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Discovery

Mediterranean diet and cardiovascular disease: a clinical review

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ABSTRACT

Cardiovascular diseases, especially coronary heart disease, remain the number one killer all over the world. It is also a leading cause of disability and financial burden. Although great strides have been made in its treatment, both pharmacological and surgical, preventive therapies have only recently garnered scientific interest. A plant based diet appears to be significantly cardio-protective. Traditional Mediterranean diet (MeD), followed by people living in the Mediterranean basin, has also been noted in epidemiological studies to be associated with a lower incidence of cardiovascular diseases. It is predominantly plant based. A host of recent prospective scientific studies have confirmed this beneficial cardiovascular connection. MeD is effective in preventing cardiovascular disease.

Key words: Mediterranean diet, cardiovascular disease, plant based diet, coronary artery disease, cardiovascular mortality.

1. INTRODUCTION

People living in the olive growing regions of the Mediterranean basin follow a diet that is high in monounsaturated fats; ethanol (predominantly wine) consumption at low to moderate levels; high consumption of vegetables, fruits, nuts, seeds, legumes, and grains; moderate consumption of milk and dairy products, mostly in the form of cheese; high intake of olive oil, more sourdough bread rather than pasta, low to moderate amounts of fish and poultry, eggs zero to four times a week and low consumption of red meat and meat products (Trichopoulou et al, 1997; Farah, 2008; Neil K Agarwal, 2014a & 2014b; Shashi K Agarwal 2014). This diet is low in saturated fat (< or = 7-8% of energy), with a high monounsaturated/saturated fat ratio and with total fat ranging from < 25% to > 35% of energy (Willett et al, 1995). The diet is usually consumed in a fixed number of meals, with a post lunch siesta and timings later during the day when compared to eating patterns for the rest of the Europeans (Bellisle, 2009). It was essentially a frugal diet, followed by the poor families and poor societies, especially in Crete, but also in much of the rest of Greece and Southern Italy (Willet et al, 1996; Bach-Faig et al, 2011).

The Traditional Mediterranean diet (MeD) has been linked with several health benefits, (Serra-Majem et al, 2006) including a decreased incidence of adult onset diabetes mellitus (Rossi et al, 2013) several cancers (Benetou et al, 2008; Trichopoulou et al, 2010; Couto et al, 2011; Bamia et al, 2013) and hip fractures, (Benetou et al, 2013) and all-cause mortality (Tognon et al, 2012). The most exciting beneficial association has been with cardiovascular diseases, (Dontas et al, 2007; Rees et al, 2013) including the incidence of (Mente et al, 2009) and survival from (de Lorgeril et al, 1994) coronary heart disease, and thrombotic stroke (Misirli et al, 2012). There is also a reduction in cardiovascular mortality (Tong et al, 2016).

2. METHODS

A comprehensive literature search was carried out using the PubMed and PubMed Central database of the US National Library of Medicine, National Institutes of Health, on 'Mediterranean diet and cardiovascular diseases'. Other contemporary and complementary medicine databases (including Medline, Google Scholar, and Quertile) databases were also queried and relevant publications were consulted. Available scientific grey material was also reviewed. Only English language literature was reviewed.

3. RESULTS

When queried under 'Mediterranean diet and cardiovascular diseases', PubMed revealed 1696 citations dating back to 1970 while PMC revealed 6217 full length publications.

4. DISCUSSION

Cardiovascular diseases (CVD's) continue to claim the dubious distinction of being the number one killer in the world, resulting in 17.5 million deaths in 2013 (Heart.org, 2017). Its global death impact is expected to grow to more than 23.6 million deaths by the year 2030. CVD's include coronary artery disease, heart failure, stroke, cardiac arrhythmias and peripheral vascular disease. CVD's are also a leading cause of disability throughout the world, and exert extensive emotional and financial burden on individuals, families, societies and states (Gaziano, 2007). The major risk factors for CVD's are well known (Fryar et al, 2012), and include hypertension (Kearney et al, 2005), diabetes mellitus (Ferrannini et al, 2012), hypercholesterolemia (CTT, 2008), obesity (Marie et al, 2014), smoking (Mons et al, 2005), stress and anxiety (Lichtman et al, 2008), inactivity (Hakim et al, 1999), and an imprudent diet (Lichtenstein et al, 2006). Several systematic reviews and meta-analyses have shown that Mediterranean diet is a heart friendly diet and effective in reducing the risk of cardiovascular disease (de Lorgeril et al,1999;Singh et al, 2002; Marita et al, 2005;Sofi et al, 2010; Sofi et al, 2014) And it is cost effective (Saulle et al, 2013).

A proper diet plays an important role in the avoidance of several chronic diseases (Simopoulos et al, 1995), including obesity, cardiovascular diseases; diabetes mellitus, and cancer (WHO, 2006). However, with industrialization, diet has become unhealthy with an increase in energy intake but a decrease in energy expenditure, an increase in protein and saturated fats, n-6 fatty acids and trans fatty acids, a decrease grains, fruits and vegetables, a decrease in n-3 fatty acids, protein and complex carbohydrates, including fiber. The modern diet is also low in calcium, phytochemicals and antioxidants. The MeD resembles the Paleolithic diet in terms of its ingredients, especiallywhen it comes to the ratio of (n-6) to (n-3) fatty acids. (de Lonrgeril et al, 1994; Singh et al, 1992). The diet of

Crete and most of Greece or the MeD is thus more in concert with the evolutionary past of humans, and has repeatedly been proven to bebeneficial for our cardiovascular system.

4.1. Mediterranean diet and hypertension.

Studies indicate that MeD may help prevent the development of hypertension (Abellan et al, 2016), reduce both systolic and diastolic blood pressure (Ndanuko et al, 2016), and help in its control (Toledo et al, 2013).

4.2. Mediterranean diet and diabetes mellitus

Several studies have shown that MeD is good for diabetic patients, leading to a better glycemic control, higher rates of diabetes remission, delayed need for diabetes medication, reduction in cardiovascular risk factors and in improving the quality of life of these patients (Toobert et al, 2003; Elhayany et al, 2010; Esposito et al, 2014; Huo et al, 2014). MeD is preventive for DM (Martinez-Gonzalez et al, 2008; Salas-Salvado et al, 2014). Metabolic syndrome is a prediabetic state (Stern et al, 2004; Lorenzo et al, 2007) and MeD is associated with reduced risk of developing metabolic syndrome ranging from 15% to 80% (Tortosa et al, 2007; Rumawas et al, 2009; Kesse-Goyot et al, 2013). MeD, as compared with control diets, may reduce HbA1c levels by 0.30–0.47%, (Esposito et al, 2015).

4.3. Mediterranean diet and obesity

Several facets of obesity are positively improved by MeD (Mendez et al, 2006; Beunza et al, 2010; Romaguera et al, 2010). There is a decrease in abdominal obesity (Romaguera et al, 2009). Several other studies have confirmed a similar negative relationship between adherence to MeD and overweight/obesity (Shubair et al, 2005; Lazarou et al, 2010; Schroder et al, 2004; Panagiotakos et al, 2006; Panagiotakos et al, 2007).

4.4. Mediterranean diet and lipids

MeD is associated with beneficial effects on the lipids as evidenced by decreased amount of cellular lipid levels and oxidized LDL (Fito et al, 2007). Virgin olive oil helps improve the HDL related atherosclerotic protection (Hernáezet al, 2017).

4.5. Mediterranean diet and Metabolic Syndrome

Several studies indicate an improvement in the metabolic syndrome with MeD (Kastonini et al, 2011).

4.6. Mediterranean diet and coronary heart disease

A host of studies on the primary prevention of CVD's show a statistically significant association between the MedDiet pattern and the incidence of CVD's (Gardener et al, 2011; Fung et al, 2009; Knoops et al, 2004; Trichopoulou et al, 2003; Estruch et al, 2013; Buchland et al, 2009; Panagiotakos et al, 2007; Martínez-González et al, 2011; Menotti et al, 2012; Guallar-Castillón et al, 2012). Addition of extra-virgin olive oil or mixed nuts to the MeD reduced the cardiovascular events by 30% (Estruch et al, 2013). Moreover, an inverse association with greater adherence to MeD was observed for deaths related to coronary heart disease (Tripochoulou et al, 2003; Knoops et al, 2004; Fung et al, 2009; Gardener et al, 2011). There was a coronary heart disease mortality reduction of 26% at 20 years and 22% reduction at 40 years in individuals with a higher adherence to the MeD in Italy (Menotti et al, 2012).

4.7. Mediterranean diet and heart failure

Heart failure biomarkers improve with MeD as evidenced by a reduction in the N-terminal pro-brain natriuretic peptide (Fito et al, 2014).

4.8. Mediterranean diet and stroke

MeD is associated with a lower risk of stroke (Fung et al, 2009).

4.9. Mediterranean diet and peripheral vascular disease

A beneficial effect has also been recognized in patients with peripheral vascular disease (Ruiz-Canela et al, 2014).

4.10. Mediterranean diet and cardiovascular mortality

The beneficial effects of MeD on cardiovascular risk factors and cardiovascular diseases also translates into a reduced cardiovascular mortality (Knoops et al, 2004; Hodge et al, 2011; Stefler et al, 2015;Tong et al, 2016).

4.11. Mediterranean diet and other illnesses

MeD is a healthy diet and its benefits extend beyond those stemming from a reduction in cardiovascular diseases and cardiovascular mortality. These include several cancers (Couto et al, 2011) including gastric, colorectal and those involving the breast (Buckland et al, 2013). There is an improvement in depression, (Psaltopoulou et al, 2013; Sanchez-Villegas et al, 2013;Lai et al, 2014; Singh et al, 2014) and cognitive impairment (Lourida et al, 2013; Estruch et al, 2013; Wu et al, 2017). There is an improvement of bone mineral density (Rivas et al, 2013; Chen et al, 2016) and a reduction in hip fractures (Benetou et al, 2013).

4.12. Mediterranean diet and all-cause mortality

Besides cardiovascular related deaths, all-cause mortality is also decreased in patients adhering to MeD (Knoops et al, 2004; Sofi et al, 2014; Tognon et al, 2012). Mediterranean diet in the Greek EPIC cohort (as reflected in the apparent reduction of total mortality), high consumption of plant foods accounted for 37.2% of the reduction (vegetables 16.2%, fruits and nuts 11.3%, legumes 9.7%), moderate alcohol intake, as contrasted to high or none for 23.5% of the reduction, whereas low meat intake accounted for 16.6% and olive oil (as reflected in the monounsaturated-to-saturated ratio) for 10.6% (Trichopoulou et al, 2009).

5. MECHANISMS

Plant based diets are rich in polyphenols, which reduce atherogenesis by positively affecting LDL oxidation, nitric oxide release, vascular inflammation, oxidative stress, cell adhesion, foam cell formation, smooth muscle cell proliferation, and platelet adhesion and aggregation (Vita, 2005; Ginter et al, 2012). Alcohol in MeD is wine, and the latter provides better cardiovascular protection because its high contents of of compounds such as reservaratol (Gronbaek et al, 2002). Red and processed meats are heart unhealthy. They lead to higher concentrations of total serum cholesterol, low-density-lipoprotein cholesterol, and triglycerides (Slattery et al, 1991). Processed meats are higher in dietary sodium, nitrates and phosphates (Kaluza et al, 2014). The benefits from olive oil are related to their high monounsaturated fatty acid content (Schwingshackl et al, 2014). Many other mechanisms are also contributive. Studies have documented an improvement in cardiovascular markers in patients adhering to the MeD (Fito et al, 2016).

6. CONCLUSIONS

The evidence regarding the protective effect of MeD against cardiovascular diseases, both in primary and secondary prevention, has been proven by several randomized controlled trials, observational studies, and meta-analyses. MeD diet is primarily a plant based diet, with only low intake of red meat. Its cardioprotective benefits accrue from its positive effects on lipid profile, endothelial function, vascular inflammation, and insulin resistance. With the increasing worldwide prevalence of cardiovascular disease, dietary incorporation and subsequent adherenceto the MeD, can greatly help in curbing this number one killer in the world.

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CONFLICT OF INTEREST

None

REFERENCE

1. AbellánAlemán J, ZafrillaRentero MP, Montoro-García S, et al. Adherence to the "Mediterranean Diet" in Spain and Its Relationship with Cardiovascular Risk (DIMERICA Study). Nutrients. 2016 Oct 28;8(11). pii: E680.
2. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, Medina FX, Battino M, Belahsen R, Miranda G, Serra-Majem L, Mediterranean Diet Foundation Expert Group Mediterranean diet pyramid today. Public Health Nutr. 2011; 14:2274–2284. doi: 10.1017/S1368980011002515.
3. Bamia C, Lagiou P, Buckland G, et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemiol. 2013;28:317–328. doi: 10.1007/s10654-013-9795-x.
4. Bellisle F. Infrequently asked questions about the Mediterranean diet. Public Health Nutr. 2009 Sep;12(9A):1644-7. doi: 10.1017/S1368980009990498.
5. Benetou V, Orfanos, P, Pettersson-Kymmer U, et al. Mediterranean diet and incidence of hip fractures in a European cohort. Osteoporos Int. 2013;24:1587–1598. doi: 10.1007/s00198-012-2187-3.

6. Benetou V, Trichopoulou A, Orfanos P, et al. Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. Br J Cancer. 2008;99:191–195. doi: 10.1038/sj.bjc.6604418.
7. Beunza J.J., Toledo E., Hu F.B., Bes-Rastrollo M., Serrano-Martínez M., Sánchez-Villegas A., Martínez J.A., Martínez-González M.A. Adherence to the Mediterranean diet, long-term weight change, and incident overweight or obesity: The Seguimiento Universidad de Navarra (SUN) cohort. Am. J. Clin. Nutr. 2010;92:1484–1493. doi: 10.3945/ajcn.2010.29764.
8. Buckland G., González C.A., Agudo A., et al. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. Am. J. Epidemiol. 2009;170:1518–1529. doi: 10.1093/aje/kwp282.
9. Buckland G, Travier N, Cottet V, et al. Adherence to the mediterranean diet and risk of breast cancer in the European prospective investigation into cancer and nutrition cohort study. Int J Cancer. 2013;132:2918–2927. doi: 10.1002/ijc.27958.
10. Chen G, Dong X, Zhu Y-Y, Tian H, He J, Chen Y. Adherence to the Mediterranean diet is associated with a higher BMD in middle-aged and elderly Chinese. Scientific Reports. 2016;6:25662. doi:10.1038/srep25662.
11. Couto E, Boffetta P, Lagiou P, et al. Mediterranean dietary pattern and cancer risk in the EPIC cohort. Br J Cancer. 2011;104:1493–1499. doi: 10.1038/bjc.2011.106.
12. CTT: Cholesterol Treatment Trialists' (CTT) Collaborators Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371(9607):117-125.
13. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994;343:1454–1459. doi: 10.1016/S0140-6736(94)92580-1.
14. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999;99:779-785.
15. Dontas S.A., Zerefos N.S., Panagiotakos D.B., Valis D.A. Mediterranean diet and prevention of coronary heart disease in the elderly. Clin. Interv. Aging. 2007;2:109–115. doi: 10.2147/ciia.2007.2.1.109.
16. Elhayany A, Lustman A, Abel R et al. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus. A one year prospective randomized intervention study. Diabetes ObesMetab 2010;12:204–9. doi:10.1111/j.1463-1326.2009.01151.x .
17. Esposito K, Maiorino MI, Petrizzo M et al. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. Diabetes Care 2014;37:1824–30.
18. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open. 2015;5(8):e008222. doi:10.1136/bmjopen-2015-008222.
19. Estruch R., Ros E., Salas-Salvadó J., et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N. Engl. J. Med. 2013;368:1279–1290.
20. Farah R, Glick Y, Farah R. [Secrets of the Mediterranean diet].[Article in Hebrew] Harefuah. 2008 May;147(5):422-7, 477.
21. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet. 2012 Aug 11;380(9841):601-10.
22. Fitó M., Guxens M., Corella D., Sáez G., et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: A randomized controlled trial. Arch. Intern. Med. 2007;167:1195–1203. doi: 10.1001/archinte.167.11.1195.
23. Fitó M, Estruch R, Salas-Salvadó J, et al.:PREDIMED Study Investigators. Effect of the Mediterranean diet on heart failure biomarkers: a randomized sample from the PREDIMED trial. Eur J Heart Fail. 2014 May;16(5):543-50. doi: 10.1002/ejhf.61. Epub 2014 Feb 24.
24. Fitó M, Melander O, Martínez JA, Toledo E, Carpéné C, Corella D. Advances in Integrating Traditional and Omic Biomarkers When Analyzing the Effects of the Mediterranean Diet Intervention in Cardiovascular Prevention. Flood V, ed. International Journal of Molecular Sciences. 2016;17(9):1469. doi:10.3390/ijms17091469.
25. Fryar CD, Chen T, Li X. Prevalence of Uncontrolled Risk Factors for Cardiovascular Disease: United States, 1999–2010. NCHS Data Brief, No. 103. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2012.
26. Fung T.T., Rexrode K.M., Mantzoros C.S., Manson J.E., Willett W.C., Hu F.B. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation. 2009;119:1093–1100. doi: 10.1161/CIRCULATIONAHA.108.816736.
27. Gardener H., Wright C.B., Gu Y., Demmer R.T., Boden-Albala B., Elkind M.S., Sacco R.L., Scarmeas N. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: The Northern Manhattan Study. Am. J. Clin. Nutr. 2011;94:1458–1464. doi: 10.3945/ajcn.111.012799.
28. Gaziano T.A.; Reducing the growing burden of cardiovascular disease in the developing world. Health Aff (Project Hope). 2007; 26:13-24.

29. Ginter E, Simko V. Plant polyphenols in prevention of heart disease. BratislLekListy. 2012;113(8):476–80.
30. Grønbaek M. Alcohol, type of alcohol, and all-cause and coronary heart disease mortality. Ann. N. Y. Acad. Sci. 2002;957:16–20. doi: 10.1111/j.1749-6632.2002.tb02902.x.
31. Guallar-Castillón P., Rodríguez-Artalejo F., Tormo M.J., et al. Major dietary patterns and risk of coronary heart disease in middle-aged persons from a Mediterranean country: The EPIC-Spain cohort study. Nutr. Metab. Cardiovasc. Dis. 2012;22:192–199.
32. Hakim AA, Curb JD, Petrovitch H, Rodriguez BL, Yano K, Ross GW, White LR, Abbott RD. Effects of walking on coronary heart disease in elderly men: the Honolulu heart program. Circulation. 1999;100:9–13.
33. Heart.org: http://www.heart.org/idc/groups/ahamah-public/@wcm/@sop/@smd/documents/downloadable/ucm_480086.pdf (accessed February 10, 2017)
34. Hernáez A, Castañer O, Elosua R, et al. Mediterranean diet improves high-density lipoprotein function in high-cardiovascular-risk individuals: A randomized controlled trial. Circulation 2017; 135:633-643.
35. Hodge AM, English DR, Itsiopoulos C, O'Dea K, Giles GG. Does a Mediterranean diet reduce the mortality risk associated with diabetes: evidence from the Melbourne Collaborative Cohort Study. NutrMetab Cardiovasc Dis. 2011;21:733–9. doi: 10.1016/j.numecd.2010.10.014.
36. Huo R, Du T, Xu Y, 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 ClinNutr 2014. Published Online First: 5 Nov 2014
37. Kaluza J, Åkesson A, Wolk A. Processed and unprocessed red meat consumption and risk of heart failure: prospective study of men. Circ Heart Fail. 2014;7:552–557.
38. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. J Am Coll Cardiol. 2011;57:1299–1313. doi: 10.1016/j.jacc.2010.09.073.
39. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 13:217–223.
40. Kesse-Guyot E, Ahluwalia N, Lassale C et al. Adherence to Mediterranean diet reduces the risk of metabolic syndrome: a 6-year prospective study. NutrMetab Cardiovasc Dis 2013;23:677–83.
41. Knoops K.T., de Groot L.C., Kromhout D., et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: The HALE project. JAMA. 2004;292:1433–1439. doi: 10.1001/jama.292.12.1433.
42. Lazarou C., Panagiotakos D.B., Matalas A.L. Physical activity mediates the protective effect of the Mediterranean diet on children's obesity status: The CYKIDS study. Nutrition. 2010;26:61–67. doi: 10.1016/j.nut.2009.05.014.
43. Lichtenstein A, Appel LJ, Brands M, et al. American Heart Association Nutrition Committee Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114(1):82–96.
44. Lichtman JH, J. Thomas Bigger Jr, James A. Blumenthal et al. Depression and Coronary Heart Disease. Circulation.2008; 118: 1768-1775.Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol. 2008 Apr 1; 51(13):1237-46.
45. Lorenzo C, Williams K, Hunt KJ et al. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;30:8–13. doi:10.2337/dc06-1414.
46. Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, Llewellyn DJ. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology. 2013;24:479–489. doi: 10.1097/EDE.0b013e3182944410.
47. Marie Ng, Tom Fleming, BS, Margaret Robinson et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2014, Volume 384, No. 9945, p766–781.
48. Marita C. Bautista, Marguerite M. Engler. The Mediterranean Diet: Is It Cardioprotective? Prog Cardiovasc Nurs. 2005;20(2):70-76.
49. Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ. 2008;336:1348–1351. doi: 10.1136/bmj.39561.501007.BE.
50. Martínez-González M.A., García-López M., Bes-Rastrollo M., et al. Mediterranean diet and the incidence of cardiovascular disease: A Spanish cohort. Nutr. Metab. Cardiovasc. Dis. 2011;21:237–244.
51. Mendez M.A., Popkin B.M., Jakszyn P., et al. Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity. J. Nutr. 2006;136:2934–2938.
52. Menotti A., Alberti-Fidanza A., Fidanza F. The association of the Mediterranean Adequacy Index with fatal coronary events in an Italian middle-aged male population followed for 40 years. Nutr. Metab. Cardiovasc. Dis. 2012;22:369–375. doi: 10.1016/j.numecd.2010.08.002.
53. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link

between dietary factors and coronary heart disease. Arch Intern Med. 2009;169:659–669.
54. Misirli G, Benetou V, Lagiou P, Bamia C, Trichopoulos D, Trichopoulou A. Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. Am J Epidemiol. 2012;176:1185–1192. doi: 10.1093/aje/kws205.
55. Mons U, Müezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. The BMJ. 2015;350:h1551.
56. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. AdvNutr. 2016 Jan 15;7(1):76-89. doi: 10.3945/an.115.009753. Print 2016 Jan.
57. Neil K Agarwal, Shashi K Agarwal. Cardiovascular Friendly Natural Foods and Supplements - A Brief Review: Part I. Medical Science, 2014a, 4(12),32-38
58. Neil K Agarwal, Shashi K Agarwal. Cardiovascular Friendly Natural Foods and Supplements - A Brief Review: Part II. Medical Science, 2014b, 5(15),8-14
59. Panagiotakos D.B., Chrysohoou C., Pitsavos C., Stefanadis C. Association between the prevalence of obesity and adherence to the Mediterranean diet: The ATTICA study. Nutrition. 2006;22:449–456. doi: 10.1016/j.nut.2005.11.004.
60. Panagiotakos D.B., Pitsavos C., Arvaniti F., Stefanadis C. Adherence to the Mediterrranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the MedDietScore. Prev. Med. 2007;44:335–340. doi: 10.1016/j.ypmed.2006.12.009.
61. Panagiotakos D.B., Polystipioti A., Papairakleous N., Polychronopoulos E. Long-Term adoption of a Mediterranean diet is associated with a better health status in elderly people; a cross-sectional survey in Cyprus. Asia Pac. J. Clin. Nutr. 2007;16:331–337.
62. 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;74:580–591. doi: 10.1002/ana.23944.
63. Rees K., Hartley L., Flowers N., Clarke A., Hooper L., Thorogood M., Stranges S. Mediterranean dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst. Rev. 2013;8 doi: 10.1002/14651858.CD009825.
64. Rivas A. et al. Mediterranean diet and bone mineral density in two age groups of women. Int J Food Sci Nutr 64, 155–161 (2013).
65. Romaguera D., Norat T., Mouw T., et al. Adherence to the Mediterranean diet is associated with lower abdominal adiposity in European men and women. J. Nutr. 2009;139:1728–1737. doi: 10.3945/jn.109.108902.
66. Romaguera D., Norat T., Vergnaud A.C., et al. Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. Am. J. Clin. Nutr. 2010;92:912–921. doi: 10.3945/ajcn.2010.29482.
67. Rossi M, Turati F, Lagiou P, Trichopoulos D, Augustin LS, La Vecchia C, Trichopoulou A. Mediterranean diet and glycaemic load in relation to incidence of type 2 diabetes: results from the Greek cohort of the population-based European Prospective Investigation into Cancer and Nutrition (EPIC) Diabetologia. 2013;56:2405–2413. doi: 10.1007/s00125-013-3013-y.
68. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvado J, Martinez-Gonzalez MA. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. JAMA. 2014;311:415–417. doi: 10.1001/jama.2013.280618.
69. Rumawas ME, Dwyer JT, McKeown NM et al. The development of the Mediterranean-style dietary pattern score and its application to the American diet in the Framingham Offspring Cohort. J Nutr 2009;139:1150–6.
70. Salas-Salvado J, Bullo M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med. 2014;160:1–10. doi: 10.7326/M13-1725.
71. Sanchez-Villegas A, Martinez-Gonzalez MA, Estruch R, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. BMC Med. 2013;11:208. doi: 10.1186/1741-7015-11-208.
72. Saulle R, Semyonov L, La Torre G. Cost and Cost-Effectiveness of the Mediterranean Diet: Results of a Systematic Review. Nutrients. 2013;5(11):4566-4586. doi:10.3390/nu5114566.
73. Schwingshackl L., Hoffmann G. Monounsaturated fatty acids, olive oil and health status: A systematic review and meta-analysis of cohort studies. Lipids Health Dis. 2014;13:154. doi: 10.1186/1476-511X-13-154.
74. Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean diet: a systematic review. Nutr Rev. 2006 Feb;64(2 Pt 2):S27-47.
75. Schroder H., Marrugat J., Vila J., Covas M.I., Elosua R. Adherence to the traditional Mediterranean diet is inversely associated with body mass index and obesity in a Spanish population. J. Nutr. 2004;134:3355–3361.
76. Shashi K Agarwal. Vitamin Supplementation for Cardiovascular Protection: Salutary, Superfluous or

Sinister? A Brief Review. Medical Science, 2014, 7(27), 106-111

77. Shubair M.M., McColl R.S., Hanning R.M. Mediterranean dietary components and body mass index in adults: The peel nutrition and heart health survey. Chronic Dis. Can. 2005;26:43–51.
78. Simopoulos, A. P., Herbert, V. & Jacobson, B. (1995) Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease. The Healing Diet Macmillan New York, NY.
79. Singh, R. R., Rastogi, S. S., Verma, R., Laxmi, B., Singh, R., Ghosh, S., &Niaz, M. A. (1992) Randomised controlled trial of cardioprotective diet inpatients with recent acute myocardial infarction: results of a one year follow-up. Br. Med. J. 304: 1015–1019.27.
80. Singh RB, Dubnov G, Niaz MA, 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;360:1455-1461.
81. Singh B, Parsaik AK, Mielke MM, Erwin PJ, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39:271–282.
82. Slattery ML, Jacobs DR Jr, Hilner JE, et al. Meat consumption and its associations with other diet and health factors in young adults: the CARDIA study. Am J ClinNutr. 1991 Nov;54(5):930-5.
83. Sofi F., Abbate R., Gensini G.F., 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;92:1189–1196. doi: 10.3945/ajcn.2010.29673.
84. Sofi F., Macchi C., Abbate R., Gensini G.F., Casini A. Mediterranean diet and health status: An updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014;17:2769–2782. doi: 10.1017/S1368980013003169.
85. Stefler D, Malyutina S, Kubinova R, Pajak A, Peasey A, Pikhart H, et al. Mediterranean diet score and total and cardiovascular mortality in Eastern Europe: the HAPIEE study. Eur J Nutr. 2015. Ahead of print.
86. Stern MP, Williams K, Gonzalez-Villalpando C et al. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004;27:2676–81. doi:10.2337/diacare.27.11.2676.
87. Tognon G, Nilsson LML, Lissner L, Johansson I, Hallmans G, Lindahl B, et al. The Mediterranean diet score and mortality are inversely associated in adults living in the subarctic region. J Nutr. 2012;142:1547–53. doi: 10.3945/jn.112.160499.
88. Toledo E, Hu FB, Estruch R, Buil-Cosiales P, et al. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial. BMC Med. 2013 Sep 19;11:207. doi: 10.1186/1741-7015-11-207.
89. Tong TYN, Wareham NJ, Khaw K-T, Imamura F, Forouhi NG. Prospective association of the Mediterranean diet with cardiovascular disease incidence and mortality and its population impact in a non-Mediterranean population: the EPIC-Norfolk study. BMC Medicine. 2016;14:135. doi:10.1186/s12916-016-0677-4.
90. Toobert DJ, Glasgow RE, Strycker LA et al. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: a randomized clinical trial. Diabetes Care 2003;26:2288–93. doi:10.2337/diacare.26.8.2288.
91. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A et al. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. Diabetes Care 2007;30:2957–9. doi:10.2337/dc07-1231.
92. Trichopoulou A, Lagiou P. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. Nutr Rev. 1997 Nov;55(11 Pt 1):383-9.
93. Trichopoulou A., Costacou T., Bamia C., Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 2003;348:2599–2608. doi: 10.1056/NEJMoa025039.
94. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ. 2009;338:b2337. doi: 10.1136/bmj.b2337.
95. Trichopoulou A, Bamia C, Lagiou P, Trichopoulos D. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Am J ClinNutr. 2010;92:620–625. doi: 10.3945/ajcn.2010.29619.10.
96. Trichopoulou A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ. 2005;330:991. doi: 10.1136/bmj.38415.644155.8F.
97. Vita JA. Polyphenols and cardiovascular disease: effects on endothelial and platelet function. Am J ClinNutr. 2005 Jan;81(1 Suppl):292S–297S
98. WHO 2006. Global Strategy on Diet, Physical Activity and Health. Diet and Physical Activity: A Public Health Priority. Available online: www.who.int/dietphysicalactivity/en/
99. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet

pyramid: a cultural model for healthy eating. Am J ClinNutr. 1995 Jun;61(6 Suppl):1402S-1406S.

100. Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. Scientific Reports. 2017;7:41317. doi:10.1038/srep41317.