

Review of Literature
The Effects of Mediterranean Diet on Cardiovascular Disease

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ABSTRACT

Background: Cardiovascular disease (CVD) affects more people in the United States than any other disease. The Mediterranean Diet (MedDiet) may prevent the risk of developing CVD, especially those at high risk.

Objective: Does following a Mediterranean style diet help reduce and/or prevent the effects of CVD.

Methods: A thorough literature review was done using multiple databases. Randomized clinical trials were investigated in order to understand the relationship between a MedDiet and CVD in humans. The dependent variable (primary outcome) assessed was whether participant suffered from a CVD event or died as a result of a CVD. The main independent variable assessed was whether participant adhered to a MedDiet. Other confounders that were investigated included age, sex, smoking status, alcohol consumption, physical activity, total energy intake, educational level, hypertension, and anthropometric measurements (height, weight, waist and hip circumference.

Results: Research consistently demonstrates that there is an inverse relationship between the development of CVD and adhering a MedDiet. Following a MedDiet also showed weight management was more effective in the long term compared to following other forms of diet. More evidence is needed to understand the role and effectiveness of olive oil, as this seems to be a major contributor along with eating lots of vegetables and legumes, to preventing CVD.

Conclusions: Evidence from several studies, starting from the first study, Seven Countries Study in 1958-1983, shows a MedDiet can help prevent those with a high risk of CVD and However, more research is needed to understand dosages of olive oil and mechanisms of such a diet.

INTRODUCTION

CVD, including heart disease and stroke, is not only the leading cause of mortality in U.S, but the world. It accounts for one in every three deaths and is a leading cause of long-term disability directly costing well over 312.6 billion dollars. CVD is a complex multifactorial disease, with no direct cause, that is characterized by increased LDL and total cholesterol, inflammation, hypertension, increased platelet aggregation, and calcification. A well-balanced diet with regular physical activity can help prevent CVD or slow its progression. With the many diet plans that are advertised to the public, it can be tricky and confusing to know which one to follow. Thanks to much research that has been done, dating back to 1958, who conform to a MedDiet appear to prevent CVD and can help in even managing the effects of CVD.

Key features of the tradition MedDiet include the high consumption of the following: fruits, vegetables, fish, whole grains, legumes, and nuts. Additionally, the consumption of olive oil makes this diet group unique. MedDiet followers also consume low amounts of meat and dairy products and moderately consume alcohol with meals. Olive oil has many healing effects and was used as traditional medicine in many cultures for centuries. Many effects of olive oil have been identified such as helping to manage type II diabetes because its richness in monosaturated fats. Olive oil also has its effect on blood pressure (BP) and has shown to reduce hypertension if one consumes olive oil daily. Consumption of olive oil helps in losing weight as well as managing weight due to its high nutrient value. Olive oil has positive effects on heart health because it slows down the heart aging process and its antioxidants help protect against red blood cells damage. Other effects of olive oil that been shown is lowering the risk of colon cancer, skin cancer, relieving earache, and bone health by preventing loss of calcium.

Many studies have analyzed the relationship between a MedDiet and CVD. The main studies analyzing this relationship include the Seven Countries Study, Lyone Heart Diet Study, EPI-Elderly Prospective Cohort Study, HALE, SENECA, and FINE studies, Nurses' Health Study, and a study

by Mitrou et al. This literature review serves the main purpose of collecting the evidence and determining the effectiveness of following a MedDiet and/or preventing CVD. Various aspects of CVD will be analyzed using different outcome variables.

METHODS

Randomized clinical trials as well as other prospective cohort studies were investigated to better understand the relationship between a MedDiet and CVD. The dependent variable (primary outcome) assessed was whether participant suffered from a CVD event or died as a result of a CVD. The main independent variable assessed was whether participant adhered to a MedDiet. Other confounders that were investigated included age, sex, smoking status, alcohol consumption, physical activity, total energy intake, educational level, hypertension, and anthropometric measurements (height, weight, waist and hip circumference. Depending on the study, other factors were also assessed such as systolic and diastolic blood pressure, total cholesterol, family history, and marital status.

All the research articles used were peer-reviewed and published within ten years. The databases used include PubMed, EBSCOhost, and Google scholar. Six of the papers are randomized clinical trials (RCT) and two of them are literature reviews of the preliminary work published on the topic. Any study that used MedDiet as the independent variable and CVD as the dependent variable or primary outcome were included. The key terms used in searching for the articles include “Mediterranean diet,” “cardiovascular disease,” which generated 347 results. After using a variety of search phrases, some of the same studies were found. The refined studies were chosen based on independent variable and specifically focusing on a MedDiet. Two systems reviews were included as they were legitimate literature reviewed providing an overview of the main studies conducted in order to assess the adherence to a MedDiet and CVD.

DISCUSSION

Mediterranean Diet and CVD Development

Several randomized clinical studies were investigated to understand the true effect of adhering to a MedDiet and the development of CVD. The study by Hoevenaar-Blom et al. was a meta-analysis of the prospective EPIC-NL Study cohort with 10-15 years of follow up with a total of 40,011 men and women between the ages of 20 to 70 years old.¹ This study aimed to examine the relationship between a Mediterranean style diet and incident fatal CVD, total CVD, and specific CVD. The secondary aim was to explore which components of this diet had the strongest association with each of these associations. The EPIC-NL cohort is the Dutch contribution to the European Prospective Investigation into Cancer and nutrition (EPIC) study. The two studies within the EPIC-NL cohort investigated were the MORGEN and PROSPECT cohorts. The MORGEN cohort consisted of 22,654 men and women aged between 20-65 years old chosen randomly from three Dutch towns. The PROSPECT cohort consisted of 17,357 women aged between 50-70 years, who participated in a breast cancer screening program. Dietary intake was assessed using a validated food frequency questionnaire (FFQ). During the 10-15 years of follow-up, 4881 CVD events occurred, and 487 persons died from CVD. Mediterranean Diet Score (MDS) was associated with a 22% lower incidence of fatal CVD, a 5% lower incidence of total CVD, and a 15% lower incidence of composite CVD. An inverse relationship between Mediterranean style diet and total CVD and more strongly so with fatal CVD. Additionally, it was found the higher the MDS score, the lower the incidence of CVD.

Another study by Trichopoulou et al. was a randomized control trial (RCT) and placebo controlled in order to determine if there is an inverse relationship between a MedDiet and fatality among European elders with coronary infarct.² Data for 100,442 participants from nine European countries, who were 60 years or older were included in the EPIC-Elderly project. Participants that had MI, but no cancer or stroke, were only included. Information on foods and beverages was assessed using a self-or interviewer-administered FFQ or quantitative dietary questionnaire.

Anthropometric measurements (height, weight, waist and hip circumference) were taken. The investigators found that after a median follow-up of 6.7 years, adherence to a modified MedDiet by 2 units was associated with 18% lower overall mortality rate in survivors of MI.

A multicenter trial study implemented in Spain by Estruch et al. was also a RCT, placebo-controlled primary prevention study with a median follow-up of 4.8 years.³ The purpose of this study was to compare the effects of a MedDiet with that of a low-fat diet for primary prevention of CVD. The subjects enrolled in this study were 7,447 men and women (57% were women) who were at high risk for developing CVD. Men were aged 55 to 80 years of age and women were between the ages of 60 to 80. Subjects were randomly assigned to the of the the three diet groups: a MedDiet supplemented with extra virgin olive oil, a MedDiet supplemented with mixed nuts, or a low-fat diet. The low-fat diet group served as the controls. Participants had no CVD at enrollment, but were identified as high risk. Participants received quarterly individual and group educational sessions, and depending on which group they were assigned to, they were given free extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point assessed was the rate of major CVD event (MI, stroke, or death). Median follow up of participants was 4.8 years. The main result of this study indicated that a MedDiet with extra-virgin olive oil or nuts is more protective against CVD than a recommended low-fat diet.

The fourth RCT study by Hu et al. investigated which socioeconomic status (SES) and lifestyle factors were associated with a lower adherence to the MedDiet.⁴ In this study, 7,447 men and women who were at high risk for developing CVD were recruited into the PREDIMED trial. Men were aged between 55 to 80 years and women were between the ages of 60 to 80 years. The PREDIMED study was analyzed for various variables to assess SES and lifestyle information. The results indicated that former smokers, physical activity, and higher educational level were associated with higher MedDiet adherence. Conversely, having a larger waist-to-height ratio, being diabetic,

being single/divorced/separated, and current smokers were associated with lower adherence to the MedDiet.

A cross-sectional, longitudinal study by Yang et al. examined the association between CVD risk markers and dietary habits conformed to a in an occupationally active, non-Mediterranean cohort.⁵ A cohort of 780 career male firefighters, aged 18 years or older from the U.S. Midwest were included in the study. MedDiet patterns from a previously developed questionnaire were assessed examining pre-existing dietary habits from participants. Clinical data from the fire department medical examinations were extracted and analyzed. The results indicated that greater adherence to a MedDiet had significant inverse relationships with negative health effects such as metabolic syndrome, LDL-cholesterol. Conversely, a significant relationship was independently associated with higher HDL-cholesterol.

The RCT and placebo-controlled intervention by Mayneris-Perxachs et al. analyzed the influence of a MedDiet pattern on the plasma fatty acid composition and its relation with metabolic syndrome (MetS) after one year of intervention.⁶ This study also analyzed data from the EPIC study. A total of 425 subjects aged 55 to 80 years at high risk of CVD, were randomly assigned to one of the three groups as mentioned in the study by Estruch et al. After one year of intervention, participants in group 1 showed significantly increased plasma concentrations of palmitic and oleic acids. The nut and olive oil diets induced a fatty acid composition that has been shown to be beneficial in the face of metabolic syndrome.

Systematic Review of the MedDiet and CVD

An overview of the literature provided by Robson summarizes the results of several studies, including the randomized, single-blind secondary prevention trial called the Lyon Heart Study in France. The objective of Robson's systematic review was to examine the history and consistency of the MedDiet in preventing and managing CVD. A total of 605 subjects were divided into one of two groups: MedDiet adherence (experimental) or diet with 34% intake of fat, who served as the

controls.⁷ Another literature review by Sofi et al. focused on all the current and updated evidence examining the beneficial effects of MedDiet in the occurrence of major chronic degenerative diseases. The results from various studies were summarized in each study outlined in the methods. The following studies that were summarized in the systematic review include: Seven Countries Study, Lyon Heart Diet Study, EPI- Elderly Prospective Cohort Study, HALE, SENECA, and FINE studies, Study by Mitrou et al. (2007), and the Nurses' Health Study. The study by Mitrou et al. was a large cohort study that analyzed data on 214,284 participants between the ages of 50 and 71 years for a follow-up period of approximately ten years.⁹ The results indicated that patients who greatly adhered to the MedDiet had a 22% decrease in cardiovascular mortality in men and a 29% decrease in women. There results of all these studies were consistent in that adherence to a MedDiet had a significant association to a favorable health outcomes and better quality of life, even long term health.

CONCLUSION

The findings in all of the articles were consistent in showing adherence to the MedDiet had a significantly positive impact on preventing CVD. All of the RCTs showed reduced mortality in participants who greatly adhered to a MedDiet. An inverse relationship between the development of CVD and following a MedDiet was found. More research needs to be conducted measuring diet at baseline. In addition, the effects and dosage of olive oil needs to be investigated in order to understand how much olive oil is recommended as well as the mechanisms of adhering to such a diet. More studies should be implemented to understand the relationship with current lifestyle factors with the MedDiet and the prevention and/or management of CVD.

Some of the limitations of the study include not accounting for certain confounders such as race/ethnic background. Also, not all studied measured physical activity. Another limitation observed in the Estruch et al. study is not using blinding in the study. Bias could have occurred in

analyzing patients with certain confounders if investigators know which group subjects are assigned to; however, it would not have changed the outcome (CVD).

As a result of a thorough literature review and evidence from several studies, starting from the first study, Seven Countries Study in 1958-1983, a MedDiet can help prevent those with a high risk of CVD. The use of olive oil should be encouraged, specifically the use of extra virgin olive oil, when cooking and for adding to foods (I.e. salad) because of the many benefits it provides for overall health and even management of certain illnesses (i.e. diabetes, hypertension, obesity).

More research is needed to understand dosages of olive oil and mechanisms of such a diet. More studies need be done in a variety of populations. For example, different SES, different race/ethnic backgrounds, and various physical activity levels need to be assessed. Some of the information assessed in the cohort studies was from European countries, which may have different lifestyles than Americans, for example. Effectiveness of medications in relation to the effectiveness of a MedDiet would be an interesting association to investigate.

APPLICATION TO DIETETIC PRACTICE

Fish, the meat of grass-grazing animals, dairy products, eggs, walnuts, figs, and wild greens are nutrient rich and have Omega 3. Omega 3, which has shown to effect overall health, were eaten at ever meal, including snacks as observed by Simopoulos. The foods listed as having Omega 3 resembles the foods consumed by people following the MedDiet as well as other traditional diets following by people of Crete and Greece in the 1960s. Also, olive oil's benefits are many as discussed in the introduction; therefore, I would recommend that people follow the MedDiet by consuming large amounts of vegetables, fruits, nuts, legumes, use olive oil, and drink wine in moderate amounts. The nutritional benefits of following a MedDiet should be recommended by practitioners, especially in patients who are at high risk of developing CVD.

SUMMARY TABLE

Author/Year/ Study Design	Subjects	Groups	Outcomes	Results
Hovenaar-Blom et al., 2012, meta-analysis, RCT	40,011	-Random sampling with dietary intake assessed through FFQ	Fatal CVD, total CVD, and specific CVD	MedDiet associated with a 22% lower incidence of fatal CVD, 5% lower incidence of total CVD, and 15% lower incidence of composite CVD.
Trichopoulou et al., 2007, RCT	100,442	-Diet groups - Placebo group	MI	Adherence to a MedDiet was associated with 18% lower mortality.
Estruch et al., 2013, RCT	7,447	-3 groups: MedDiet with olive oil, MedDiet with nuts, Low-fat diet (controls) - Placebo group	LDL, BP	A MedDiet with extra-virgin olive oil or nuts is more protective against CVD than a recommended low-fat diet.
Hu et al., 2013, RCT	7,447	-2 Time-released garlic powder pills - Placebo group	SES Smoking status Educational level	Former smoking, physical activity, and higher educational level were associated with higher MedDiet adherence.
Yang et al., 2014	780	- Firefighters in the U.S. Midwest	CVD	Greater adherence to a MedDiet had significant and independently associated with higher HDL-cholesterol.
Mayneris-Perxachs et al., 2014, RCT	425	-3 groups: MedDiet with olive oil, MedDiet with nuts, Low-fat diet (controls) - Placebo	LDL, HDL, BP, CVD	After 1 year of intervention, participants in group 1 showed significantly increased plasma concentrations of palmitic and oleic acids
Robson et al., 2014, lit review	605	-2 groups: MedDiet, diet with 34% less fat intake (controls)	CVD, LDL, HDL	Major reductions of the rates of fatal and non-fatal CVD complications were reported in the experimental group.

Sofi et al., 2013, RCT	169	- Raw garlic - Garlic powder - AGE - Placebo	LDL, HDL, TC, and TAG	No statistically significant findings between the groups.
Higashikawa et al., 2012, lit rev	varies	- All studies	CVD and all outcomes	All studies were consistent in that adherence to a MedDiet had a significant association to a favorable health outcomes and better quality of life, even long term.

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