Mediterranean Diet and Cardiovascular Disease Prevention: What do We Know?

Jordi Salas-Salvadó[a,b,c,d], Nerea Becerra-Tomás[a,b,c,d], Jesús Francisco García-Gavilán[a,b,c,d], Mònica Bulló[a,b,c,d] and Laura Barrubés [a,b,c].

[a]Rovira i Virgili University, Department of Biochemistry and Biotechnology, Human Nutrition Unit, Reus, Spain

[b]University Hospital of Sant Joan de Reus, Nutrition Unit, Reus, Spain

[c]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain

[d]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain

Short title: Mediterranean diet and cardiovascular disease

Corresponding authors: Prof. Jordi Salas-Salvadó, MD, PhD. Human Nutrition Unit, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili. C/ Sant Llorenç 21, 43201 Reus (Spain). Telephone number: +34977759312; Fax number: +34977759322; e-mail address: jordi.salas@urv.cat

Key words: Mediterranean diet; Cardiovascular disease; Coronary heart disease, Stroke, Myocardial infarction; Heart failure.

Word count: 2499 (excluding title page, abstract, references, figures and tables)

Number of Figures: 3 **Number of Tables**: 1

List of abbreviations: CHD, Coronary heart disease; CV, Cariovascular;CVDs, Cardiovascular diseases;HF, Heart failure;LDL-C, Low-density lipoprotein cholesterol; MedDiet, Mediterranean Diet;MI, Myocardial infarction; RCTs, Randomized clinical

trials; SCFA, Short-chain fatty acid; SFAs, Saturated fatty acids; TMAO, Trimethylamine N-Oxide.

Abstract

Cardiovascular disease (CVD) morbidity and mortality is increasing, representing an important public health issue worldwide. It is well-known that risk of CVD is substantially influenced by lifestyle, including poor diet, tobacco smoking and physical inactivity. In the last years, the so-called Mediterranean Diet (MedDiet) has been associated with broad healthy benefits on human health, including protection against CVD. The present narrative review aimed to summarize and discuss the evidence from meta-analyses of epidemiological and clinical trials analyzing MedDiet and CVD risk. The MedDiet is one of the best dietary patterns analyzed in relation to CVD risk and other health outcomes. Studies demonstrated that MedDiet has beneficial effects in the prevention of total and specific types of CVD, albeit a moderate-high degree of inconsistency has been reported and few studies have been included in most of the meta-analyses. As consequence, more high-quality prospective cohorts and randomized clinical trials are warranted in order to increase the confidence in the effect estimates.

Cardiovascular (CV) diseases (CVDs) are considered the predominant cause of mortality worldwide, accounting for a 31% of all global deaths in 2015 (1). Evidence so far suggests that CVDs are in highly measure preventable by tackling their well-known risk factors, such as increased blood pressure (BP) and plasma cholesterol levels, diabetes mellitus control, obesity, and unhealthy lifestyle (2). In this regard, epidemiological and randomized clinical trials (RCTs) have shown that changes in lifestyle, including a healthy dietary pattern, should be promoted for CVDs prevention (3). The so-called Mediterranean Diet (MedDiet), is one of the dietary patterns that has been in the spotlight of research during the last decades due to its broad healthy reported benefits. The purpose of the present review is to summarize the key findings from meta-analyses of epidemiological and clinical trials, regarding MedDiet and CVDs and its specific risk factors.

Mediterranean Diet: a Historical Perspective

The MedDiet refers to the traditional dietary pattern characteristic of populations bordering the Mediterranean Sea in the sixties. The term appeared in the mid of the last century with the pioneering landmark 7 countries study, conducted by Ancel Keys, which compared the dietary habits from different countries (United States, Japan, Finland, Netherlands, former Yugoslavia, Greece and Italy) in relation to the CVDs risk (4). The results showed a lower coronary heart disease (CHD) mortality rate in the Mediterranean countries. These findings were mainly explained by the low consumption of saturated fatty acids (SFAs) of these Mediterranean populations (5). Over the years, the definition of the MedDiet has changed from the original proposed by Keys. Nowadays, it can be described as a dietary pattern characterized by: a) olive oil as the main source of dietary fat; b) high intake of plant foods (vegetables, fruits, whole cereals, potatoes, legumes,

nuts and seeds); c) low to moderate amounts of animal foods (dairy products, fish, poultry, red meat and eggs); and d) wine in moderation within meals (6). Although this definition is broadly accepted, it is noteworthy that the MedDiet has variants depending on the characteristics of each Mediterranean population, which actually makes difficult to stablish a unique universal definition. Despite this limitation, different approaches to assess the adherence to this traditional dietary pattern, including *a priori* and *a posteriori* scores or even screener questionnaires, have been proposed based on the aforementioned definition. In epidemiological settings, the *a priori* score is the most-used method. The discussion of these different scores is out of the scope of the present review, and has been systematically and critically evaluated in detail elsewhere (7).

Mediterranean Diet and CVD Risk Factors

Several epidemiological and clinical trials have assessed the effect of MedDiet on recognized CVD risk factors, the findings of which have been summarized in different meta-analyses. The results from the most recent (**Table 1**), suggest that MedDiet adherence is not only inversely associated with the risk of diabetes (8) and metabolic syndrome (9) incidence, but also has beneficial effects on BP (10), triglycerides (10), low-density lipoprotein cholesterol (LDL-C) (11) and body weight (12). However, it is noteworthy that overall, a high degree of inconsistency in the results across studies was evident (I^2 ranging from 26% to 99.42%), which reduces the confidence in the effect estimates.

Mediterranean Diet and CVD Risk and Mortality

After the Keys et al., observation in relation to MedDiet and CVDs, many researchers have centered their efforts to study this association. Most of the scientific evidence comes from prospective cohort studies, while few randomized controlled trials (RCTS) have been conducted in this field. Importantly, several meta-analyses have summarized these

findings (**Figure 1 and Figure 2**), thereby providing the highest level of evidence in this topic.

Total CVD

Total CVD risk in relation with MedDiet adherence has been extensively investigated in the last years, which is reflected in the publication of seven meta-analyses of observational studies (13–19) since 2008. Overall, the results are in the same line demonstrating an inverse association between adherence to the MedDiet and the risk of total CVD. In the most recent meta-analysis of 11 prospective cohort studies (18), a 19% lower risk of total CVD was reported comparing highest versus lowest categories of adherence to the MedDiet (RR: 0.81; 95%CI: 0.74-0.88; I^2 = 79.9%). However, this meta-analysis did not include those studies evaluating only the association between the MedDiet and CHD or stroke risk because they were analyzed separately as specific outcomes. Nonetheless, these results were in line with a previous meta-analysis conducted by Grosso et al, that pooled 30 studies (also including those that had as outcome only fatal and/or non-fatal CHD and stroke), showing a 29% lower risk of total CVD comparing highest versus lowest adherence to the MedDiet (RR: 0.71; 95%CI: 0.65, 0.78; I^2 = 78%) (17). Recently, a cumulative meta-analysis of prospective cohort studies and RCTs reported a strong inverse association between adherence to the MedDiet and risk of mortality from, or incidence of cardiovascular disease (RR: 0.89; 95%CI: 0.86, 0.91; I^2 = 75.9%)(19). Although evidence so far from all the meta-analyses supports a beneficial association between MedDiet adherence and the risk of total CVD, it is noteworthy that the inter-study heterogeneity is moderate to high, ranging from 32.6% to 79.9% (**Figure 1**), which relatively reduces the overall confidence in the effect estimates. This heterogeneity could be explained by the inclusion in the meta-analyses of studies with diverse CVD outcomes. Instead of encompass only those studies evaluating a cluster

of different types of CVD events incidence and mortality, authors included in the meta-analyses a mix of studies analyzing either cause-specific CVD incidence (e.g. only CHD), or a combination of different types of CVD events incidence, or cause-specific CVD mortality (e.g. only fatal CHD), or a combination of different CVD mortality causes, or a composite of CVD incidence and mortality. Therefore a homogeneous definition of total CVD across meta-analyses would be imperative to reduce the heterogeneity between studies and make the results comparable.

CVD Incidence

Four meta-analyses (one of prospective cohort studies and 3 of clinical trials) have analyzed MedDiet and CVD incidence. Results from the observational studies meta-analysis (**Figure 1**) revealed a 27% lower risk of CVD incidence after comparing highest versus lowest categories of adherence to the MedDiet, with a lower to moderate inter-study heterogeneity (I^2 = 36%) (17). These results are in line with those from meta-analyses of clinical trials (**Figure 2**). In the most recent meta-analysis (17) including 4 clinical trials, results revealed that MedDiet reduced the risk of CVD incidence by a 45%, with a substantial inter-study heterogeneity (I^2 = 68%). However, it is important to highlight that the analysis included the GOSPEL study (20), which actually did not evaluate the MedDiet solely, because the intervention also included smoking cessation, physical activity promotion and stress management. Moreover, authors also included the Indo-Mediterranean Diet Heart trial, a study with low reliability due to concerns about the integrity of its data (21), which could affect the magnitude of the effect estimates because it contributes to a 25.5% of the total weight. Importantly, no sensitivity analysis excluding this study was performed. However, the results were consistent with those from a previous meta-analysis conducted by Liyanage et al., (22) where the GOSPEL study was not included and where the removing of the Indo-Mediterranean Diet Heart study

from the main analysis did not change the direction of the effect (RR: 0.69; 95%CI: 0.55, 0.86).

CVD Mortality

As far as we know one meta-analysis of prospective studies and two of clinical trials have evaluated the association between the MedDiet adherence and the risk of CVD mortality (17,22). The meta-analysis of epidemiological studies (17) included 16 comparisons and a 25% lower risk of CVD mortality was reported when comparing highest versus lowest categories of MedDiet adherence, with a high degree of inter-study heterogeneity (I^2 = 75%). These results are in line with those from the most recent meta-analysis of RCTs, where MedDiet interventions decreased CVD mortality risk by 41% after pooling findings from 4 RCTs (including the Indo-Mediterranean Diet Heart study (21) and the GOSPEL study (20)). However, a previous meta-analysis of RCTs (22) that did not include the GOSPEL study, revealed that MedDiet had not effect on CVD mortality compared to control diets (RR: 0.90; 95%CI: 0.72, 1.11) and, the results remained unchanged even after the exclusion of Singh et al., trial (22). However, a RCT in which the dietary intervention do not followed the actual definition of MedDiet (23) was included in this meta-analysis. Importantly, no sensitivity analysis was performed excluding this study, which represented a 42.8% of the total weight of the analysis, and could affect the direction and magnitude of the effect estimates because, although non-significant, the intervention group had a trend toward higher risk of CVD mortality compared to the control group.

CHD

Three meta-analyses have been published up-to-date evaluating the association between MedDiet and risk of CHD. Results from meta-analyses of observational studies (17,18) are consistent, showing a lower risk of CHD ranging from 28% to 30%, even taking into

account that one of them mixed results from cross-sectional and prospective studies (18). These findings are in line with those from a meta-analysis of RCTs, which demonstrated that the MedDiet reduced the risk of CHD by a 35% compared to control diets (22). It is noteworthy, that the exclusion of the Indo-Mediterranean Diet Heart study modified the effect estimates, becoming non-significant (RR: 0.73; 95%CI: 0.51, 1.05). Therefore, results regarding CHD should be interpreted with caution.

Stroke

Three meta-analyses of observational studies (17,18,24) and two of RCTs (17,22) have investigated the association between MedDiet adherence and the risk of stroke, reporting a beneficial effect on this specific type of CVD. Although meta-analyses of observational studies are heterogeneous in terms of the study design (**Figure 1**), results are consistent, showing a ~30% lower risk of stroke when comparing highest versus lowest categories of adherence to MedDiet, with a degree of inter-study heterogeneity ranging from 46.1% to 69.1%. These results have been confirmed by meta-analyses of clinical trials (**Figure 2**), albeit few and different studies were included in both analyses. According to the pooled effect estimates, MedDiet reduced the risk of stroke by a ~35%.

Myocardial Infarction(MI)

One meta-analysis of three prospective cohort studies assessed the relationship between MedDiet adherence and MI risk (17). An inverse association was reported between myocardial infarction and higher categories of MedDiet adherence compared to lower categories (RR: 0.67; 95%CI: 0.54, 0.83). These results were consistent with those from another meta-analysis of three clinical trials assessing the effect of the MedDiet on stroke risk (17). MedDiet, compared with control diets, reduced the risk of MI by a 40%, with a good consistency across the included studies (I^2 = 26%). Nonetheless, the analysis

included the Indo-Mediterranean Heart study (21) and the GOSPEL study (20), which decreases the confidence in the effect estimates.

Heart Failure (HF)

A meta-analysis of prospective cohort studies (25) reported that higher adherence to the MedDiet compared to a lower adherence was associated with 8% lower risk of HF, with no evidence of inter-study heterogeneity (I^2 = 0%). These results are in line with those from a meta-analysis of two RCTs, where the results showed that the MedDiet reduced the risk of HF by 70% (22). It is important to point out that the analysis included the Indo-Mediterranean Diet Heart study, and therefore the confidence in the estimates of effect is low.

Potential Mechanisms Implicated in CVD Prevention

In last decades, several studies have tried to identify potential mechanisms explaining the benefits of the MedDiet on CVD. In this sense, its high fiber content, the specific lipid profile (rich in monounsaturated fatty acids and polyunsaturated fatty acids) and its richness in other components such as polyphenols, with recognized antioxidant and anti-inflammatory properties, have been proposed as the main actors in the protection against CVD (10,26,27) through the modulation of its surrogates such as blood pressure, lipid profile, body weight and fasting blood glucose (**Figure 3**). It is recognized that the beneficial effects of the MedDiet can only be explained by the synergy between all the nutrient components included that can attenuate or exacerbate the deleterious or beneficial effects respectively produced by a single nutrient.

For example, legumes, nuts, fruits and vegetables are food sources of fiber, which contributes to improve CV health through the control of body weight and the long-term weight loss maintenance by lowering energy intake and triggering satiety cues (28). Moreover, fiber contributes to down-lowering cholesterol as demonstrated in a meta-

analysis of RCTs in which a 2-10 g/day increase in soluble fiber resulted in a significant decreases in LDL-C (29).

The abundance of plant-based foods and the moderate presence of animal products, favors a low saturated fat and high unsaturated fat content, which would contribute to improve the cardiometabolic risk factors by lowering LDL-C levels and ameliorating the oxidative stress and inflammation by limited content of heme groups that are related to oxidative reactions which damaged proteins and cell membrane lipids (27,30,31).

Some key foods of the Mediterranean diet, such as nuts, vegetables, fruits, olive oil and wine, are especially rich in antioxidant and anti-inflammatory components. Its consumption has been broadly associated with an improvement of several inflammatory and oxidant biomarkers (32–34). In this sense, some *in vitro* studies have shown that polyphenols such as resveratrol or hydroxytyrosol, exerts anti-oxidant and anti-inflammatory effects by scavenging and neutralizing free oxygen and nitrogen species, inhibiting platelet aggregation, reducing vascular inflammation and apoptotic processes, or protecting LDL against oxidation mediated by peroxynitrites (31,35,36).

The MedDiet is also rich in several vitamins (mainly E and C) and minerals (magnesium, and potassium), which have been associated with reductions in blood pressure, markers of inflammation and oxidation, and with improvements in endothelial function and insulin sensitivity (37–41).

Finally, MedDiet because of its richness in legumes, nuts, fruits and vegetables could modulate gut microbiota and influence the production of metabolites thereof, affecting CVD risk. For instance, it has been reported that adherence to the MedDiet is associated with an increase fecal short chain fatty acids (SCFA) levels and reduced levels of urinary trimethylamine–N-oxide (TMAO) (42). SFCA could protect against CVD because it has been reported that increase fatty acid oxidation, and decrease in the liver the novo fatty

acid synthesis and plasma glucose and cholesterol levels (43). Contrary, TMAO has been associated to a higher risk of CVD. Despite mechanisms are not well understood, TMAO seems to directly influence macrophages to accumulate cholesterol and form foam cells and also contributes to modifies cholesterol and sterol metabolism (44).

Conclusion

The MedDiet is probably one of the best-studied dietary patterns in relation to CVDs prevention, which is reflected in the large amount of meta-analyses published in this field. As illustrated in the present review, it has been proven by several meta-analyses that MedDiet exerts a beneficial role in CVD prevention. However, the moderate to high inter-study heterogeneity observed across most of the different types of CVD outcomes and the inclusion of few studies in some of the meta-analyses, confirms the need for more high-quality prospective cohorts and RCTs to provide more reliable results from which evidence-based recommendations could be drawn. Although MedDiet is the dietary pattern with more scientific evidence in terms of CVD prevention, future RCTs demonstrating that MedDiet could be achievable in other non-Mediterranean countries are warranted in order to demonstrate the transferability of the MedDiet recommendations.

Acknowledgements: This work has been supported in part by the Spanish Ministry of Health (Carlos III Health Institute) through the Fondo de Investigación para la Salud (FIS), which is co-funded by the European Regional Development Fund. Laura Barrubés-Piñol has been granted by the Ministry of Education, Culture and Sports of Spain (FPU 16/00165).

Author Contributions: JS-S, NB-T, JF.G-G, MB and LB-P designed the review; NB-T, JF.G-G and LB-P performed the literature research; JS-S, NB-T, JF.G-G, MB and LB-P wrote the manuscript; all authors approved the final version of the manuscript.

Conflicts of interest: Nerea Becerra-Tomás, Jesús F. García-Gavilán, Mònica Bulló and Laura Barrubés-Piñol have nothing to declare. Jordi Salas-Salvadó is a nonpaid member of the Scientific Advisory Council of the International Nut Council (INC). Jordi Salas-Salvadó is member of the Executive Committee of the Instituto Danone Spain and his institution received grants from Danone SA and INC.

References

1. World Health Organization. WHO | Cardiovascular diseases (CVDs) [Internet]. World Health Organization; 2017 [cited 2017 Apr 28]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/
2. Joseph P, Leong D, McKee M, Anand SS, Schwalm J-D, Teo K, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res. 2017 Sep 1;121(6):677–94.
3. Bowen KJ, Sullivan VK, Kris-Etherton PM, Petersen KS. Nutrition and Cardiovascular Disease—an Update. Curr Atheroscler Rep. 2018 Feb;20(2):8.
4. Keys A, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, et al. Seven Countries A Multivariate Analysis of Death and Coronary Heart Disease. Harvard University Press; 1980.
5. Keys A, Mienotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. Am J Epidemiol. 1986 Dec 1;124(6):903–15.
6. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995 Jun 1;61(6):1402S–1406S.
7. D'Alessandro A, De Pergola G. Mediterranean Diet and Cardiovascular Disease: A Critical Evaluation of A Priori Dietary Indexes. Nutrients. 2015 Sep 16;7(9):7863–88.
8. Jannasch F, Kr?ger J, Schulze MB. Dietary Patterns and Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Prospective Studies. J Nutr. 2017 Jun 1;147(6):1174–82.
9. Godos J, Zappalà G, Bernardini S, Giambini I, Bes-Rastrollo M, Martinez-

Gonzalez M. Adherence to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of observational studies. Int J Food Sci Nutr. 2017 Mar 17;68(2):138–48.

10. Garcia M, Bihuniak JD, Shook J, Kenny A, Kerstetter J, Huedo-Medina TB. The Effect of the Traditional Mediterranean-Style Diet on Metabolic Risk Factors: A Meta-Analysis. Nutrients. 2016 Mar 15;8(3):168.
11. Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, et al. "Mediterranean" dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013 Aug 12;(8):CD009825.
12. Esposito K, Kastorini C-M, Panagiotakos DB, Giugliano D. Mediterranean Diet and Weight Loss: Meta-Analysis of Randomized Controlled Trials. Metab Syndr Relat Disord. 2011 Feb;9(1):1–12.
13. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008 Sep 11;337:a1344.
14. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010 Nov 1;92(5):1189–96.
15. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014 Dec 29;17(12):2769–82.
16. Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. Curr Opin Lipidol. 2014 Feb;25(1):20–6.
17. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? Crit Rev Food Sci

Nutr. 2017 Oct 13;57(15):3218–32.

18. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2017 Nov 25;

19. Martínez-González MÁ, Hershey MS, Zazpe I, Trichopoulou A. Transferability of the Mediterranean Diet to Non-Mediterranean Countries. What Is and What Is Not the Mediterranean Diet. Nutrients. 2017 Nov 8;9(11):1226.

20. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni A Pietro, Balestroni G, Ceci V, et al. Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction. Arch Intern Med. 2008 Nov 10;168(20):2194.

21. Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet. 2002 Nov 9;360(9344):1455–61.

22. Liyanage T, Ninomiya T, Wang A, Neal B, Jun M, Wong MG, et al. Effects of the Mediterranean Diet on Cardiovascular Outcomes-A Systematic Review and Meta-Analysis. Wright JM, editor. PLoS One. 2016 Aug 10;11(8):e0159252.

23. Burr ML, Ashfield-Watt PAL, Dunstan FDJ, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr. 2003 Feb 6;57(2):193–200.

24. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol. 2013 Oct;74(4):580–91.

25. Papadaki A, Martínez-González MÁ, Alonso-Gómez A, Rekondo J, Salas-Salvadó J, Corella D, et al. Mediterranean diet and risk of heart failure: results

from the PREDIMED randomized controlled trial. Eur J Heart Fail. 2017 Sep;19(9):1179–85.

26. Kastorini C-M, Panagiotakos DB, Chrysohoou C, Georgousopoulou E, Pitaraki E, Puddu PE, et al. Metabolic syndrome, adherence to the Mediterranean diet and 10-year cardiovascular disease incidence: The ATTICA study. Atherosclerosis. 2016 Mar;246:87–93.

27. Huo R, Du T, Xu Y, Xu W, Chen X, Sun K, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. Eur J Clin Nutr [Internet]. 2015 Nov 5 [cited 2018 Feb 19];69(11):1200–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25369829

28. Wanders AJ, van den Borne JJGC, de Graaf C, Hulshof T, Jonathan MC, Kristensen M, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. Obes Rev. 2011 Jul 1;12(9):no-no.

29. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr. 1999 Jan 1;69(1):30–42.

30. Kim K, Hyeon J, Lee SA, Kwon SO, Lee H, Keum N, et al. Role of Total, Red, Processed, and White Meat Consumption in Stroke Incidence and Mortality: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. J Am Heart Assoc. 2017 Aug;6(9):e005983.

31. Annuzzi G, Bozzetto L, Costabile G, Giacco R, Mangione A, Anniballi G, et al. Diets naturally rich in polyphenols improve fasting and postprandial dyslipidemia and reduce oxidative stress: a randomized controlled trial. Am J Clin Nutr. 2014 Mar;99(3):463–71.

32. Razquin C, Martinez JA, Martinez-Gonzalez MA, Mitjavila MT, Estruch R, Marti A. A 3 years follow-up of a Mediterranean diet rich in virgin olive oil is associated with high plasma antioxidant capacity and reduced body weight gain. Eur J Clin Nutr. 2009 Dec 26;63(12):1387–93.

33. Mena M-P, Sacanella E, Vazquez-Agell M, Morales M, Fitó M, Escoda R, et al. Inhibition of circulating immune cell activation: a molecular antiinflammatory effect of the Mediterranean diet. Am J Clin Nutr. 2009 Jan 1;89(1):248–56.

34. Zhu F, Du B, Xu B. Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review. Crit Rev Food Sci Nutr. 2017 Jun 12;1–11.

35. Tangney CC, Rasmussen HE. Polyphenols, inflammation, and cardiovascular disease. Curr Atheroscler Rep. 2013 May;15(5):324.

36. Yamagata K, Tagami M, Yamori Y. Dietary polyphenols regulate endothelial function and prevent cardiovascular disease. Nutrition. 2015 Jan;31(1):28–37.

37. Saremi A, Arora R. Vitamin E and Cardiovascular Disease. Am J Ther. 2010 May;17(3):e56–65.

38. Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G, Lefebvre PJ. Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications? Diabetes Care. 1991 Jan;14(1):68–72.

39. Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee J-H, et al. Vitamin C as an Antioxidant: Evaluation of Its Role in Disease Prevention. J Am Coll Nutr. 2003 Feb;22(1):18–35.

40. Rosique-Esteban N, Guasch-Ferré M, Hernández-Alonso P, Salas-Salvadó J. Dietary Magnesium and Cardiovascular Disease: A Review with Emphasis in Epidemiological Studies. Nutrients [Internet]. 2018 Feb 1 [cited 2018 Feb

23];10(2):168. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29389872

41. Aaron KJ, Sanders PW. Role of Dietary Salt and Potassium Intake in Cardiovascular Health and Disease: A Review of the Evidence. Mayo Clin Proc. 2013 Sep;88(9):987–95.

42. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut. 2016 Nov;65(11):1812–21.

43. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud D-J, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013 Sep;54(9):2325–40.

44. Tang WHW, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk. N Engl J Med. 2013 Apr 25;368(17):1575–84.

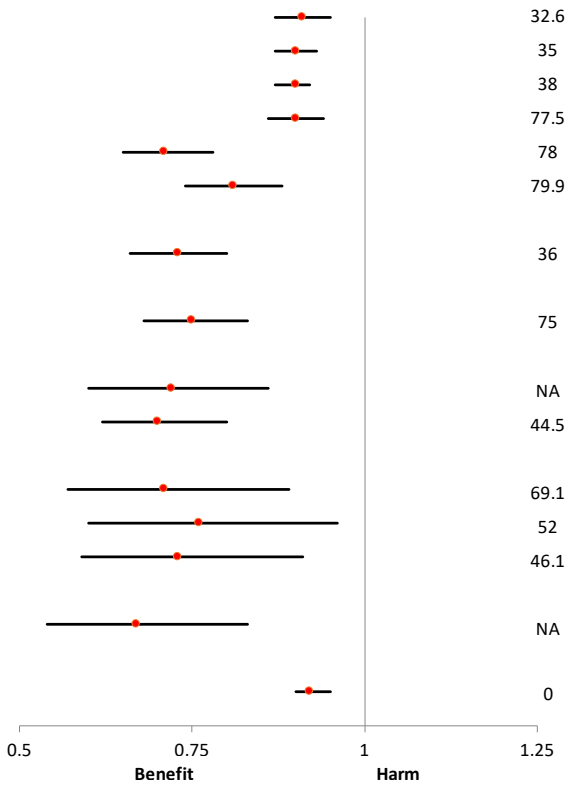
Table 1. Summary of the most recent meta-analyses of prospective cohorts studies and randomized clinical trials on Mediterranean diet and cardiovascular risk factors*

Outcome	Effect size	Number of studies	Pooled effect size and 95%CI	I^2 (%)
Meta-analyses of cohort studies				
Diabetes (8)	Relative risk	6	0.87 (0.82, 0.93)	26.0
Metabolic syndrome (9)	Relative risk	4	0.73 (0.54, 0.98)	69.0
Meta-analyses of randomized clinical trials				
Fating blood glucose (10)	Mean difference	23	-0.50 (-0.81, -0.20)	96.7
Systolic blood pressure (10)	Mean difference	25	-0.72 (-1.03, -0.42)	97.0
Diastolic blood pressure (10)	Mean difference	25	-0.94 (-1.45, -0.44)	99.4
HDL-c (10)	Mean difference	27	0.19 (-0.07, 0.46)	94.0
Triglycerides (10)	Mean difference	25	-0.46 (-0.72, -0.21)	93.7
LDL-c (11)	Mean difference	6	-0.07 (-0.13, -0.01)	22.0
Waist circumference(10)	Mean difference	39	-0.54 (0.77, -0.31)	96.4
Body weight (12)	Mean difference	19	-1.75 (-2.86, -0.64)	94.9

*Meta-analyses including studies conducted in specific populations (e.g. only diabetic patients) were not considered.

Figure 1. Summary of meta-analyses of observational studies on Mediterranean Diet adherence and cardiovascular disease outcomes.

CVD outcomes	No. of studies	Pooled RR [95% CI]	RR and 95%CI	Residual I^2 [%]
Total CVD[¥]				
Sofi et al 2008 (12)	4	0.91 [0.87, 0.95]		32.6
Sofi et al 2010 (13)	8	0.90 [0.87, 0.93]		35
Sofi et al 2013 (14)	20	0.90 [0.87, 0.92]		38
Martínez-González et al 2014 (15)	16	0.90 [0.86, 0.94]		77.5
Grosso et al 2017 (16)	30	0.71 [0.65, 0.78]		78
Rosato et al 2017 (17)	11	0.81 [0.74, 0.88]		79.9
CVD incidence[§]				
Grosso et al 2017 (16)	14	0.73 [0.66, 0.80]		36
CVD mortality*				
Grosso et al 2017 (16)	16	0.75 [0.68, 0.83]		75
Coronary heart disease				
Grosso et al 2017 (16)	4	0.72 [0.60, 0.86]		NA
Rosato et al 2017[†] (17)	11	0.70 [0.62, 0.80]		44.5
Stroke				
Psaltopoulou et al 2013[‡] (23)	12	0.71 [0.57, 0.89]		69.1
Grosso et al 2017 (16)	5	0.76 [0.60, 0.96]		52
Rosato et al 2017[†] (17)	6	0.73 [0.59, 0.91]		46.1
Mycoardial infarction				
Grosso et al 2017 (16)	3	0.67 [0.54, 0.83]		NA
Heart failure				
Papadaki et al 2017 (24)	3	0.92 [0.90, 0.95]		0



[¥]Includes a mix of studies analyzing either: a) cause-specific cardiovascular disease event incidence (e.g. only coronary heart disease); or b) a combination of different types of cardiovascular disease events incidence; or c) a cause-specific cardiovascular disease mortality (e.g. only fatal coronary heart disease); or d) a combination of different cardiovascular disease mortality causes; or e) a composite of incidence and mortality from cardiovascular disease.

[§]Includes studies analyzing either: a) cause-specific cardiovascular disease event incidence (e.g. coronary heart disease); or b) a combination of different types of cardiovascular disease events incidence; or c) a composite of incidence and mortality from cardiovascular disease.

*Includes studies analyzing either: a) cause-specific cardiovascular disease mortality (e.g. fatal coronary heart disease); or b) a combination of different cardiovascular disease mortality causes.

All meta-analyses included only prospective cohort studies, unless otherwise indicated.

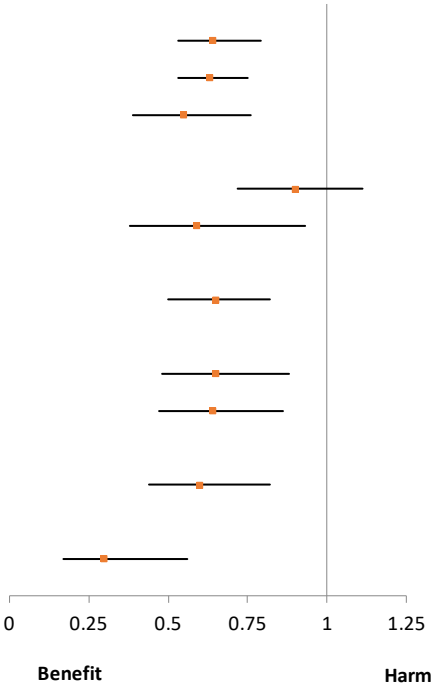
†Includes prospective and cross-sectional studies

‡Includes prospective and case-control studies

Abbreviations: CVD, cardiovascular disease; RR, Relative Risk; NA, non-available.

Figure 2. Summary of meta-analyses of clinical trials on Mediterranean Diet adherence and cardiovascular disease outcomes

CVD outcomes	No. of Trials	Pooled RR [95% CI]	RR and 95%CI	Residual I^2 [%]
CVD incidence[¥]				
Martínez-González et al 2014 (15)	2	0.64 [0.53, 0.79]		54.5
Liyanage et al 2016 (21)	3	0.63 [0.53, 0.75]		NA
Grosso et al 2017 (16)	4	0.55 [0.39, 0.76]		68
CVD mortality[§]				
Liyanage et al 2016 (21)	4	0.90 [0.72, 1.11]		NA
Grosso et al 2017 (16)	4	0.59 [0.38, 0.93]		75
Coronary heart disease				
Liyanage et al 2016 (21)	3	0.65 [0.50, 0.85]		NA
Stroke				
Liyanage et al 2016 (21)	3	0.65 [0.48, 0.88]		NA
Grosso et al 2017 (16)	2	0.64 [0.47, 0.86]		0
Mycoardial infarction				
Grosso et al 2017 (16)	3	0.60 [0.44, 0.82]		26
Heart failure				
Liyanage et al 2016 (21)	2	0.30 [0.17, 0.56]		NA

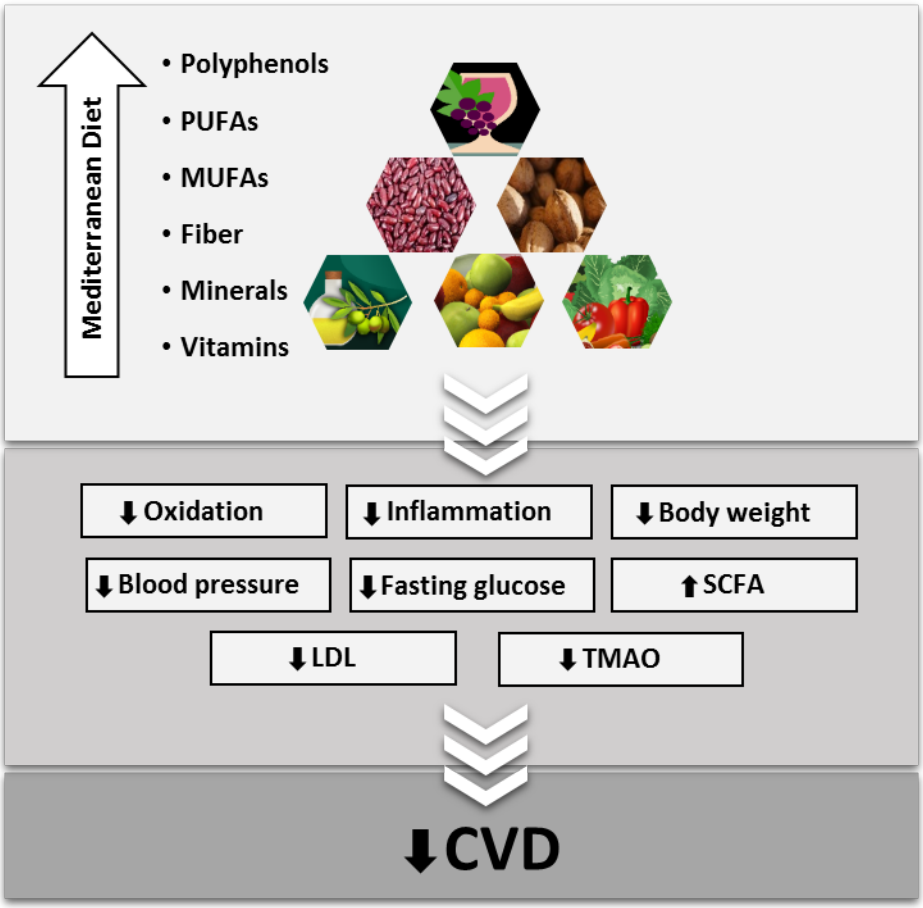


[§]Includes studies analyzing a composite of incidence of and mortality from cardiovascular disease

*Includes studies analyzing a combination of different cardiovascular disease mortality causes.

Abbreviations: CVD, cardiovascular disease; RR, Relative Risk; NA, non-available.

Figure 3. Potential mechanisms by which Mediterranean diet could protect against cardiovascular disease



Abbreviations: MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SCFA, short-chain fatty acids; TMAO, Trimethylamine N-oxide.

In this figure we represent in the upper part some Mediterranean diet nutrients implicated in the beneficial effects of this dietary pattern on cardiovascular disease. Most of these nutrients are present especially in plant-based diets and act synergistically. Mediterranean diet also refrains from animal nutrient sources and is low in processed food rich in salt, saturated and trans fatty acids, sugar, iron and other nutrients that have demonstrated detrimental effects on the mechanisms implicated in the atherogenesis processes (some of them represented in the bottom part of the figure).