



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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EXECUTIVE SUMMARY

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	1 RCT WHI-DM (48,835)	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.
		Observational Lowered risk	3 Observational (591,002)	
Breast Cancer Incidence	Low	RCT Mixed	2 RCTs WHI-DM (48,835) PREDIMED (4,152)	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.
		Observational Similar	12 Observational (range 1,598 to 355,062)	
Colorectal Cancer Incidence	Low	RCT Similar	1 RCT WHI-DM (48,835)	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.
		Observational Lowered risk	9 Observational (range 19,133 to 397,641)	
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

^aStrength 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 included 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