals or fatty acids, monounsaturated or seafood):kw
3. ((high or more or increase or elevat or much or rais) near (intake or consumption or consume or eat or amount))
4. (#1 or #2) and #3
5. red next meat or red next wine
6. MeSH descriptor: [Dairy Products] explode all trees
7. ((low or little or medium or moderate or less or decrease or reduc or restrict) near (intake or consumption or consume or eat or amount))
8. (#5 or #6) and #7
9. mediterranean near diet
10. MeSH descriptor: [Diet, Mediterranean] explode all trees
11. #4 or #8 or #10 (Publication year from 1990 to 2015)
12. Cancer
13. MeSH descriptor: [Neoplasms] explode all trees
14. #12 or #13
15. #14 and #11

Key Questions 1 and 2 Rheumatoid Arthritis

1. fruit or vegetable or legume or nut? or bread or cereal or grain or (olive next oil) or (monounsaturated next fat) or (mono unsaturated next fat) or fish
2. (fruit or vegetable or nuts or bread or cereals or fatty acids, monounsaturated or seafood):kw
3. ((high or more or increase or elevat or much or rais) near (intake or consumption or consume or eat or amount))
4. (#1 or #2) and #3
5. red next meat or red next wine
6. MeSH descriptor: [Dairy Products] explode all trees
7. ((low or little or medium or moderate or less or decrease or reduc or restrict) near (intake or consumption or consume or eat or amount))
8. (#5 or #6) and #7
9. mediterranean near diet
10. MeSH descriptor: [Diet, Mediterranean] explode all trees
11. #4 or #8 or #10 (Publication year from 1990 to 2015)
12. MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
13. #11 and #12

Key Questions 1 and 2 Cognitive Function

1. fruit or vegetable or legume or nut? or bread or cereal or grain or (olive next oil) or (monounsaturated next fat) or (mono unsaturated next fat) or fish
2. (fruit or vegetable or nuts or bread or cereals or fatty acids, monounsaturated or seafood):kw
3. ((high or more or increase or elevat or much or rais) near (intake or consumption or consume or eat or amount))
4. (#1 or #2) and #3
5. red next meat or red next wine
6. MeSH descriptor: [Dairy Products] explode all trees
7. ((low or little or medium or moderate or less or decrease or reduc or restrict) near (intake or consumption or consume or eat or amount))
8. (#5 or #6) and #7
9. mediterranean near diet
10. MeSH descriptor: [Diet, Mediterranean] explode all trees
11. #4 or #8 or #10 (Publication year from 1990 to 2015)
12. Mild cognitive impairment
13. MeSH descriptor: [Dementia] explode all trees
14. MeSH descriptor: [Alzheimer Disease] explode all trees
15. #12 or #13 or #14
16. #15 or #11

Key Question 3

1. fruit or vegetable or legume or nut? or bread or cereal or grain or (olive next oil) or (monounsaturated next fat) or (mono unsaturated next fat) or fish
2. (fruit or vegetable or nuts or bread or cereals or fatty acids, monounsaturated or seafood):kw

3. ((high or more or increase or elevat or much or rais) near (intake or consumption or consume or eat or amount))
4. (#1 or #2) and #3
5. red next meat or red next wine
6. MeSH descriptor: [Dairy Products] explode all trees
7. ((low or little or medium or moderate or less or decrease or reduc or restrict) near (intake or consumption or consume or eat or amount))
8. (#5 or #6) and #7
9. mediterranean near diet
10. MeSH descriptor: [Diet, Mediterranean] explode all trees
11. #4 or #8 or #10 (Publication year from 1990 to 2015)
12. Adherence
13. MeSH descriptor: [Patient Compliance] explode all trees
14. #12 or #13
15. #11 or #14

CINAHL

Key Questions 1 and 2 Randomized Controlled Trials

1. Fruit* vegetable* legume* nut nuts bread breads cereal* “olive oil” “monounsaturared fat*” “mono-unsaturated fat*” fish
2. (MH “Fruit+”) OR (MH “Vegetables+”) OR (MH “Legumes+”) OR (MH “Nuts+”) OR (MH “BREAD”) OR (MH “Cereals+”) OR (MH “Olive Oil”) OR (MH “Fatty Acids, Monounsaturated+”) OR (MH “Seafood+”)
3. High more increase elevat* much rais*
4. Intake consumption consume eat* amount*
5. 3 AND 4
6. 1 OR 2
7. 5 AND 6
8. “red meat*” “red wine*”
9. (MH “Dairy Products+”)
10. Low little medium moderate less decreas* reduc* restrict*
11. 4 AND 10
12. 8 OR 9
13. 11 AND 12
14. (MH “Mediterranean Diet”)
15. 7 OR 13 OR 14 (published date: 19900101-2015; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult)

Key Questions 1 and 2 Cancer

1. Fruit* vegetable* legume* nut nuts bread breads cereal* “olive oil” “monounsaturared fat*” “mono-unsaturated fat*” fish
2. (MH “Fruit+”) OR (MH “Vegetables+”) OR (MH “Legumes+”) OR (MH “Nuts+”) OR (MH “BREAD”) OR (MH “Cereals+”) OR (MH “Olive Oil”) OR (MH “Fatty Acids, Monounsaturated+”) OR (MH “Seafood+”)
3. High more increase elevat* much rais*

4. Intake consumption consume eat* amount*
5. 3 AND 4
6. 1 OR 2
7. 5 AND 6
8. "red meat*" "red wine*"
9. (MH "Dairy Products+")
10. Low little medium moderate less decreas* reduc* restrict*
11. 4 AND 10
12. 8 OR 9
13. 11 AND 12
14. (MH "Mediterranean Diet")
15. 7 OR 13 OR 14 (published date: 19900101-2015; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult)
16. Cancer
17. 15 AND 16

Key Questions 1 and 2 Rheumatoid Arthritis

1. Fruit* vegetable* legume* nut nuts bread breads cereal* "olive oil" "monounsaturared fat*" "mono-unsaturated fat*" fish
2. (MH "Fruit+") OR (MH "Vegetables+") OR (MH "Legumes+") OR (MH "Nuts+") OR (MH "BREAD") OR (MH "Cereals+") OR (MH "Olive Oil") OR (MH "Fatty Acids, Monounsaturated+") OR (MH "Seafood+")
3. High more increase elevat* much rais*
4. Intake consumption consume eat* amount*
5. 3 AND 4
6. 1 OR 2
7. 5 AND 6
8. "red meat*" "red wine*"
9. (MH "Dairy Products+")
10. Low little medium moderate less decreas* reduc* restrict*
11. 4 AND 10
12. 8 OR 9
13. 11 AND 12
14. (MH "Mediterranean Diet")
15. 7 OR 13 OR 14 (published date: 19900101-2015; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult)
16. Rheumatoid arthritis
17. Arthritis
18. 16 OR 17
19. 15 AND 18

Key Questions 1 and 2 Cognitive Function

1. Fruit* vegetable* legume* nut nuts bread breads cereal* "olive oil" "monounsaturared fat*" "mono-unsaturated fat*" fish

2. (MH “Fruit+”) OR (MH “Vegetables+”) OR (MH “Legumes+”) OR (MH “Nuts+”) OR (MH “BREAD”) OR (MH “Cereals+”) OR (MH “Olive Oil”) OR (MH “Fatty Acids, Monounsaturated+”) OR (MH “Seafood+”)
3. High more increase elevat* much rais*
4. Intake consumption consume eat* amount*
5. 3 AND 4
6. 1 OR 2
7. 5 AND 6
8. “red meat*” “red wine*”
9. (MH “Dairy Products+”)
10. Low little medium moderate less decreas* reduc* restrict*
11. 4 AND 10
12. 8 OR 9
13. 11 AND 12
14. (MH “Mediterranean Diet”)
15. 7 OR 13 OR 14 (published date: 19900101-2015; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult)
16. Mild cognitive impairment
17. Dementia
18. Alzheimer disease
19. 16 OR 17 OR 18
20. 15 AND 19

Key Question 3

1. Fruit* vegetable* legume* nut nuts bread breads cereal* “olive oil” “monounsaturared fat*” “mono-unsaturated fat*” fish
2. (MH “Fruit+”) OR (MH “Vegetables+”) OR (MH “Legumes+”) OR (MH “Nuts+”) OR (MH “BREAD”) OR (MH “Cereals+”) OR (MH “Olive Oil”) OR (MH “Fatty Acids, Monounsaturated+”) OR (MH “Seafood+”)
3. High more increase elevat* much rais*
4. Intake consumption consume eat* amount*
5. 3 AND 4
6. 1 OR 2
7. 5 AND 6
8. “red meat*” “red wine*”
9. (MH “Dairy Products+”)
10. Low little medium moderate less decreas* reduc* restrict*
11. 4 AND 10
12. 8 OR 9
13. 11 AND 12
14. (MH “Mediterranean Diet”)
15. 7 OR 13 OR 14 (published date: 19900101-2015; English Language; Exclude MEDLINE records; Human; Age Groups: All Adult)
16. Adherence
17. 15 AND 16

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Question Text	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	Yes	Thank you
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	
Is there any indication of bias in our synthesis of the evidence?	No	Thank you
	No	
	No	
	No	
	No	
	No	
Are there any published or unpublished studies that we may have overlooked?	No	No response needed
	No	
	No	
	No	
	No	
	No	
Additional suggestions or comments can be provided below. If applicable, please indicate the page and	page 5 lines 45-53. The Women's Health Initiative is called out in the text but PREDIMED is not. Seems that consistency should be greater. page 6, line 41 and page 44, line 25. is there really evidence that a low fat diet is healthy? Isn't this all called into question? I think there is greater evidence of the healthiness of a vegetarian diet. Page 12: What is the "T" in "PICOTS"? Pge 18, line 23. It would help to define "k" somewhere. Some readers may not be acquainted with the terminology. Page 43, line 12; I wonder whether you want to use "possibly" rather than "likely". Although I would really like to believe that the difference in outcomes for WHI compared with PREDIMED is the difference in the diet, do we have enough evidence	page 5. We have named the PREDIMED study in this statement. page 6. Thank you for the suggestion. We have removed low fat diet from these lines. page 12. The “T” is for Timing (now added to the PICOTS) page 18. We have defined k in several places. page 43 and General comment: We revised

line numbers from the draft report.	to write that it is "likely"? General comment: I would like to see text in the conclusion that states something to the effect that "in retrospect, the definition of 'Mediterranean diet' may have been overly broad, and in turn, this may have influenced the conclusions of the analysis. For example, a diet of hamburgers and French fries would qualify as long at it was eaten with red wine and no milk." I acknowledge the paragraph about asking which components are the active ingredients in the Mediterranean diet, but I think that directly pointing to the issue of defining the diet is also very important.	the language in the report to address both of these comments.
	The authors reviewed and synthesized the literature and conducted a meta-analysis for randomized clinical trials and observations studies about the benefits (or not) of the Mediterranean diet (MedDiet) pattern in the primary and secondary prevention of disease or chronic conditions. Comments: 1. Title: I suggest changing the title of the paper as not all studies included in the meta-analysis were interventions. Dietary intake as an exposure in an observational study was observed. 2. I disagree with the authors' definition of the MedDiet and the statement (page 14 Methods) that 'there is no universally accepted definition of the Mediterranean diet'. There are a numerous publications and a couple reviews below about the MedDiet which clearly describe the components of the MedDiet pattern (references a and b). a) Trichopoulou et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Medicine 2014, 12:112. b) Willett WC et al; Mediterranean Diet Pyramid: A cultural model for healthy eating. Am J Clin Nutr. 1995; 61(suppl): 1402S-1406S. In addition, the MedDiet is not a 'low fat' diet even though the 'low fat' diet may include many of the components the authors describe in their definition. The key component of the MedDiet is olive oil, as reported in numerous publications including the ones I suggest above. Therefore, it seems that the definition of a MedDiet should include olive oil plus 2 of the other components. The authors use a commonly used ratio [monounsaturated fat (MUFA)/saturated fat ratio] as one of the components to define the MedDiet and further explain that most of the MUFA should come from olive oil. However, it is not clear to me if the source of monounsaturated fat intake is known (ie, was the source of MUFA reported in published papers). Given that most of the instruments used in studies to assess dietary intake are food frequency questionnaires, it is not clear if source of MUFA was available. As you may know, a large source of MUFA in the US diet is from meat. And meat has been positively related to numerous chronic diseases. In the U.S., very little olive oil is consumed. Olive oil is not the main cooking oil used in the U.S. Finally, several studies categorized as 'Mediterranean' in the current study were in fact 'low fat' diets (e.g. WHI diet modification trial). In WHI, one of the goals of the	1. Thank you for the suggestion. We have changed the title 2. We chose our definition based on the recent Cochrane review and with approval from our stakeholders and Technical Expert Panel. We have examined the references cited in the reviewer comment and believe that these references, and others, do, in fact, emphasize that there is no universally accepted definition of the Mediterranean diet. 3. We did an exploratory analysis creating forest plots with outcomes based on country and found no pattern. 4. We have added more references to the text.

	diet intervention was to reduce fat intake to 20% of calories which is clearly low fat. However, fat intake for a MedDiet pattern is about 40% from calories. Further, the PREDIMED study investigators compared a MedDiet pattern to a low fat diet pattern – and found the MedDiet to be beneficial in reducing incident CVD events compared to the low fat diet pattern. So it is puzzling that the WHI diet pattern (which is low fat) was labeled as 'Mediterranean-like diet' in this review. Thus, the study investigators meta-analyzed very different diet patterns (although according to their study definition – they were labeled the Mediterranean diet). I believe the authors have combined diet patterns that are very different - apples and oranges – which may explain their study results. If the authors changed their definition for the MedDiet pattern, then the meta-analysis should be conducted again. 3. For key question 3, I suggest the authors compare the results of studies conducted in European countries to the studies conducted in the U.S. given that the diet patterns defined as 'Mediterranean' would be quite different between the 2 continents. In Europe – the Mediterranean diet would include 'olive oil' while in the U.S. the Med diet pattern would not include 'olive oil' and most likely be 'low fat' diet patterns. 4. Throughout the text, the authors refer to some number of RCTs and observational studies. Perhaps these studies can be referenced so the reader is aware of which study the author is referring. Also, in the Discussion – mention is made of a 'high quality RCT or lower quality RCT…..', so again, please reference these.	
	Thank you for the opportunity to serve as an expert reviewer for this comprehensive evidence-based review of the impact of the Mediterranean diet on health outcomes important to our nation's veterans. My comments follow. My principal concern is how predominantly findings from the Women's Health Initiative - Dietary Modification (WHI-DM) trial are featured throughout the document. I understand that the authors decided to adhere to the Cochrane definition of a Mediterranean diet and included studies that reported at least two of the following components: • high monounsaturated/saturated fat ratio • low to moderate red wine consumption • high consumption of legumes • high consumption of grains and cereals • high consumption of fruits and vegetables • low consumption of meat and meat products and increased consumption of fish • moderate consumption of milk and dairy products	As noted, the WHI-DM trial met our study inclusion criteria. We have clarified the dietary components in WHI-DM and noted how they differ from PREDIMED. We have clarified that the diabetes outcome was type 2 diabetes mellitus (T2DM) throughout the report. Page 31, Table 2. We have added definitions to the Strength of Evidence Tables. For the outcome noted, consistency is unknown because there is a single trial. The assessment of precision is based on the width of the confidence interval. The suggested thresholds for precision are 0.75 to 1.25 and the lower bound of the PREDIMED study was

	The WHI-DM intervention diet met this low bar of having 2 of the 7 components. However, the WHI-DM intervention diet was missing one of the key components - a high monounsaturated/saturated fat ratio. Several papers stress the importance of the inclusion of a source of monounsaturated fats in the Mediterranean diet. For example, see the following: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3916858/ The Mediterranean diet is a plant-based pattern, where vegetables, fruits, cereals (preferably as whole grain), legumes, and nuts should be consumed in high amount and frequency. The Mediterranean dietary pattern (MDP) also includes moderate consumption of fish and shellfish, white meat, eggs, and dairy products. On the contrary, consumption of red meat, processed meats, and foods rich in sugars and in fats should be small in both quantity and frequency. The principal source of dietary lipids of the MDP is olive oil and an adequate daily intake of water should be guaranteed, as well as moderate consumption of wine is recommended. And, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222885/ The traditional Mediterranean diet is characterized by high consumption of vegetables, fruits and nuts, legumes, and unprocessed cereals; low consumption of meat and meat products; and low consumption of dairy products (with the exception of the long-preservable cheeses). Alcohol consumption was common in the traditional Mediterranean diet, but generally in moderation and in the form of wine and, as a rule, during meals- in the spirit of the ancient Greek word 'symposium'. Total intake of lipids could be high (around or in excess of 40% of total energy intake, as in Greece), or moderate (around 30% of total energy intake, as in Italy) but, in all instances, the ratio of the beneficial monounsaturated to the non-beneficial saturated lipids is high, because of the high monounsaturated content of the liberally used olive oil. Finally, fish consumption has in the past been a function of the distance from the sea but has been, overall, at a moderate level. Including the WHI-DM as a randomized controlled clinical trial testing the efficacy of the Mediterranean diet seems like an immense leap when one of the key features of the WHI-DM intervention was a low-fat diet. See the NIH WHI website (https://www.nhlbi.nih.gov/whi/diet.htm) where it states that the dietary modification (DM) clinical trial component of the WHI studied the effect of a low-fat, high fruit, vegetable and grain diet on breast cancer, colorectal cancer and heart disease in postmenopausal women. Furthermore, the participants were counseled to decrease	0.71. Page 39. We have modified this statement. Page 42. Thank you for the suggestion. We have added this information to the Executive Summary. Page 45. Thank you for the suggestion. We have removed low fat diet from the statements about other healthy diets.

	their fat intake to 20 percent of their total daily calories. This reviewer would like further justification for defining a Mediterranean diet as one that only includes two of the key components of the diet and most importantly prominently featuring the WHI-DM in the Executive Summary, Findings and Conclusions when it did not include one of the key, critical components of a Mediterranean diet; a high intake of monounsaturated fat. Please be clear throughout the manuscript that you are referring to type II diabetes mellitus and not "diabetes." Page 31 - Table 2 Please explain how you defined consistency and precision in the studies. For example, in the first row of Table 2 you stated that "consistency is unknown and there was imprecision (PREDIMED)." What benchmark did you use to make this statement? Page 39 The statement "We evaluated strength of evidence for all-cause mortality finding insufficient evidence that mortality was similar between Mediterranean diet and control diet groups" is confusing. This could be interpreted to mean you found sufficient evidence that mortality was different between the Mediterranean diet and control diet groups. However, I don't think this was the intent of this statement. Page 42 - paragraph 3 The authors provide a good explanation of why the results are likely different between the PREDIMED studies and the WHI studies. This discussion should be prominent in the Executive Summary. Page 45 - Research Gaps - The authors refer to a "low fat diet" as another "healthy diet." A diet low in total fat is no longer promoted by government and other important health organizations. For example the 2015 Dietary Guidelines Advisory Committee recommended dropping past recommendations to restrict total fat and rather emphasize the importance of reducing saturated fat and replace it with monounsaturated and polyunsaturated fats (see http://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf). Furthermore, the American	

	Heart Association no longer promotes a “low-fat” diet but rather stresses the importance of including monounsaturated and polyunsaturated fats in a heart healthy diet (see http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyEating/The-American-Heart-Associations-Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp). Thus, I recommend not including a “low fat” diet as an example of a healthy diet.	
	1. I would like to see more details about the subjects in the PREDIMED study (age, CVD risk factors, etc.). The number of subjects should be noted consistently ("7000 people" on page 3, line 44 and page 42, line 14 but "7447 people" on page 19, line 14). 2. Why does the Strength of Evidence table (Executive Summary, page 7-8, and paragraph on page 30 and Table 2 on pages 31-32) NOT include cardiovascular incidence and mortality, with the other outcomes? 3. The comments differentiating the PREDIMED study and the WHI study address the concerns raised by reviewers on the conference call earlier.	1. We have added more details about the subjects and have made sure that we consistently report the number of subjects. 2. Systematic reviews typically only assess Strength of Evidence for key outcomes. We focused on outcomes we considered most clinically relevant. We have added more information in the Methods section. 3. Thank you.
	Pages 5 - 6; Key Findings and Strength of Evidence - 3rd bullet: As noted on the conference call, and in the complete results section of the ESP below, the intervention diet in this study was more similar to the control diet than the intervention diet in the PREDIMED trial! Suggest including this in the bullet in both this Summary section and the Summary section of the complete ESP. Page 6; Key Findings and Strength of Evidence - 6th bullet: Suggest the following edit to this bullet: "can be achieved in the setting of a controlled trial, but may require labor intensive behavioral interventions and monitoring." Same comment applies to the corresponding sections in the complete ESP Page 6: Applicability: As noted in the Research Gaps section below, applicability of the available data to Veterans is limited by the presence of only 1 RCT in a comparable North American population and 1 RCT in an all-female population. Shouldn't this be included as a comment? Same comment applies to the corresponding sections in the complete ESP. Page 7: Executive Summary Table - Strength of Evidence. For Key Question #1, the Table is missing the evidence regarding reduction in CV events. Not sure why this key finding was not included in the Table. Same comment applies to the corresponding Table in the complete ESP.	Pages 5-6, Thank you. We have modified the Discussion/Conclusions section and this bullet has been eliminated. We emphasize differences between the trials. Page 6, We have modified the Discussion/Conclusions Section and eliminated the bullet points. We have included the suggested language. Page 6. Thank you. We have modified the Applicability section.

	Page 43, 3rd Paragraph from bottom on Total Cancer Incidence and Mortality- ; Again, the fact that the WHI intervention diet is a very low intensity Mediterranean diet should be mentioned here as well.	Page 7. As noted above, systematic reviews typically only assess Strength of Evidence for key outcomes. We focused on outcomes we considered most clinically relevant. Page 43. Thank you. The WHI-DM diet is noted in this section.

APPENDIX C. EVIDENCE TABLES

KEY QUESTION 1

Table 1. Key Question 1 – Study, Intervention, and Patient Characteristics

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Buckland 2015[36] Europe (10 countries) EPIC Funding: World Cancer Research Fund Cohort	Cohort: -520,000 apparently healthy men and women -aged 25-70 -recruited between 1992 and 2000 in 23 centers from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through a center-specific FFQ that addressed usual diet over previous year Excluded: -prevalent cancer at recruitment -incomplete follow-up -missing dietary and lifestyle data -ratio for energy intake versus energy expenditure in the top and bottom 1% -missing information for the components used to construct the healthy lifestyle index	rMED: incorporates fruit, vegetables, olive oil, legumes, dairy, fish, seafood, and cereals; alcohol excluded Scored from 0 to 16 Follow-up: 11.4 years	N = 461,550 Gender (% male) 29.8 BMI: 25.4 Age: 51.2	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Catsburg 2015[35] Canada CSDLH and NBSS Funding: Breast Cancer Research Foundation Cohort	Cohorts: CSDLH -Canadian men and women predominantly alumni of Universities of Alberta, Toronto, and Western Ontario (1995 to1998) -small contingent also recruited through Canadian cancer society in 1992 -actually used a sub-cohort of 3,320 randomly selected women NBSS -RCT of breast cancer screening -women aged 40-59 from 15 Canadian clinical centers between 1980 and 1985	Healthy pattern: predominantly vegetable and legume food groups Follow-Up: CSDLH 13 years NBSS 20-25 years	CSDLH N = 3,320 women Age: 60 BMI: 23.8 Race: 95.8% white NBSS N = 89,835 women	Population: low Outcomes: low Measurement: unclear Confounding: unclear Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Gardener 2015[79] Australia Australian Imaging, Biomarkers and Lifestyle (ABL) Funding: CSIRO Flagship Collaboration Fund, Science and Industry Endowment Fund, National Health and Medical Research Council, and other government and foundation sources Cohort	Included: -Healthy (cognitively "normal") participants from ABL study who completed FFQ at baseline -ABL participants were age 60 or over at baseline Excluded: -Alzheimer's disease or mild cognitive impairment -non-Alzheimer's disease dementia, schizophrenia, bipolar disorder, significant current depression, Parkinson's disease, cancer (other than basal cell skin carcinoma) in past 2 years, symptomatic stroke, insulin-dependent diabetes, uncontrolled diabetes mellitus, or current regular alcohol use exceeding 2 standard drinks/day (women) or 4/day (men)	FFQ (Cancer Council of Victoria): used to determined Australian-style Mediterranean Diet (AusMeDi) score, Western dietary pattern, and prudent Follow-up: 3 years	N = 527 Age (mean): 69 Gender (% male): 40 BMI: 26	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Harmon 2015[34] USA Multiethnic Cohort Funding: National Cancer Institute Cohort	Cohort: -recruited a multiethnic population ->215,000 men and women aged 45-75y at recruitment living in Hawaii or Los Angeles -enrolled between 1993-1996 -baseline questionnaire including food intake over past 12m Included: -identified with one of 5 main MEC ethnic groups (white, African American, Japanese American, native Hawaiian, and Latino) -valid dietary information -no previous history of cancer, heart attack, or stroke at baseline	aMED: a) 1 point for ≥ median consumption of vegetables (excluding potatoes), total fruit, nuts, legumes, fish, whole grains, and MUFA:SA ratio b) 1 point for < median consumption of red and processed meats c) 1 point for alcohol consumption between 5-15g/d for women or 10-25g/d for men Follow-up: 13-18 years	Men N = 70,170 (45%) Age: 56.6-61.3 BMI: 25.9-26.9 Women N = 86,634 (55%) Age: 56.4-61.5 BMI: 25.3-27.2	Population: Unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Hu 2015[93] USA Nurses' Health Study (NHS) and Nurses' Health Study II Funding: National Institutes of Health Cohort	Included: -Nurses' Health Study (NHS) (1976): female registered nurse, age 30-55 -Nurses' Health Study II (NHS II) (1989): female registered nurse, age 25-42 Excluded: -70 or more missing items on FFQ -total energy intake < 500 or > 3,500 kcal/day -missing aMED score	FFQ in 1980 for NHS, 191 for NHS II; updated approximately every 4 years; aMED score (0 to 9 points, higher score indicated stronger conformity Follow-up: 28 years for NHS, 20 years for NHS II	Total N = 174,638 N = 83,245 NHS N = 91,393 NHS II Age (mean): 43.4 Gender (% male): 0 BMI: 24.9	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Koyama 2015[92] USA Health, Aging, and Body Composition (Health ABC) Funding: National Institute of Aging and Alzheimer's Association Cohort	Included: -Medicare-eligible -community-dwelling -age 70-79 -residing in Memphis, TN or Pittsburgh, PA -no difficulty walking a quarter of a mile, climbing 10 steps without resting, and performing any activities of daily living -free of life-threatening cancers (no treatment in past 3 years) -plan to remain in study area for at least 3 years	FFQ (Block Dietary Data System); participants interviewed by trained examiners; information used to construct MedDiet scores (0-55 with higher score representing stronger conformity Follow-up: 8 years	N = 2,326 Age (mean): 75 Gender (% male): 49 BMI: 27.3	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Toledo 2015[27] Spain PREDIMED Funding: Instituto de Salud Carlos III RCT	Included: -women aged 60-80 -free of CVD at enrollment -either type II diabetes mellitus or at least 3 of the following major cardiovascular risk factors: smoking, hypertension, elevated LDL, low HDL, overweight or obesity, or family history of premature coronary heart disease Excluded: -prior diagnosis of breast cancer -probable breast tumors	MeDiet +EVOO, MeDiet+ nuts, or advice to reduce dietary fat -dietary training at baseline visit -personalized advice -group sessions Follow-up: 4.8 years	N = 4,284 women Age: 67.7 BMI: 30.4	Sequence generation: low Allocation concealment: low Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low
Vormund 2015[33] Switzerland Swiss National Cohort Group	Cohort: -pooled data from 2 cross-sectional studies in Switzerland: National Research Program 1A (1977-1979) and the Swiss Monitoring of Trends	Individuals assigned a value of 1 for each beneficial component preferred (salad, vegetables, fruits, whole grains, white meat, fish,	N = 17,861 8,665 men 9,196 women Mean age 45.2	Population: low Outcomes: low Measurement: unclear

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Funding: Swiss National Science Foundation Cohort	and Determinants in Cardiovascular Disease (MONICA) study -diet assessed using a simplified 24-h recall	monounsaturated lipids, and alcohol) or detrimental component avoided (red or processed meat); also assigned a value of 1 for consumption of dairy products Follow-up: 21.4 years	Normal BMI: 52.9% Underweight: 2.5% Overweight: 34.3% Obese: 10.2%	Confounding: low Risk of Bias: low
Ax 2014[44] Sweden ULSAM Funding: Uppsala University, Uppsala City Council Research Fund, and Swedish Research Council Cohort	Cohort: -initiated in 1970 -all men born between 1920 and 1924 living in Uppsala municipality were invited Included: -participated in 70-year investigation between 1991 and 1995 Excluded: -self-reported type II diabetes -reported extreme energy intake -for subgroup of adequate reports excluded inadequate reporters, as defined by the Golderg equation -previously diagnosed prostate cancer	mMDS: a) 1 point for > median fat quality (MUFA:SFA) and consumption of vegetables, fruits, cereals including potatoes, and fish b) 1 point for below median consumption of meat c) 1 point for alcohol intake between 10-50g/day Follow-up: 13.2 years	N = 1,044 Adequate reporters n = 566 BMI: 26.1	Population: unclear Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Buckland 2014[75] Europe EPIC Funding: Europe Against Cancer Program of the European Commission and other government agencies Cohort	Cohort: -520,000 apparently healthy men and women -aged 25-70 -recruited between 1992 and 2000 in 23 centers from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through center-specific FFQ that addressed usual diet over previous year Excluded: -registered as having cancer previously -missing end of follow-up data -missing information on diet or lifestyle -ratio for energy intake versus energy expenditure in the top or bottom 1%	Relative Mediterranean Diet Score: 18pt linear score that incorporates 9 key dietary components; 7 components presumed to reflect the MD (fruit, nuts and seeds, vegetables, legumes, fish, olive oil, and cereals) and 2 components presumed not to reflect the MD (dairy products and meat); calculated as a function of energy density and divided into tertiles; also includes alcohol, scored by assigning 2 to moderate consumers (5-25g/day for women, 10-50g/day for men) and 0 to participants outside this range Follow-up: 11 years	N = 477,312 Gender (% male): 30 Age at enrollment: 51.2 (9.9) BMI: 25.4 (4.3)	Population: unclear Outcomes: unclear Measurement: low Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Cuenca-Garcia 2014[43] USA Aerobics Center Longitudinal Study (ACLS) Funding: National Institutes of Health, Coca-Cola Company, and Spanish Grants from the Ministry of Economy and Competitiveness Cohort	Cohort: -received a preventive medical examination at the Cooper Clinic in Dallas, TX Included: -completed a standardized medical history questionnaire -underwent an extensive clinical evaluation -completed a 3-day dietary record -Complete and valid data for all the main exposures and confounders studied Excluded: -personal history of CVD or cancer -didn't achieve at least 85% of their age-predicted maximal heart rate during the graded modified Balke treadmill exercise testing -less than one year of follow-up	MDS (using sex-specific median cut-offs) a) 1 point for above median intake of vegetables, legumes, fruits and nuts, cereals, fish and seafood, and monounsaturated/saturated fats ratio b) 1 point for below median intake of dairy products and meat/meat products c) 1 point for alcohol intake 2 drinks or less per day in men and 1 drink or less per day for women Follow-up: 11.6 years	N = 12,449 Gender (% male): 78 Age: 20-82	Population: unclear Outcomes: low Measurement: low Confounding: low Risk of Bias: Low
George 2014[42] USA Women's Health Initiative Observational Study (WHI OS) Funding: National Heart, Lung, and Blood Institute Cohort	Cohort: -between 1993 and 1998 -40 clinical centers -postmenopausal women age 50-79 at study entry -clinical trial component and WHI OS study closed in 2004-2005, extension study continued through 2010 -diet measured at enrollment using a self-administered FFQ Included: -93,676 women participating in the WHI OS Excluded: -incomplete diet data -implausible energy intakes of < 600kcals/day or > 5,000 kcals/day -prior diagnosis of CVD or cancer	aMED: a) 5-15g alcohol b) ≥ median consumption of fish, fruit, legumes, nuts and seeds, ratio of MUFA to SFA, vegetables, and whole grains c) < median consumption of red and processed meats Follow-up: 12.9 years	N = 63,805 women aMED Quintile 1: 11,685 aMED Quintile 5: 15,708 Age, years: 61.9 to 64.2 BMI: 25.6 to 28.9	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Kenfield 2014[41] USA Health Professionals Follow-up Study (HPFS) Funding: National Cancer Institute and the Prostate Cancer Foundation Cohort	Cohort: -initiated in 1986 among US male health professionals aged 40-75 yr -completed FFQ for past year, updated every 4 years Excluded: -men reporting implausible energy intake (<800 or >4200 kcal/d) -missing ≥70 food items on the baseline FFQ -men diagnosed with cancer, except non-melanoma skin cancer	Traditional Mediterranean diet score: a) 1 point each for < median dairy and meat intake b) 1 point for alcohol intake 10-50g/day c) 1 point each for >median intake of vegetables, legumes, fruits and nuts, grains, fish, and the ratio of polyunsaturated to saturated lipids Follow-Up: 23.2 years	N = 47,867 men Age at start: 52.6-55.3 BMI: 25.1-25.8	Population: unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Li 2014[40] USA-6 states or 2 metropolitan areas NIH-AARP Funding: National Cancer Institute Cohort	Cohort: -mailed population-based survey linked with cancer registry data and death databases (for outcomes) Included: -age 50-71 Excluded: -proxy respondents -extreme daily caloric intake (either high or low) -cancer at baseline	Dietary Assessment: 2 dietary quality indices HEI-2005 and aMED constructed based on FFQ Follow-up: Men – 1,466 head and neck cancer cases over 2,838,422 person-years Women – 402 cases over 1,964,936 person-years	N = 494,967 Age: 62.1 (men); 61.9 (women) Gender (% male): 60 BMI: 27 (men and women)	Population: low Outcomes: unclear Measurement: low Confounding: low Risk of Bias: low
Lopez-Garcia 2014[39] USA HPFS/NHS Funding: National Institutes of Health Cohort	Cohort: HPFS -initiated in 1986 among US male health professionals aged 40-75 yr -completed FFQ for past year, updated every 4 years NHS -female, registered nurse, 30-55 years in 1976 (start of NHS), residing in 11 US states; completed mailed questionnaire about health and lifestyle Included: -men and women with a nonfatal CVD event (myocardial infarction, stroke, angina pectoris, coronary bypass, and coronary angioplasty) diagnosed from beginning of follow-up through 2006	aMED: a) 1 point if intake > cohort-specific median for vegetables, legumes, fruit, nuts, whole grain cereals, fish, and MUFA:SFA b) 1 point for intake < cohort-specific median for red and processed meats c) 1 point for alcohol intake of 5-15 g/d for women and 10-15 g/d for men Follow-up: 7.7 years for men and 5.8 years for women	N = 17,415 (6,137 men, 11,278 women) Men: Age: 69 BMI: 26 Women: Age: 67 BMI: 26.6	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Reedy 2014[38] USA-6 states or 2 metropolitan areas NIH-AARP Funding: Not reported Cohort	Cohort: -mailed population-based survey linked with cancer registry data and death databases (for outcomes) Included: -age 50-71 Excluded: -proxy respondents -cancer, ESRD, heart disease, stroke, or diabetes at baseline -extreme daily caloric intake (either high or low)	Dietary Assessment: aMED constructed based on FFQ Follow-up: 15 years	N = 242,321 men 182,342 women Age: 62 (men), 62 (women) Gender (% male): 57 BMI: 26 (men), 25 (women)	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Salas-Salvadó 2014[26] See Estruch 2013[7] RCT	Cohort: See Estruch 2013 Included: -no diabetes at baseline -incidence of diabetes could be ascertained during follow-up -required to meet American Diabetes Association criteria for diabetes on 2 tests within 3 months to be included as an incident case (fasting glucose 126.1 mg/dL or higher or 2-hour glucose 200 mg/dL or higher after 75-g oral glucose load)	Same as Estruch 2013 Follow-up: 4.1 years	N = 3,541 (of 7,447 in trial) Age (mean): 67 Gender (% male): 38 Race: NR BMI: 30	Sequence generation: low Allocation concealment: low Blinding: low Confounding: low Incomplete outcome data: high Selective outcome reporting: low Risk of Bias: medium
Tangney 2014[90] USA Memory and Aging Project (MAP) Funding: National Institute on Aging Cohort	Cohort: -started in MAP (cognitively normal older persons living in retirement communities and subsidized housing) in 1997 Included: -dementia-free at start of study -agreed to annual clinical neurologic evaluations -agreed to be in nutrition component of study (started in 2004) -had 2 or more cognitive assessments and completed valid FFQ	FFQ data used to determine MedDietScore (0-55); higher scores connote greater accordance with diets Follow-up: 4.1 years (range 1 to 10)	N = 826 Age (mean): 82 Gender (% male): 26 Race: NR BMI: 27.1	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Xie 2014[37] USA NHS Funding: National Institutes of Health	Cohort: -female, registered nurses, 30-55 years in 1976 (start of NHS) -residing in 11 US states -completed mailed questionnaire about health and lifestyle	aMDS: considers the consumption of certain fatty acids, legumes, cereals, fruits, nuts, vegetables, meat, dairy, and alcohol and ranges from 0 to 10 Follow-up: 24 years	N = 82,984 women Age: 64 BMI: 27	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Cohort				
Bamia 2013[53] Europe (10 countries) with France also reported separately[64] EPIC Funding: World Cancer Research Fund Cohort	Cohort: -520,000 apparently healthy men and women -age 25-70 -recruited between 1992 and 2000 in 23 centers from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through center-specific FFQ that addressed usual diet over previous year Excluded: -verified or self-reported prevalent cancer -insufficient follow-up information or no dietary information	MMDS: a) 1 point for intake ≥ cohort sex-specific medians for each component (vegetables, legumes, fruit/nuts, fish/seafood, and cereals) b) 1 point for consumption of meat/meat products and dairy products < median c) 1 point for ethanol intake between 5-25g/d for women and 10-50g/d for men d) 1 point for ≥ median ratio of unsaturated to saturated fats CSMMDS (center-specific): -calculated MMDS using sex and center specific medians Follow-up: 11.6 years	N = 143,752 men Age <45: 23% 45 to <55: 35% 55 to <65: 34% ≥ 65: 7% BMI ≤25: 36% >25 to <30: 49% ≥30: 15% N = 336,556 women Age <45: 26% 45 to <55: 41% 55 to <65: 27% ≥65: 6% BMI ≤25: 58% >25 to <30: 29% ≥30: 13% France[64] N = 68,442 Healthy Pattern: Age: 52.7-52.8 BMI: 22.5-23.6	Population: unclear Outcomes: unclear Measurement: low Confounding: low Risk of Bias: medium
Bosire, 2013[52] USA-6 states or 2 metropolitan areas NIH-AARP Funding: National Cancer Institute Cohort	Cohort: -mailed population-based survey linked with cancer registry data and death databases (for outcomes) Included: -men age 50-71 Excluded: -proxy respondents -people with other cancers (except non-melanoma skin); ESRD -extreme daily caloric intake (either high or low)	Dietary Assessment: 3 dietary quality indices HEI-2005, AHEI-2010, and aMED constructed based on FFQ Follow-up: 8.9 years	N = 293,464 Age (mean): 62 Gender (% male): 100 Race (%white): 93 BMI: 27	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Buckland 2013[51] Europe EPIC Funding: The	Cohort: -520,000 apparently healthy men and women -age 25-70 -recruited between 1992 and 2000 in 23 centers	Adapted relative Mediterranean diet score (ARMED); 16 point scale: a) score of 0-2 assigned to country	N = 355,062 Age at Recruitment: 50.8 BMI: 25.0	Population: unclear Outcomes: low Measurement: low Confounding: low

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European Commission FP5 Project Cohort	from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through center-specific FFQ that addressed usual diet over the previous year Excluded: -no follow-up information -prevalent cancer at recruitment -incomplete information on diet or lifestyle -implausible dietary data top and bottom 1% of the total energy intake to energy requirement ratio	specific tertiles of intake for 6 components presumed to fit MD; fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (fresh or frozen, excluding fish products and preserved fish), olive oil, and cereals b) scoring inverted for components presumed to not fit MD (meat and dairy products) c) for olive oil: 0 to non-consumers, 1 for subjects< median, and 2 for subjects ≥median Follow-up: 11.0 years		Risk of Bias: low
Couto, 2013[50] Sweden Swedish Women's Lifestyle and Health (SWLH) Funding: Swedish Research Council and Swedish Cancer Society Cohort	Cohort: -from 1991-1992, women age 30-49 living in Uppsala Health Care Region -96,000 women randomly selected from Swedish central population registry to receive an invitation letter and questionnaire -follow-up questionnaire mailed to previous respondents in 2003 -questionnaires asked about diet in previous 6 months Included: -completed a baseline questionnaire Excluded: -diagnosed with breast cancer before or at recruitment -total energy intake outside the 1st and 99th percentiles -missing information on BMI, height, age at first birth and total number of children, age at menarche, or use of oral contraceptives	-Conformity measured using variant of the Mediterranean diet score (Low = 0, High = 9) a) 1 point for > median consumption of vegetables, fruits and nuts, legumes, cereals, fish, and high ratio of unsaturated to saturated fat b) 1 point for < median consumption of dairy and meat products c) 1 point for alcohol consumption between 5-25 g/day Follow-up: 16 years	At baseline: N = 44,840 Age: 30-49 BMI: ≤20: 12% 21-24: 62% ≥25: 26%	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Estruch, 2013[7] Valls-Predret 2015[28] Martinez-Lapiscina 2013[25]	Included: -community-dwelling women 60-80 years or men 55-80 years -no CV disease but high CV risk (either type II diabetes, or at least 3 major risk factors)	MD+EVOO (approx. 1 liter/week): n = 2,543 MD+nuts (30 g/day); n = 2,454 (both MD groups had individual and group dietary training at	N = 7,447 Age (mean): 67 Gender (% male): 43 Race: 97% white (from Europe); 1.4%	Sequence generation: low Allocation concealment: low Blinding: low

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Spain PREDIMED Funding: Instituto de Salud Carlos III (ISCIII) RCT	Excluded: -documented history of previous CV disease -severe medical condition that may impair ability to participate in nutrition intervention study -life expectancy <1 year -immunodeficiency or HIV-positive status -illegal drug use or chronic alcoholism or total daily alcohol intake >80g/day -BMI >40 kg/m^2 -impossible to follow Mediterranean-type diet -low predicted likelihood to change dietary habits -history of food allergy to any components -participation in any drug trial or use of investigational drug in last year -unable to attend clinic visits every 3 months -illiteracy	baseline and quarterly thereafter with conformity evaluation) Control: n = 2,450 (low fat diet) Dietary training at baseline with conformity evaluation; yearly leaflet explaining low-fat diet[a] No total caloric restriction advised No promotion of physical activity Follow-up: 4.8 years	Hispanic (Central or South America) BMI: 30	Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low
Gamba 2013[29] USA Women's Health Initiative Dietary Modification Trial (WHI-DM) Funding: National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Heart, Lung, and Blood Institute; National Institutes of Health; and US Department of Health and Human Services RCT	Included: -postmenopausal women -age 50-79 years Included: -interested in one or more components of the clinical trials -willing to be randomized to intervention or comparison group -fat intake at baseline of 32% or more Excluded: -previous history of breast, colorectal, or any cancer other than non-melanoma skin cancer in the past 10 years -predicted survival of less than 3 years -type I diabetes mellitus and other conditions that posed adherence and retention concerns (*eg,* alcoholism, dementia). Participants had to have a baseline fat intake 32% or more of total energy	Intervention: intensive behavioral modification program using 18 group sessions in first year and then quarterly sessions decrease total fat intake to 20% or less of energy and consume 5 or more servings per day of vegetables and fruits and 6 or more servings per day of grains; Comparison: received a copy of the US Department of Health and Human Services ' *Dietary Guidelines for Americans* Follow-up: 8.1 years	N = 48,835 IG: 19,541 CG: 29,294 Age (mean): 62.3 BMI: 29.1	Sequence generation: low Allocation concealment: low Blinding: unclear Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low

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Gnagnarella 2013[49] Italy COSMOS Funding: Italian Association for Cancer Research, Italian Foundation for Cancer Research, and European Institute of Oncology Cohort	Cohort: -5203 asymptomatic volunteers -age ≥ 50 years -current smoker or had quit smoking for <10 years and had smoked at least 20 pack-years -Enrolled between October 2004 and October 2005 -underwent annual LD-CT -baseline FFQ about intake over preceding year Included: -completed FFQ returned Excluded: -abnormal dietary values (total caloric intake less than or greater than 3 standard deviations)	aMED score: a) 1 point for intakes > median value reported by all participants for vegetables, fruits, nuts, cereals, legumes, and fish (otherwise 0 points) b) 1 point for red and processed meat consumption < median c) 1 point for alcohol intake of 5-15g/day Follow-up: 5.7 years	N = 4,336 Gender (% male): 66 Age (median): 57 BMI ≤18.5: 1% BMI 18.5-24: 45.2% BMI 25-30: 41.4% BMI ≥30: 11.6%	Population: unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Kesse-Guyot 2013[80] France SU.VI.MAX (Supplementation with Vitamins and Mineral Antioxidants) Funding: Agence Nationale de la Recherche, Direction Generale de la Sante (Ministry of Health), Mederic, Sodexo, Ipsen, Mutuelle Generale de l'Education Nationale (MGEN), and Pierre Fabre Cohort	Cohort: -participants from SU.VI.MAX and SU.VI.MAX -dietary pattern assessed 1994-1996 and cognitive outcomes assessed 2007-2009 Excluded: -missing neuropsychological test scores -<3 dietary records during first 2 years of follow-up -younger than 45 years at baseline -missing data on one or more covariates	Food and nutrient intakes determined from patient-completed 24-hr dietary records during first 2 years of follow-up *Mediterranean Diet Score (MDS)* (max score of 9; higher scores indicated better conformity) a) 1 point for > sex-specific mean consumption of vegetables, fruits, grains, fish, nuts, legumes, and the ratio of MUFAs to SFAs b) 1 point for < median consumption of meat and dairy products c) 1 point for alcohol consumption between 5-25g/d for women and 10-50g/day for men *Mediterranean-Style Dietary Pattern Score (MSDPS) (*scores range from 0 (0%) to 1 (100%) reflecting % of energy from foods included in Med Diet pyramid) a) each component (except olive oil) scored 0-10 according to level	N = 3083 Age (mean): 52 at baseline; 65 at time of cognitive evaluation Gender (% male): 54 Race: NR BMI: 24	Population: unclear Outcomes: low Measurement: low Confounding: low Risk of Bias: low

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		of conformity b) exclusive olive oil use = 10 points, no use = 0, and use of olive oil and other fats = 5 Follow-up: 13 years		
Kyro 2013[48] Denmark Funding: NordForsk and the Danish Cancer Society Cohort	Included: -age 50-64 years -born in Denmark -reside in certain areas of Denmark Excluded: -cancer	Dietary Assessment: self-administered FFQ converted into a "healthy Nordic food index" comprised of fish, cabbage, rye bread, oatmeal, apples & pears, and root vegetables Follow-up: 13 years	N = 57,053 Men (n = 26,664): Age: median 56 BMI: median 26 Women (n = 29,216): Age: median 56 BMI: median 25	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Li 2013[47] USA-6 states or 2 metropolitan areas NIH-AARP Funding: National Cancer Institute Cohort	Cohort: -mailed population-based survey linked with cancer registry data and death databases (for outcomes) Included: -age 50-71 Excluded: -proxy respondents -extreme daily caloric intake (either high or low) -cancer at baseline	Dietary Assessment: 2 dietary quality indices HEI-2005 and aMED constructed based on FFQ Follow-up: 9.7 years	N = 494,968 Age (mean): 62 Gender (% male): 60 Race (%white): 93 BMI: 27	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Link 2013[46] USA California Teachers Study (CTS) Funding: National Cancer Institute, California Breast Cancer Research Fund, and other government sources Cohort	Included: -active and retired female teachers and administrators residing in California Excluded: -history of breast cancer -extremely low or high caloric intake	Dietary assessment: self-administered FFQ reduced to 5 patterns using factor analysis; "salad and wine" and "ethnic" diets fit our definition of Mediterranean diet Follow-up: 14.1 years	N = 91,779 Age (median): 50 Gender (% male): 0 Race 88% non-Latina white BMI: median 23.7	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium

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Mursu 2013[45] USA IWHS Funding: National Cancer Institute, Academy of Finland, Finnish Cultural Foundation, and Fulbright program Cohort	Cohort: -started in 1986, 41,836 women age 55-69 completed a 16-page self-administered questionnaire Included: -for 2004 follow-up analysis only women with complete baseline and FFQ follow-up data Excluded: -premenopausal, diabetes, CVD, cancer -did not adequately complete a FFQ at baseline in 1986	AHEI components (each component had potential to contribute 0-10 points to total score): vegetables, whole fruit, whole grains, sugar-sweetened beverages/fruit juices, nuts and legumes, red and processed meat, fat quality, sodium, and alcohol intake	Baseline N = 29,634 2004 follow-up analysis: n = 15,076 Age: 61.2 BMI: 26.7	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Samieri 2013[84] USA NHS Funding: National Cancer Institute, Fulbright Research Scholar program, and Pole de Recherche et d"Enseignement Superieur Cohort	Cohort: NHS: female, registered nurse, 30-55 years in 1976 (start of NHS), residing in 11 US states; completed mailed questionnaire about health and lifestyle Cognitive sub-study: age 70 or older in 1995, free of stroke, completed at least one expanded FFQ in 1984 or 1986, completed at least one cognitive assessment, no missing data for energy intake and physical activity	FFQ: expanded 116-item version introduced in 1984; used information to estimate daily energy intake and construct alternative MD 9 point score a) 1 point for > median intake of vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, and MUFA:SFA ratio b) 1 point for < median intake of red/processed meats c) 1 point for alcohol intake of 5-15g/d Follow-up: 6 years	N = 16,058 Age (mean): 74 at first cognitive exam Gender (% male): 0 Race: NR BMI: 20% 21 or lower 17% 30 or higher	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Samieri 2013[83] USA Women's Health Study Funding: National Cancer Institute, Fulbright Research Scholar program, and Pole de	Included: -no history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or chronic kidney or liver disease -age 65 years or older (for sub-study) -complete dietary data -at least one complete cognitive assessment	FFQ completed at baseline; used to construct alternate Mediterranean diet conformity score (9 point) Follow-up: 4 years	N = 6,174 Age (mean): 72 Gender (% male): 0 BMI: 26	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium

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Recherche et d"Enseignement Superieur Cohort				
Wengreen 2013[91] USA Cache County Memory Study (CCMS) Funding: National Institutes of Health, General Mills Bell Institute of Health, and Utah State University Cohort	Cohort: -elderly (age 65 and older) residents of Cache County, UT -completed baseline interview and FFQ Invited to participate: 1995-96 Reassessed: 1998-99, 2003-03, 2005-06 Excluded: -dementia at baseline -implausible energy intakes on FFQ	FFQ: 142-item, self-administered MD score: 8 components (no moderate alcohol consumption component) -participants ranked on consumption of fruit, vegetables, total grains, nuts and legumes, MUFA:SFA ratio, and fish -ranked in reverse order of intake of red and processed meat and full-fat dairy -rank scores summed and participants put into quintiles Follow-up: 10.6 years	N = 3,580 Age (mean): 74 Gender (% male): 43 Race: NR BMI: 26	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Cherbuin 2012[76] Australia PATH Through Life Funding: National Health and Medical Research Council Cohort	Included: -resident of Canberra, Australia -randomly selected from electoral roll -middle-aged cohort (age 60-64 at Wave 1 [2001-2]) -valid neuropsychological assessment at Wave 1 and follow-up (5 years) -available dietary and *APOE*E4* data	FFQ: 215 food items (from Commonwealth Scientific and Industrial Research Organisation); used to calculate daily nutrient intake and caloric intake; weekly alcohol consumption determined with Alcohol Use Disorders Identification Test Follow-up: 4 years	N = 1,557 Gender (% male): 49 Age (mean): 62.5 BMI: NR	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Chiuve 2012[56] USA NHS/HPFS Funding: National Institutes of Health and American Heart	Cohort: HPFS -initiated in 1986 among US male health professionals age 40-75 yr -completed FFQ for past year, updated every 4 years NHS -female, registered nurse, 30-55 years in 1976	AHEI: food and nutrients that have been associated consistently with lower risk of chronic disease in clinical and epidemiologic investigations (vegetables, fruits, whole grains, nuts and legumes, fat quality, low-sugar beverages, and red/processed meat plus low	N = 71,495 women (NHS) N = 41,029 men (HPFS) Age: NR BMI: NR	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Association Cohort	(start of NHS), residing in 11 US state -completed mailed questionnaire about health and lifestyle Excluded: -previously diagnosed CVD, diabetes, or cancer -invalid FFQ data	sodium and alcohol intake 0.5-1.5 or 2g/d depending on gender Follow-up: NHS 24 years, HPFS 22 years		
Gardener 2012[78] Australia Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL) Funding: CSIRO Flagship Collaboration Fund and Science and Industry Endowment Fund with other sources Cohort	Cohort: -volunteers -healthy control, MCI, and AD individuals -age ≥60 (longitudinal analysis of healthy controls reported) Included: -completed the CCVFFQ, returned for follow-up assessment at 18m Excluded: -history of non-AD dementia, schizophrenia, bipolar disorder, significant current depression, Parkinson's disease, cancer (other than basal cell skin carcinoma) within last 2 years -symptomatic stroke, insulin-dependent diabetes, uncontrolled diabetes mellitus -current regular alcohol use exceeding 2 standard drinks/day for women or 4/day for men -incomplete neuropsychological test results	Cancer Council of Victoria FFQ: 74 items, self-administered, assesses intake over preceding 12 months *MD Score* (0-low conformity, 9 = high conformity): a) 1 point for >sex-specific median consumption of fruits, vegetables, legumes, cereals, fish, and MUFA:SFA b) 1 point for < median consumption of meat and dairy products c) 1 point for alcohol consumption 5-25g/d for women, 10-50g/d for men. Follow-up: 1.5 years	N = 723 healthy controls (652 in analysis) Age (mean): 70 Gender (% male): 42 Race: NR (72% born in Australia) BMI: 26.5	Population: unclear Outcomes: unclear Measurement: low Confounding: low Risk of Bias: medium
Kwok 2012[24] Hong Kong Funding: Tung Wah Group RCT	Included: -old-age hostel resident -75 or older Excluded: tube-fed -on special diet due to chronic renal failure	Control (CG): PI and dietician gave 1h talk to residents/staff on prevention of dementia; promoted brain preservation diet (2 portions of fruit/day, 3 portions of vegetables/day, 5 portions of fish/wk, avoidance of salty foods) Intervention (IG): Control plus dietary support groups every 3 weeks for first year and then every 6 weeks for 21 months; at each group session: information sharing, interactive games to reinforce learning, and promotion of brain preservation diet; dietician also liaised closely with hostel and	N = 429 Age (mean): 83 Gender (% male) IG: 22 CG: 9.3 BMI: 23	Sequence generation: unclear Allocation concealment: unclear Blinding: unclear Incomplete outcome data: low Selective outcome reporting: unclear Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
		kitchen staff on menu and cooking methods Follow-up: 33 months		
Tognon 2012[54] Sweden Funding: Swedish Council on Working Life and Social Research EpiLife Center, Nordic Health Whole Grain Food/NordForsk, Swedish Council for Working Life and Social Research, and Swedish Research Council Cohort	Cohort: -between Jan 1, 1990 to Dec 31, 2008 residents of Vasterbotten county in northern Sweden invited to participate in a health survey when turning 30 (between 1990-1996), 40, 50, or 60 -in 1996 and 2008, 70-year-olds were also included in cohort Included: -underwent anthropometric measurements as well as measurement of blood pressure, lipids, and oral glucose tolerance -completed a dietary questionnaire Excluded: -missing body weight or height -unrealistic food intake levels (lowest 5% or highest 2.5%) -completed <10% of food items on questionnaire -reported alcohol intake >50g/d	Modified Mediterranean Diet Score: a) 1 point for > sex/questionnaire-specific median consumption of vegetables and potatoes, fruit and juices, whole-grain cereals, fish and fish products, ratio of MUFA + PUFA to SFA, and alcohol intake b) 1 point for < median consumption of meat/meat products and dairy products Follow-up: 10 years for all-cause mortality 9 years for cause-specific	N = 77,151 Age: predominantly 30-60 y olds Gender (% male): 47 BMI ≥ 30 (obese): 61%	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Cade 2011[58] United Kingdom UKWCS Funding: World Cancer Research Fund Cohort	Cohort: -recruited 35,372 women aged 35-69y between 1995 and 1998 -cohort was selected from about 500,000 responders to a survey -selected each vegetarian then the next non-vegetarian in the survey aged within 10 years of the vegetarian -Baseline FFQ Excluded: -prevalent breast cancer -couldn't be flagged for cancer registration with the Office of National Statistics -energy intake outside of the expected levels -no form date	Mediterranean Diet Score: a) 0 or 1 point for each component using the cohort median as cut off b) 1 point for > median intake of vegetables, legumes, fruit and nuts, cereal, fish, and ratio of monounsaturated fatty acids to saturated fatty acids c) 1 point for < median intake of meat, poultry, and dairy products d) 1 point for alcohol consumption of 5-25g/d Follow-up: 9 years	N = 33,731 women Age (mean): 52 BMI: 24.5	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium

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Couto 2011[57] Europe EPIC Funding: European Commission and International Agency for Research on Cancer Cohort	Cohort: -520,000 apparently healthy men and women -age 25-70 -recruited between 1992 and 2000 in 23 centers from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through center-specific FFQ that addressed usual diet over previous year Included: -complete exposure information Excluded: -prevalent cases of cancer -incomplete follow-up - ratio of energy intake vs energy expenditure in the top or bottom 1%	a) 1 point for > country sex-specific median consumption of vegetables, legumes, fruits and nuts, cereals, fish, and a high ratio of unsaturated to saturated lipids b) 1 point for < median consumption of dairy, meat, and meat products c) 1 point for alcohol consumption between 10-50g/d for men, 5-25g/d for women Follow-up: 8.7 years	N = 478,478 Men (n = 142,605) Age (mean): 52 Mean BMI: 26.5 Women, (n = 335,873) Age (mean): 51 BMI: 25	Population: unclear Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Menotti 2011[55] Italy Seven Countries Study Funding: No funding received Cohort	Cohort: -population-based prospective cohort Included: -men age 40-59 in 2 communities in Italy Excluded: -none	Dietary Assessment: food intake data collected by dietitians and categorized into 17 food groups; factor analysis reduced diet to 3 factors, one of which (factor 2) "was similar to the pattern considered a typical Mediterranean diet rich in vegetables, oil, and fish" Follow-up: 40 years for mortality, 20 years for CHD events	N = 1,221 for mortality N = 1,153 for CHD events For mortality sample: Age (mean): 54.9 Gender (% male): 100 Race: NR BMI: 25.7	Population: low Outcomes: low Measurement: unclear Confounding: unclear Risk of Bias: medium
Tangney 2011[89] USA Chicago Health and Aging Project (CHAP) Funding: National Institute on Aging Cohort	Cohort: -enrollment beginning in 1993 -age ≥65 -≥2 cognitive assessments Included: -living on south side of Chicago; Excluded: -died before follow-up -invalid dietary data -only one cognitive assessment	*MedDiet score* based on FFQ (139 items) over past year; maximum score of 55 (greatest conformity) a) consumption of fruit, vegetables, legumes, nuts and beans, fish, olive oil, potatoes, and nonrefined cereals assigned a score of 5 for at least daily consumption and < 5 points for fewer servings (0 if rarely consumed) b) opposite scoring for red meat and meat products (0 if > 10 times/week and 5 if ≤ 1 time/ week) c) 0 for alcohol intake >700 mL/d or	N = 3,790 Age (mean): 75 Gender (% male): 38 Race: 60% black BMI: 27.1	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
		none at all; 5 for < 300 mL/d *MedDiet Wine* score same as above but alcohol consumption only includes wine Follow-up: 7.6 years (mean)		
Fung 2010[59] USA NHS and HPFS Funding: National Institutes of Health Cohort	Cohort: NHS -121,700 female nurses, age 30-55 -questionnaires sent biennially since 1976 -first FFQ in 1980, expanded in 1984 (baseline); designed to measure intake for previous year Included: -completed 1980 FFQ with <10 missing items -realistic total energy intake (500-3500 kcal/d) HPFS: -initiated in 1986 among US male health professionals age 40-75 years -completed FFQ for past year, updated every 4 years Excluded: -history of cancer, except non-melanoma skin cancers or ulcerative colitis	aMED a) 1 point if intake is >median for vegetables, legumes, fruit, nuts, whole-grain cereals, fish, and monounsaturated:saturated fat ratio b) 1 point for intake< median for red and processed meats c) 1 point for alcohol intake of 5-15g/d Follow-up: 26 years	NHS N = 87,312 women HPFS N = 45,080 men Age: 30-55 for women, 40-75 for men) BMI = 24	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Roberts 2010[82] USA Mayo Clinic Study of Aging Funding: National Institutes of Health and private foundation Cohort	Cohort: -randomly selected from all Olmsted County (MN) residents age 70-89 on 10/1/2004 (longitudinal analysis of cognitively normal or MCI reported) Excluded: -died before contacted -terminally ill and in hospice -previously diagnosed confirmed dementia -could not be contacted -missing FFQ or responses on more than 10 questions -reported extreme caloric intake	Health Habits and History Questionnaire (128 items) to assess eating habits in past year; portion size and frequency; used to calculate MD score (0 = minimal, 9 = maximal conformity) a) 1 point for ≥ median consumption of vegetables, legumes, fruits, cereal, MUFA:SFA, and fish b) 1 point for < median consumption of meat and dairy products c) 1 point for alcohol consumption of 0-30g/d Follow-up: 2.2 years	N = 1141 in follow-up cohort (1233 with baseline data) Age (median): 80 Gender (% male): 51% Race: NR BMI <25: 32% 25-29: 40% ≥30: 28%	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Agurs-Collins 2009[60]	Cohort: -African-American women from across US	Prudent Pattern: higher intakes of cruciferous and other vegetables,	N = 50,778 Age (mean): 38.5	Population: unclear Outcomes: low

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USA Black Women's Health Study Funding: National Cancer Institute Cohort	-enrolled 59,000 women in 1995 -age 21-69 -baseline FFQ to assess average food intake over previous year -follow-up questionnaires sent every 2 years Included: -completed 1995 baseline FFQ -missing data on ≤ 10 questions on FFQ -total caloric intake of 500 to 3800 kcal/d -completed at least one follow-up questionnaire -did not report breast cancer at baseline	fruit, whole grains, cereals, beans, low-fat dairy products, fish, and poultry Follow-up: 12 years	BMI: 27.9	Measurement: unclear Confounding: low Risk of Bias: medium
Féart 2009[77] France Three-City (3C) Study Funding: Institut National de la Sante et de la Recherche Medicale, Institut de Sante Publique et Developpement, and Sanofi-Aventis Cohort	Cohort: -community-dwelling, identified in 1999-2000 from electoral rolls in Bordeaux Included: -age ≥65 -at least one follow-up re-examination over 5 years Excluded: -missing dietary data -did not complete screening for dementia -dementia at baseline	*FFQ*: aggregated into 20 food and beverage groups with focus on MD foods: vegetables, fruits, legumes, cereals, fish, meat, dairy, and alcohol; score from 0 to 9 (higher score = higher conformity) a) 1 point for > sex median of vegetables, fruits, legumes, cereals, and fish b) 1 point for < median consumption of meat and dairy products c) 1 point for 10-20g/d of alcohol for men and 1.4-5.7g/d for women d) 1 point for > median ratio of MUFA:SFA *24-hour Dietary Recall*: for nutrient intake, total energy intake, and ratio of MSFA to SFAs Follow-up: 2, 4, and 7 years	N = 1410 Age (mean): 76 Gender (% male): 40% Race: NR BMI: 26	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Scarmeas 2009[85] See Scarmeas 2006[88] Cohort	Cohort: see below Excluded: -missing dietary or physical activity evaluation -death or loss to follow-up	Same as above Follow-up: 5.4 years	N = 1880 Age (mean): 77 Gender (% male): 31 BMI: 27.4	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Scarmeas 2009[87] See Scarmeas 2006[88]	Cohort: see below Excluded: -dementia or MCI at baseline (including CDR = 0.5)	Same as above Follow-up: 4.5 years	N = 1393 cognitively normal at baseline Age (mean): 77 Gender (% male): 32	Population: low Outcomes: low Measurement: low Confounding: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Cohort	-missing dietary information		BMI: 27.5	Risk of Bias: low
Psaltopoulou 2008[81] Greece ILIDA (nested in EPIC-Greece) Funding: European Commission, Greek Ministry of Health, Greek Ministry of Education, private grant, and Hellenic Health Foundation Cohort	Included: -residence in Attica region -age ≥60 at enrollment -agreed to participate Excluded: -died during follow-up -missing information on diet, anthropometric, or lifestyle variables -reported a stroke at baseline	Conformity to MD based on 9 components: vegetables, legumes, fruit and nuts, cereals, fish, meat, dairy, ethanol, and lipids; 10-point score (0 = minimal conformity, 9 = maximal conformity) a) 1 point for > median consumption of vegetables, legumes, fruit and nuts, cereals, and fish b) 1 point for < median consumption of meat and dairy c) 1 point for 10-50g/d alcohol for men 5-25g/d for women d) 1 point for ≥ median MUFA:SFA ratio Follow-up: 8 years	N = 732 Age (mean) 60-64 yrs: 40% 65-69 yrs: 33% ≥70 yrs: 26% Gender (% male): 35 Race: NR BMI: ≤24.99: 15% 25.00-29.00: 45% ≥30.00: 40%	Population: low Outcomes: low Measurement: low Confounding: unclear Risk of Bias: low
Reedy 2008[61] USA-6 states or 2 metropolitan areas NIH-AARP Funding: National Cancer Institute Cohort	Cohort: -Mailed population-based survey linked with cancer registry data and death databases (for outcomes) Included: -age 50-71 Excluded: -proxy respondents -cancer, ESRD -extreme daily caloric intake (either high or low)	Dietary Assessment: MED score constructed based on FFQ Follow-up: 5 years	N = 492,382	Population: low Outcomes: unclear Measurement: low Confounding: low Risk of Bias: low
Tinker 2008[30] USA WHI-DM Funding: National Heart, Lung, and Blood Institute RCT	Cohort: -postmenopausal women -age 50-79 years -interested in one or more components of the clinical trials Included: -willing to be randomized to an intervention or comparison group -fat intake at baseline of 32% or more Excluded: -any prior colorectal or breast cancer -other cancers in the last 10 years except non-	Intervention (IG): intensive behavioral modification program using 18 group sessions in first year and then quarterly sessions a) reduce total fat to 20% of energy intake b) increase vegetables and fruits to at least 5 servings daily and grains to at least 6 servings daily c) anticipated that saturated fat would also be reduced Comparison (CG): received US	N = 45,887 IG: 18,376 CG: 27,511 Age (mean): 62 Race: 82% white 10% black 8% other BMI: 28.9	Sequence generation: low Allocation concealment: low Blinding: unclear Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
	melanoma skin cancer -medical conditions with predicted survival < 3 years -adherence or retention concerns -current dietary intake of <32% of energy from fat -type 1 diabetes mellitus	Department of Health and Human Services *Dietary Guidelines for Americans* and other health-related materials but not asked to make any dietary changes Follow-up: 8.1 years		
Prentice 2007[31] USA WHI-RCDM Funding: National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, and US Department of Health and Human Services RCT	Cohort: -postmenopausal women -age 50-79 years -interested in one or more components of the clinical trials Included: -willingness to be randomized to an intervention or comparison group Excluded: -prior breast or colorectal cancer -other cancer except non-melanoma skin cancer within the past 10 years -medical conditions yielding predicted survival of < 3 years -adherence or retention concerns -baseline diet estimated to have less than 32% of energy from fat	Intervention (IG): intensive behavioral modification program using 18 group sessions in first year and then quarterly sessions a) decrease total fat intake to 20% or less of energy b) consume 5 or more servings per day of vegetables and fruits and 6 or more servings per day of grains Comparison (CG): received US Department of Health and Human Services *Dietary Guidelines for Americans* Follow-up: 8.1 years	N = 48,835 IG: 19,541 (40%); CG: 29,294 (60%) Age (mean): 62.3 BMI≥25: 75%	Sequence generation: low Allocation concealment: low Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low
Sant 2007 and Sieri 2004 [62,70] Italy ORDET study Funding: Italian Association for Research on Cancer Cohort	Cohort: -population-based, prospective Included: -healthy women age 34-70 in one Northern Italy province Excluded: -history of cancer, bilateral oophorectomy, or chronic or acute liver disease -on hormone therapy in the 3 months before recruitment	Dietary Assessment: self-administered semi-quantitative FFQ from which 4 diet patterns were derived (2 relevant for Mediterranean diet review) a) *salad vegetables*: raw vegetables and olive oil b) *prudent*: cooked vegetables, rice, poultry, fish, and low alcohol consumption Follow-up: 9.5 years (Sieri 2004)	N = 8,984 Age: NR Gender (% male): 0 Race: NR BMI: NR	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Beresford 2006[23] USA WHI-DM Funding:	Cohort: -postmenopausal women -age 50-79 years -interested in one or more components of the	Intervention (IG): intensive behavioral modification program using 18 group sessions in first year then quarterly sessions	N = 48,835 IG: 19,541 (40%) CG: 29,294 (60%) Age 50-59: 36.9%	Sequence generation: low Allocation concealment: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
National Heart, Lung, and Blood Institute and Department of Health and Human Services RCT	clinical trials Included: -willing to be randomized to an intervention or comparison group -fat intake at baseline of 32% or more Excluded: -any prior colorectal or breast cancer -other cancers in the last 10 years -type 1 diabetes -medical conditions with predicted survival of < 3 years -adherence concerns	a) reduce total fat to 20% of energy intake b) increase vegetables and fruits to at least 5 servings daily and grains to at least 6 servings daily c) anticipated that saturated fat would also be reduced Comparison (CG): received US Department of Health and Human Services *Dietary Guidelines for Americans* and other health-related materials but not asked to make any dietary changes Follow-up: 8.1 years	60-69: 46.5% 70-79: 16.6% Gender (% male): 0 Race: 81% black, 11% white, 4% Hispanic, 0.5% American Indian, 2% Asian/pacific islander, and 1.3% unknown BMI: NR	Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low
Fung 2006[65] USA NHS Funding: National Institutes of Health Cohort	Cohort: -121,700 female nurses, aged 30-55, questionnaires sent out biennially since 1976 -First FFQ in 1980, expanded in 1984 (baseline), designed to measure intake for previous year Included: -completed the 1984 FFQ with fewer than 70 missing items -total caloric range between 500 and 3500 kcal/day Excluded: -women with a history of cancer, except non-melanoma skin cancers	aMED (higher score is more healthful): vegetables (except potatoes), legumes, fruits, nuts, cereals (whole grain only), red and processed meat, fish, alcohol, and the monounsaturated:saturated fat ratio a) 1 point for > median intake of foods listed except 1 point for < median consumption of meat b) 1 point for alcohol consumption 5-15g/d. Follow-up:18 years	N = 71,058 BMI: 24.5	Population: unclear Outcomes: unclear Measurement: low Confounding: low Risk of Bias: medium
Howard 2006[32] USA WHI-DM Funding: National Heart, Lung, and Blood Institute, Department of Health and Human Services RCT	Cohort: -postmenopausal women -age 50-79 years Included: -fat intake at baseline of 32% or more Excluded: -any prior colorectal or breast cancer -other cancers except non-melanoma skin cancer in the last 10 years -type 1 diabetes -medical conditions with predicted survival of < 3 years -adherence concerns (alcoholism)	Intervention (IG): intensive behavioral modification program using 18 group sessions in first year then quarterly sessions a) reduce total fat to 20% of energy intake b) increase vegetables and fruits to at least 5 servings daily and grains to at least 6 servings daily c) anticipated that saturated fat would also be reduced Comparison (CG): received US Department of Health and Human	N = 48,835 IG: 19,541 (40%) CG: 29,294 (60%) Age (mean): 62.3 BMI: 29.1	Sequence generation: low Allocation concealment: low Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
	-frequent consumption of meals not made at home	Services *Dietary Guidelines for Americans* and other health-related materials but not asked to make any dietary changes Follow-up: 8.1 years		
Lagiou, 2006[63] Sweden Swedish WLH Funding: Swedish Research Council and Swedish Cancer Society Cohort	Cohort: -from 1991-1992 recruited women age 30-49 years who lived in Uppsala Health Care Region -96,000 women randomly selected from Swedish central population registry to receive invitation letter and questionnaire -follow up questionnaire mailed to previous respondents in 2003 -questionnaires asked about diet in previous 6 months Included: -completed a baseline questionnaire Excluded: -emigrated without re-immigration prior to start of study -prevalent cancer (excluding non-melanoma skin cancer), CHD, or diabetes at enrollment -missing information on any covariates studied -total energy intake outside 1st and 99th percentiles	Dietary Assessment: FFQ about diet for 6 preceding months; conformity measured using variant of Mediterranean diet score (Low = 0 High = 9): a) 1 point for > median consumption of vegetables, fruits and nuts, legumes, cereals, fish, and high ratio of unsaturated to saturated fat b) 1 point for < median consumption of dairy and meat products c) 1 point for alcohol consumption between 5-25 g/day Follow-up: 12.01 years	n = 42,237 Age 29-34: 24% 35-39: 26% 40-44: 26% 45-49: 24% BMI <25: 73% 25-29.9: 22% ≥30: 5%	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Scarmeas 2006[88] USA Washington Heights-Inwood Columbia Aging Project (WHICAP) Funding: National Institute on Aging and private foundation Cohort	Cohort: -participant in cohort (WHICAP 1992, WHICAP 1999) -identified from probability sample of Medicare beneficiaries residing in an area of 3 contiguous census tracts in northern Manhattan Excluded: -missing or incomplete dietary information -died within 1.5 years from baseline assessment -follow-up not available	Semi-quantitative FFQ (61 items) used to determine MD score (0 = minimal conformity, 9 = maximum) a) 1 point for > median consumption of fruits, vegetables, legumes, cereals, and fish b) 1 point for < median consumption of meat and dairy c) 1 point for > median ratio of MUFA:SFA d) 1 point for alcohol 0-30gm/d. Follow-up: 4 years	N = 2226 Age (mean): 77 Gender (% male): 32 BMI: 27.4	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Scarmeas 2006-2[86] See above Cohort	Cohort: see above Excluded: -non-demented at baseline but developed dementia at follow-up -deemed non-demented but had Clinical Dementia Rating (CDR) > 0 -deemed demented but had either a non-AD diagnosis or a CDR > 1 -missing dietary information	Same as above	N = 1984 Age (mean): 76 Gender (% male): 32 BMI: 27.7	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Adebamowo 2005[69] USA NHS II Funding: Not reported Cohort	Cohort: -116,671 female registered nurses -age 25-42 -questionnaires mailed biennially Included: -free of cancer -responded to baseline questionnaire Excluded: -implausible values for total energy intake (<600kcal or >3500kcal/day) -left more than 70 items on the FFQ blank -diagnosis of cancer, except non-melanoma skin cancer before the start of follow-up -in situ breast cancer -postmenopausal at baseline	Prudent: vegetables, fruit, legumes, whole grains, fish, poultry, and low-fat dairy products Follow-up: 8 years	Mean age: 36 (4.6) Prudent: Quartile 1 (lowest): N = 17934, Age 35.5, BMI: 24.7 Q3: N = 18452, Age 36, BMI: 24.4 Q5: N = 17470, age 36.4, BMI: 24.7	Population: unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Kim 2005[68] Japan JPHC Funding: Ministry of Health, Labor, and Welfare of Japan Cohort	Cohort: -54,498 residents -age 40-59 years at beginning of study (1/1990) -FFQ covered past month Included: -returned questionnaire Excluded: -self-reported serious illness (cancer, ischemic heart disease, cerebrovascular disease, or chronic liver disease) at baseline -not Japanese -moved away at baseline -reported extreme total energy intake (upper 2.5% or lower 2.5%) -reported a past history of cancer	Healthy: heavily loaded with vegetables, fruits, soy products, seaweeds, mushroom, milk, beans, and yogurt Follow-up: 9 years	N = 42,112 Men (n = 20,300) Age: 48-50.7 BMI: 23-24 Women (n = 21,812) Age: 48.6-50.9 BMI: 23-24	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Mannisto 2005[74] Europe DIETSCAN (NLCS) Funding: Dutch Cancer Society and Commission of the European Communities Cohort	Cohort: -DIETSCAN looked at 3 cohorts (NLCS, SMC, and ORDET); only NLCS was extracted because data from other studies had been reported previously Included: -women selected from 204 Dutch municipalities -age 55-69 years	Vegetable pattern: high intake of vegetables, legumes, fruit, pasta, fish, and oil Follow-up: 7 years	N = 62,537 Age (mean): 61.4 Gender (% male): 0 BMI: 25.1	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low
Michaud 2005[67] USA NHS/HPFS Funding: Public Health Service Grants from National Institutes of Health Cohort	NHS Cohort: -121,700 female nurses -age 30-55 years -questionnaires sent out biennially since 1976 -first FFQ in 1980, expanded in 1984 (baseline), designed to measure intake for previous year Inclusion: -responded to 1984 FFQ Excluded: -diagnosed with cancer other than non-melanoma skin cancer before 1984 -implausibly low or high daily energy intake (<500 or >3500kcal/day) HPFS Cohort: -initiated in 1986 among US male health professionals -age 40-75 years -completed FFQ for past year, updated every 4 years Excluded: -men reporting implausible energy intake (<800 or >4200 kcal/d) -missing ≥70 food items on baseline FFQ -diagnosed with cancer, except non-melanoma skin cancer	Prudent: high consumption of vegetables, legumes, fruit, whole grains, fish, and poultry. Follow up: 16 years	NHS: N = 77,179 Prudent Q1: N = 16,351, age 50.8, BMI: 24.9 Q3: N = 16,352 age 50.8, BMI: 25.1 Q5: N = 16,351, age 50.9, BMI: 25.3 HPFS: N = 47,493 Prudent Q1: N = 9,175, age 54.3, BMI: 25.1 Q2: N = 9,659, age 54.3, BMI: 25, Q3: N = 9,374, age 54.4, BMI: 24.8	Population: unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Velie 2005[66] USA BCDDP Funding: National Cancer Institute Cancer Prevention Fellowship Program Cohort	Cohort: -participants selected from >280,000 past participants in BCDDP breast cancer screening program (1973 to 1981) Included: -diagnosis of breast cancer, non-malignant or benign breast disease determined by biopsy or surgery -recommended for biopsy or breast surgery but did not have surgery performed -sample of women with no evidence of breast disease also included -data collected 5 times -FFQ about food intake over past year -completed survey Excluded: -caloric intake <400 or ≥3800kcal/day -≥ 300 skipped food items -premenopausal at fourth data collection -received diagnosis of breast cancer before or at time of 2nd data collection -unknown or missing menopausal data -did not complete 2nd data collection -FFQ unusable -inappropriate entry and exit dates -missing information for parity, age at first live birth, and education	Vegetable-Fish/Poultry-Fruit: a) high intakes of vegetables, broiled or baked fish, and chicken b) low intakes of sweets and white bread Follow-up: 8 years	N = 40,559 women, 4005 lost to follow-up Age (mean); 62 (range 40-91 at study start) BMI <18.5: 2-3.1% 18.5 to <25: 46.8-61.8% 25 to <30: 28-34.4% ≥30: 7.2-16.7%	Population: low Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Dixon 2004[72] Europe DIETSCAN Funding: Commission of the European Communities Cohort	Cohort: -3 European cohorts* -ATBC: RCT of male smokers in Northern Finland, 29,113 men, age 50-69y, completed FFQ before randomization asking about diet for previous year -NLCS on Diet and Cancer: prospective cohort study of 58,279 men and 62,5347 women age 55-69y -SMC: 61,462 women from Sweden born between 1914-1948 and invited to participate in population-based mammography screening program in 1987-1990; FFQ about intake for	Vegetable pattern: characterized by intake of vegetables and legumes, citrus fruit and berries, pasta and rice, poultry and fish, and oil and salad dressings. Correlated with intakes of Vitamins A,C, and E; folate; and polyunsaturated fatty acids Follow-up: 6-14 years	ATBC men: N = 29,133 Age (mean): 57.2 BMI: 26.3 NLCS men: N = 58,279 Age (mean): 61.4 BMI: 25 NLCS women: N = 62,573 Age (mean): 61.4 BMI: 25.1 SMC women:	Population: unclear Outcomes: low Measurement: low Confounding: unclear Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
	previous 6 months *Fourth cohort (ORDET) in DIETSCAN did not provide necessary follow-up data		N = 61,463 Age (mean): 53.7 BMI: 24.8 (4.4)	
Knoops 2004[71] Europe HALE Funding: European Union Cohort	Cohort: -SENECA started in 1988, random age- and sex-stratified sample of inhabitants, born 1913-1918 of 19 towns; HALE project included13 centers that carried out mortality follow-up; survey at baseline and repeated in 1993 and 1999; asked about diet in month before -FINE: survivors of 5 cohorts of the Seven Countries Study in Finland, Italy, and the Netherlands; started in 1984 and continued to 2000; recruited men born 1900-1920; HALE included 1989-1991 baseline measurement of men aged 70-90; asked about previous 2-4wk diet Excluded: -CHD, CVD, cancer, or diabetes at baseline	Modified Mediterranean Diet Score: a) 1 point for > sex specific median consumption of monounsaturated fatty acids to saturated fatty acids ratio, fruits and fruit products, vegetable and potatoes, legumes, nuts and seeds, fish, and grains b) 1 point for < median consumption of meat and meat products and dairy products Follow-up: 10 years	SENECA Women (n = 832) Age (mean): 73 BMI <25 : 41% Men (n = 781) Age (mean): 73 BMI <25: 39% FINE Men (n = 726) Age (mean): 77 BMI <25: 42%	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Trichopoulou 2003[4] Greece EPIC-Greek cohort Funding: Europe Against Cancer Program (European Commission), Greek Ministry of Health, and Greek Ministry of Education Cohort	Cohort: -520,000 apparently healthy men and women -age 25-70 -recruited between 1992 and 2000 in 23 centers from 10 European countries, some countries had specialized cohorts (*eg,* just women in France) -usual dietary intakes at enrollment assessed through center-specific FFQ that addressed usual diet over previous year Included: -Greek component of EPIC -vital status could be ascertained -complete information on dietary, lifestyle, and anthropometric variables Excluded: -diagnoses of coronary heart disease, diabetes mellitus, or cancer at enrollment	a) 1 point for > sex-specific median consumption of vegetables, legumes, fruits and nuts, cereal, and fish b) 1 point for < median consumption of meat, poultry, and dairy products c) 1 point for alcohol consumption between 10-50g/day for men or 5-25g/day for women d) fat intake measured using ratio of monounsaturated lipids to saturated lipids. Follow-up: 3.7 years	N = 22,043 Age <55: 57% 55-64: 23% ≥65: 20% Gender (% male): 40 BMI Men: 28.1 Women: 28.8	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Terry 2001[73] Sweden Swedish Mammography Screening Cohort Funding: Swedish Cancer Society, Swedish Research Council, and World Cancer Research Fund Cohort	Cohort: -questionnaires and mailed invitations to be screened by mammography sent to women born between 1917 and 1948 in Vastmanland county and women born between 1914 and 1948 in Uppsala County -questionnaire asked about diet for previous 6 months Excluded: -women outside the age range 40-76y -missing or incorrect identification numbers -lacking date on questionnaire, date for moving out of study area, or date of death -extreme energy intake estimates below 416kcal or above 3,729kcal (+/- 3SDs) -previous cancer diagnosis other than non-melanoma skin cancer	Healthy: fruit and vegetables, fish and poultry, cereal and whole grain breads, fruit juice, and low fat dairy products Follow-up: 9.6 years	61,463 women Healthy: Q1: median 54y, BMI: 24.3 Q3: 52y, BMI: 24.1 Q5: 52y ,BMI: 24.2	Population: low Outcomes: low Measurement: unclear Confounding: unclear Risk of Bias: medium

[a] Protocol modified approximately half-way through enrollment to follow intervention schedule of MD groups including completion of 9-item conformity scale
AD = Alzheimer's disease; aMED = alternate Mediterranean diet score; BMI = body mass index; CV = cardiovascular; EVOO = Extra Virgin Olive Oil; FFQ = food frequency questionnaire; MCI = mild cognitive impairment; MD = Mediterranean diet; MUF = monounsaturated fat; NR = not reported; Q = quantile; RCT = randomized controlled trial; SF = saturated fat

Table 2. Key Question 1 – Mortality, Quality of Life, Adverse Events, and Patient Satisfaction

Study Intervention (n) Control (n)	All-cause Mortality % (n/N)		Health-related Quality of Life (*describe*)		Patients with any Adverse Event % (n/N)		Adverse Events Related to Diet (*describe*) % (n/N)		Patient Satisfaction *(describe)*	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cancer										
Beresford 2006[23] *N = 48,835*	950/19541 (0.6%) End points accrued through 3/05	1454 (0.61%) HR 0.97 (0.89, 1.05)								
Cardiovascular Disease										
Estruch 2013[7] *N = 7,447*	Group 1: 4.6% (118/2543) 10.0/ 1000 p-y HR 0.82 (0.64, 1.07) Group 2: 4.7% (116/2454) 11.2/ 1000 p-y HR 0.97 (0.74, 1.26)	4.7% (114/2450) 11.7 1000 p-y (P = NS)					No relevant diet-related adverse events reported			
Cognitive Impairment										
Kwok 2012[24] *N = 429*	13% (27/204)	11% (25/225)								

HR = hazard ratio; NS = not statistically significant

Table 3. Key Question 1 – New Onset of Cardiovascular-related Conditions (Myocardial Infarction, Stroke, Congestive Heart Failure) and Rhematoid Arthritis

Study Intervention (n) Control (n)	MI % (n/N)		Stroke % (n/N)		Rheumatoid Arthritis % (n/N)		Other *(specify)* % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cardiovascular Disease										
Estruch 2013[7] *N = 7,447*	Group 1: 1.5% (37/2543) 3.1/1000 p-y HR 0.80 (0.51, 1.26) Group 2: 1.3% (31/2454) 3.0/1000 p-y HR 0.74 (0.46, 1.19)	1.6% (38/2450) 3.9/ 1000 p-y (P = NS)	Group 1: 1.9% (49/2543) 4.1/1000 p-y HR 0.67 (0.46, 0.98) Group 2: 1.3% (32/2454) 3.1/1000 p-y HR 0.54 (0.35, 0.84)	2.4% (58/2450) 5.9/ 1000 p-y (P < .05 vs Groups 1 and 2)			Death from CV Cause Group 1: 1.0% 26/2543 2.2/1000 p-y HR 0.69 (0.41, 1.16) Group 2: 1.3% 31/2454 3.0/1000 p-y HR 1.01 (0.61, 1.66)	1.2% 30/2450 3.1/ 1000 p-y (P = NS)	MI, Stroke, Death from CV Cause Group 1: 2.7% 69/2543 8.1/1000 p-y HR adj 0.70 (0.54, 0.92) Group 2: 3.4% 83/2454 8.0/1000 p-y HR adj 0.72 (0.54, 0.96)	4.4% 109/2450 11.2/ 1000 p-y (P < .05 vs Groups 1 and 2)
Howard 2006[32] *N = 48,835*	435/19541 HR 0.98 (0.87, 1.11)	671/29,294	379/19541 HR 1.03 (0.90, 1.06)	556/29294			CHD death 158/19541 HR 1.02 (0.84, 1.25) CABG/PCI 717/19541 HR 0.96 (0.88, 1.06) Composite CHD 1000/19541 HR 0.97 (0.90, 1.06)	CHD death 234/29294 CABG/PCI 1113/29294 Composite CHD 1549/29294		

Study Intervention (n) Control (n)	MI % (n/N)		Stroke % (n/N)		Rheumatoid Arthritis % (n/N)		Other *(specify)* % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Diabetes										
Salas-Salvado 2014[26] *N = 3,541*							Diabetes New cases Group 1: 6.9% (80/1154) 16.0 per 1000 PY HR 0.60 (0.43, 0.85) vs control Group 2: 7.4% (92/1240) 18.7 per 1000 PY HR 0.82 (0.61, 1.10) vs control	8.8% (101/ 1147) 23.6 per 1000 PY		
Tinker 2008[30] *N = 45,887*							New diagnoses of diabetes 1303 (7.1%)	2039 (7.4%) HR 0.96 (0.9, 1.03)		
Rheumatoid Arthritis (RA)										
Hu 2015[93] N = 174,638					Highest quartile vs lowest quartile HR of RA: 0.98 (0.80, 1.20), P = .85 for trend					

CABG = coronary artery bypass graft; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MD = Mediterranean diet; MI = myocardial infarction; NR = not reported; PY = person year; RR = risk ratio

Table 4. Key Question 1 – New Onset of Kidney Disease, Cancer, and Cognitive Impairment

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cancer								
Buckland 2015[36] *N = 461,550*			Gastric Cancer Risk >8 points 220/192,337 HR 0.87 (0.69, 1.09) P = .22					
Catsburg 2015[35] *CSDLH N = 3,320* *NBSS N = 89,835*			CSDLH Healthy Q5: 452 cases/14,799 py HR 0.73 (0.58, 0.91) P trend = .001 NBSS Healthy Q5: 688 cases/160,145 py HR 0.84 (0.65, 1.10) P trend = .199					
Harmon 2015[34] *N = 156,804*							Cancer Mortality Men aMED Q1: 1267 Q2: 1053 HR 0.92 (0.88, 1.00) Q3: 1165 HR 0.92 (0.85, 0.99) Q4: 1032 HR 0.88 (0.81, 0.96) Q5: 1336 HR 0.81 (0.75, 0.89) Women aMED Q1: 1107 Q2: 939 HR 0.96 (0.88, 1.05) Q3: 886 HR 0.85 (0.77, 0.93) Q4: 946 HR 0.95 (0.86, 1.04) Q5: 1152 HR 0.84 (0.76, 0.92)	

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Toledo 2015[27] *N = 4,282*			Breast Cancer Risk MeDiet+EVOO 8/1,476 HR 0.32 (0.12, 0.79) MeDiet+nuts 10/1,285 HR 0.59 (0.26, 1.35) Both 18/2,761 HR 0.43 (0.21, 0.88) Both MDs ≤67: HR 0.16 (0.05, 0.5) >67: HR 0.92 (0.34, 2.47) BMI<30: HR 0.29 (0.11, 0.83) BMI≥30: HR 0.57 (0.22, 1.49)	17/1391				
Vormund 2015[33] *N = 17,861*							Cancer Mortality Per 1 point increase in MDS Classical MDS, dairy bad HR 0.97 (0.93, 1) Men HR 0.94 (0.89, 0.99) P<.05 Women HR 1.0 (0.94, 1.06) Alternative MDS, dairy good HR 0.95 (0.92, 0.99) P<.05 Men HR 0.92 (0.88, 0.97) P<.05 Women HR 0.98 (0.93, 1.04) Compared to MDS<4 MDS 4-6 HR 0.87 MDS 6-9 HR 0.86	

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Ax 2014[44] *N = 1,044* *Adequate reporters 566*			Risk of Prostate Cancer Entire study population (1,044) P trend = .32 Adequate reporters (566) Continuous HR 1.01 (0.75, 1.37) High Score 9/73 HR 1.04 (0.43, 2.49) P = .9					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Buckland 2014[75] *N = 477,312*			Per 4-unit increase in rMED for Urothelial Cell Carcinomas (UCC) HR 0.95 (0.87, 1.03) In current smokers, UCC, high versus low rMED score HR 0.66 (0.47, 0.93) Overall 1,425cases/477,312 Low score: 588/131,522 HR 1 Medium score: 565/206,353 HR 0.94 (0.83, 1.07) High Score: 272/139,437 HR 0.84 (0.69, 1.03), P trend = .107 Age at diagnosis <65 Low score: HR 1 Medium Score: HR 0.84 (0.69, 1.02) High Score: HR 0.81 (0.61, 1.07) P = .102 Age>65 Low score HR 1 Medium score HR 1.02 (0.86, 1.21) High Score HR 0.86 (0.64, 1.14) P trend = .504 Men: Medium score: HR 0.95 (0.81, 1.01) High score: HR 0.79 (0.62, 1.01) P trend = .094 Women Medium score: HR 0.92 (0.73, 1.18) High Score: HR 0.95 (0.68, 1.33) P trend = .692 BMI<25 Medium: HR 0.98 (0.79, 1.21) High: HR 0.92 (0.66, 1.28) P trend = .637 BMI>25 Medium: HR 0.93 (0.79, 1.10) High: HR 0.82 (0.64, 1.06) P trend = .138					
Cuenca-Garcia 2014[43] *N = 12,449*							Cancer Mortality Q4: 33 deaths/2,123 HR 1.63 (0.91, 2.92) P trend = .432	

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
George 2014[42] *N = 63,805*							Cancer Deaths aMED Q1: 509/11,685 HR 1 Q2: 428/11,416 HR 0.87 (0.76, 0.99) Q3: 485/12,919 HR 0.88 (0.77, 1.00) Q4: 428/12,077 HR 0.83 (0.73, 0.95) Q5: 534/15,708 HR 0.8 (0.7, 0.92) P = .001 BMI<25: HR 0.73 (0.59, 0.9) P = .003 BMI 25-29.9: HR 0.78 (0.62, 0.98) P = .032 BMI≥30: HR 0.98 (0.75, 1.27) P = .87, $P_{interaction}$ = .331	
Kenfield 2014[41] *N = 47,867*			Risk of Prostate Cancer Score 6-9: 2,054 cases HR 0.95 (0.9, 1.02), P trend = .13					
Li 2014[40] *N = 494,967*			MVA HR (comparing highest quintile to lowest quintile on aMED score) Men: 0.80 (0.64, 1.01), P trend = .002) Women: 0.42 (0.24, 0.74) P trend <.0001					
Lopez-Garcia 2014[39] *N = 17,415*							Death from Cancer Men Q5: 71 cases RR 0.88 (0.63, 1.21), P trend = .14 2-point increase RR 0.9 (0.79, 1.03) Women Q5: 26 cases RR 0.80 (0.48, 1.33), P trend = .48 2 point increase RR 0.94 (0.78, 1.13) Pooled Q5: RR 0.85 (0.65, 1.11) P trend = .1 2 point increase RR 0.91 (0.82, 1.02)	

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Reedy 2014[38] *N = 424,662*							Cancer Mortality MVA HR (comparing highest to lowest aMED score quintile) Women: 0.79 (0.74, 0.85) Men: 0.80 (0.77, 0.84)	
Xie 2014[37] *N = 82,984*			Ovarian cancer Q5: 159 cases, HR 0.91 (0.71, 1.18) P trend = .44					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bamia 2013[53] *N = 397,641*			Colorectal Cancer MMDS* HR 0.96 (0.92, 1.00) 6-9: HR 0.89 (0.80, 0.99) P = .02 CSMMDS* HR 0.97 (0.93, 1.01) 6-9: 0.92 (0.84, 1.00) P = .05 Men MMDS* HR 0.97 (0.90, 1.03) 6-9: 0.89 (0.76, 1.04) P trend = .14 CSMMDS* HR 0.98 (0.92, 1.04) 6-9: 0.91 (0.8, 1.03) P trend = .14 Women MMDS* HR 0.95 (0.90, 1.01) 6-9: 0.88 (0.77, 1.01) P trend = .05 CSMMDS* HR 0.96 (0.91, 1.01) 6-9: 0.93 (0.83, 1.05) P trend = .19 MMDS Colon Cancer* HR 0.95 (0.89, 1.00) 6-9: HR 0.88 (0.78, 1.00) P = .03 Proximal colon cancer* HR 0.98 (0.90, 1.06) 6-9: HR 0.92 (0.76, 1.11) P = .31 Distal colon cancer* HR 0.92 (0.84, 0.99) 6-9: HR 0.83 (0.68, 1.00) P = .04 Rectal Cancer* HR 0.99 (0.92, 1.07) 6-9: HR 0.90 (0.76, 1.07) P = .3 France[64] Relative Risks of Colorectal Cancer Healthy Q1: RR 1 Q2: RR 0.92 (0.61, 1.38) Q3: RR 0.81 (0.53, 1.23) Q4: RR 0.77 (0.49, 1.20) P trend = .20 *Per 2 unit increment in scale				France[64] Adenomas (RR) Healthy: Q2: 0.97 (0.76, 1.25) Q3: 1.02 (0.79, 1.30) Q4:0.85 (0.65, 1.10) P trend = .29 *Also looked at RR for high-risk adenomas, no significant results[64]	Western: Q2: 0.98 (0.76, 1.27) Q3: 1.21 (0.92, 1.59) Q4: 1.39 (1, 1.94) P trend = .03 Drinker Q2:1.06 (0.83, 1.36) Q3:1.09 (0.85, 1.41) Q4:1.42 (1.10, 1.83) P trend = .01 Meat Eaters Q2: 1.23 (0.96, 1.57) Q3: 1.03 (0.80, 1.33) Q4: 1.13 (0.87, 1.46)
Bosire 2013[52] *N = 293,464*			Total Prostate Cancer (with reported PSA screening in preceding 3 years) MVA HR (aMED score) 0.97 (0.91, 1.03), P trend = .09				Advanced Prostate Cancer MVA HR (aMED score) 1.0 (0.87, 1.15), P trend = .82 Fatal Prostate Cancer 0.8 (0.59, 1.10), P trend = .23	

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Buckland 2013[51] *N = 355,062*			arMED score Low(0-5): 2,187 tumors/68,676 women HR 1 Medium(6-9): 5,664/182,710 HR 0.97 (0.92, 1.02) High (10-16): 2,374/83,676 HR 0.94 (0.88, 1.00) P trend = .048					
Couto 2013[50] *N = 44,840*			Breast Cancer Cases 6-7: 297 RR 1.10 (0.92, 1.33) 8-9: 35 RR 1.42 (0.99, 2.05) 2-point increment in score: 1,278 cases RR 1.08 (1.00, 1.15)					
Gamba 2013[29] *N = 48,835*			Non-Melanoma Skin Cancer Cases: IG:1,923 CG: 2,984 HR 0.98 (0.92, 1.04) Age 50-59: 505 HR 0.93 (0.83, 1.04) 60-69: 953 HR 0.98 (0.91, 1.07) 70-79: 465 HR 1.03 (0.91, 1.15) P = .17 BMI: <25: 641 HR 1.06 (0.96, 1.17) 25 to <30: 687 HR 0.92 (0.84, 1.01) ≥30: 589 HR 0.97 (0.88, 1.08) P = .26 Melanoma cases: IG: 114 HR 1.04 (0.82, 1.32) Age 50-59: 41 HR 0.99 (0.67, 1.47) 60-69: 54 HR 1.04 (0.73, 1.46) 70-79: 19 HR 1.15 (0.63, 2.09) P = .25 BMI: <25: 28 HR 0.91 (0.57, 1.46) 25 to <30: 36 HR 0.83 (0.55, 1.24) ≥30: 50 HR 1.43 (0.97, 2.11) P = .13					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Gnagnarella 2013[49] *N = 4,336*			Lung Cancers N (rate/100-year) 6-7: 38 (0.68) HR 0.63 (0.35, 1.14) 8-9: 1.0 (0.11) HR 0.10 (0.01, 0.77) P trend = .045					
Kyro 2013[48] *N = 57,053*			Colorectal Cancer HR (highest to lowest quintile) Men: 0.87 (0.61, 1.25), P trend = .94 Women: 0.65 (0.46, 0.94), P trend = .02					
Li 2013[47] *N = 494,968*			Cardia adenocarcinoma HR 1.10 (0.76, 1.61) Noncardia adenocarcinoma HR 0.75 (0.52, 1.09) Esophageal Squamous Cell HR (highest quintile to lowest quintile aMED score): 0.44 (0.22, 0.88); P trend = .03					
Link 2013[46] *N = 91,779*			HR (highest to lowest quintile) Salad: 1.12 (1.01, 1.25), P trend = 0.01 Ethnic: 0.94 (0.85, 1.05), P trend = 0.24					
Mursu 2013[45] *Baseline N = 29,634 Follow-up N = 15,076*							Cancer Mortality Baseline cohort 757 cases/7,408 RR 0.88 (0.79, 0.98) P trend<.001 Follow-up cohort 98 cases/3,769 RR 0.83 (0.63, 1.09) P trend = .037	
Chiuve 2012[56] *N = 112,524*			Cancer Risk Women (NHS) Q4: 2,627 cases RR 0.93 (0.88, 0.99) P trend = .01 Men (HPFS) Q4: 1,205 cases RR 0.94 (0.87, 1.03) P trend = .13 Pooled Q4: RR 0.94 (0.89, 0.98), P trend = .003					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tognon 2012[54] *N = 77,151*							Cancer Specific Mortality All Cancer Men: 493 cases HR 0.92 (0.87, 0.98) Women: 481 HR 0.98 (0.92, 1.03) Pancreas Men: 47 cases HR 0.82 (0.68, 0.99) Women: 45 HR 0.83 (0.69, 1.00) Breast Women: 80 HR 1.12 (0.97, 1.28) Colorectal Men: 73 HR 1.07 (0.93, 1.24) Women: 54 HR 0.91 (0.77, 1.08) Stomach Men: 31 HR 1.07 (0.85, 1.34) Women: 21 HR 1.24 (0.95, 1.64) Prostate Men: 61 HR 0.88 (0.74, 1.03) Respiratory Men: 68 HR 0.86 (0.73, 1.00) Women: 54 HR 1.05 (0.88, 1.24)	
Cade 2011[58] *N = 33,731*			Med diet Score 0-2: 94 cases/3,668 HR 1 3: 123/4,486; HR 1.06 (0.77, 1.46) 4: 140/6,008; HR 0.98 (0.72, 1.33) 5: 165/6,272; HR 0.99 (0.73, 1.35) 6: 124/5,755; HR 0.84 (0.60, 1.17) 7-10: 182/7,542; HR 0.96 (0.70, 1.32) P trend = .4					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Couto 2011[57] *N = 478,478*			All Cancers HR for 2 point increment of MD score All: 30,731 cases; HR 0.96 (0.95, 0.98) Males: 9,669 cases; HR 0.97 (0.95, 1.00) Females: 21,062; HR 0.96 (0.95, 0.98) Score 6-9: 7308/118,818; HR 0.93 (0.9, 0.96); P trend = .00001 Men 6-9: 2,455/38,908; HR 0.93 (0.88, 0.99) P trend = .02 Women 6-9: 4,853/79,910; HR 0.93 (0.89, 0.96) P trend = .0001					
Menotti 2011[55] *N = 1,221*							Cancer mortality Factor 2 HR 0.84 (0.74, 0.96)	
Fung 2010[59] *N = 87,312*			aMED Colorectal P = .14 Men: Q5 RR 0.88 (0.71, 1.09) Women: Q5: RR 0.88 (0.74, 1.05)					
Agurs-Collins 2009[60] *N = 50,778*			Breast Cancer Cases Prudent Q1:182/87,582py RR 1 Q2: 202/88,780py RR 0.97 (0.78, 1.20) Q3: 239/89,353py RR 0.99 (0.79, 1.22) Q4: 214/89,554py RR 0.80 (0.64, 0.99) Q5: 257/88,473py RR 0.86 (0.68, 1.08) P trend = .06 BMI<25* Q1: 55/28,165py RR 1 Q5: 72/27,862py RR 0.64 (0.43, 0.93) P trend = .01 BMI: 25 to <30* Q1: 61/27,143py RR 1 Q5: 94/30,528 RR 1.11 (0.73, 1.66) P trend = .88 BMI≥30* Q1: 66/32,274py RR 1 Q5: 90/30,083 py RR 0.94 (0.62, 1.42) P trend = .44					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Reedy 2008[61] *N = 492,382*			Colorectal Cancer MVA HR (highest to lowest quintile of Mediterranean diet score0 Men: 0.72 (0.63, 0.83) Women: 0.89 (0.72, 1.11)					
Prentice 2007[31] *N = 48,835*			Invasive Cancer Ovary 0.36 (57)* HR 0.83 (0.60, 1.14) Endometrium 0.79 (125)* HR 1.11 (0.88, 1.40) Breast 4.15 (655)* HR 0.91 (0.83, 1.01) Colorectal 1.27 (201)* HR 1.08 (0.90, 1.29) All other sites 4.56 (720)* HR 0.95 (0.86, 1.04) Total 10.69 (1,687)* HR 0.95 (0.89, 1.01) *Incidence of Invasive Cancer per 1000 py (N cases) for Intervention Group Invasive Ovarian Cancer (57 cases) Age 50-59: 0.26 (16) HR 0.70 (0.39, 1.27) 60-69: 0.32 (23) HR 0.65 (0.40, 1.05) 70-79: 0.72 (18) HR 1.69 (0.86, 3.31); BMI: <25.9: 0.42 (22) HR 1.01 (0.59, 1.73) 25.9 to <30.9: 0.3 (16) HR 0.60 (0.34, 1.07) ≥30.9: 0.35 (18) HR 0.89 (0.50, 1.60) Total Invasive Cancer (1,687 cases) Age 50-59: 7.95 (483) HR 0.94 (0.84, 1.06) 60-69: 11.41 (821) HR 0.93 (0.86, 1.02) 70-79: 15.27 (383) HR 0.99 (0.87, 1.13) BMI: <24.9 9.56 (396) HR 0.91 (0.81, 1.04) 24.9 to <28.2: 10.61 (596) HR 0.97 (0.88, 1.08) 28.2 to <32.5: 11.5 (412) HR 0.94 (0.83, 1.06) ≥32.5: 11.59 (275) HR 0.98 (0.84, 1.14)			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Sant 2007, Sieri 2004 [62,70] *N = 8,861*			Breast Cancer MVA HR (highest tertile to lowest tertile of dietary conformity) (Sieri 2004) Salad vegetable 0.66 (0.47, 0.95); P trend = .016 Prudent: 1.28 (0.90, 1.83); P trend = .169 HER-2 positive (Sant 2007) Salad vegetable: 0.25 (0.10, 0.64) P trend = .001) Prudent: 0.72 (0.35, 1.48); P trend = .372) HER-2 negative (Sant 2007) No associations between any diet and breast cancer incidence					
Beresford 2006[23] *N = 48,835*			Invasive Colorectal Cancer 201/19,541 (0.13%) HR 1.08 (0.90, 1.29) Colon Cancer 153/19,541 (0.1%) HR 1.05 (0.85, 1.30) Rectal cancer 50/19,541 (0.03%) HR 1.11 (0.77, 1.61)				Colorectal Cancer Mortality 47 (0.03%) HR 1.26 (0.85, 1.85) Polyps/Adenoma Incidence: 3,402 (2.16%) HR 0.91 (0.87, 0.95) Total Cancer Incidence 1,946 (1.24%) HR 0.97 (0.89, 1.05) Total Cancer Mortality 436 (0.28%) HR 0.96 (0.90, 1.01)	
Fung 2006[65] *N = 71,058*			Breast Cancer Risk (aMED quintiles) Q1:629 cases RR 1 Q2: 679 RR 0.92 (0.83, 1.03) Q3: 669 RR 0.89 (0.80, 1.00) Q4:750 RR 0.94 (0.84, 1.05) Q5: 853 RR 0.98 (0.88, 1.10) P = .69 ER+ cases Q1 to Q5 RR 1.05 (0.91, 1.18) P trend = .23 ER- cases Q1 to Q5 RR 0.79 (0.6, 1.03) P trend = .03 Change in risk for ER-BC with a 10% increase in score: 7% reduction P = .02					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Lagiou 2006 *N = 42,237*[63]							Death from Cancer Trend per 2 point increase in diet score: All ages 280/42,237 MR = 0.89 (0.77, 1.04); P trend = .2 Age <40 76/21,149 MR = 1.07 (0.79, 1.43) Age ≥40 204/21,068 MR = 0.84 (0.71, 1.01) P = .184 for interaction Score 6-9: 54/9,453 MR = 0.8 (0.57, 1.13)	
Adebamowo 2005[69] *N = 90,638*			Breast Cancer, Prudent Q1 = 127 cases/139,864py RR 1 Q2 = 124 cases/143,717py RR 0.96 (0.75, 1.23) Q3 = 147 cases/144,021py RR 1.02 (0.80, 1.31) Q4 = 169 cases/136,359py RR 0.90 (0.68, 1.18) P = .36					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Kim 2005[68] *N = 42,112*			Men, Healthy pattern Colorectal Cancer Q4: 53/47,710py HR 0.81 (0.52, 1.24) P trend = .8 Colon Cancer Q4: 36 HR 0.83 (0.49, 1.41) P trend = .62 Rectal cancer Q4: 17 HR 0.76 (0.37, 1.58) P trend = .76 Women, Healthy pattern Colorectal Cancer Q4: 36/52,289py HR 0.98 (0.58, 1.65) P trend = .82 Colon Cancer Q4: 20 HR 0.76 (0.39, 1.50) P trend = .68 Rectal cancer Q4: 16 HR 1.43 (0.62, 3.28) P trend = .34					
Mannisto 2005[74] *N = 1,598*			Breast Cancer Q4: RR 0.90 (0.67, 1.20)					
Michaud 2005[67] *N = 124,672*			Pancreatic Cancer Risk, Prudent NHS Q5 41/239,717py RR 0.93 (0.52, 1.64) P = .57 HPFS Q5: 37/119,513py RR 1.88 (1.06, 3.32) P trend = .09 Pooled Q5: RR 1.32 (0.66, 2.63) P trend = .83					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Velie 2005[66] *N = 40,559*			Breast Cancer Vegetable-fish/poultry-fruit Q1: 341 cases RH = 1 Q2: 391 cases RH = 1.12 (0.90, 1.3) Q3: 378 RH 1.07 (0.92, 1.24) Q4: 386 RH 1.07 (0.92, 1.25) Q5: 372 RH 1.03 (0.88, 1.20) P trend = .95 Invasive Breast Cancer Q1: 245 RH = 1 Q2: 290 RH 1.15 (0.97, 1.37) Q3: 272 RH 1.06 (0.89, 1.27) Q4: 284 RH 1.09 (0.91, 1.3) Q5: 274 TH = 1.04 (0.87, 1.26) P trend = .77 *No evidence of interaction with BMI					

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Dixon 2004[72] *ATBC = 19,133* *NLCS = 120,852* *SMC = 61,463*			Vegetable Pattern, Colorectal Cancer ATBC: 322cases/286,967py Linear RR 1.07 (0.95, 1.20) Q4 RR 1.22 (0.87, 1.73); P trend = .09 NLCS men: 660 cases/10,496py Linear RR 1.03 (0.93, 1.15) Q4 RR 1.04 (0.78, 1.39); P trend = .41 NLCS women: 512 cases/11,328py Linear RR 0.92 (0.81, 1.03) Q4 RR 0.91 (0.65, 1.27); P trend = .78 SMC women: 586cases/749,282py Linear RR 1.03 (0.93, 1.14) Q4 RR 0.99 (0.77, 1.27); P trend = .9 Colon Cancer ATBC men: 191cases/287,375py Linear RR 1.02 (0.87, 1.19) Q4 RR 1.05 (0.66, 1.67); P trend = .66 NLCS men: 400cases/10,509py Linear RR 1.02 (0.89, 1.16) Q4 RR 0.93 (0.65, 1.32); P trend = .93 NLCS women: 360cases/11,334py Linear RR 0.87 (0.76, 1.01) Q4 RR 0.78 (0.54, 1.15); P trend = .29 SMC women: 396cases/749,964py Linear RR 1.03 (0.91, 1.16) Q4 RR 0.96 (0.71, 1.30) P trend = .87 Rectal cancer ATBC men: 133cases /287,486py Linear RR 1.14 (0.95, 1.36) Q4 RR 1.48 (0.88, 2.49) P trend = .04 NLCS men: 260cases/10,525py Linear RR 1.05 (0.91, 1.21) Q5 RR 1.23 (0.83, 1.83) P trend = .16 NLCS women: 152cases/11,355py Linear RR 1.01 (0.85, 1.21) Q4 RR 1.33 (0.76, 2.35); P trend = .24 SMC women: 193cases/750,318py Linear RR 1.06 (0.87, 1.29) Q5 RR 1.12 (0.70, 1.79); P trend = .84				

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Knoops 2004[71] *N = 1,507*							Cancer Mortality Med Diet score ≥4 HR 0.90 (0.70, 1.17) 233 deaths/2,152 at risk	
Trichopoulou 2003[4] *N = 22,043*							Death from Cancer 97/22,043 HR (2-pt increment in MD score): 0.76 (0.59, 0.98)	
Terry 2001[73] *N = 61,463*			Breast Cancer, Healthy Pattern (Rate Ratios) Ages 40-76, P trend = .52 Q1: 1 Q2: 0.94 (0.79, 1.12) Q3: 0.96 (0.80, 1.14) Q4: 0.95 (0.79, 1.14) Q5: 0.92 (0.76, 1.13) Ages 40-49, P trend = .68 Q1: 1 Q2: 0.87 (0.63, 1.20) Q3: 1.12 (0.83, 1.53) Q4: 0.86 (0.61, 1.20) Q5: 0.91 (0.63, 1.31) Ages 50-76. P trend = .52 Q1: 1 Q2: 0.97 (0.79, 1.19) Q3: 0.86 (0.70, 1.07) Q4: 0.99 (0.79, 1.23) Q5: 0.91 (0.72, 1.16)					
Cognitive Impairment								
Gardener 2015[79] *N = 527*					Authors' conclusion: Higher baseline conformity to AusMeDi associated with better performance in executive function cognitive domain after 36 months in APOE $_{E}$4 allele carriers (positive trend in cohort as a whole); no significant relationships between prudent diet conformity and cognitive function			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Koyama 2015[92] *N = 2,326*					Mean difference in slope of 3MS scores (high vs lower scores [points/year]) Whites: 0.09 (-0.03, 0.21), P = .14 Blacks: 0.22 (0.05, 0.39), P = .01			
Valls-Pedret 2015[28] *Group 1: MD+EVOO (n = 127)* *Group 2: MD+nuts (n = 112)* *Group 3: Usual care (n = 95)*					Global Cognition Outcome[b] (adjusted change from baseline) Group 1: 0.05 Group 2: -0.05 Incidence of MCI[c] Group 1: 13.4% (17/127) Group 1: 7.1% (8/112)	Global Cognition -0.38 (P = .005 for Group 1 vs control) MCI 12.6% (12/95) (P = .28)	MMSE (adjusted change from baseline) Group 1: 0.16 Group 2: -0.07	-0.26 (P = NS)
Tangney 2014[90] *N = 826*					Rate of decline in global cognitive score (based on 19 cognitive tests) MD: per one unit higher MedDietScore rate of decline was slower by 0.002 standardized units (P = .01)[a] Only the upper tertile of MedDietScores was associated with rates of global cognitive change (P = .003) No evidence of modification by age or sex			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Kesse-Guyot 2013[80] *n = 3,083*					Association between diet conformity and composite cognitive score (adjusted mean differences with high conformity as reference) MDS: Low conformity: -0.18 (-1.09, 0.73) Medium conformity: 0.58 (-0.21, 1.37) (P = .27 with conformity as continuous variable) No interaction between conformity and sex with regard to cognitive performance			
Martinez-Lapiscina 2013[25] *Group 1: MD+EVOO (n = 224)* *Group 2: MD+nuts (n = 166)* *Group 3: Usual care (n = 132)*					Incidence of MCI Group 1: 8.0% (18/224) Group 2: 11.4% (19/166) Incidence of Dementia Group 1: 5.4% (12/224) Group 2: 3.6% (6/166)	MCI 17.4% (23/132) Dementia 12.9% (17/132)	MMSE at Follow-up (adj means) Group 1: 27.7 Group 2: 27.7 CDR at Follow-up (adj means) Group 1: 5.3 Group 2: 5.1	27.1 (P < .05 for both groups vs control) 4.8 (P < .05 for both groups vs control)
Samieri 2013[84] *N = 16,058*					MD score not significantly associated with change over time in TICS, global cognitive score, or verbal memory score (P trends = .31, .84, and .70)			
Samieri 2013[83] *N = 6,174*					Q5 vs Q1 Global Cognition Mean Difference: 0.02 (-0.03, 0.06), P = .63 Verbal Memory Mean Difference: 0.03 (-0.02, 0.07); P = .44			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Wengreen 2013[91] *N = 3,580*					Participants in highest quintile of Med Diet Score scored 0.94 points higher on baseline assessment than did subjects in lowest quintile (P = .001) Time X quintile of DASH or MD score not significant (difference in 3MS scores between quintiles consistent over time)			
Cherbuin 2012[76] *N = 1,557*					MCI: 10 new cases OR 1.41 (0.95, 2.10)* CDR (0.5): 19 new cases OR 1.18 (0.88, 1.57)* Any MCD: 37 new cases OR 1.20 (0.98, 1.47)* *per one unit change in MeDi			
Gardener 2012[78] *N = 723*					Correlation between baseline MD score and change in cognitive performance at 18 months (n = 652): MMSE: Correlation = .098, P = .014 Logical Memory II: Correlation = -.011, P = .779 Delis-Kaplan Executive Function System: Correlation = .042, P = .294 California Verbal Learning Test II: Correlation = .029, P = .472			
Kwok 2012[24] *N = 429*					Demented 22/162 (13.6%) Worse 36/162 (22.2%)	Demented 30/180 (16.7%) P = .427 Worse 49/180 (27.2%) P = .285		

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tangney 2011 [89] *N = 3,790*					MedDiet and Med Diet Wine scores associated with higher baseline global cognitive scores and reduced declines in cognitive function (P<.001) (adjusted for age, gender, race, education, participation in cognitive activities, and energy)			
Roberts 2010 [82] *N = 1,141*					No significant association of MD score with incident events HR (incident MCI or dementia): Second tertile: 0.79 (0.51, 1.21) Upper tertile: 0.75 (0.46, 1.21)			
Féart 2009 [77] *N = 1,410*					Cognitive Function MD conformity as continuous variable: each additional unit of diet score associated with fewer MMSE errors, diet score X time (P = .04) No association with other cognitive tests MD conformity as a categorical variable: no association with cognitive function No association between MD conformity and risk for incident dementia or AD			
Scarmeas 2009 [85] *N = 1,880*					Decrease in AD risk with increasing physical activity and diet conformity (low physical activity/ low MD conformity as reference) Adjusted (n = 1,598) Low activity/high MD: HR 0.77 (0.53, 1.13) High activity/low MD: HR 0.81 (0.57, 1.16) High activity/high MD: HR 0.65 (0.44, 0.96)			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Scarmeas 2009-2[87] *N = 1,383*					Higher MD conformity associated with borderline trend for lower risk of developing MCI MD Continuous Adjusted (n = 1,199) HR 0.92 (0.85, 0.99) MD Tertiles (Low as reference) Middle: HR 0.83 (0.62, 1.12) High: HR 0.72 (0.52, 1.00)			
Psaltopoulou 2008[81] *N = 732*					Multiple regression-derived adjusted differences in mean score on MMSE per specified differences in possible predictor variables at enrollment No significant differences: gender, BMI, MD score (overall)			
Scarmeas 2006[88] *N = 2,226*					Development of AD MD Continuous Adjusted (n = 1,759): HR 0.91 (0.83, 0.98), P = .015 MD Tertiles Adjusted (n = 1,759); low tertile (score 0-3) as reference Middle tertile (score 4-5): HR 0.85 (0.63, 1.16) High tertile (score 6-9): HR 0.60 (0.42, 0.87) P = .007 Significant MD X time interaction: higher conformity to MD associated with slower cognitive decline (*B* = 0.003; P = .047)			

Study Intervention (n) Control (n)	Kidney Disease % (n/N)		Cancer % (n/N)		Cognitive Impairment % (n/N)		Other *(specify)* % (n/N)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Scarmeas 2006-2[86] *N = 1,790*					Risk for AD Adjusted (n = 1,300); low tertile (score 0-3) as reference Middle tertile (score 4-5): OR 0.47 (0.29, 0.76) High tertile (score 6-9): OR 0.32 (0.17, 0.59) With all vascular variables in model Adjusted (n = 1,259); low tertile (score 0-3) as reference Middle tertile (score 4-5): OR 0.48 (0.29, 0.79) High tertile (score 6-9): OR 0.31 (0.16, 0.58)			

BC = breast cancer; CDR = Clinical Dementia Rating; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; MCD = mild cognitive disorder (any); MCI = mild cognitive impairment; MD = Mediterranean diet; MMSE = Mini Mental State Examination; MR = mortality ratio; MVA = multivariate analysis; NR = not reported; NS = not statistically significant; Q = quantile; RR = risk ratio

KEY QUESTION 2

Table 5. Key Question 2 – Study, Intervention, and Patient Characteristics

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Cancer				
Yang 2015[110] USA Physicians' Health Study (PHS) Funding: Department of Defense, National Institutes of Health, and Prostate Cancer Foundation Cohort	Cohort: -men participating in PHS I or II and continued to be followed with annual questionnaires -PHS I: initiated in 1982, randomized trial of aspirin and beta-carotene in US physicians age 40-84 -PHS II: initiated in 1997, randomized trial of vitamin E, C, and a multivitamin, male US physicians Included: -diagnosed with non-metastatic prostate cancer -completed a dietary assessment after prostate cancer diagnosis	Prudent Pattern: higher intake of legumes, vegetables, fruits, whole grains, garlic soy products, fish, and oil and vinegar Follow-up: 9.9 years	926 men Age (at diagnosis): 68.8 BMI <25: 46.7% BMI 25-30: 47.3% BMI >30: 6.1%	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Fung 2014[104] USA NHS Funding: National Institute of Health Cohort	Cohort: -121,701 women, registered nurses age 30-55 at enrollment (1976) -questionnaire every 2 years, diet every 4 years Included: -diagnosed with stage I-III colorectal cancer (1986-2008) Excluded: -history of cancer within 3 years of colorectal cancer diagnosis -died within first 6 months after return of first post-diagnosis biennial questionnaire or FFQ	Diet assessed with first FFQ collected at least 6 months after diagnosis aMED a) 1 point for intake > cohort specific median in vegetables, legumes, fruits, nuts, whole grains, fish, and monounsaturated: saturated fat ratio b) 1 point if intake was < median in meat, c) 1 point if alcohol intake 5-15g/day Follow-up: 11.2 years	N = 1,201 Age (at entry to analysis): 66.5 BMI: 25.4	Population: unclear Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Kenfield 2014[41] USA HPFS Funding: National Institutes of Health/National Cancer Institute and Prostate Cancer Foundation	Cohort: -initiated in 1986 among US male health professionals age 40-75 yr -completed FFQ for past year, updated every 4 years Excluded: -reported implausible energy intake (<800 or >4200 kcal/d) -missing ≥70 food items on baseline FFQ -diagnosed with cancer, except non-melanoma	Traditional Mediterranean diet score: a) 1 point each for < median in dairy and meat intake b) 1 point for alcohol intake of 10-50 g/day c) 1 point each for >median intake of vegetables, legumes, fruits and nuts, grains, fish, and the ratio of polyunsaturated to saturated lipids. Follow-Up: 9 years	N = 4,538 Age (at diagnosis): 69-69.7 BMI: 25.2-26.2	Population: unclear Outcomes: unclear Measurement: low Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Cohort	skin cancer -advanced cancer at diagnosis -missing clinical stage -no post diagnosis diet data			
Vrieling 2013[109] Germany MARIE Funding: Deutsche Krebshilife Cohort	Cohort: -recruited in 2002-2005 -Hamburg and Rhein-Neckar-Karlsruhe region of Germany Included: -histologically confirmed primary invasive (stage I-IV) or *in situ* breast cancer -age 50-74 at diagnosis in 2001-2005 -FFQ referred to the year before diagnosis Excluded: -missing FFQ -previous cancer -in situ breast cancer -energy intake in the top or bottom 1.0%	Healthy: high vegetables, fruits, vegetable oil, sauces/condiments, and soups/bouillons intake Follow-up: 5.5 years	N = 2,522	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium
Kim 2011[105] USA NHS Funding: National Institutes of Health Cohort	Cohort: -121,701 women, registered nurses age 30-55 at enrollment (1976) -questionnaire every 2 years, diet every 4 years Included: -stage 1-3 breast cancer cases (1978-1998) Excluded: -stage 4 breast cancer -4 or more positive lymph nodes without a complete negative metastatic work up -missing disease stage -death or recurrence within 1y of breast cancer diagnosis -cancer before 1978 -missing diet -diet assessment during treatment or calculated recurrence date	aMED: a) 1 point for > median intake of vegetables, legumes, fruits, nuts, whole grains, fish, and monounsaturated:saturated fat ratio b) 1 point for < median intake of meat and dairy c) 1 point for alcohol intake of 5-15g/d. Follow-up: 6-26 years	N = 2,729 BMI: 26	Population: low Outcomes: unclear Measurement: low Confounding: low Risk of Bias: low
Kwan 2009[107] USA Life After Cancer Epidemiology (LACE)	Cohort: -2280 women diagnosed with invasive breast cancer (1997-2000) Included: -age 18-79	Prudent Diet: cruciferous vegetables, other vegetables, tomatoes, dark yellow vegetables, fruits, legumes, onions, leafy vegetables, fish, soups, whole grains, poultry (not fried),	N = 1,901 women Prudent: Age: 58 BMI: 27-28	Population: low Outcomes: low Measurement: unclear Confounding: low Risk of Bias: low

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Funding: National Cancer Institute, Utah Cancer Registry, and State of Utah Department of Health Cohort	-diagnosis of early-stage primary breast cancer (stage I ≥1cm, stage II, or stage IIIA) -enrollment 11-39 months after diagnosis -completion of breast cancer treatment (except for adjuvant hormonal therapy) -free of recurrence -no history of other cancers in prior 5 years Excluded: -breast cancer recurrence -new primary breast cancer -death between diagnosis and 3 months after study enrollment -incorrect stage -prior breast cancer -> 39 months since diagnosis -incomplete demographic and medical data -didn't complete a dietary questionnaire at baseline (asked about previous yr) -receiving treatment -language difficulty -extremes of dietary intake <500 or >4000kcal -excessive number of skipped items	salad dressings (all type), rice, grains, plain pasta, fruit juice, low-fat dairy, nuts, potatoes (not fried), and cold cereals. Follow up: 5.93 years		
Meyerhardt 2007[108] USA Funding: National Cancer Institute and Pfizer Oncology Cohort	Cohort: -prospective -1,009 patients enrolled in randomized adjuvant chemotherapy trial Included: -had complete surgical resection of primary tumor within 56 days of study entry -had regional lymph node metastases but no distant metastases -ECOG performance status of 0 to 2 -adequate bone marrow, renal, and hepatic function	Dietary Assessment: based on self-administered FFQ. Prudent (high fruits and vegetables, poultry, and fish) Follow-up: 5.3 years	N = 1,009	Population: unclear Outcomes: low Measurement: unclear Confounding: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Kroenke 2005[106] (Sub-study of Kim 2011) USA NHS Funding: National Cancer Institute Cohort	Cohort: -121,701 women, registered nurses age 30-55 at enrollment (1976) -questionnaire every 2 years, diet every 4 years Included: -diagnosed with invasive breast cancer (1982-1998) -completed a dietary questionnaire in 1984 AND at least 1yr after breast cancer diagnosis Excluded: in situ disease or metastatic breast cancer at diagnosis -4 or more positive nodes but lacking a complete metastatic work-up -previous cancer	Prudent: a) higher amounts of fruit, vegetables, whole grains, low-fat dairy products, protein, and fiber b) lower amounts of trans-unsaturated and saturated fats c) lower glycemic load Follow-up: 9 years	N = 2,619 BMI: 26	Population: unclear Outcomes: unclear Measurement: unclear Confounding: low Risk of Bias: medium
Cardiovascular Disease				
Tuttle 2008[8] USA The Heart Institute of Spokane Diet Intervention and Evaluation Trial (THIS-DIET) Funding: Washington State and intramural support from investigators' clinical institutions RCT	Included: -enrolled within 6 weeks of a first MI Excluded: -NYHA class III or IV -ventricular arrhythmias requiring medication or a defibrillator -uncontrolled hypertension.	Intervention 1: low fat (AHA Step II diet) Intervention 2: "Mediterranean style diet" not otherwise described Intervention participants received a) 2 individual diet counselling sessions within first month b) additional individual sessions at 2, 6, 12, and 24 months c) 6 different-content group sessions Controls: non-randomized, identified through databases, met all inclusion and exclusion criteria, matched 1:1 with intervention patients within 6 months after randomization, received standard dietary advice from medical center dietitians Follow-up: 46 months	Low fat (n = 50) Med (n = 51) NR controls: (n = 101) Age (mean) Low fat: 58 Med: 58 Control: 58 Gender (% male) Low fat: 68 Med: 80 Control: 74 BMI Low fat :31 Med: 30 Control: 29	Sequence generation: unclear Allocation concealment: unclear Blinding: low Incomplete outcome data: low Selective outcome reporting: unclear Risk of Bias: medium
Burr 2003[94] Wales Funding: British Heart Foundation, Seven Seas Ltd, Novex Pharma,	Included: -men<70 yr being treated for angina Excluded: -awaiting CABG -already eating oily fish twice a week -intolerance to fish or fish oil	4 groups: 1. 2 portions of oily fish each week or up to 3 gm fish oil (N = 764) 2. 4-5 portions of fruits and vegetables, at least one glass orange juice, and increased oat intake (N =	N = 3,114 Age (mean): 61 Gender (% male): 100 BMI: 28	Sequence generation: unclear Allocation concealment: unclear Blinding: unclear Incomplete outcome

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
and the Fish Foundation RCT	-other serious illness or likelihood of a move out of the area	779) 3. both intervention 1 and 2 (N = 807) 4. “sensible eating’ - nonspecific advice (N = 764) Follow-up: 5 years		data: unclear Selective outcome reporting: unclear Risk of Bias: medium
Singh, 2002[98] India Funding: Centre of Nutrition and Heart RCT	Included: -≥ 1 major risk factor for coronary artery disease (hypertension, hypercholesterolemia, diabetes mellitus, angina pectoris, or previous myocardial infarction) -> 25 years old Excluded: -absence of major risk factors -cancer, chronic diarrhea or dysentery -a blood urea >6.6mmol/L -arthritis -dislike of intervention diet -refusal of laboratory testing -death before randomization	Intervention (Mediterranean-style): same diet and lifestyle advice as comparator group PLUS at least 400-500g of fruits, vegetables, and nuts per day; 400-500g of whole grains, legumes, rice, maize, and wheat daily; mustard seed or soybean oil in 3-4 servings per day Comparator: a) advised to be active, take proper medications, not smoke or consume alcohol, and engage in mentally relaxing activities b) suggested diet similar to NCEP step I prudent diet (<30% of energy from total fat, <10% from saturated fat, and <300 mg of cholesterol per day) Follow-up: 2 years	N = 1,000 IG: 499; CG: 501 Age (mean): Intervention: 49 Control: 48 Gender (male) Intervention: 91% Control: 88% BMI Intervention: 24.3 Control: 24.1	Sequence generation: high Allocation concealment: unclear Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: medium
De Lorgeril 1998, 1999[6,97] France Lyon Heart Study Funding: Institut National de la Sante et de la Recherche Medicale (INSERM); Ministry of Research; CNAMTS, CETIOM, and ONIDOL; Astra-Calve BSN; and Foundation pour	Included: -<70 years -MI within past 6 months Exclusion: -stage 3 or 4 heart failure -hypertension (SBP>180, DBP>110) -inability to complete an exercise test due to recurrent angina -ventric arrhythmias or AV block -any condition thought to limit survival or ability to participate in a long-term trial	Intervention: a) more bread, more root vegetables and green vegetables, more fish, less meat (beef, lamb and pork to be replaced with poultry), no day without fruit, and butter and cream replaced with canola oil-based margarine supplied free by study b) initial one-hour diet advice session followed by “further counselling at subsequent visits” (visit schedule: 8 weeks then annual) Comparator: no dietary advice apart from whatever they received as part of routine care Follow-up: Intervention 46.7 months; Control 44.9 months	N = 584, Intervention 303, Control:302 Age (mean): Intervention: 53.5 Control: 53.5 Gender (% male) Intervention: 89.4 Control: 92.1 BMI Intervention: 25.8 Control: 25.8	Sequence generation: unclear Allocation concealment: low Blinding: low Incomplete outcome data: unclear Selective outcome reporting: low Risk of Bias: medium

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
la Recherche Medicale RCT				
De Lorgeril, 1994, 1996[95,96] France Lyon Heart Study Funding: see De Lorgeril 1998, 1999 (above) RCT	See above	See above Follow-up: Intervention 26.9 months, Control 27.1 months	N = 605, Intervention 303, Control 302 Age (mean) Intervention: 53.5 Control: 53.5 Gender (% male) Intervention: 89.4 Control: 92.1 BMI Intervention: 25.8 Control: 25.8	Sequence generation: unclear Allocation concealment: low Blinding: low Incomplete outcome data: unclear Selective outcome reporting: low Risk of Bias: medium
Singh, 1992[99] India Funding: Not reported RCT	Included: -admission to hospital in previous 24 hours for acute MI or unstable angina Excluded: -patient refusal -cancer, diarrhea, or dysentery -death before randomization -BUN > 400mg/l -non-cardiac chest pain	Intervention (indo-Mediterranean): a) meat, eggs, hydrogenated oils, butter, and clarified butter replaced with vegetarian meat substitutes and soya bean, sunflower, and ground nut oils b) advice to eat fruits, vegetables, pulses, nuts, and fish plus general health advice (regularly reinforced) Comparator (Step 1 NCEP): a) meat, eggs, hydrogenated oils, butter, and clarified butter replaced with vegetarian meat substitutes and soya bean, sunflower, and ground nut oils b) general health advice that was NOT reinforced Follow-up: 1 year	N = 406/505 Intervention: 204, Control: 202 Age (mean) Intervention: 50.5 Control: 52.0 Gender (% male) Intervention:(88% Control: 92% BMI Intervention: 24.3 Control: 23.3	Sequence generation: unclear Allocation concealment: unclear Blinding: low Incomplete outcome data: unclear Selective outcome reporting: unclear Risk of Bias: Medium *An article published in BMJ 2005 331 (7511) outlines serious doubts about Singh and this paper in particular and whether results are true or fabricated. A check of the raw data didn't match the figures published and some methods have been questioned.
Singh 1991[100] India Funding: Not	Included: -responded to ads in local newspapers, clubs, and clinics	Intervention: a) meat and eggs replaced with fish or protein and fat-rich cereals and	N = 463 Intervention: N = 228 Age (mean): 45.2	Sequence generation: unclear Allocation

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
reported RCT	Excluded: -respondents with cancer, chronic renal failure, diarrhea, or dysentery -those who did not like diet protocol	cottage cheese b) low in saturated fat; many fruits, vegetables, cereals, peas, beans, nuts, and soybean/sunflower oils* c) follow-up at 1-4-wk intervals d) counseling sessions with dietitian and one of the physicians, "the dietitian also made home visits to educate housewives regarding the maintenance of dietary compliance" Control: usual care/diet *Diets for obese and hyperlipidemic individuals lower in fat content and had same ratio of polyunsaturated to saturated fatty acids Follow-up: 1 year	Gender (% male): 91 Obese: 36% Control: N = 230 Age (mean): 47.5 Gender (% male): 90, Obese: 34%	concealment: low Blinding: low Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low
Cognitive				
Scarmeas 2009[87] USA Washington Heights-Inwood Columbia Aging Project (WHICAP) Funding: National Institute on Aging Cohort	Cohort: -WHICAP 1992, WHICAP 1999 -identified from probability sample of Medicare beneficiaries -residing in area of 3 contiguous census tracts in northern Manhattan Included: -diagnosis of MCI defined as 1) subjective memory complaint, 2) objective impairment in at least one cognitive domain (memory, executive, language, visuospatial), 3) essentially preserved activities of daily living, 4) no diagnosis of dementia Excluded: -missing or incomplete dietary information -insufficient data for MCI diagnosis	Semi-quantitative FFQ (61 items) used to determine MD score (0 = minimal conformity, 9 = maximum) a) 1 point for >median consumption of fruits, vegetables, legumes, cereals, and fish b) 1 point for < median consumption of meat and dairy c) 1 point for > median ratio of MUFA:SFA d) 1 point for alcohol 0-30gm/d Follow-up: 4.3 years	N = 482 with MCI at baseline Age (mean): 78 Gender (% male): 32 BMI: 27.2	Population: low Outcomes: low Measurement: low Confounding: low Risk of Bias: low
Rheumatoid Arthritis				
McKellar 2007[101] United Kingdom Funding: Scottish Society of Physicians	Cohort: -recruitment aimed at residents from Social Inclusion Partnership areas in Glasgow (areas of social deprivation) Included: -female	Intervention (n = 75): a) 6 week (2 hrs/wk) "hands-on" cookery course with emphasis on Mediterranean-type diet b) written information on diet including recipes	N = 130 Age (mean): 54 Gender (% male): 0 BMI: 27.3 Disease duration: 9.4 years	Sequence generation: high Allocation concealment: unclear Blinding: unclear Incomplete outcome

Author, year Country Study name Funding Source Study type	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
RCT	-age 30-70 years Excluded: NR	c) information about food hygiene, nutrition, and local accessibility of affordable ingredients (fruits, vegetables, legumes, MUFA>SFA, olive oil) Comparator (n = 55): received readily available written information on healthy eating Follow-up: 6 months		data: low Selective outcome reporting: low Risk of Bias: medium
Sköldstam 2003[102] Sweden Funding: Faculty of Social Sciences (Umea University), Swedish Foundation for Health Care Sciences and Allergy Research, Health Research Council, and other foundations RCT	Cohort: -recruited from Kalmar in SE Sweden Included: -RA (per 1987 American College of Rheumatology criteria) -disease duration ≥ 2 years -disease clinically stable and under adequate control (per patient's rheumatology specialist) -disease modifying anti-rheumatic drugs unchanged for ≥3 months -corticosteroids unchanged for ≥4 weeks, and NSAIDs unchanged for ≥10 days before starting trial Excluded: -daily dose of oral corticosteroids (Prednisolone) >12.5 mg -DAS28 > 2.0 (active disease) -no condition other than RA that demanded active medical attention -vegetarian -already living on Mediterranean-like diet	Intervention (n = 26): Cretan MD* a) olive and canola oil for food preparation, baking, and salad dressings; canola oil margarine for cooking and as a spread b) 6 diet lessons (plus consultations if needed) c) written instructions and recipes d) some food supplied free (oils, margarine, frozen vegetables, and tea) Comparator (n = 25): usual diet NOTES: 1) both groups participated in 3-week outpatient rehabilitation program (8 hrs/day, 5 days/wk); lunch and dinner provided (either MD or usual diet, as randomized); study continued for 9 additional weeks with participants preparing their own meals 2) daily doses of anti-rheumatic drugs, corticosteroids, and supplementary prescriptions remained constant throughout study; NSAID doses could be adjusted Follow-up: 3 months *dairy and alcohol components modified for Swedish subjects	N = 51 Age (mean): 58 Gender (% male): 20% Race: NR BMI: 27* Disease duration: 13.6 years* *Intervention group participants had significantly higher BMI and longer disease duration	Sequence generation: unclear Allocation concealment: unclear Blinding: unclear Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: low

AD = Alzheimer's disease; aMED = alternative Mediterranean diet score; BMI = body mass index; FFQ = food frequency questionnaire; MCI = mild cognitive impairment; MD = Mediterranean diet; MUF = monounsaturated fat; NR = not reported; NSAID = non-steroidal anti-inflammatory; SF = saturated fat

Table 6. Key Question 2 – Outcomes for Populations with Diabetes, Heart Disease, Kidney Disease, and/or Hypertension (Part 1)

Study Intervention (n) Control (n)	All-cause Mortality % (n/N)		Quality of Life (*describe*)		Patients with any Adverse Event % (n/N)		Adverse Events Related to Diet (*describe*) % (n/N)		Other *(describe)*	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cardiovascular Disease										
Tuttle 2008[8] *N = 101*	Med Diet: 0/51	Low fat diet: 0/50 P = 1.0					None described		Cardiac Death Med Diet 0/51	Cardiac Death Low-Fat diet 0/50 P = 1.0
Burr 2003[94] *N = 3,114*	1. 18.4% (141/764) 2. 17.1% (133/779) 3. 17/6% (142/807)	14/3% (109/764)							Cardiac Deaths Fish+Fruit 10.7% (86/807)	Cardiac Deaths Sensible eating 8.8% (67/764)
Singh 2002[98] *N = 1,000*	5% (24/299)	8% (38/501) P = .064			Total cardiac endpoints: 7.8% (39/499)	Total cardiac endpoints: 15.2% (76/501) ARR 0.48 (0.33, 0.71)			Suspected cardiac deaths 0.4% (2/499)	Suspected cardiac deaths 0.2% (1/501) P = .56
De Lorgeril 1998,1999[6,97] *N = 605*	4.6% (14/302)	7.9% (24/303) RR 0.44 (0.21, 0.94)							Cardiac Deaths 2.0% (6/302)	Cardiac deaths 6.3% (19/303) RR 0.35 (0.15, 0.83)
De Lorgeril 1994, 1996[95,96] *N = 605*	2.6% (8/302)	6.6% (20/303) HR 0.30 (0.11, 0.82)					2 pts reported "margarine related side effects": "colitis" and "diarrhea"			

Study Intervention (n) Control (n)	All-cause Mortality % (n/N)		Quality of Life (*describe*)		Patients with any Adverse Event % (n/N)		Adverse Events Related to Diet (*describe*) % (n/N)		Other *(describe)*	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Singh 1992 [99] *N = 406*	10% (21/204)	19% (38/202) RR 0.55 (0.34, 0.75)					"mild belching and fullness in a few patients"		Total Cardiac Mortality 9.8% (20/204)	Total Cardiac Mortality 16.8% (34/202) RR 0.58 (0.34, 0.83)
Singh 1991[100] *N = 458*	3.5% (8/228)	4.8% (11/230) NS			Complica-tions Angina: 12 Resistant HTN: 5 Total: 101	Angina: 28 HTN: 10 Total: 165 P<.02-total				

CI = confidence interval; HR = hazard ratio; HTN = hypertension; MD = Mediterranean diet; NR = not reported; NS = not statistically significant; RR = risk ratio

Table 7. Key Question 2 – Outcomes for Populations with Diabetes, Heart Disease, Kidney Disease, and/or Hypertension (Part 2)

Study Intervention (n) Control (n)	New MI % (n/N)		New Stroke % (n/N)		New Revascularization Procedure % (n/N)		New Amputation % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cardiovascular Disease								
Tuttle 2008[8] *N = 101*	Med Diet 2% (1/51)	Low-fat 6% (3/50) P = .36	Med Diet 6% (3/51)	Low-fat 2% (1/50) P = .62	Med Diet 22% (11/51)	Low-fat 16% (8/50)		
Singh 2002[98] *N = 1,000*	33/499 (6.6%) Non-fatal: 21/499 (4.2%) Adj RR 0.47 (0.28, 0.79) Fatal: 12/499 (2.4%) Adj RR 0.67 (0.31, 1.42)	60/501 (12%) Non-fatal: 43/501 (8.6%) Fatal: 17/501 (3.4%) *adjusted for age, gender, BMI, cholesterol, and blood pressure	7/499 (1.4%) Stroke death: 2/499 (0.4%)	13/501 (2.6%) P = .17 Stroke death: 3/501 (0.6%)	CABG or angioplasty 6/499 (1.2%)	CABG or angioplasty 16/501 (3.2%) P = .03		
De Lorgeril 1999[6] *N = 605*	Nonfatal MI: 2.6% (8/302)	Nonfatal MI: 8.3% (25/303)						
De Lorgeril 1994, 1996[95,96] *N = 605*	Nonfatal MI: 1.6% (5/302)	Nonfatal MI: 5.6% (17/303)	0/302	3/303	10% (31/302)	14% (41/303)		
Singh 1992[99] *N = 406*	21% (43/204) RR 0.62 (-0.42, 0.83)	33% (67/202)						
Singh 1991[100] *N = 458*	12.3% (28/228)	20.0% (46/230)	0.4% (1/228)	1.3% (3/230)				

CABG = coronary artery bypass graft; RR = risk ratio

Table 8. Key Question 2 – Outcomes for Populations with Diabetes, Heart Disease, Kidney Disease, and/or Hypertension (Part 3)

Study Intervention (n) Control (n)	Development of Retinopathy % (n/N)		Development of Neuropathy % (n/N)		Development of End-stage Renal Disease % (n/N)		Development of Congestive Heart Failure % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cardiovascular Disease								
Tuttle 2008[8] *N = 101*							0/51	0/50 P = 1.0
Singh 2002[98] *N = 1,000*							Heart Failure: 2.2% (11/499)	Heart Failure: 7% (35/501) P = .0003
De Lorgeril 1999[6] *N = 605*							2.0% (6/302)	3.6% (11/303)
De Lorgeril 1994, 1996[95,96] *N = 605*							0.7% (2/302)	2.6% (8/303)
Singh 1991[100] *N = 458*							0.9% (2/228)	0.9% (2/230)

Table 9. Key Question 2 – Outcomes for Populations with Cancer

Study Intervention (n) Control (n)	Cancer-specific Mortality % (n/N)		Quality of Life *(specify)*		Cancer Progression % (n/N)		Cancer Recurrence % (n/N)		Adverse Events % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Yang 2015[110] *N = 926*	Prostate Cancer Mortality Q4: 10 events/213 HR 0.46 (0.17, 1.24) P trend = .11									
Fung 2014[104] *N = 1,201*	Colorectal Cancer Mortality aMED (P = .19) Q1:39 RR 1 Q2:32 RR 1.18 (0.73, 1.91) Q3:32 RR 0.96 (0.58, 1.56) Q4:23 RR 0.73 (0.42, 1.28) Q5:36 RR 0.84 (0.50, 1.42) Prudent (P = .16) Q1:39 RR 1 Q2:26 RR 0.67 (0.40, 1.12) Q3: 30 RR 0.62 (0.37, 1.05) Q4:35 RR 0.91 (0.53, 1.55) Q5: 32 RR 0.67 (0.37, 1.22)									
Kenfield 2014[41] *N = 4,538*	Fatal Prostate Cancer 6-9: 85 cases HR 1.01 (0.75, 1.38) P = .95									
Vrieling 2013[109] *N = 2,522*	Breast Cancer Mortality – Healthy Diet Pattern Q1: 72/614 Q2: 46/616 HR 0.76 (0.51, 1.14) Q3: 55/617 HR 0.83 (0.56, 1.23) Q4: 50/609 HR 0.89 (0.59, 1.35) P = .25						Breast Cancer Recurrence – Healthy Diet Pattern Q1: 67 recurrences/517 (stage I-IIIa) Q2: 56/542 HR 0.84 (0.58, 1.21) Q3: 61/543 HR 0.77 (0.54, 1.12) Q4: 55/533 HR 0.71 (0.48, 1.06) P = .02			

Study Intervention (n) Control (n)	Cancer-specific Mortality % (n/N)		Quality of Life *(specify)*		Cancer Progression % (n/N)		Cancer Recurrence % (n/N)		Adverse Events % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Kim 2011[105] *N = 2,729*	Breast Cancer Deaths aMED Q1: 51 RR 1 Q2: 48 RR 0.97 (0.63, 1.50) Q3: 56 RR 0.72 (0.47, 1.10) Q4: 73 RR 1.25 (0.83, 1.89) Q5: 75 RR 1.15 (0.74, 1.77) P = .21 Pre-diagnosis diet not associated with mortality									
Kwan 2009[107] *N = 1,901*	Death from Breast Cancer Prudent Q1: 34/451 Q2: 27/449 HR 0.78 (0.46, 1.32) Q3: 34/456 HR 0.94 (0.57, 1.57) Q4: 26/454 HR 0.79 (0.43, 1.43) P trend = .57						Breast Cancer Recurrence Prudent Q1: 62/451 Q2: 60/449 HR 0.95 (0.66, 1.37) Q3: 71/456 HR 1.09 (0.76, 1.56) Q4: 63/454 HR 0.95 (0.63, 1.43) P trend = .94			
Meyerhardt 2007[108] *N = 1,009*							Colon Cancer Recurrence 1.13 (0.77, 1.67)			
Kroenke 2005[106] *(Sub-study of Kim 2011) N = 2,619*	Breast Cancer Deaths Q1: 38 RR 1 Q2: 38 RR 0.85 (0.53, 1.34) Q3: 53 RR 1.17 (0.74, 1.84) Q4: 56 RR 1.18 (0.75, 1.87) Q5: 57 RR 1.07 (0.66, 1.73) P = .57									

aMed = alternative Mediterranean diet score; HR = hazard ratio; Q = quantile; RR = relative risk

Table 10. Key Question 2 – Outcomes for Populations with Rheumatoid Arthritis

Study Intervention (n) Control (n)	Pain *(specify)* % (n/N)		Quality of Life *(specify)*		Functional Status *(specify)*		Adverse Events % (n/N)	
	Intervention	Control	Intervention	Intervention	Control	Control	Intervention	Control
McKellar 2007[101] *N = 130*	Global pain score (VAS 0-100) (median) Baseline: 50 6 months: 50	Baseline: 55 6 months: 63 (P = .049)			DAS28 (median) Baseline: 4.7 6 months: 4.4 HAQ (median) Baseline: 1.75 6 months: 1.63	Baseline: 5.0 6 months: 4.8 (P = NR; change reflects "no response") Baseline: 1.75 6 months: 1.88 (P = NR at 6m)		
Sköldstam 2003[102] *N = 51*	Pain score (VAS 0-100) (mean) Baseline: 32 12 weeks: 20	Baseline: 31 12 weeks: 34 (P = .006 for difference between groups for change from baseline to 12 weeks)	SF-36 Significant change from baseline to 12 weeks for 1 of 8 dimensions (Vitality)	No significant changes from baseline to 12 weeks	DAS28 (mean (SD)) Baseline: 4.4 (1.2) 12 weeks: 3.9 (1.2) HAQ (mean (SD)) Baseline: 0.7 (0.5) 12 weeks: 0.6 (0.4)	Baseline: 4.3 (1.4) (n = 23) 12 weeks: 4.3 (1.5) (n = 23) (P = .047 for difference between groups for change from baseline to 12 weeks) Baseline: 0.8 (0.6) (n = 23) 12 weeks: 0.8 (0.6) (n = 23) (P = .012 for difference between groups for change from baseline to 12 weeks)	2 withdrawals: 1 due to dyspepsia (diet related); 1 relapse of rheumatoid pleuritis (not diet-related, required increased prednisolone)	None reported

DAS = Disease Activity Score; HAQ = Health Assessment Questionnaire; NR = not reported; SD = standard deviation; SF – 36 = Short Form – 36; VAS = visual analog scale

Table 11. Key Question 2 – Outcomes for Populations with Cognitive Impairment

Study Intervention (n) Control (n)	Diagnosis of Dementia *(specify)* % (n/N)		Quality of Life *(specify)*		Functional Status *(specify)*		Adverse Events % (n/N)	
	Intervention	Control	Intervention	Intervention	Control	Control	Intervention	Control
Scarmeas 2009-2[87] *N = 482*	Higher conformity to MD associated with lower risk of developing AD MD Continuous Adjusted (n = 406) HR 0.89 (0.78, 1.02) MD Tertiles (Low as reference) Middle: HR 0.55 (0.34, 0.90) High: HR 0.52 (0.30, 0.91) Results similar for patients with MCI without memory impairment No significant association for subjects with MCI with memory impairment							

AD = Alzheimer's disease; HR = hazard ratio; MCI = mild cognitive impairment; MD = Mediterranean diet

KEY QUESTION 3

Table 12. Key Question 3 – Study, Intervention, and Patient Characteristics

Author, year Country Study name Funding Source	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
Elmer 2006[111] USA PREMIER Funding: National Heart, Lung and Blood Institute RCT	Included: -generally healthy adults -25y or older -prehypertension or stage 1 hypertension and met Joint National Committee VI criteria for a 6-month trial of non-pharmacologic therapy -not taking antihypertensive medication and blood pressure of 120-159/80-95 mmHg Excluded: -BMI <18.5 or >45 -use of antihypertensive drugs or other drugs that affect blood pressure -JNC VI risk category C (target organ damage or diabetes) -use of prescription weight loss medications -previous cardiovascular event, congestive heart failure, angina, or cancer -consumption of > 21 alcoholic drinks per week	Established (comparator): a) goals included weight loss of at least 15 lbs if BMI >25, at least 180 min/wk week of moderate physical activity, reduced sodium (<100mmol/day), and no more than 30 (men) or15 (women) ml of alcohol b) attended 14 group sessions and 4 individual during first 6 months; monthly group sessions and 3 individual for remaining year Established + DASH (intervention): a) everything from established intervention (above) b) counseling on DASH diet with goals for increased consumption of fruits and vegetables (9-12 servings/day) and low-fat dairy products (2-3 s/d) and reduced consumption of saturated fat (≤7%) and total fat (≤ 25%) Advice Only: advised to follow National 'High Blood Pressure Education program lifestyle recommendations for blood pressure control (outcomes not extracted for this group) Follow-up: 1.5 years	N = 810, all middle aged Gender (% male): 38 Race: 34% African American BMI: 33	Sequence generation: low Allocation concealment: low Blinding: low Incomplete outcome data: low Selective Outcome reporting: unclear Risk of Bias: low

Author, year Country Study name Funding Source	Inclusion/Exclusion Criteria	Intervention Comparator Follow-up	Patient Characteristics	Risk of Bias
WHI Study Group 2004[113] Beresford 2006[23] USA WHI-DM Funding: National Heart, Lung, and Blood Institute and Department of Health and Human Services	Included: -postmenopausal women -age 50-79 years -interested in one or more components of the clinical trials -willing to be randomized to an intervention or comparison group Excluded: -baseline diet estimated to have less than 32% of energy from fat	Intervention: intensive behavioral modification program using 18 group sessions in first year and then quarterly sessions a) decrease total fat intake to 20% or less of energy b) consume 5 or more servings per day of vegetables and fruits and 6 or more servings per day of grains Comparison: received US Department of Health and Human Services *Dietary Guidelines for Americans* Follow-up: 5 years	Intervention, n = 19,542 Control, n = 29,294 1yr post randomization: 50-54: 13.8% 55-59: 22.4% 60-64: 26.1% 65-69: 21% 70-74: 12.3% 75-79: 4.4% BMI <25: 25.9% 25-29.9: 36.2% 30-34.9: 22.9% ≥35: 15%	Sequence generation: unclear Allocation concealment: unclear Blinding: unclear Incomplete outcome data: low Selective outcome reporting: low Risk of Bias: medium

BMI = body mass index

Table 13. Key Question 3 – Adherence

Study Intervention (n) Control (n)	Adherence to Diet *(describe)*	
	Intervention	Control
Elmer 2006[111] *N = 537*	Change at 18 months, mean servings/day Fruit and vegetable intake: 2.8 (SD 3.4) Dairy intake: 0.4 (1.5) Change at 18m, mean saturated fat (%): -2.9% (3.4)	Change at 18 months, mean servings/day Fruit and vegetable intake: 0.1 (2.7) Dairy intake: -0.2 (1.5) Change at 18m, mean saturated fat (%): -1.1% (3.7)
WHI 2004[113] ***Beresford 2006[23]*** *N = 48,836*	Difference between control and intervention (C-I) Fat intake: Year 1 10.9%, Year 5 9% Saturated Fat: Year 1 4%, Year 5 3.5% Servings of fruits and vegetables: Year 1 -1.2, Year 5 -1.3 Servings per day of grains: Year 1 -0.8, Year 5 -0.5 All P<.001 Mean difference (intervention - comparison) in change in consumption at year 3 (Beresford 2006[23]) Red meat: -20.2% (-25.5, -14.8) Fish: -3.9% (-13.1, 5.2) Poultry: 2.3% (-4.9, 9.5) Vegetables and fruits: 47.4% (42.5, 52.2) Grains: 17.6% (12.7, 22.4)	

APPENDIX D. LITERATURE FLOW

Figure 1. Literature Flow Key Questions 1 and 2 Randomized Controlled Trials

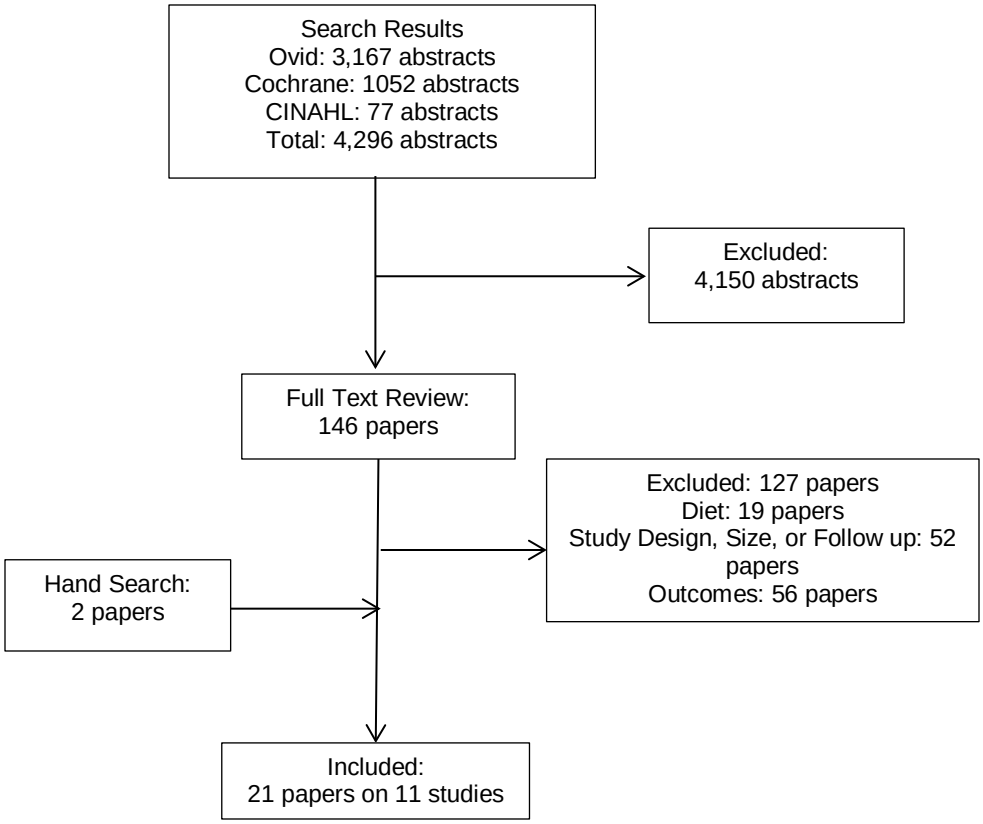

Figure 2. Literature Flow Key Questions 1 and 2 Cohort Studies (Cancer, RA, Cognitive)

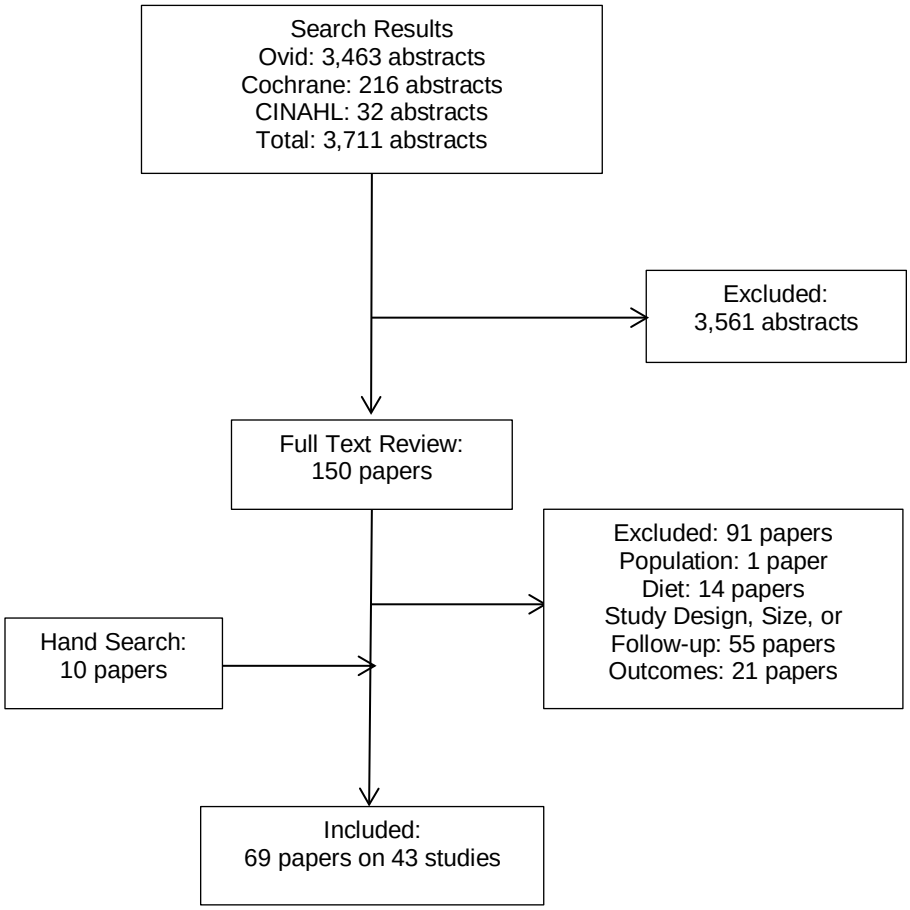

Figure 3. Literature Flow Key Question 3