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Mediterranean diet impact on cardiovascular diseases: a narrative review

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Cardiovascular disease (CVD) accounts for more than 17 million deaths per year worldwide. It has been estimated that the influence of lifestyle on CVD mortality amounts to 13.7% for smoking, 13.2% for poor diet, and 12% for inactive lifestyle. These results deeply impact both the healthy status of individuals and their skills in working. The impact of CVD on productivity loss accounts for the 24% in total costs for CVD management.

Mediterranean diet (MedD) can positively impact on natural history of CVD. It is characterized by a relatively high consumption of inexpensive and genuine food such as cereals, vegetables, legumes, nuts, fish, fresh fruits, and olive oil as the principal source of fat, low meat consumption and low-to-moderate consumption of milk, dairy products, and wine.

Its effects on cardiovascular health are related to the significant improvements in arterial stiffness. Peripheral artery disease, coronary artery disease, and chronic heart failure are all positively influenced by the MedD.

Furthermore, MedD lowers the risk of sudden cardiac death due to arrhythmias.

The present narrative review aims to analyze the effects of MedD on CVD.

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Introduction

Cardiovascular disease (CVD) is the primary global cause of death, responsible for more than 17 million deaths per year.[1,2] The contribution of unhealthy lifestyle to the development of CVD in high-income and middle-income countries is unquestionable.[3,4] It has been estimated that the impact on CVD mortality of lifestyle amounts to 13.7% for smoking, 13.2% for poor diet, and 12% for inactive lifestyle.[5,6] Smoking, poor diet, inactive lifestyle, and excessive alcohol consumption are responsible for almost 40% of all deaths and 80% of chronic diseases in the United States.[5] Improving cardiovascular health is a strategic goal in public health, and improving the average quality of diet is fundamental in achieving such a therapeutic goal.[1–7]

The present narrative review aims to analyze the effects of healthy Mediterranean diet (MedD) on CVD.

'Mediterranean diet' definition and state of the art

MedD refers to the eating habits found in some Mediterranean populations (particularly Crete and southern Italy)

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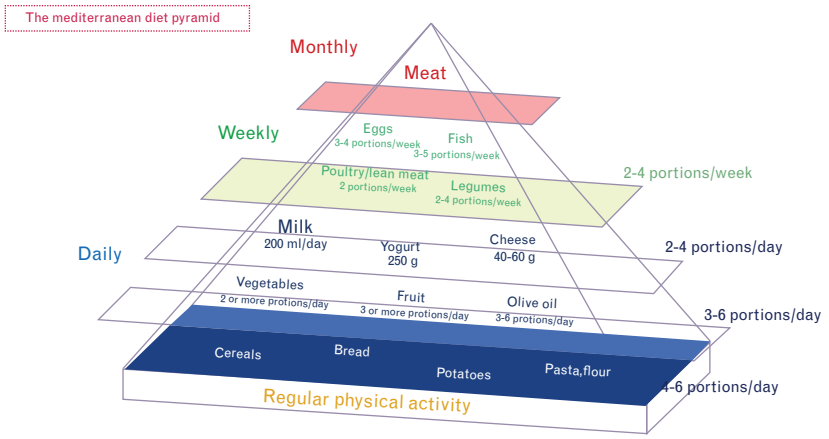
Fig. 1



The pyramid of Mediterranean diet: components and quantities for health protection.

in the mid-20th century. In this area, after the Second World War nutrition was scarce and characterized by a relatively high consumption of inexpensive and genuine food such as cereals, vegetables, legumes, nuts, fish, fresh fruits, and olive oil as the principal source of fat (Fig. 1). The consumption of meat was low, whereas the consumption of milk, dairy products and wine was low–moderate (Fig. 1). The intake of sophisticated food was almost null.[8]

Baseline dietary data showed large differences in saturated fat intake across worldwide cohorts. Intake of saturated fat was low in southern European Mediterranean cohorts and in Japan.[9] Cereals and wine consumption is typical in Italy; bread consumption was high in the Yugoslavian cohorts apart from in Belgrade, with large amounts of vegetables and fish in Dalmatia; olive oil and fruit consumption was high in Greece; fish, rice, and soy products were typical of the Japanese cohorts.[10]

It was observed that there were strong and significant associations between saturated fat (as total energy intake proportions) and coronary artery disease (CAD) incidence or mortality. Moreover, there were high inverse relationships between polyunsaturated/saturated fat and monounsaturated/saturated fat ratios on one side and CAD mortality on the other.[11,12] In the Mediterranean areas, the high monounsaturated/saturated fat ratios reflected the extensive use of olive oil. Although individual saturated fatty acids (FAs), overall fat and dietary cholesterol intake were directly associated with CAD mortality, this was not the case for oleic acid and polyunsaturated FAs. On the other hand, carbohydrate intake was inversely and significantly correlated with CAD rates. These results were compatible with the causal hypothesis that diets high in saturated fat intake – leading to high average levels of serum cholesterol – were responsible for greater CAD incidence and mortality rates across populations.

It was hypothesized that decreasing the consumption of dairy products by half might be associated with a 20% decline in CAD mortality over a 25-year period. A 25% lower consumption of animal foods and a concomitant increase of plant foods by 25% might be associated with a 32% decline in 25-year CAD mortality.[12]

A systematic evaluation of eating patterns was carried out over a 25-year follow-up (starting with a testing sample of people aged 45–64 years) in five cohorts (two in Finland, one in the Netherlands, and two in Italy). The general eating habits remained the same throughout the 25 years. Saturated fat decreased by 3% of total energy in Finland and by less than 1% in Italy.[13]

New research has confirmed and expanded the concept of MedD and the results of the Seven Country Study.[14,15] The European Prospective Investigation into Cancer and Nutrition (EPIC) has provided important evidence, based on analyses on large numbers of patients.[16] MedD proved protective on renal function, levels of serum uric acid, weight control, metabolic syndrome, and on developing ischemic stroke.[17–20] More recently, a study on the MedD has stimulated important comparative procedures between the a-priori and the a-posteriori approach for the definition of dietary patterns.[21] This research period has enabled the concept of MedD to gradually take form and its benefits, regarding low incidence, prevalence, and mortality from CHD, have been expanded to other CVDs, and all-causes mortality including cancer.[22]

The characteristics and virtues of the MedD were recently accompanied by a declaration from United Nations Educational, Scientific and Cultural Organization, which classified the MedD as a 'cultural heritage of humanity'. It is however important to stress that there are probably no longer populations homogeneous to the MedD patterns, although within most populations it is certainly possible to identify subgroups of people whose eating habits, casually or deliberately, have enjoyed better health and longevity, by adopting the traditional Seven Countries Study Mediterranean Diet.

Prevalence of unhealthy lifestyle habits

With few exceptions, age-standardized mortality rates from CVD have fallen in European countries from 2000 to 2010; nonetheless, CVD still caused 1.48 million premature deaths and 37% of all deaths in 2010.[2] It has been estimated that 24% of the total costs for CVD in Europe are due to productivity losses.[23]

Improving cardiovascular health is a strategic goal in public health.[1,24,25] The contribution of unhealthy lifestyle behaviors to the development of CVD in high-income and middle-income countries is unquestionable.[5] Sustainable health policies are needed to promote healthy lifestyle behaviors including not smoking, having a healthy dietary pattern and a normal BMI, abstaining from excessive alcohol use, and maintaining regular physical activity.[3,6,23] Smoking cessation is associated with decreased risk for CVD.[4] Regular physical activity is associated with decreased risk for CVD and cardiovascular mortality.[4] A moderate-intensity physical activity for at least 30 min a day five times a week is recommended.[3] Only 27% of adult European citizens meet these activity recommendations.[23]

Dietary habits influence CVD risk.[3] In the 2013 WHO Ministerial Conference on Nutrition and NonCommunicable Diseases, it was recognized that 'a healthy diet can contribute to achieving the global targets on NCDs adopted by the Sixty-sixth World Health Assembly, including achieving a 25% relative reduction in premature mortality from NonCommunicable Diseases by 2025'.[26] Core components of a healthy diet include limiting intakes of saturated and trans fats, carbohydrate, alcohol, and sodium and increasing intakes of fruit, vegetables, and dietary fibers. The MedD meets these healthy diet requirements. The cost-effectiveness analysis performed by Abdullah *et al.*[27] confirms this statement. The analysis estimates that reduction in costs, consequent to an improve management of CVD events, will be of $ 41.9 million in Canada and $1.0 billion in the United States in the 'worst case' scenario represented by a 5% of the population switching to MedD and having a 10% reduction in CVD.[27]

Mediterranean diet and peripheral artery disease

Peripheral artery disease (PAD) is one of the most important manifestations of atherosclerotic disease.[28] The overall prevalence of the disease, assessed in several epidemiological studies, ranges from 3 to 10%, being incremented to 15–20% over the age of 70.[29] The cardiovascular risk factors associated with an increased incidence of PAD are diabetes mellitus and cigarette smoking, followed by arterial hypertension, obesity, and dyslipidemia. In many patients with PAD, these risk factors are simultaneously present, determining the metabolic syndrome.[30]

MedD can dramatically improve prognosis, clinical course of PAD, and reduction in negative outcomes (Table 1).

Table 1 The effects of Mediterranean diet on peripheral artery disease: the overview from literature

Reference	Name of the study	Type of study	Design	Patients	Main results
Ruiz-Canela *et al.*[31]	PREDIMED	Multicenter, randomized, primary prevention trial	Randomization 1 : 1 : 1	3 groups: MedD + olive oil (2539 pts); MedD + nuts (2452 pts); controls (2444 pts)	↓ 66% PAD incidence [HR: 0.34 (0.20–0.58)] in MedD + olive oil ↓ 50% PAD incidence [HR: 0.50 (0.30–0.81)] in MedD + nuts NNT = 336 (95% CI 269–566) for MedD + olive oil NNT = 448 (95% CI 316–1536) for MedD + nuts
Martínez-González *et al.*[34]	PREDIMED	Multicenter, randomized, primary prevention trial	Randomization 1 : 1 : 1	3 groups: MedD + olive oil (2539 pts); MedD + nuts (2452 pts); controls (2444 pts)	Number expected prevented PAD cases: 10 cases in a hypothetical cohort of 1000 pts
Ciccarone *et al.*[35]		Prospective cohort study	Not randomized	144 PAD pts 288 type 2 diabetes pts	Lowest MedD score tertiles: - 2.63 (diabetes duration <10 years) higher risk of PAD progression - 3.9-fold (diabetes duration >10 years) higher risk of PAD progression - 5.9-fold (hypertensive) higher risk of PAD progression
Hoevenaar-Blom *et al.*[36]	EPIC-NL	Prospective cohort study	Not randomized	40 011 pts	↓ 26% [HR: 0.74 (95% CI 0.45–1.21)] in PAD risk in highly adherent to MedD
van de Laar *et al.*[39]	AGAHLS	Observational study	Not randomized	196 pts	Increased arterial stiffness in less adherent to MedD
Gardener *et al.*[40]	NOMAS	Observational study	Not randomized	1374 pts	−0.049 mm reduction in plaque thickness each 1-point increase in MedD score, $P = 0.03$ −0.371 mm^2 reduction in plaque area each 1-point increase in MedD score, $P = 0.03$
Sala-Vila *et al.*[41]	PREDIMED subcohort	Multicenter, randomized, primary prevention trial	Randomization 1 : 1 : 1	175 pts	MedD group + nuts vs. controls: ↓ 0.084 mm (−0.158 to −0.010 mm, $P = 0.024$) c-IMT ↓ 0.030 mm (−0.153 to 0.093 mm, $P = 0.034$) maximum internal c-IMT

AGAHLS, Amsterdam Growth and Health Longitudinal Study; CI, confidential index; c-IMT, carotid intima–media thickness; EPIC-NL, European Prospective Investigation into Cancer and Nutrition – NL (Dutch contribution); HR, hazard ratio; MedD, Mediterranean diet; NNT, number-need-to-treat; NOMAS, Northern Manhattan Study; PAD, peripheral artery diseases; PREDIMED, PREvención con DIeta MEDiterránea; pts, patients.

The PREDIMED study, performed from October 2003 to December 2010 in Spain, tested the effect of the MedD enriched with olive oil or dry nuts in 7477 participants with type 2 diabetes mellitus or at least three cardiovascular risk factors, aged 55–80 years and without baseline overt clinical PAD or CVD. PREDIMED was a primary prevention trial. Authors observed a 66% reduction in PAD incidence [hazard ratio: 0.34 (95% confidential index 0.20–0.58)] in patients undergone MedD plus extra-virgin olive oil and a 50% reduction in PAD incidence [hazard ratio: 0.50 (95% confidential index 0.30–0.81)] in the group treated with MedD plus nuts, compared with the control group.[31] All results were obtained after adjusting for confounding factors. Furthermore, the number-need-to-treat (NNT) was 336 (95% confidential index 269–566) for the MedD plus extra-virgin olive oil group and 448 (95% confidential index 316–1536) for the MedD plus nuts group. Although these numbers are far from those of well established pharmacological treatments (i.e. NNT for PAD primary prevention with statins: from 24 to 42[32]; NNT for PAD primary prevention with ACE-inhibitors: 7 (95% confidential index 5–12)[33]), they suggest an important role of eating habits on PAD progression. A further analysis revealed a number of expected prevented PAD cases of 10 out of 1000 patients.[34]

Ciccarone *et al.*[35] showed the protective role of the MedD in counteracting PAD development in patients with type 2 diabetes mellitus. They observed that the higher the MedD score – representing greater adherence to MedD – the lower the risk of PAD. Although diabetes duration and hypertensive condition can negatively impact PAD occurrence, a high MedD score is associated with a decrease progression of the disease. Patients in the lowest score tertile showed a 2.63 (diabetes duration <10 years) and 3.9-fold (diabetes duration >10 years) higher risk of PAD progression as compared with their higher counterparts.[35] Such differences dramatically increased when considering hypertensive condition: hypertensive individuals who poorly followed MedD displayed a 5.9-fold higher risk of PAD than those adhering to MedD.[35]

The EPIC-NL cohort study supported the previous findings.[36] The Authors prospectively followed up 40 011 men and women aged 20–70 years. They were enrolled between 1993 and 1997 and followed for 10–15 years (mean 11.8 years).[36] The study was design for investigating the influence of MedD on cardiovascular outcomes occurrence. By splitting results, the authors observed a 26% [hazard ratio: 0.74 (95% confidential index 0.45–1.21), after correction for confounding factors] reduction in PAD occurrence in patients highly adherent to MedD, as assessed by means of the modified Mediterranean diet score.[36]

The reasons for such improvements in the overall cardiovascular risk burden of individuals prone to or suffering from PAD are not fully understood. Klonizakis *et al.*[37] showed that vascular function may benefit from MedD. The lower limb vascular endothelial cutaneous vascular conductance improved in patients who had undergone MedD even at 1-year follow-up.[37] Although the study was not set for PAD patients – the authors enrolled 20 healthy individuals – it provides insights on possible mechanisms explaining the positive effects of MedD in such patients.

The reasons behind the improvement of disease and the prevention of PAD in patients following MedD regimen can be related to the positive effect on arterial walls.[38] The Amsterdam Growth and Health Longitudinal Study compared longitudinal levels of adherence with MedD, during adolescence and adulthood (two to eight repeated measures obtained between the ages of 13 and 36 years) between individuals, with different levels of arterial stiffness in adulthood.[39] The study population included 373 (196 women) apparently healthy adults who underwent carotid, brachial, and femoral arteries ultrasound evaluations at 36 years of age. After adjustments for confounders, individuals with stiffer carotid arteries had lower adherence scores and were less likely to have adhered to this dietary pattern during the preceding 24 years compared with those with less stiff arteries. Therefore, MedD may prevent arterial stiffness in adulthood, and consequently the development of PAD.[39]

MedD can also influence the peripheral atherosclerotic burden. Gardener *et al.*[40] outlined the positive effect of MedD on carotid plaque thickness and median plaque area progression: the 1374 patients enrolled in the Northern Manhattan Study showed that the increase in 1 point of MedD score was able to significantly reduce the 75th percentile of plaque thickness (-0.049 mm, $P = 0.03$, after adjusting for confounding factors) and the median of plaque area (-0.371 mm^2, $P = 0.03$).[40]

A substudy from PREDIMED[41] also revealed a relative regression of internal carotid intima–media thickness (c-IMT) in MedD group plus nuts [-0.084 mm (-0.158 to -0.010 mm); $P = 0.024$ vs. control], as well as maximum internal c-IMT [-0.030 mm (-0.153 to 0.093 mm); $P = 0.034$], even after adjusting for confounding factors.

Although the pathophysiological mechanisms are not yet clarified, several studies show the effectiveness of the MedD in preventing the development of PAD especially in young patients.[42]

Mediterranean diet in chronic coronary artery disease patients

CAD is the most common cause of death in developed countries, responsible for about one out of five deaths. Chronic stable angina (CSA) is the first presentation of CAD in about 50% of patients, affecting about 17 million people in the United States.[43] Nutrition plays an increasingly significant role for secondary prevention of cardiovascular events in CSA.[44–47]

Table 2 The effects of Mediterranean diet on chronic coronary artery disease: the overview from literature

Reference	Name of the study	Type of study	Design	Patients	Main results
Estruch *et al.*[22]	PREDIMED	Multicenter, randomized, primary prevention trial	Randomization 1 : 1 : 1	3 groups: MedD + olive oil (2539 pts); MedD + nuts (2452 pts); controls (2444 pts)	Primary Endpoint (AMI, stroke, or death from cardiovascular causes): ↓ 30% (MedD + olive oil: HR: 0.70, 95% CI 0.53–0.91, $P = 0.009$) ↓ 30% (MedD + nuts: HR: 0.70, 95% CI 0.53–0.94, $P = 0.02$)
Gardener *et al.*[48]	NOMAS	Observational study	Not randomized	2568 pts	No influence in AMI occurrence: HR: 0.65, 95% CI 0.38–1.12, $P = 0.27$
Hoevenaar-Blom *et al.*[36]	EPIC-NL	Prospective cohort study	Not randomized	40 011 pts	↓ in AMI occurrence (HR: 0.86, 95% CI 0.79–0.93)
Buckland *et al.*[50]	EPIC	Prospective cohort study	Not randomized	41 078 pts	↓ 40% (HR: 0.60, 95% CI 0.47–0.77, $P < 0.001$) CHD occurrence in highly adherent
De Lorgeril *et al.*[51,52]	Lyon Diet Heart Study	Randomized single-blind trial		605 pts	↓ 72% (CRR: 0.28, 0.15–0.53, $P < 0.05$) in myocardial infarction + cardiovascular death
Barzi *et al.*[53]	GISSI-Prevenzione Study	Clinical trial	Randomization	11 246 pts	↓ 15% in mortality after AMI (95% CI 12–18%) ↓ 14% in mortality after 6.5-year follow-up
Iestra *et al.*[54]		Prospective cohort study	Not randomized	426 pts	↓ 15% in mortality after AMI (HR: 0.75; 95% CI 0.57–0.97)

AMI, acute myocardial infarction; CI, confidential index; CRR, conditional risk ratios; EPIC-NL, European Prospective Investigation into Cancer and Nutrition – NL (Dutch contribution); GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HR, hazard ratio; MedD, Mediterranean diet; NOMAS, Northern Manhattan Study; PREDIMED, PREvención con DIeta MEDiterránea; pts, patients.

MedD can further improve the outcomes of these patients (Table 2). The PREDIMED study[22] on primary prevention of adverse outcomes revealed a significant reduction in the primary composite endpoint of the study [acute myocardial infarction (MI), stroke, or death from cardiovascular causes]: the use of MedD plus olive oil (hazard ratio: 0.70, 95% confidential index 0.53–0.91, $P = 0.009$) and MedD plus nuts (hazard ratio: 0.70, 95% confidential index 0.53–0.94, $P = 0.02$) both decreased the incidence of the composite endpoint of 30%. Nevertheless, when splitting the single endpoints, they found that previous results were triggered by the significant reduction in stroke occurrence rather than acute MI of death from cardiovascular causes. Similar results came from the analyses of the Northern Manhattan Study[48]: higher adherence to MedD did not significantly reduce the occurrence of MI (hazard ratio: 0.65, 95% confidential index 0.38–1.12, $P = 0.27$). Nevertheless, the EPIC-NL cohort study[36] in apparently healthy individuals outlined the significant reduction in the occurrence of MI after adjusting for confounders in patients showing higher adherence to MedD (hazard ratio: 0.86, 95% confidential index 0.79–0.93).

The cardiovascular Spanish section of the EPIC study – a prospective European study involving healthy individuals – pointed out a further 40% reduction in the risk of CAD occurrence in the patients highly adherent to MedD (hazard ratio: 0.60, 95% confidential index 0.47–0.77, $P < 0.001$), even after the adjustment for confounders.[49,50]

The Lyon Diet Heart Study provided information about the role of MedD in the secondary prevention of adverse outcomes after acute MI.[51,52] This was a randomized, single-blind secondary prevention trial in patients analyzing the incidence of three composite outcomes: MI plus cardiovascular death (composite outcome 1); MI plus cardiovascular death plus major secondary events (unstable angina occurrence, overt heart failure, stroke, or pulmonary or peripheral embolism) (composite outcome 2); the preceding plus minor events requiring hospital admission, including recurrent stable angina, postangioplasty restenosis, surgical or medical myocardial revascularization, and thrombophlebitis (composite outcome 3). MedD was able to significantly reduce the occurrence of all-cause and cardiovascular death ($P < 0.05$). All the three composite outcomes were significantly reduced ($P = 0.0001$ for composite outcome 1 and composite outcome 2 and $P = 0.0002$ according to composite outcome 3). At multivariate proportional-hazards analyses, MedD was able to reduce the occurrence of composite outcome 1 of 72% [conditional risk ratios (CRRs) 0.28, 0.15–0.53, $P < 0.05$], composite outcome 2 of 67% (CRR 0.33, 0.21–0.52, $P < 0.05$), and composite outcome 3 of 47% (CCR 0.53, 0.38–0.74, $P < 0.05$).[51]

A subanalysis[53] of the GISSI-Prevenzione study involving patients surviving recent (3 months or less) MI

pointed out a 15% (95% confidential index 12–18%) reduction in the occurrence of mortality each unit increase in the MedD score. The authors calculated a 14% reduction in the overall risk of mortality after 6.5-year follow-up.[53] Although this subanalysis did not reveal the incidence of further coronary events, data on mortality are fundamental to consider the overall impact of MedD on health.

The prospective analysis from Iestra *et al.*[54] outlined the reduction in mortality risk (hazard ratio: 0.75; 95% confidential index 0.57–0.97) in patients following MedD and recently suffering from MI.[54]

The hypotheses accounting for the positive effects of MedD on cardiovascular outcomes of patients suffering from CAD are different, but not conclusive. A subanalysis from PREDIMED study pointed out the reduction in CD40 expression on monocytes surface (34%, $P = 0.03$), and a further decrease in C-reactive protein and IL-6 in both MedD groups (plus olive oil and plus nuts).[55] Accordingly, the expression of adhesion molecules such as soluble intracellular Cell Adhesion Molecule and P-selectin was significantly reduced in both groups as compared with controls ($P = 0.04$).[55] All of these molecular changes suggest a protection of atherosclerotic plaques from instability and/or negative progression related to the adherence to MedD, which was persistent even at 12-month follow-up. The 5-year follow-up of this group of patients confirmed the statistical significant reduction in inflammatory markers[56]: IL-6 and IL-8, monocyte chemotactic protein-1, TNF-α, adhesion molecules were significantly reduced following MedD treatment, acting as a possible mechanism for cardiovascular risk prevention.

Therefore, as confirmed by literature, MedD may play a crucial role in primary and secondary prevention of CADs.[57]

Mediterranean diet in patients with chronic heart failure

Despite significant advances in pharmacological and non-pharmacological therapy, heart failure continues to have high morbidity and mortality and its prevalence is increasing in most regions of the world.[58,59] There is consequently an evident need for novel therapeutic approaches. Nutritional interventions appear to be particularly attractive because they could work additively with established therapies without exerting negative hemodynamic effects.

Healthy dietary patterns in general, including some components of the MedD, have been associated with lower incidence of heart failure in some observational studies (Table 3).[60–62] Recently, Tektonidis *et al.*[63] in a prospective study that included 37 308 men from Sweden free from CVD at baseline, firstly demonstrated that high adherence to MedD (assessed by a MedD score) was

Table 3 The effects of Mediterranean diet on chronic heart failure: the overview from literature

Reference	Name of the study	Type of study	Design	Patients	Main results
Tektonidis *et al.*[63]	COSM	Prospective cohort study	Not randomized	37 308 pts	↓ 31% in HF occurrence in highly MedD adherent pts (RR: 0.69, 95% CI 0.57–0.83; *P* for trend <0.001) ↓ 45% in mortality related to HF in highly MedD adherent pts (RR: 0.55, 95% CI 0.31–0.98; *P* for trend = 0.007)
Papadaki *et al.*[64]	PREDIMED	Multicenter, randomized, primary prevention trial	randomization 1 : 1 : 1	3 groups: MedD + olive oil (2539 pts); MedD + nuts (2452 pts); controls (2444 pts)	No influence MedD on HF occurrence
Wirth *et al.*[66]	EPIC-Potsdam substudy	Prospective cohort study	Not randomized	24 008 pts	No influence MedD on HF occurrence
Levitan *et al.*[67]	MESA	Prospective cohort study	Not randomized	4497 pts	Higher MedD score related to: - Higher LVM - Higher LVV - Higher LVSV - Higher LVEF
Levitan *et al.*[68]	WHI	Prospective cohort study	Not randomized	3215 pts	Higher MedD adherence related to reduced HF occurrence (HR: 0.85, 95% CI 0.70–1.02, $P = 0.08$)
Chrysohoou *et al.*[70]		Prospective cohort study	Not randomized	372 pts	MedD adherence slightly associated with better LVFP and biventricular systolic function in chronic HF patients with LVEF < 40%

CI, confidential index; COSM, Cohort of Swedish Men; EPIC, European Prospective Investigation into Cancer and Nutrition; HF, heart failure; HR, hazard ratio; LVEF, left ventricle ejection fraction; LVFP, left ventricle filling pressure; LVM, left ventricle mass; LVSV, left ventricle stroke volume; LVV, left ventricle volume; MedD, Mediterranean diet; MESA, Multi-Ethnic Study of Atherosclerosis; PREDIMED, PREvención con Dieta MEDiterránea; pts, patients; WHI, Women's Health Initiative.

associated with a 31% [relative risk (RR): 0.69, 95% confidential index 0.57–0.83; *P* for trend <0.001] reduction in risk of heart failure development over a median follow-up time of 10.9 years. Moreover, mortality related to heart failure was significantly reduced in patients highly adherent to MedD (RR: 0.55, 95% confidential index 0.31–0.98; *P* for trend = 0.007), after adjusting for confounding factors.[63]

Data from 'PREDIMED' did not show reduction in heart failure occurrence in the population following MedD combined with extra-virgin oil or nuts as compared with controls.[64] Despite the strict adherence to the dietetic regimens, there was a similar incidence of heart failure among the three groups at 4.8-year median follow-up. Heart failure was a secondary outcome of the PREDIMED study and, probably, was underpowered for the final analysis. Authors suggested a further controlled trial designed *ad hoc* for this purpose. Despite this lack of difference among groups, Fitó *et al.*[65] observed a significant reduction in plasma N-terminal pro-brain natriuretic peptide in MedD groups as compared with controls, whereas no variation was observed in urinary albumin or albumin/creatinine ratio.

The EPIC-Potsdam substudy confirmed the PREDIMED results[66]: among the 9225 men and 14 783 women enrolled in the study, there was no relationship between heart failure occurrence and adherence to MedD. Although the gross analysis revealed a significant reduction in heart failure occurrence, the multivariate regression analysis did not confirm the results (highest adherence group: hazard ratio: 0.66, 95% confidential index 0.41–1.08, *P* for trend 0.10).[66] Further analysis should be considered in the adoption of MedD in the setting of strategies for primary prevention of heart failure.

An interesting point of view about this matter comes from the analysis of the Multi-Ethnic Study of Atherosclerosis study.[67] The authors applied the MedD score for the evaluation of these patients whose cardiac function and morphology were also combined for the final evaluation. The higher the MedD score the higher the left ventricle (LV) mass and volume, as well as stroke volume and LV ejection fraction. This cross-sectional association revealed the skills of MedD to enhance the structure and the function of the LV in apparently healthy individuals.

Different results come from the analysis of secondary prevention studies. A subanalysis from the Women's Health Initiative study involved about 3215 participants who experienced hospitalization for heart failure.[68] These women were followed up for a median time of 4.6 years, and their daily dietary patterns were also periodically evaluated. Patients showing higher MedD adherence showed a trend for reduced mortality for heart failure (hazard ratio: 0.85, 95% confidential index 0.70–1.02, *P* = 0.08) after adjusting for several confounding factors.[68] A good adherence to MedD after acute coronary syndrome (ACS) was significantly associated with reduced incidence of LV dysfunction during hospitalization, whereas higher MedD score showed a trend toward reduced negative LV remodeling within 3 months after the acute event.[69]

Significantly, Chrysohoou *et al.*[70] observed that greater adherence to MedD was slightly associated with better LV filling pressure and better biventricular systolic function in chronic heart failure patients with LV ejection fraction less than 40%. In particular, after adjusting for potential confounding factors (e.g. age, sex, physical inactivity, smoking habits, obesity, history of hypertension, hypercholesterolemia and diabetes mellitus, ejection fraction, and years of heart failure), log E wave/A wave ratio was inversely associated with the MedD score.[70] Furthermore, aliment-specific analysis revealed the potential beneficial effect of vegetables, fish, and olive oil on LV and right ventricular systolic and diastolic indices, suggesting a further nonpharmacological therapeutic strategy in these patients.[70]

In conclusion, even though evidence is not conclusive, MedD may positively impact on reverse remodeling in heart failure patients or in patients likely to develop heart failure.

Mediterranean diet effects on arrhythmias and sudden cardiac death

The effects of MedD on arrhythmias prevention and/or sudden cardiac death (SCD) are poorly established (Table 4).[71] The GISSI-Prevenzione Investigators demonstrated that early administration of ω-3 poly-unsatured fatty acids (PUFA) supplementation (a well established component of MedD) in patients recently suffering from ACS can reduce the occurrence of SCD.[72] The authors suggested a possible antiarrhythmic role of ω-3 PUFA on heart as the key role for SCD prevention.

The Women's Health Initiative substudy involved 93 122 postmenopausal women who were evaluated for the MedD and, in parallel, for the occurrence of SCD.[73] The research found a total of 237 SCD. The statistical analyses and the corresponding adjustment for confounding factors did not outline the superiority of higher adherence to MedD in prevention of SCD. Nevertheless, women in the highest quintile showed a not significant 36% reduction (highest to lowest quintile hazard ratio: 0.64, 95% confidential index 0.43–0.94, *P* = 0.21) in SCD reduction as compared with those poorly adherent to MedD.[73] The Isfahan Cohort Study considered a composite endpoint of fatal MI, fatal stroke (i.e. death from cerebrovascular disease) and SCD; it demonstrated that MedD was effectively able to strongly reduce the occurrence of the primary endpoint (hazard ratio: 0.42, 95% confidential index 0.19–0.96, *P* for trend = 0.02 after adjusting for confounding factors) more than other

Table 4 The effects of Mediterranean diet on arrhythmias and sudden cardiac death: the overview from literature

Reference	Name of the study	Type of study	Design	Patients	Main results
Bertoia *et al.*[73]	WHI	Prospective cohort study	Not randomized	93 122 pts	Not-significant 36% reduction in SCD in higher MedD adherent pts (highest to lowest quintile HR: 0.64, 95% CI 0.43–0.94, $P=0.21$)
Mohammadifard *et al.*[74]	ISF	Prospective cohort study	Not randomized	4834 pts	↓ Composite endpoint o(fatal AMI, fatal stroke and SCD): HR: 0.42, 95% CI 0.19–0.96, P for trend $=0.02$
Martínez-González *et al.*[77]	PREDIMED	Multicenter, randomized, primary prevention trial	randomization 1 : 1 : 1	3 groups: MedD + olive oil (2539 pts); MedD + nuts (2452 pts); controls (2444 pts)	↓ 38% (HR: 0.62; 95% CI 0.45–0.85) AF occurrence in MedD + olive oil
Mattioli *et al.*[76]		Case–control study	Not randomized	800 pts	OR: 1.90, 95% CI 1.58–2.81, $P=0.001$ for fast AF conversion in MedD

AF, atrial fibrillation; AMI, acute myocardial infarction; CI, confidential index; HR, hazard ratio; ISF, Isfahan Cohort Study; MedD, Mediterranean diet; OR, odds ratio; PREDIMED, PREvención con DIeta MEDiterránea; pts, patients; SCD, sudden cardiac death; WHI, Women's Health Initiative.

Table 5 Mediterranean diet and cardiovascular disease: what is known and potential beneficial mechanisms related to high intake of fruit and vegetables, strongly present in Mediterranean diet

MedD and cardiovascular disease
MedD reduces mortality for cardiovascular disease[83]
MedD significantly reduced the risk of metabolic syndrome and protected against risk factors such as waist circumference, lipids, glucose, and blood pressure in primary prevention[20]
MedD provided a more robust reduction in cardiovascular disease risk factors and inflammatory markers[55,56]
Nutrition plays an increasingly significant role for secondary prevention of CV events in CSA[47]
MedD have been associated with lower incidence of HF in some observational studies[60–62]
Potential beneficial mechanisms related to high intake of fruit and vegetables, strongly present in MedD
Antioxidant properties of fruit and vegetables[84]
Well known health benefits of high flavonol intake[85]
Potential increase in nitric oxide species[86]
Concomitant weight loss associated with diets high in fruits and vegetables.
Reduction of blood pressure[87]
Reduction of inflammatory markers

CSA, chronic stable angina; CV, cardiovascular; HF, heart failure; MedD, Mediterranean diet.

dietary patterns (i.e. Western diet, animal fat diet, and fast food diet).[74]

Data on the relationship between MedD and atrial fibrillation occurrence/recurrences are controversial (Table 4). The changes in nutritional habits might reduce the occurrence of arrhythmias.[75–77] According to MedD, a post-hoc analysis of the PREDIMED study revealed a 38% (hazard ratio: 0.62; 95% confidential index 0.45–0.85 vs. control group) reduction in atrial fibrillation occurrence when adopting MedD plus olive oil. These data were obtained after adjusting for confounding factors.[77]

Mattioli *et al.*[76] confirmed the lower incidence of atrial fibrillation in patients following MedD as compared with controls. The interesting result of their research was related to the higher probability of sinus rhythm conversion in patients highly adherent to MedD. They observed a 90% (odds ratio 1.90, 95% confidential index 1.58–2.81, $P=0.001$) probability of fast rhythm conversion in patients declaring high MedD score.[76] An interesting insight from Mattioli *et al.*[76] was related to a possible role of antioxidant properties of MedD on atrial fibrillation expression. Pastori *et al.*[78,79] confirmed such pathogenetic hypothesis. This group observed that higher adherent atrial fibrillation patients showed reduced levels of soluble NADPH oxidase 2-derived peptide and F2-isoprostanes,[78] and increased levels of glutathione peroxidase 3.[79] These results confirmed the antioxidant properties of MedD in atrial fibrillation, thus suggesting positive effects for the conversion or reduction of its occurrence/recurrence.

Furthermore, MedD can prevent major cardiovascular events related to atrial fibrillation.[78,80] Beyond antioxidant properties, the demonstration of stable time-in-therapeutic range for warfarin-treated patients[80,81] as well as the reduction in thromboxane A2 production (i.e.

reduced tendency to platelets to aggregate)[82] accounts for the reduced rate of atrial fibrillation-related adverse events.

Although confirmatory, structured, randomized trials should be adopted for these issues, the scientific background seems to favor the MedD in possible, positive influence on outcomes of SCD and/or atrial fibrillation patients.

Conclusion

The MedD is a reliable weapon against CVD progression. It positively affects endothelial function, arterial stiffness, and cardiac remodeling (Fig. 1 and Table 5).[83–87] The consequence is a reduction in the occurrence of PADs, improvements in the outcomes of CADs and heart failure (Fig. 1 and Table 5).[83–87] Therefore, the adoption of MedD can reduce the CVD manifestations and consequences, promoting healthy lifestyle and best management of body care.

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Conflicts of interest

There are no conflicts of interest.

References

1 Smith SC Jr, Collins A, Ferrari R, *et al.* Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). *J Am Coll Cardiol* 2012; **60**:2343–2348.
2 Nichols M, Townsend N, Scarborough P, *et al.* Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014; **35**:2950–2959.
3 Mozaffarian D, Benjamin EJ, Go AS, *et al.* Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. *Circulation* 2016; **133**:e38–e360.
4 Fuster V, Kelly BB. *Promoting cardiovascular health in the developing world. A critical challenge to achieve global health*. Washington, DC: National Academies Press (US); 2010.
5 Mokdad AH, Marks JS, Stroup DF, *et al.* Actual causes of death in the United States, 2000. *JAMA* 2004; **291**:1238–1245.
6 Arena R, Guazzi M, Lianov L, *et al.* Healthy lifestyle interventions to combat noncommunicable disease – a novel nonhierarchical connectivity model for key stakeholders: a policy statement from the American Heart Association, European Society of Cardiology, European Association for Cardiovascular Prevention and Rehabilitation, and American College of Preventive Medicine. *Mayo Clin Proc* 2015; **90**:1082–1103.
7 Scicchitano P, Cameli M, Maiello M, *et al.* Nutraceuticals and dyslipidaemia: beyond the common therapeutics. *J Funct Foods* 2014; **6**:11–32.
8 Menotti A, Puddu PE. How the Seven Countries Study contributed to the definition and development of the Mediterranean diet concept: a 50-year journey. *Nutr Metab Cardiovasc Dis* 2015; **25**:245–252.
9 Keys A, Blackburn H, Menotti A, *et al.* Coronary heart disease in seven countries. *Circulation* 1970; **41**:1–211.
10 Kromhout D, Keys A, Aravanis C, *et al.* Food consumption patterns in the 1960s in Seven Countries. *Am J Clin Nutr* 1989; **49**:889–894.
11 Hertog MGL, Kromhout D, Aravanis C, *et al.* Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. *Arch Intern Med* 1995; **155**:381–386.
12 Menotti A, Kromhout D, Blackburn H, *et al.* Food intake patterns and 25-year mortality from coronary heart disease: cross-cultural correlations in the Seven Countries Study. *Eur J Epidemiol* 1999; **15**:507–515.
13 Huijbregts PP, Feskens EJ, Räsänen L, *et al.* Dietary intake in five aging cohorts of men in Finland, Italy and The Netherlands. *Eur J Clin Nutr* 1995; **49**:852–860.
14 Trichopoulou A, Kouris-Iazos A, Wahlqvist ML, *et al.* Diet and overall survival in elderly people. *Br Med J* 1995; **311**:1457–1460.
15 Trichopoulou A, Tina Costacou T, Christina Bamia C, *et al.* Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; **348**:2599–2608.
16 Dilis V, Katsoulis M, Lagiou P, *et al.* Mediterranean diet and CHD: the Greek European Prospective Investigation into Cancer and Nutrition cohort. *Br J Nutr* 2012; **108**:699–709.
17 Chrysohoou C, Panagiotakos DB, Pitsavos C, *et al.* Adherence to the Mediterranean diet is associated with renal function among healthy adults: the ATTICA study. *J Ren Nutr* 2010; **20**:176–184.
18 Kontogianni MD, Chrysohoou C, Panagiotakos DB, *et al.* Adherence to the Mediterranean diet and serum uric acid: the ATTICA study. *Scand J Rheumatol* 2012; **41**:442–449.
19 Esposito K, Kastorini CM, Panagiotakos DB, *et al.* Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. *Metab Syndr Relat Disord* 2011; **9**:1–12.
20 Kastorini CM, Milionis HJ, Esposito K, *et al.* The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies on 534,906 individuals. *J Am Coll Cardiol* 2011; **57**:1299–1313.
21 Kastorini CM, Papadakis G, Milionis HJ, *et al.* Comparative of a-priori and a-posteriori dietary patterns using state-of-the-art classification algorithms: a case/case–control study. *Artif Intell Med* 2013; **59**:175–183.
22 Estruch R, Ros E, Salas-Salvado J, PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368**:1279–1290.
23 Nichols M, Townsend N, Scarborough P, *et al. European cardiovascular disease statistics 2012*. Brussels; Sophia Antipolis: European Heart Network; European Society of Cardiology; 2012.
24 Lloyd-Jones DM, Hong Y, Labarthe D, *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010; **121**:586–613.
25 Smith SC Jr, Chen D, Collins A, *et al.* Moving from political declaration to action on reducing the global burden of cardiovascular diseases: a statement from the Global Cardiovascular Disease Taskforce. *J Am Coll Cardiol* 2013; **62**:2151–2153.
26 WHO Regional Office for Europe. *Declaration on Nutrition and Non Communicable diseases in the context of health 2020*. Copenhagen: WHO Regional Office for Europe; 2013; Available at http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/publications/2013/vienna-declaration-on-nutrition-and-noncommunicable-diseases-in-the-context-of-health-2020.
27 Abdullah MM, Jones JP, Jones PJ. Economic benefits of the Mediterranean-style diet consumption in Canada and the United States. *Food Nutr Res* 2015; **59**:27541.
28 Criqui MH, Fronek A, Barrett-Connor E, *et al.* The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; **71**:510–551.
29 Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteriaon the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995; **91**:1472–1479.
30 Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 2004; **110**:738–743.
31 Ruiz-Canela M, Estruch R, Corella D, *et al.* Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA* 2014; **311**:415–417.
32 Coppola G, Novo S. Statins and peripheral arterial disease: effects on claudication, disease progression, and prevention of cardiovascular events. *Arch Med Res* 2007; **38**:479–488.

33 Hackam DG, Sultan NM, Criqui MH. Vascular protection in peripheral artery disease: systematic review and modelling study. *Heart* 2009; **95**:1098–1102.

34 Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E, PREDIMED INVESTIGATORS. Benefits of the Mediterranean diet: insights from the PREDIMED study. *Prog Cardiovasc Dis* 2015; **58**:50–60.

35 Ciccarone E, Di Castelnuovo A, Salcuni M, *et al.*, Gendiabe Investigators. A high-score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. *J Thromb Haemost* 2003; **1**:1744–1752.

36 Hoevenaar-Blom MP, Nooyens AC, Kromhout D, *et al.* Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. *PLoS One* 2012; **7**:e45458.

37 Klonizakis M, Alkhatib A, Middleton G. Long-term effects of an exercise and Mediterranean diet intervention in the vascular function of an older, healthy population. *Microvasc Res* 2014; **95C**:103–107.

38 Lydakis C, Stefanaki E, Stefanaki S, *et al.* Correlation of blood pressure, obesity, and adherence to the Mediterranean diet with indices of arterial stiffness in children. *Eur J Pediatr* 2012; **171**:1373–1382.

39 van de Laar RJ, Stehouwer CD, van Bussel BC, *et al.* Adherence to a Mediterranean dietary pattern in early life is associated with lower arterial stiffness in adulthood: the Amsterdam Growth and Health Longitudinal Study. *J Intern Med* 2013; **273**:79–93.

40 Gardener H, Wright CB, Cabral D, *et al.* Mediterranean diet and carotid atherosclerosis in the Northern Manhattan Study. *Atherosclerosis* 2014; **234**:303–310.

41 Sala-Vila A, Romero-Mamani ES, Gilabert R, Núñez I, *et al.* Changes in ultrasound-assessed carotid intima–media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. *Arterioscler Thromb Vasc Biol* 2014; **34**:439–445.

42 Sucato V, Novo G, Evola S, *et al.* Coronary microvascular dysfunction in patients with diabetes, hypertension and metabolic syndrome. *Int J Cardiol* 2015; **186**:96–97.

43 Montalescot G, Sechtem U, Achenbach S, *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2014; **35**:2260–2261.

44 Lichtenstein AH, Appel LJ, Brands M, *et al.* Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006; **114**:82–96.

45 Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation* 2011; **123**:2870–2891.

46 Trichopoulou A, Orfanos P, Norat T, *et al.* Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ* 2005; **330**:991.

47 Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr* 2017; doi: 10.1038/ejcn.2017.58. [Epub ahead of print].

48 Gardener H, Wright CB, Gu Y, *et al.* 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.

49 Danesh J, Saracci R, Berglund G, *et al.* EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. *Eur J Epidemiol* 2007; **22**:129–141.

50 Buckland G, González CA, 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.

51 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.

52 De Lorgeril M, Salen P, Martin JL, *et al.* Effect of a Mediterranean type of diet on the rate of cardiovascular complications in patients with coronary artery disease. Insights into the cardioprotective effect of certain nutriments. *J Am Coll Cardiol* 1996; **28**:1103–1108.

53 Barzi F, Woodward M, Marfisi RM, Tavazzi L, Valagussa F, Marchioli R, GISSI-Prevenzione Investigators. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. *Eur J Clin Nutr* 2003; **57**:604–611.

54 Iestra J, Knoops K, Kromhout D, de Groot L, Grobbee D, van Staveren W. Lifestyle, Mediterranean diet and survival in European postmyocardial infarction patients. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:894–900.

55 Casas R, Sacanella E, Urpi-Sardà M, *et al.* The effects of the Mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease: a randomized trial. *PLoS One* 2014; **9**:e100084.

56 Casas R, Urpi-Sardà M, Sacanella E, *et al.* Anti-inflammatory effects of the Mediterranean diet in the early and late stages of atheroma plaque development. *Mediators Inflamm* 2017; **2017**:3674390.

57 Panagiotakos DB, Pitsavos C, Stefanadis C, *et al.* Short-term prognosis of patients with acute coronary syndromes through the evaluation of physical activity status, the adoption of Mediterranean diet and smoking habits: the Greek Acute Coronary Syndromes (GREECS) study. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:901–908.

58 Aranda JM, Johnson JW, Conti JB. Current trends in heart failure readmission rates: analysis of Medicare data. *Clin Cardiol* 2009; **32**:47–52.

59 Schreiner G, Spertus JA, Vidán MT, *et al.* Recent national trends in readmission rates after heart failure hospitalization. *Circ Heart Fail* 2010; **3**:97–103.

60 Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. *Arch Intern Med* 2009; **169**:851–857.

61 Levitan EB, Wolk A, Mittleman MA. Relation of consistency with the dietary approaches to stop hypertension diet and incidence of heart failure in men aged 45–79 years. *Am J Cardiol* 2009; **104**:1416–1420.

62 Belin RJ, Greenland P, Allison M, *et al.* Diet quality and the risk of cardiovascular disease: the Women's Health Initiative (WHI). *Am J Clin Nutr* 2011; **94**:49–57.

63 Tektonidis TG, Åkesson A, Gigante B, *et al.* Adherence to a Mediterranean diet is associated with reduced risk of heart failure in men. *Eur J Heart Fail* 2016; **18**:253–259.

64 Papadaki A, Martínez-González MÁ, Alonso-Gómez A, *et al.* Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial. *Eur J Heart Fail* 2017; doi: 10.1002/ejhf.750. [Epub ahead of print].

65 Fitó M, Estruch R, Salas-Salvadó J, *et al.* Effect of the Mediterranean diet on heart failure biomarkers: a randomized sample from the PREDIMED trial. *Eur J Heart Fail* 2014; **16**:543–550.

66 Wirth J, di Giuseppe R, Boeing H, Weikert C. A Mediterranean-style diet, its components and the risk of heart failure: a prospective population-based study in a non-Mediterranean country. *Eur J Clin Nutr* 2016; **70**:1015–1021.

67 Levitan EB, Ahmed A, Arnett DK, *et al.* Mediterranean diet score and left ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr* 2016; **104**:595–602.

68 Levitan EB, Lewis CE, Tinker LF, *et al.* Mediterranean and dash diet scores and mortality in women with heart failure: the women's health initiative. *Circ Heart Fail* 2013; **6**:1116–1123.

69 Chrysohoou C, Panagiotakos DB, Aggelopoulos P, *et al.* The Mediterranean diet contributes to the preservation of left ventricular systolic function and to the long-term favorable prognosis of patients who have had an acute coronary event. *Am J Clin Nutr* 2010; **92**:47–54.

70 Chrysohoou C, Pitsavos C, Metallinos G, *et al.* Cross-sectional relationship of a Mediterranean type diet to diastolic heart function in chronic heart failure patients. *Heart Vessels* 2012; **27**:576–584.

71 Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary artery disease. *Circulation* 2012; **125**:1043–1052.

72 [No authors listed]. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 1999; **354**:447–455.

73 Bertoia ML, Trche EW, Michaud DS, *et al.* Mediterranean and dietary approaches to stop hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women. *Am J Clin Nutr* 2014; **99**:344–351.

74 Mohammadifard N, Talaei M, Sadeghi M, *et al.* Dietary patterns and mortality from cardiovascular disease: Isfahan Cohort Study. *Eur J Clin Nutr* 2017; **71**:252–258.

75 Mattioli AV. Lifestyle and atrial fibrillation. *Expert Rev Cardiovasc Ther* 2011; **9**:895–902.

76 Mattioli AV, Miloro C, Pennella S, *et al.* Adherence to Mediterranean diet and intake of antioxidants influence spontaneous conversion of atrial fibrillation. *Nutr Metab Cardiovasc Dis* 2013; **23**:115–121.

77 Martínez-González MÁ, Toledo E, Arós F, *et al.* Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation* 2014; **130**:18–26.

78 Pastori D, Carnevale R, Bartimoccia S, *et al.* Does Mediterranean diet reduce cardiovascular events and oxidative stress in atrial fibrillation? *Antioxid Redox Signal* 2015; **23**:682–687.

79 Pastori D, Carnevale R, Menichelli D, *et al.* Is there an interplay between adherence to Mediterranean diet, antioxidant status, and vascular disease in atrial fibrillation patients? *Antioxid Redox Signal* 2016; **25**:751–755.

80 Pastori D, Carnevale R, Nocella C, *et al.* Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular events in atrial fibrillation: effect of adherence to Mediterranean diet. *J Am Heart Assoc* 2017; **6**:; doi: 10.1161/JAHA.117.005784.
81 Pignatelli P, Pastori D, Vicario T, *et al.* Relationship between Mediterranean diet and time in therapeutic range in atrial fibrillation patients taking vitamin K antagonists. *Europace* 2015; **17**:1223–1228.
82 Pignatelli P, Pastori D, Farcomeni A, *et al.* Mediterranean diet reduces thromboxane A2 production in atrial fibrillation patients. *Clin Nutr* 2015; **34**:899–903.
83 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; **337**:a1344.
84 Knekt P, Ritz J, Pereira MA, *et al.* Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr* 2004; **80**:1508–1520.
85 Huxley R, Neil HA. The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. *Eur J Clin Nutr* 2003; **57**:904–908.
86 Hollman P, Cassidy A, Comte B, *et al.* The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established. *J Nutr* 2011; **141**:989S–1009S.
87 John J, Ziebland S, Yudkin P, Roe LS, Neil HAW, Oxford Fruit and Vegetable Study Group. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomized controlled trial. *Lancet* 2002; **359**:1969–1974.