

The association between olive oil consumption and primary prevention of cardiovascular diseases

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ABSTRACT

Introduction: American Heart Association and many other recommend Mediterranean diet for patients with cardiovascular risk. This systematic review and meta-analysis are conducted to review the effects of Mediterranean diet on the cardiovascular events as reported in randomized controlled trials (RCTs). **Methods:** A systematic research is conducted on MEDLINE via Ovid, Embase, PubMed, Google Scholar, Web of Science, and Informit. Databases of studies conducted between 2000 and 2017 were included in the analysis. All the collected studies were screened, and at the end, seven RCTs met the inclusion criteria. All the characteristics of trails such as study design, interventions, follow-up duration, and primary and secondary outcomes were recorded. RevMan was used to evaluate risk reduction in each trial individual using forest plot and fixed effects. **Results:** Four studies were included in the review, having a total of 25,195 participants. The effects of Mediterranean diet were found in cardiovascular events (627), coronary events (251), and all-cause death (887). The analysis revealed that there is a statistically significant relationship between Mediterranean diet and reduction in cardiovascular events at $P = 0.02$. However, other parameters did not show any statistically significant results that need further investigation. **Conclusion:** The individual RCT provides evidence of protective effects of the Mediterranean diet on cardiovascular events. However, the quality and quantity of data available in those trails are not reliable and limited. Therefore, the results of those trails must be cautiously interpreted.

Keywords: Cardiovascular risk, coronary artery disease, Mediterranean diet, meta-analysis, olive oil, systematic review

Introduction

Cardiovascular diseases cause approximately 52 million deaths worldwide^[1,2] and present huge burden on the healthcare system of the entire world. According to some studies, the incidence of cardiovascular disease is slightly lower in Mediterranean region.^[1,3] These varied patterns of cardiovascular disease can be associated with different dietary patterns in the region.

In the Mediterranean region, the traditional diet is mainly Mediterranean diet. It includes grains, pulses, cereals, fruits, nuts, legumes, olive oils, milk and dairy products, low intake of meat, and beef. Trichopoulou *et al.* devised *a priori* score to determine adherence to Mediterranean diet.^[4] One study reported a lower

rate of cardiovascular diseases in the Mediterranean region when compared with European region.^[5] Two other studies demonstrated lower incidence of cardiovascular events with high consumption of Mediterranean diet such as nuts, olive oil, fruits, and vegetables.^[6,7] Besides reducing the risk of cardiovascular diseases, Mediterranean diet also maintains healthy lipid levels in the body.^[8,9] Mediterranean diet is also associated with improving the status of metabolic syndrome and hence reducing mortality rate.^[10,11] Other major benefits of Mediterranean diet include a reduction in cognitive impairment,^[7,8] the risk of cancer,^[4] hypertension, hyperlipidemia, and total mortality.^[12]

There are several randomized controlled trials (RCTs) on the effectiveness of Mediterranean diet to reducing cardiovascular risk.^[13] However, some of the trials have a methodological bias which renders their quality.^[14] To evaluate the effectiveness of Mediterranean diet in cardiovascular disease, the current

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systematic review and meta-analysis were conducted on the latest RCTs. The findings of this review will enhance our current knowledge on the beneficial impacts of the Mediterranean diet in cardiovascular events.

Methods

Search strategies

A thorough literature research was conducted using PRISMA guidelines for meta-analysis to evaluate the effectiveness of interventions. The following databases were explored using targeted Boolean search strategy: MEDLINE through Ovid, Embase, PubMed, Google Scholar, Web of Science, and Informit. The initial search was broad and included all types of studies, without any language restriction. The keywords used to research the database include (“Mediterranean diet” [mesh] OR Olive oil * [tw] OR “Virgin Olive oil” [tw] OR “dietary intervention” [tw] AND (“Cardiovascular diseases” [mesh] OR ischemic heart disease * [tw] OR coronary artery disease* [tw])). Mesh search was conducted to target the core 10% articles, which are often ignored. These keywords helped to gather maximum-targeted articles.

Selection of study

Two independent authors following a standard approach carried out the literature search. The studies included in the systematic review on the basis of a defined inclusion and exclusion criteria. All the included studies assessed the impact of Mediterranean diet on adults and compared it to the control diet. The follow-up period of all the included studies is not less than 3 months. The studies are included in the systematic review on the basis of a defined inclusion and exclusion criteria. The Mediterranean diet includes one of these five components: (1) consumption of olive oil, (2) intake of nuts and legumes, (3) high intake of grains and other cereal food, (4) high intake of green vegetables and fruits, and (5) moderate consumption of dairy products. The eligibility criteria were developed using PICO strategy (Population, intervention, control, and outcome). Based on this strategy, a specific criterion was designed in which included studies have the following features:

Inclusion criteria

- Participants with no previous history of cardiovascular events and living in either Mediterranean region or non-Mediterranean region
- Participants adhering to Mediterranean diet
- Study design of RCTs
- Studies not older than 2000
- Only human studies in English language
- Outcome measures of cardiovascular disease, stroke, heart failure, and cardiovascular mortalities.

Exclusion criteria

- Prospective cohort studies and all other reviews
- Studies reporting outcomes other than cardiovascular events
- Non-human studies
- Trails older than 2010.

Mediterranean diet consumed

Participants of the study had taken Mediterranean diet, and their dietary scores were calculated according to the dietary pattern and the traditionally consumed Mediterranean pattern.^[12] The participants who consumed at least one food item from the category of diet considered as Mediterranean diet (whole grain breads, rice, and pasta; dairy products; poultry; eggs; fish and seafood; legumes, nuts and seeds; potatoes; fruit juice and drinks) were given a value of one. Whereas participants who consumed food among this category less than once in a week were given a value of 0. Participants who have consumed olive oil in their cooking and taken other nuts and vegetables once per day were given a value of 1. Contrary to that, participants who had consumed diet such as meat, pickled food, salty snacks, pizza, and beverages once in a week were given a value of 0. We stick to the dietary scores as defined in the included studies.

Data extraction

Reports of published trials were obtained and all the relevant information were recorded in Excel spreadsheet. All the data summary of trails was recorded including age, gender, history of hypertension, body mass index and family history of cardiovascular disease, follow-up duration, outcome of interest, dietary intervention, and any adverse effect reported. All four included studies were assessed through Cochrane risk of bias tool to find any selection bias.^[15]

Main outcomes

In the current systematic review and meta-analysis, the following primary outcomes were recorded: cardiovascular events (myocardial infarction, stroke), cardiovascular deaths, heart failure, all-cause death, and any reported adverse event.

Statistical analysis

RevMan review manager version (5.3) was used to perform statistical analysis on the included studies. Relative risks (RRs) and confidence intervals (CIs) at 95% were calculated from each study using the number of events reported in each trail. In multicenter PREDIMED studies, three interventions were given: we considered the intervention of olive oil with nuts and extra virgin olive oil jointly, presented their combined results, and compared it with low-fat control diet intervention. Random fixed effects model was applied to evaluate the estimates of RRs. A *P* value of 0.05 was taken statistically significant for our results.

Results

Characteristics of included studies

Database search yielded some articles. After screening, full text of 94 articles was retrieved and reviewed. Of these, only seven randomized controlled trails having 25,195 participants fulfilled the inclusion criteria of the current systematic review. Table 1 lists the characteristics of the included studies. Among these seven RCTs, a total of 627 cardiovascular events, 251 other coronary

Table 1: Characteristics of the included studies

Study/author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Completion rate (%) (treatment/placebo)	Intention-to-treat described	Incomplete outcome data adequately addressed	Selective outcome reporting	Inclusion criteria	Treatment Group		
Ng <i>et al.</i> , 2011	Yes	Yes	No	No	68/82.6	Yes	Yes	No	>18 years with HIV	Advice on high fruit, vegetables, nuts, white meat, canola or olive oil as main cooking oil		
PREDIMED study, Estruch <i>et al.</i>	Yes	Yes	No	Yes	95.1/88.7	Yes	Yes	No	Male (80 years) and female (60-80 years) with type 2 DM or ≥3 major cardiac risk factor	Mediterranean diet+extra virgin olive oil; Mediterranean diet+nuts; both intervention groups received supplements		
Guasch-Ferré <i>et al.</i> , 2014	Yes	Yes	No	No	100/100	No	Yes	No	Male (80 years) and female (60-80 years) with type 2 DM or ≥3 major cardiac risk factor	Mediterranean diet + extra virgin olive oil; Mediterranean diet + nuts; both intervention groups received supplements		
Papadaki <i>et al.</i> , 2017	Yes	Yes	Yes	Yes	100/100	No	Yes	Yes	Male (80 years) and female (60-80 years) ≥3 CVD risk factors	Mediterranean diet + extra virgin olive oil; Mediterranean diet + nuts; both intervention groups received supplements		
Author	Control group	Setting	Duration of follow up (mean)	Total number of patients	Mean age (years)	Male n (%)	DM (%)	Primary or secondary prevention	Number of composite CV events [#]	Number of coronary events	Number of cerebrovascular events	Number of all-cause death
Ng <i>et al.</i> , 2011	Dietary advice according to NCEP guidelines	Single center Hong Kong	1 year	48	41	37 (77)	NR	Primary	NR	NR	NR	4
PREDIMED study, Estruch <i>et al.</i>	Low-fat control diet	Multicenter Spain	4.8 years (median)	7447	67	3165 (42.5)	3614 (48.5)	Primary	288	106	139	348
Guasch-Ferré <i>et al.</i> , 2014	Low-fat diet (control)	Multicenter	4.8 years (median)	7447	67	3071 (42.2)	NR	Primary	194	NR	NR	222
Papadaki <i>et al.</i> , 2017	Low-fat diet (control)	Multicenter	4.8 years (median)	7403	67	NR	NR	Primary	NR	52	NR	NR

[#]p<0.05. CVD: Cardiovascular disease; DM: Diabetes mellitus; NCEP: National Cholesterol Education Program; CV: Cardiovascular; NR: Not reported; PREDIMED: Prevention with Mediterranean Diet

events, and 887 total deaths were reported. The studies excluded from the systematic review were prospective cohort study and did not fulfill the criteria of comparison of dietary interventions on cardiovascular events. Figure 1 shows the literature survey and study selection processes made according to PRISMA guidelines.

RCTs included in the review had population size ranging from 48 to 7447 participants. Three of the included studies were multicenter PREDIMED trails and only one study was a pilot RCT. In all four studies, dietary interventions were given to the participants. Studies included in the review were conducted between 2000 and 2017. The mean age of all the participants was 67 years. In one study, only women were enrolled while other contained both genders. The quality of all the studies was assessed through Cochrane risk of selection bias tool. It was found that all the studies have randomized sequence generation and allocation concealment. Only one study had to blind participants, and two studies had been blinded by the outcome. The process of intention-to-treat analysis is described in two studies and all the studies adequately addressed incomplete outcome data.

Evaluating the impact of Mediterranean diet on cardiovascular health and death

Reported cardiovascular events

Two trials reported the impacts of the Mediterranean diet on the outcome related to cardiovascular events. In these two studies, the risk of cardiovascular disease is reduced by (RR 0.83, 95%

CI: 0.72–0.97, $P = 0.02$).^[13,16,17] However, these findings suggest a statistically significant relation and provide an evidence of Mediterranean diet reducing major cardiovascular events.

Reported cardiovascular deaths

Two studies reported cardiovascular deaths; however, the findings suggest that the death may not be associated with Mediterranean diet as the RR is not statistically significant (RR 1.03, 95% CI: 0.84–1.26, $P = 0.74$).^[13,16-18]

Reported all-cause death

All the four trials reported an all-cause death; there is no evidence which shows that Mediterranean diet has any impact on all-cause death in trials.^[13,16-20] The relations are statistically insignificant at $P = 0.77$, having RR 1.02 and 95% CI: 0.90–1.15. All these findings and forest plot is presented in Figure 2.

Discussion

The aim of this review was to determine the beneficial impact of Mediterranean diet such as olive oil on positive cardiovascular outcomes. The study was limited to RCTs and an intensive research revealed few studies, but most of the studies were excluded, as they did not meet the inclusion criteria. Therefore, this study contains only seven RCTs that have reported on cardiovascular outcomes based on dietary intervention of Mediterranean diet. Data in these studies were also limited and do not have any information on adverse effects. Therefore, it was difficult to maintain the balance of risk and benefits incurred by Mediterranean diet. However, the trails included in the review show a positive impact of Mediterranean diet on cardiovascular events and suggest that it reduces the risk of cardiovascular-related events.

There are a number of prospective cohort studies that reported a significant association between dietary intake of Mediterranean diet and reduction in all-cause mortality risk.^[21,22] In the current systematic review and meta-analysis, a statistically significant relation is found between Mediterranean diet and reduction in cardiovascular event at $P = 0.02$.^[13,16,17] These findings are supported by smaller RCTs which have reported the beneficial effects of Mediterranean diet on various vascular events.^[23,24] When these reviews are evaluated, it was found that systolic blood pressure reduces by 2.4 mmHg and diastolic blood pressure reduced by 1.6 mmHg. Moreover, Mediterranean diet also reduces low-density lipoprotein (LDL) cholesterol by 2.71 mg/dL, thereby reducing the risk of any adverse cardiovascular event.^[25]

However, most of the cohort studies and RCTs reporting intermediate outcomes of the Mediterranean diet have shown some beneficial impact of large estimates as reported by many individual RCTs included in the current systematic review. In addition to large estimates, some studies have also reported the antioxidant effects of Mediterranean diet making it a diet for every age group.^[26,27] Contrary to these findings, many of the large dietary intervention trails reported negative outcomes.^[28]

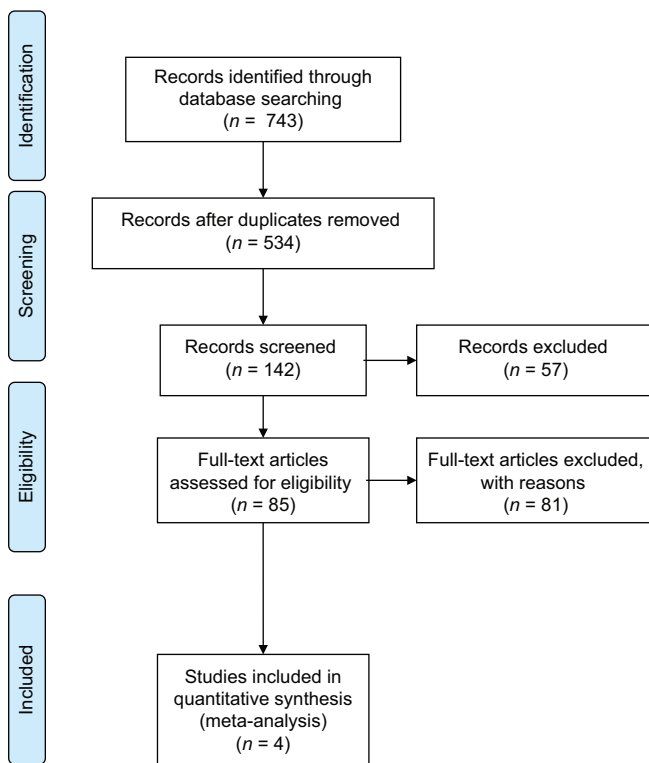


Figure 1: Flowchart of the systematic review and meta-analysis according to the preferred reporting items for systematic reviews and meta-analyze guidelines

Figure 2: Forest plot of meta-analysis

First author (year)	Forest plot	RR (95% CI) fixed effect	Treatment n/N	Control n/N	Weight (%)
Cardiovascular events					
Estruch <i>et al.</i> , 2013		0.81 (0.64-1.02)	179/4997	109/2450	53.9
Guasch-Ferre <i>et al.</i> , 2014		1.17 (0.91-1.50)	194/4811	83/2405	46.1
All trials, $P=0.41$		1.06 (0.771-1.47)	373/9808	192/4855	100
Cardiovascular deaths					
Estruch <i>et al.</i> , 2013		0.93 (0.60-1.45)	57/4997	30/2450	54.5
Guasch-Ferre <i>et al.</i> , 2014		1.26 (0.78-2.04)	58/4811	23/2405	45.5
All trials, $P=0.36$		1.07 (0.77-1.48)	115/9808	53/4855	100
All-cause death					
Estruch <i>et al.</i> , 2013		0.96 (0.77-1.20)	224/4997	114/2450	45.8
Guasch-Ferre <i>et al.</i> , 2014		1.10 (0.87-1.38)	222/4811	101/2405	40.4
Ng <i>et al.</i> , 2011		0.31 (0.03-2.74)	1/25	3/23	0.9
Papadaki <i>et al.</i> , 2017		0.80 (0.511-1.23)	52/4971	32/2432	12.9
All trials $P=0.41$		0.99 (0.85-1.15)	499/14804	250/7310	100

RR: Relative risk; CI: Confidence interval

Therefore, researchers raise a question about the validity of the claim made by some of the individual RCTs about significant beneficial effects of Mediterranean diet on cardiovascular outcomes. Moreover, data available for comparison are limited and do not provide the opportunity for comparative investigation of the impact of Mediterranean diet on cardiovascular events. One significant systematic errors associated with the poor result is the trial design of un-masking which provides differential outcomes in randomized groups.

This review provides a comprehensive and detailed systematic approach to obtain relevant trials that focus on important endpoints. However, it also faces a number of restrictions. The results of this review do not investigate the heterogeneity that exists between the individual studies, and the current analysis is limited to the published summaries of the RCT data. In these individual studies, heterogeneity seems to significantly affect the outcome of intervention due to several combinational factors which alter and the variation in follow-up time. Furthermore, significantly large benefit of the Mediterranean diet is reported in single-centered studies, but they also had an overestimation of beneficial outcomes. Another important shortcoming identified in these RCTs is the lack of data on adverse events. However, there are some studies that reported small beneficial impacts of Mediterranean diet on metabolic syndrome,^[11,29] blood cholesterol, LDL, triglyceride, and blood glucose.^[30] No such elements were reported in the current trails. Therefore, if researchers seek registration of the Mediterranean diet for any regulatory assessment programs, they need to come up with all the data to support their claim of the beneficial impact of the Mediterranean diet on the cardiovascular events.

Conclusion

Mediterranean diet is recommended by the American Heart Association/American College of Cardiology,^[31] the National Heart Foundation of Australia, and the European Society of Cardiology^[32] for patients with cardiovascular risk. These institutes recommend Mediterranean diet on the evidence of modest dietary effects on a

Mediterranean diet on reducing the risk of cardiovascular disease. However, the current RCTs do not provide definitive clinical outcomes of Mediterranean diet on the cardiovascular events. Therefore, this weakness of the current evidence requires further strong clinical research. To answer the question of plausibility of Mediterranean diet on cardiovascular events, researchers need to conduct an adequately powered trail with reliable data to document the beneficial impacts of Mediterranean diet.

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Conflicts of interest

There are no conflicts of interest.

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