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Symposium on 'Dietary management of disease'

Session 4: CVD, diabetes and cancer
Evidence for the use of the Mediterranean diet in patients with CHD

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Diet is associated with the development of CHD. The incidence of CHD is lower in southern European countries than in northern European countries and it has been proposed that this difference may be a result of diet. The traditional Mediterranean diet emphasises a high intake of fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts and seeds. It includes olive oil as a major fat source and dairy products, fish and poultry are consumed in low to moderate amounts. Many observational studies have shown that the Mediterranean diet is associated with reduced risk of CHD, and this result has been confirmed by meta-analysis, while a single randomised controlled trial, the Lyon Diet Heart study, has shown a reduction in CHD risk in subjects following the Mediterranean diet in the secondary prevention setting. However, it is uncertain whether the benefits of the Mediterranean diet are transferable to other non-Mediterranean populations and whether the effects of the Mediterranean diet will still be feasible in light of the changes in pharmacological therapy seen in patients with CHD since the Lyon Diet Heart study was conducted. Further randomised controlled trials are required and if the risk-reducing effect is confirmed then the best methods to effectively deliver this public health message worldwide need to be considered.

Mediterranean diet: CHD: Reduction in CHD risk: Non-Mediterranean populations

The WHO has reported that on a global scale in the period up to 2030 there will be a dramatic shift in the distribution of deaths from younger to older ages and from communicable to non-communicable diseases, with the leading causes of death likely to be CHD, cerebrovascular disease, HIV infection and chronic obstructive pulmonary disease[1]. Most of these diseases are complex, reflecting the interaction between genetic and environmental influences, including diet and physical activity.

CVD, which includes CHD, cerebrovascular disease and peripheral vascular disease, is still the leading cause of death in the UK, being responsible for 35% of all deaths[2]. Thus, both the management and prevention of CVD are major public health issues in the UK. Although mortality from CHD in the UK has been falling in the last four decades[2], it remains the major cause of premature death (before 75 years of age) in most affluent societies[3].

CHD

The major underlying disease process leading to CHD is atherosclerosis, a chronic inflammatory disease[4], which starts in early life and has stable and unstable phases[5]. Patients with the disease may be asymptomatic, have symptoms of chest pain or may present with sudden cardiac death. The transition from a stable to an unstable phase results from the rupture of an atherosclerotic plaque with associated partial or complete thrombosis of the artery[6] (Fig. 1). Typically, the patient then presents with increasing symptoms leading to the development of an acute coronary syndrome or myocardial infarction (MI)[5,7]. The diagnosis is based on clinical history and the results of various investigations including electrocardiography, exercise stress testing, imaging of the coronary arteries and measurement of cardiac biomarkers.

Abbreviations: ALA, α-linolenic acid; MI, myocardial infarction; PREDIMED, Prevención con Dieta Mediterránea; RR, relative risk.

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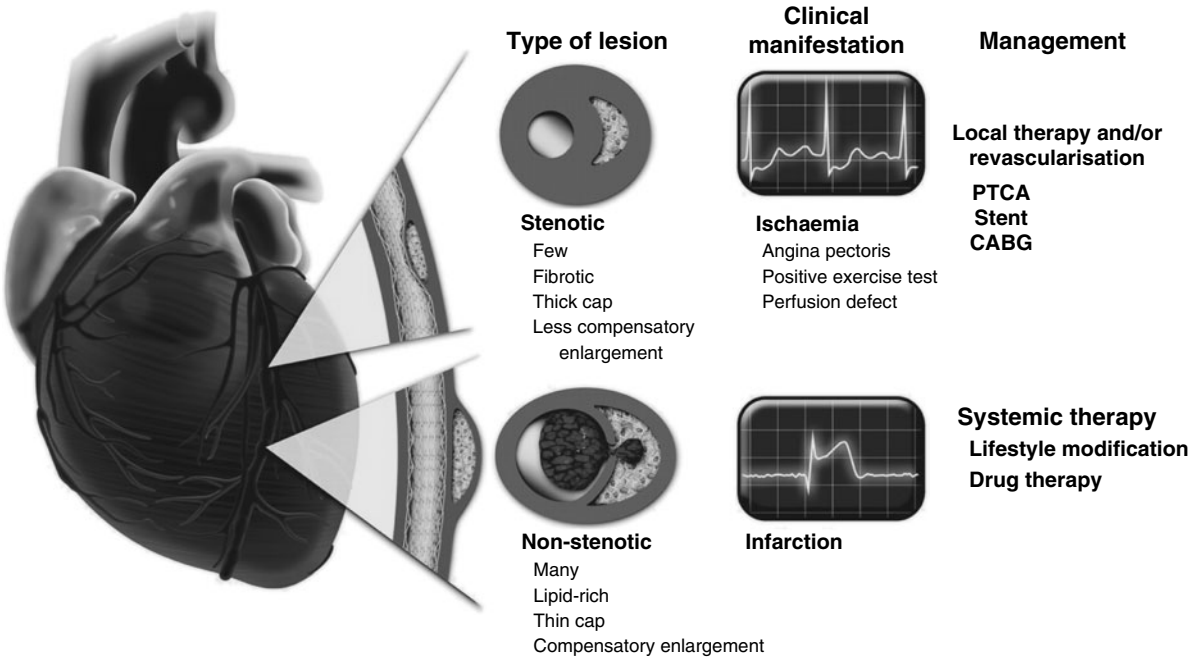

Fig. 1. Simplified schema of diversity of lesions in human coronary atherosclerosis. This schematic depicts two morphological extremes of coronary atherosclerotic plaques. Stenotic lesions tend to have: smaller lipid cores, more fibrosis and calcification; thick fibrous caps; less compensatory enlargement (positive remodelling) Non-stenotic lesions generally outnumber stenotic plaques and tend to have large lipid cores and thin fibrous caps susceptible to rupture and thrombosis. They often undergo substantial compensatory enlargement that leads to underestimation of lesion size by angiography. Non-stenotic plaques may cause no symptoms for many years but when disrupted can provoke an episode of unstable angina or myocardial infarction. Enlarged segments of the schematic show longitudinal section (left) and cross section (right) Many coronary atherosclerotic lesions may lie between these two extremes, produce mixed clinical manifestations and require multipronged management. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft. (From Libby & Theroux[6]; reproduced with permission.)

Risk factors for CHD

The non-modifiable risk factors for CHD include genetic predisposition, gender and age[8,9]. However, the majority of risk factors that contribute to CHD risk, including dyslipidaemia, hypertension, smoking and diabetes, are modifiable[10]. Diet is also thought to be a major factor in the development of CHD[11]. An association between the risk of developing CHD and obesity has been reported[10], while rates of overweight and obesity are increasing[12] and are high in patients with CHD[13]. However, the relationship between obesity and CHD is complex, in that obesity is known to increase the risk of developing type 2 diabetes, dyslipidaemia and hypertension[14], all of which are risk factors for CHD.

Diet and CHD

Lifestyle modifications (including diet) form part of strategies to prevent and delay the progression of CHD[15]. The development of CHD has traditionally been related to an increased consumption of cholesterol and saturated fat with low intakes of polyunsaturated fat[16] and possibly also a suboptimal intake of micronutrients[17]. However, the results of cohort studies and randomised controlled trials have not been in agreement, e.g. for vitamin E and β-carotene[17]. Various explanations have been offered in relation to the discordance between cohort studies and randomised controlled trials; it has been proposed that the trials conducted were too short in duration, that such interventions may have been more successful if conducted at an earlier stage in the CHD process and that the significant results linking micronutrient intake with disease risk observed in cohort studies may have been attributable to other diet and lifestyle behaviours. In addition, it is plausible that the complex mixture of micronutrients found, for example, in a diet high in fruit and vegetables may be more effective than large supplemental doses of a small number of micronutrients that were employed in the randomised controlled trials investigating antioxidants[17].

A recent systematic review of the evidence supporting a causal link between dietary factors and CHD concludes that current evidence only supports a valid association between a limited number of dietary factors, including vegetable, nut and MUFA intake (negative association) and *trans*-fatty acid and foods with a high glycaemic index or load (positive association), and CHD[18].

Assessment of whole dietary patterns *v.* single nutrients

The classical approach to assessing the relationship between diet and disease has been to focus on single nutrients or food items[19,20]. However, this approach often

does not take into account the potential interactions between combinations of food items in a whole diet[21]. There is now much interest in analysing whole dietary patterns in relation to disease risk[19,22,23] and some of these patterns have been considered in a systematic review[18]. It has been suggested that the relationship between diet and CVD is likely to be multifaceted, involving a wide variety of dietary constituents rather than individual nutrients[24]. It is thought that an optimal diet for cardiovascular health is likely to have an extensive overlap with the traditional Mediterranean diet[25]. In an overview of research on the Mediterranean diet it has been stated that >80% of CHD could be avoided by healthy food choices that are consistent with the traditional Mediterranean diet[26].

The Mediterranean diet

CHD has traditionally a low incidence in the Mediterranean region of Europe, leading to a higher life expectancy in these areas when compared with northern European countries[20]. The benefits of the Mediterranean diet were first highlighted in the Seven Countries Study[27] and the MONICA Project confirmed a north–south gradient in Europe in the incidence of CHD[28]. This outcome was supported by the Prospective Epidemiological Study of Myocardial Infarction, a cohort study of 10 000 men from Belfast and France in which a higher incidence of angina pectoris, MI and cardiac death was noted in Belfast compared with France[29]. The lower incidence of CVD in the Mediterranean region of Europe is thought to be at least partly a result of diet[20,30].

Definition of the Mediterranean diet

Defining the Mediterranean diet is difficult, given the broad geographical area that constitutes the Mediterranean region. There are cultural, ethnic, religious, economic and agricultural production differences that result in different dietary practices in these areas[15,31]. For example, the fat content of the Mediterranean diet varies between the countries, being higher in Greece and lower in Spain[32].

However, the diet has been described as a pattern that emphasises a high intake of fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts and seeds. It includes olive oil as a major fat source and dairy products, fish and poultry are consumed in low to moderate amounts, eggs are consumed zero to four times weekly and little red meat is consumed; in addition, wine is consumed in low to moderate amounts[15]. The key features of the dietary pattern have been expressed in the form of a diet pyramid (Fig. 2).

The Mediterranean diet has been described in more detail as a dietary pattern implying: (a) daily consumption of unrefined cereals and cereal products, vegetables (two to three servings), fruits (four to six servings), olive oil (as the main added lipid) and non-fat or low-fat dairy products (one to two servings); (b) weekly consumption of potatoes (four to five servings), fish (four to five servings), olives, pulses and nuts (more than four servings) and eggs and sweets (one to three servings); (c) monthly consumption of red meat and meat products (four to five servings) and a moderate wine consumption (one to two wine glasses daily)[33]. It is reported that the Mediterranean diet encourages an adequate intake of carotenoids, vitamin C, tocopherols, α-linolenic acid (ALA) and several possibly beneficial non-nutrient substances such as polyphenols and anthocyanins. The diet is low in saturated fat (approximately <9% energy), with total fat intake ranging from <30% energy to >40% energy[33]. In general, the diet contains: a high monounsaturated : saturated fat; moderate alcohol intake; high intakes of fibre, vitamins, folate and natural antioxidants; low intake of animal protein[34,35].

Dietary patterns in Mediterranean countries have, however, changed substantially over the last number of years[36], including in children[37,38]. For example, an examination of the dietary habits of 520 clinically-healthy individuals from Florence, Italy has concluded that, in general, these individuals do not follow a typical Mediterranean diet[39]. The prevalence of obesity in Greece has increased substantially, probably as a result of Westernisation of the diet, increased energy intake and decreased levels of physical activity[31], while the prevalence of MI and cardiovascular risk factors other than obesity have also increased[40]. Thus, it is now more common to think of the Mediterranean diet as the traditional diet that was consumed in Mediterranean countries in the 1960s.

Assessment of the Mediterranean dietary patterns: the Mediterranean diet score

The data collection process to assess whole diets can be complex and time consuming[41]. While patterns of food intake in the Mediterranean region are diverse, many attempts have been made to create a score that would reflect the intake of components of the Mediterranean diet. Three main methods have been adopted[42]:

1. those based on scoring (positive or negative) of components, e.g. the Mediterranean diet score[43–45];
2. those that add or subtract standardised components[46];
3. those based on ratios of components[47].

The scoring systems have used between seven and sixteen components of the diet and have been modified for use in children and adolescents. For example, the Mediterranean Adequacy Index is obtained by dividing the sum of the percentage total energy from typical Mediterranean food groups by the sum of the percentage total energy from non-typical Mediterranean food groups[47]; for full details of the scoring systems, see Bach *et al.*[42]. However, the most-widely-used scores will be summarised.

One of the first scores to be described calculates a diet score based on eight component characteristics of the traditional Mediterranean diet: high monounsaturated : saturated fat; moderate ethanol consumption; high consumption of legumes; high consumption of cereals (including bread and potatoes); high consumption of fruits; high consumption of vegetables; low consumption of meat and meat products; low consumption of milk and dairy products[43]. The gender-specific median is used as the cut-off for each component. In a later population-based

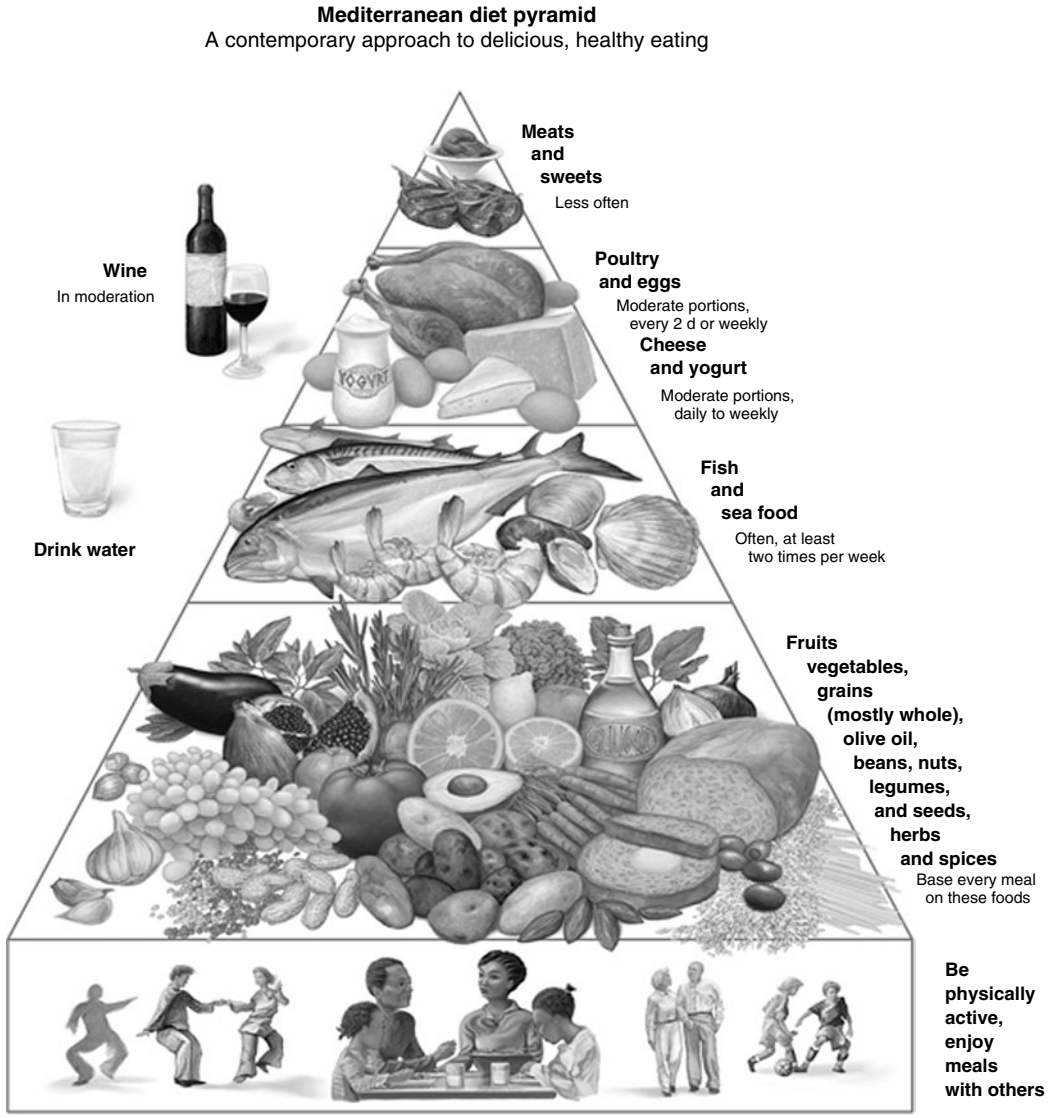

Fig. 2. Key features of the Mediterranean diet expressed as a Mediterranean diet pyramid. (From Oldways Preservation & Exchange Trust[149]; reproduced with permission.)

prospective study of 22 043 Greek adults this initial scoring scheme was adapted to include fish intake[44].

A shorter dietary intake questionnaire has been developed that assesses the frequency of consumption for a typical serving of nine food items thought to represent the cardioprotective elements of the Mediterranean diet[41]. The resulting score ranges from zero to nine points. The dietary items in the questionnaire include: olive oil (one or more spoons daily); fruit (one or more servings daily); vegetables or salad (one or more servings daily); fruit (one or more servings daily) and vegetables (one or more servings daily; one point is added when one or more servings daily of both fruit and vegetables is consumed); legumes (two or more servings weekly); fish (three or more servings per week); wine (one or more glasses daily); meat (less than one serving daily); white bread (less than once daily) and rice (less than once weekly) or wholegrain bread (more than five times weekly; one point is added when either consumption of both white bread and rice is low or consumption of wholegrain bread is high). The benefit of this questionnaire is that it provides a relatively simple means of assessing the Mediterranean diet and can reduce data collection time compared with other dietary scores, as it is not necessary to calculate the population- and gender-specific median to determine the value assigned to each of the individual components of the score, thus allowing the score to be quickly calculated and immediate feedback given to participants. The same research group has more recently proposed an extension of this score to include fourteen items for monitoring adherence to a Mediterranean dietary intervention[48].

An adaptation of the original traditional Mediterranean diet scores[43,44] was proposed for the analysis of the Nurses' Health Study, termed the alternate Mediterranean diet score, which focuses on a diet higher in plant food consumption, monounsaturated fat and fish and lower consumption of animal products and saturated fat[45]. Specific differences from the traditional Mediterranean diet

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scores include: excluding potatoes from the vegetable group; separating fruits and nuts into two categories; eliminating a score for dairy products; including whole-grain products only (rather than cereals as a whole); including only red and processed meats (rather than all meats); specifying the same range of alcohol intake for males and females. Both the alternate and traditional Mediterranean diet scores were used in a prospective analysis of Mediterranean diet and all-cause mortality and similar associations with mortality were found no matter which score was used[49].

Despite these findings of a similar association with overall mortality regardless of the Mediterranean diet score used, there is still uncertainty as to whether currently-popular and widely-used Mediterranean diet scores are appropriate for non-Mediterranean populations. Other scores are in development, including most recently the Mediterranean-style Dietary Pattern Score applied to the Framingham Offspring Cohort (7th examination)[50].

The Mediterranean diet and disease

The Mediterranean diet has been associated with a lower incidence of CHD, but it has also been associated with reduced all-cause mortality, a lower incidence of several types of cancer[44,51–54] and better self-perceived mental and physical health[55].

The Mediterranean diet and total mortality

The traditional Mediterranean diet has been associated with a reduction in total mortality in both population-based cohort studies[43,44,51] and in an intervention study[56] (discussed later in relation to the Mediterranean diet and CHD). In a cohort study of the Greek elderly a one unit increase in Mediterranean diet score has been found to be associated with a 17% reduction in overall mortality[43]. Meanwhile, the HALE project, a cohort study of elderly European men and women (1507 apparently-healthy males and 832 females aged 70–90 years) carried out in eleven European countries, has reported that adherence to a Mediterranean diet and healthy lifestyle is associated with lower risk of all-cause mortality (hazard ratio 0·77 (95% CI 0·67, 0·91)) after 10 years of follow-up[51].

Another population-based cohort study involving 22 043 adults in Greece has investigated the relationship between the Mediterranean diet and overall mortality[44]. Results have shown that a higher adherence to a Mediterranean diet is associated with a reduction in total mortality after 44 months of follow-up. A two-point increment in Mediterranean diet score is associated with a 25% reduction in total mortality[44] and a similar, although weaker, association has been shown recently after 8·5 years (14% reduction in risk per two-point increase in score; adjusted mortality ratio per two unit increase in score 0·86 (95% CI 0·80, 0·93))[57]. Similarly, among 74 607 subjects in the EPIC study a two-unit increase in Mediterranean diet score has been found to be associated with an 8% reduction in mortality[54].

A meta-analysis has been undertaken of prospective cohort studies that have in a primary prevention setting examined the relationship between adherence to a Mediterranean diet and mortality or chronic disease incidence[53]. Based on data for >500 000 subjects and >33 000 deaths it has been reported that a two-point increase in the adherence score is significantly associated with a reduced risk of mortality (pooled relative risk (RR) 0·91 (95% CI 0·89, 0·94)), cardiovascular mortality (RR 0·91 (95% CI 0·87, 0·95)), incidence of or mortality from cancer (RR 0·94 (95% CI 0·92, 0·96)) and incidence of Parkinson's disease and Alzheimer's disease (RR 0·87 (95% CI 0·80, 0·96)). This meta-analysis included the first prospective cohort study with US participants[49].

The Mediterranean diet and CHD

Much of the interest in the role of the Mediterranean diet has concentrated on CHD. There has been a number of population-based studies and intervention studies that have examined the relationship between the Mediterranean diet and CHD.

Population-based observational studies. A number of case–control studies[58,59] and prospective cohort studies[44,51] have reported associations between increased adherence to the Mediterranean diet and reduced risk of CHD. More recently, a reduced risk of CVD mortality has been reported in those individuals with the highest *v.* lowest Mediterranean diet score in men (hazard ratio 0·78 (95% CI 0·69, 0·87)) and women (hazard ratio 0·81 (95% CI 0·68, 0·97)) from the National Institutes of Health – American Association of Retired Persons Diet and Health Study, which included 214 284 men and 166 012 women aged 50–71 years[49]. Although the association was found to be more pronounced in smokers, it was also found to be present in patients who had never smoked.

The prospective cohort studies that have in a primary prevention setting examined the relationship between adherence to a Mediterranean diet and CVD incidence have been subjected to meta-analysis[53]. A two-point increase in the adherence score was shown to be significantly associated with a reduced risk of cardiovascular mortality (RR 0·91 (95% CI 0·87, 0·95); Fig. 3).

Since this meta-analysis was published an analysis of the Nurses' Health Study with 20 years of follow-up has been reported in which women in the top alternate Mediterranean diet score quintile were found to be at lower risk of both CHD and stroke compared with those in the bottom quintile (for CHD, RR 0·71 (95% CI 0·62, 0·82), $P<0·0001$ for trend; for stroke, RR 0·87 (95% CI 0·73, 1·02), $P=0·03$ for trend) [60]. CVD mortality was shown to be significantly lower among women in the top quintile of the alternate Mediterranean diet score (RR 0·61 (95% CI 0·49, 0·76), $P<0·0001$ for trend).

Not only is the Mediterranean diet associated with a decreased incidence of CHD, but it has been reported that a Mediterranean diet is associated with an improved prognosis among those individuals with existing CHD. In a prospective cohort study, but in a secondary prevention setting, the relationship between the level of adherence to a Mediterranean diet and survival has been examined in 1302 Greek individuals with a diagnosis of CHD (subset of the EPIC study population); mean follow-up was 3·78

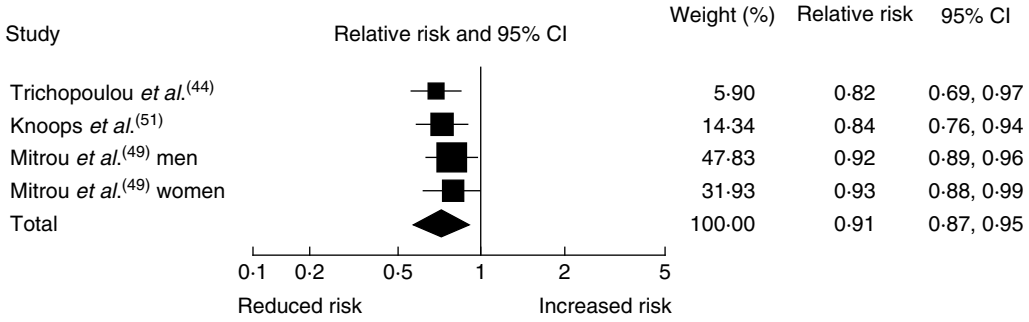

Fig. 3. Risk of mortality from CVD associated with two-point increase in adherence score for Mediterranean diet. (■), Effect size and 95% CI represented by horizontal lines; (◆), total effect size. (From Sofi *et al.*[53]; reproduced with permission from BMJ Publishing Group Ltd.)

years[61]. A Mediterranean diet scale was used to assess compliance with the diet, with a value of $\geqslant 0$ being assigned to each of nine components of the Mediterranean diet. It was found that a two-unit increase in the score is associated with a 31% lower cardiac mortality. A similar analysis in the larger EPIC elderly study of 2671 participants with 6·7 years follow-up has revealed a similar association (18 (95% CI 7, 27) % overall lower mortality rate for a two-unit increase in score)[62].

Intervention studies with clinical end points. In the GISSI-Prevenzione Study[24] a supplement of vitamin E and *n*-3 fatty acid was given to survivors of a recent MI. Patients were also given simple advice to increase intake of Mediterranean foods (fish, fruit, raw and cooked vegetables and olive oil). In an analysis adjusted for treatment allocation (therefore in effect corresponding to a cohort analysis) those individuals with a high consumption of Mediterranean foods were reported to have a relatively lower chance of premature death compared with those with a lower intake. It was found that all foods (fish, fruit, raw and cooked vegetables and olive oil) appear to have protective effects[24].

The Lyon Diet Heart Study has reported a reduction in major coronary events over a 4-year follow-up period[63]. The study was a prospective randomised single-blinded secondary prevention trial aimed at reducing the risk of cardiovascular deaths by diet modification and of recurrent MI in survivors of a first MI. A total of 605 patients were studied (303 control subjects and 302 study patients). Patients were recruited between 1988 and 1992 and less than one-third were on lipid-lowering drugs[56].

Patients in the experimental group were advised to adopt a Mediterranean-type diet. The patients were advised to include more bread, more root vegetables and green vegetables, more fish, less meat (beef, lamb and pork to be replaced with poultry), to have no day without fruit and to replace butter and cream with a margarine supplied by the researchers. This margarine had a composition similar to olive oil with 15% SFA and 48% oleic acid, but had 5·4% 18:1 *trans*-fatty acids; it was also slightly higher in linoleic acid (16·4% *v.* 8·6%) and much higher in ALA (4·8% *v.* 0·6%). The oils recommended for salads and food preparation were rapeseed and olive oils exclusively. Moderate alcohol consumption, in the form of wine, was allowed with meals. Control subjects did not receive dietary information from the study investigators; instead, they were expected to follow the dietary advice given to them by their physicians, similar to that of step 1 of the prudent diet of the American Heart Association[56].

As an interim analysis of the study after 27 months of follow-up demonstrated a protective effect of the Mediterranean intervention, with a reduction in the rate of coronary events of 73% and total mortality of 70%[64], the study was stopped early. The researchers have reported that one of the most remarkable differences between the experimental and control groups is plasma ALA concentration, which was found to increase by 68% in the experimental group[56].

In terms of dietary change, subjects in the control group were found to average (% energy) 34 from fat, 12 from saturated fat, 11 from monounsaturated fat and 6 from polyunsaturated fat, and 312 mg cholesterol/d. In contrast, subjects on the Mediterranean-style diet were found to average (% energy) 30 from fat, 8 from saturated fat, 13 from monounsaturated fat and 5 from polyunsaturated fat, and 203 mg cholesterol/d. The subjects on the Mediterranean diet were found to consume (% energy) less linoleic acid (3·6 *v.* 5·3) and more oleic acid (12·9 *v.* 10·8) and ALA (0·84 *v.* 0·29) and to consume more dietary fibre. Plasma fatty acid analysis conducted after 52 weeks of follow-up was found to confirm the dietary fatty acid data. The plasma levels of ALA were shown to be associated with composite outcome 1 (cardiac death and non-fatal MI)[56].

The final report of the study has shown that longer follow-up (mean follow-up of 46 months) and inclusion of more events in the analyses confirm the results of the interim analysis[63]. Significant reductions were found in three composite outcomes (composite outcome 1 (Fig. 4), composite outcome 2 (composite outcome 1 plus unstable angina, stroke, heart failure, pulmonary or peripheral embolism) and composite outcome 3 (composite outcome 2 plus minor events requiring hospital admission)), with the adjusted risk ratio ranging from 0·28 to 0·53. The reduction in risk in the Lyon Diet Heart Study was not found to be associated with differences in total cholesterol between the control and experimental groups and the survival curves were found to show a very early separation quite unlike that seen in the statin trials[65]. It was also reported that several years after randomisation most

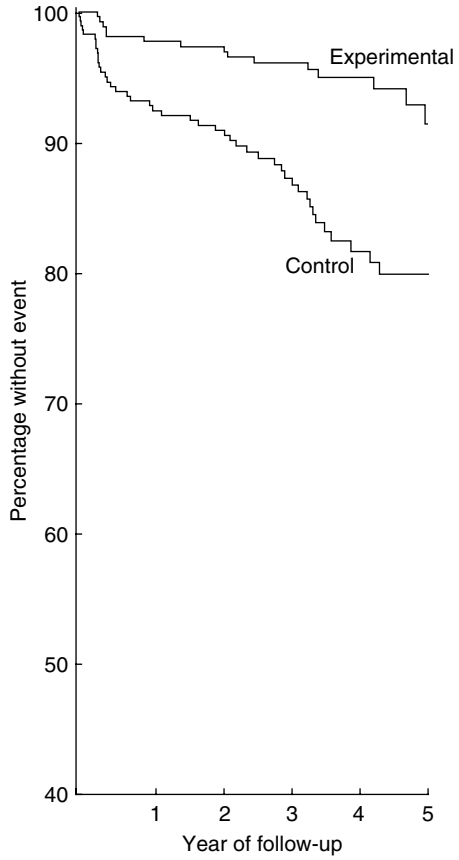

Fig. 4. Cumulative survival without non-fatal myocardial infarction (composite outcome 1; cardiac death and non-fatal myocardial infarction) among experimental (Mediterranean group) patients and control subjects in the Lyon Diet Heart Study. Cumulative survival was significantly different between groups ($P = 0{\cdot}0001$). (From de Lorgeril *et al.*[63]; reproduced with permission.)

experimental patients were still closely following the Mediterranean diet[63].

Although the results of the Lyon Diet Heart Study are impressive, there were some methodological limitations to the study. As the study was stopped early, because of beneficial effects noted in the original cohort, there may have been an overestimation of risk reduction. Baseline diet was only assessed in the experimental group and the diet of the control group was assumed to be comparable. Thus, it is unclear whether any dietary changes were made by the control group. In addition, dietary data are reported for only eighty-three (of 303 randomised into the study) and 144 (of 302 randomised into the study) subjects in the control and experimental groups respectively. Only 30 % of the total control cohort and <50 % of the total experimental group provided dietary data at the conclusion of the study and the diet of the other subjects who completed the study is not known.

Another intervention study, the Indo-Mediterranean Diet Heart Study, has reported fewer cardiac end points, sudden cardiac deaths and non-fatal MI in the intervention compared with the control group[66]. However, concern has recently been expressed about the reliability of the study[67], although the paper has not formally been withdrawn.

Effectively, therefore, there is only a single randomised controlled trial that has examined the effect of the Mediterranean diet in the secondary prevention of CHD. The American Heart Association has highlighted the need for further research in this area, taking into account the design limitations of the Lyon Diet Heart Study[68], while it has also been recognised that the results of this single trial need to be corroborated in both primary and secondary prevention models[15]. A systematic review of all dietary factors and CHD risk has ranked the evidence for the Mediterranean diet as strong, but also recommends further evaluation of dietary patterns in cohort studies and randomised trials[18].

There are a number of ongoing studies of the Mediterranean diet with CHD end points. The Prevención con Dieta Mediterránea (PREDIMED) study (recruitment aim *n* 9000) is a parallel group randomised trial that is designed to assess whether implementation of a Mediterranean diet will reduce CVD in a primary prevention setting[69]. Eligible patients include males (55–80 years) and females (60–80 years) with either diabetes or at least three major cardiovascular risk factors. The primary end point is a composite of cardiovascular death, non-fatal MI and non-fatal stroke. There are various secondary outcome measures, including death of any cause, heart failure, cancer, dementia, as well as changes in blood pressure, lipid profile and markers of inflammation. There are two intervention groups and one control group. Both intervention groups are advised to adopt a Mediterranean diet, one group is supplemented with olive oil and the other with nuts, while the control group are given advice to follow a low-fat diet. The rationale for using two types of Mediterranean diet is that the olive oil arm is enriched with MUFA and phenolic antioxidants whereas the nut diet is supplemented with PUFA and ALA. Recruitment started in 2003 and finished in 2006. Follow-up is for a minimum of 4 years so results will become available in 2010–11. What is lacking are studies in populations (e.g. northern European populations) for whom compliance may be less good.

Costs of the Mediterranean diet and cost-effectiveness considerations

A Canadian study of healthy women recruited from Quebec City has shown that adherence to the Mediterranean diet does increase the costs related to certain positive components (vegetables, fruits, legumes, nuts, rapeseed or olive oil, whole grains, poultry and fish) but this increase is balanced by a reduction in costs for other components (red meat, desserts and sweets and fast food) such that the overall effect is cost-neutral[70]. However, this cost balance may not be the case in all settings.

The cost-effectiveness of a Mediterranean diet after MI has also been evaluated, based on data from the Lyon Diet Heart Study, and the conclusion is that the intervention is highly cost-effective and represents an exceptional return on investment[71]; a similar conclusion has been drawn from the ATTICA Study[72].

Cardioprotective components of the Mediterranean diet

At this stage it is uncertain which components of the Mediterranean diet are protective against CVD. There is evidence that olive oil has beneficial properties[25,73] and the diet allows the consumption of large quantities of vegetables, salads and legumes[33]. *n*-3 Fatty acids are also thought to be important[68]. The following is a review of the evidence for the cardioprotective effect of some of the components of the Mediterranean diet.

Olive oil. In Mediterranean countries olive oil has traditionally been consumed in large quantities, which has resulted in high levels of dietary fat as a percentage of total energy, with values ranging from 25 to $\geqslant 40$[74]. Evidence suggests that olive oil may play a role in the prevention of CHD[75], most likely as a result of its high levels of MUFA and polyphenolic compounds[31,73]. MUFA, found in olive oil and rapeseed oil, are known to have beneficial effects on LDL- and HDL-cholesterol profiles[73–76] and also decrease platelet sensitivity and aggregation, as well as increase fibrinolysis[73]. The polyphenols found in olive oil may also have antioxidant effects[77] and MUFA are not substrates for lipid peroxidation.

n-*3 Fatty acids.* Oily fish is an important source of *n*-3 fatty acids, although grains, oils and some nuts are alternative sources. Marine sources provide EPA and DHA. Vegetable sources, including flaxseed, rapeseed oil, certain nuts and vegetables, provide ALA[78,79]. ALA is a known precursor of long-chain *n*-3 fatty acids; however, bioconversion of ALA to EPA and DHA is very limited in human subjects, particularly in males[80]. Consumption of fish and fish oils is known to decrease total cholesterol, serum TAG and LDL-cholesterol and may slightly increase HDL-cholesterol[76].

A number of studies have examined both fish consumption and *n*-3 fatty acid intake in relation to CHD risk. Using data from the observational Nurses' Health Study the association between fish and long-chain *n*-3 fatty acid intake has been examined and it was found that high consumption of fish and *n*-3 fatty acids is associated with a lower risk of CHD[81]. In the Diet And Reinfarction Trial subjects ($n>2000$, patients after MI) who were advised to eat oily fish were found to have a 29% reduction in 2-year all-cause mortality[82]. However, in the Diet And Reinfarction Trial-2 in which 3114 men with stable angina were advised to eat oily fish or take fish oil supplements and followed up for 3–9 years there was no effect on all-cause mortality and an increase in cardiac death, which was largely confined to the fish oil supplement group[83,84]. A weakness of the study, however, is a lack of objective markers of dietary compliance, and the authors postulate that compliance with the intervention may have been low.

In addition to the Diet And Reinfarction Trial-2 described earlier, two further large intervention trials of fish oil supplementation have been carried out[79]. In the GISSI-Prevenzione trial 11 000 patients with recent MI were given supplements of *n*-3 fatty acids, vitamin E, both or no treatment. Total mortality and sudden death were found to be lower in the patients supplemented with *n*-3 fatty acids as soon as 3 months after treatment commenced[85,86]. The Japan EPA Lipid Intervention Study, conducted in Japan in >18 000 patients with hypercholesterolaemia, has shown that EPA supplementation reduces non-fatal coronary events, but has little effect on cardiac death[87]. This result is in contrast with findings of previous studies that have suggested little effect of fish oils on non-fatal coronary events, but an effect on cardiac death[88]. The lack of effect on cardiac death may not be surprising, as fish intake is already high in Japan and therefore most of the population may already have been above the threshold for an effect of fish oil consumption on cardiac death; a dose-dependent effect has been suggested[88].

A systematic review of the evidence of the effects of long-chain *n*-3 fatty acids and *n*-3 SCFA has found no strong evidence of a reduced risk of total mortality or combined cardiovascular risk in those subjects taking additional *n*-3 fats[89], but the review does not include the Japan EPA lipid intervention study results. The most recent systematic review looking at dietary factors and CHD has described the strength of evidence as moderate for marine *n*-3 fatty acids and the evidence of benefit as observed predominantly in female cohorts and secondary prevention randomised controlled trials[18]. A further trial, the Alpha Omega Trial in patients post MI, is currently ongoing[90].

The suggested mechanism by which fish oils may reduce risk of cardiac events is through antiarrhythmic effects[84,88], antithrombotic effects[78] or possibly enhanced plaque stability[91]. However, it has been suggested that in certain subgroups of patients fish oils may not be protective and may even increase arrhythmias[84]. An increased risk of recurrent ventricular arrhythmias or fibrillation has been observed in patients with implantable defibrillators in response to fish oil[92], although when the study was combined with two others and a meta-analysis carried out no effect was found[93].

Dietary ALA intake has been associated with reduced risk of fatal CHD after 10 years of follow-up in the Nurses' Health Study[94], although by 18 years of follow-up the observed association was found to be largely confined to sudden cardiac death[95]. The Health Professionals' Follow-up Study, a cohort study of 44 895 men in the USA, has also reported an inverse relationship between ALA and CHD risk. The intake of marine *n*-3 fatty acids was not found to be inversely related to CHD risk, indicating that the protective effects of ALA may not be the same as those of the marine *n*-3 fatty acids[96].

In the Lyon Diet Heart Study patients were given margarine high in ALA (containing approximately 5% ALA). At the end of the 52-week follow-up plasma ALA concentration was found to have increased by 68% in the experimental group[56]. Plasma ALA was found to be the only fatty acid associated with an improved prognosis[63]. The investigators suggest that the protective effect observed in the experimental group was likely to be at least partly a result of ALA[63].

It has been suggested that ALA may exert an antiarrhythmic effect[95]. However, a systematic review has shown no effect of ALA on cardiovascular risk factors[97], and it is recognised that more research needs to be done on the potential cardioprotective effects of ALA[18,78]. A further trial, the Alpha Omega Trial using a factorial

design to examine the effects of marine *n*-3 fatty acids *v.* plant *n*-3 fatty acids in patients after MI, is currently ongoing[90].

Fruit and vegetables. The Mediterranean diet is rich in fruit and vegetables and epidemiological evidence, including meta-analyses, tends to support the notion that fruit and vegetables are protective against CHD[98–100]. It has been estimated that increasing fruit and vegetable intake to 600 g/d could reduce the global burden of CHD by 31 %[101], but evidence from randomised controlled trials examining the effect of increased fruit and vegetable consumption on cardiovascular end points is not currently available. Two studies have shown increased fruit and vegetable intake to reduce blood pressure[102,103], whilst another has shown that increasing fruit and vegetable consumption in subjects who are hypertensive improves arterial function[104]. In the Lyon Diet Heart Study vitamin C, a biomarker of fruit and vegetables consumption, was found to be increased in the intervention group[64].

Wine. Red wine leads to increased plasma concentrations of antioxidant polyphenols and has beneficial effects on endothelial function[20]. The *in vitro* inhibition of LDL-cholesterol oxidation by flavonoids, found in red wine, has also been demonstrated[105]. It has been stated that the French Paradox, the high intake of saturated fat but low CHD mortality seen in France, may be partly explained by a high wine consumption[106]. Using the Lyon Diet Heart Study data to study the association between alcohol intake and risk of recurrence in survivors of a first MI it was found that moderate wine drinking is associated with a reduction in cardiovascular complications[107]. These observations have been confirmed by meta-analysis for overall wine consumption[108], although some studies have questioned whether the type of alcohol consumed is important[109]. Determining the independent effect of alcohol as opposed to other lifestyle factors in observational studies is difficult[110]. The evidence for a benefit of overall alcohol consumption on CHD risk has been described as moderate[18].

Other dietary effects. In addition to the main components of the Mediterranean diet thought to be associated with a reduced risk of CHD, there will be other dietary changes (e.g. increased fibre consumption and reduced red meat consumption) that may also be beneficial. From the results of the Lyon Diet Heart Study it was concluded that *n*-3 fatty acids, oleic acid and antioxidant vitamins are likely to be cardioprotective[64]. However, it is interesting to note that in an assessment of the associations between Mediterranean diet score and survival (after a median of 44 months of follow-up) no strong associations were found for each of the individual dietary components of the Mediterranean diet score, suggesting that it is the overall pattern that is protective[44]. Analysis of the same cohort after 8·5 years has shown that certain components of the Mediterranean diet do contribute more than others; moderate ethanol consumption, low consumption of meat and meat products, high vegetable consumption, high fruit and nut consumption, high MUFA : SFA and high legume consumption contribute, whereas high cereal consumption, low dairy consumption and high fish consumption do not contribute[57]. The authors suggest a lack of association with cereal and dairy consumption because of the heterogeneity of these food groups (this factor has been dealt with in later Mediterranean diet scores) and that the lack of association with fish is because of the low fish consumption in this population[57].

Mechanism of action

Mediterranean diet and inflammation. CHD is, in part, an inflammatory disease[4] and inflammatory mechanisms are known to be important in determining the stability of atherosclerotic plaques[111]. Plasma levels of some markers of inflammation, including C-reactive protein and IL-6 have been shown to predict future cardiovascular risk[111]. A number of studies have examined associations between the Mediterranean diet and inflammatory markers.

In the ATTICA Study those participants in the highest tertile of Mediterranean diet score were found to have on average 20 % lower C-reactive protein levels, 17 % lower IL-6 levels, 15 % lower homocysteine levels, 14 % lower leucocyte counts and 6 % lower fibrinogen levels compared with those in the lowest tertile[112]. A similar negative association between adherence to the Mediterranean diet and C-reactive protein and IL-6 concentrations has recently been shown in survivors of MI[113], with a twin study also showing a negative association for IL-6, but not C-reactive protein[114].

A randomised trial has assessed the effect of a Mediterranean-style diet on endothelial function and vascular inflammatory markers in patients with metabolic syndrome[115]. Patients in the intervention group received advice on a Mediterranean-style diet, while those in the control group were given general advice on healthy food choices. After 2 years of follow-up patients following the Mediterranean-style diet were found to have significantly reduced serum concentrations of high-sensitivity C-reactive protein ($P = 0{\cdot}01$), IL-6 ($P = 0{\cdot}04$), IL-7 ($P = 0{\cdot}04$) and IL-18 ($P = 0{\cdot}03$), as well as decreased insulin resistance ($P < 0{\cdot}001$). It was concluded that one of the mechanisms responsible for the cardioprotective effect of the Mediterranean diet may be through reduction of a low-grade inflammatory state associated with the metabolic syndrome[115].

The PREDIMED investigation has looked at the effect of the Mediterranean diet on immune cell activation and inflammation in a subset of the participants (112 older subjects with diabetes or three or more CVD risk factors)[116]. Both Mediterranean diet intervention groups (one supplemented with olive oil, the other with nuts) were found to have decreased IL-6 and soluble intercellular adhesion molecule-1 after 3 months, while monocyte expression of CD49d (an adhesion molecule important for leucocyte homing) and CD40 (a pro-inflammatory mediator) were also found to be decreased in the two Mediterranean diet groups.

Two studies have recently examined the association between the Mediterranean diet and adiponectin concentrations, because of the proposed anti-inflammatory effect of adiponectin in addition to its effects on insulin resistance. Adherence to the Mediterranean diet was found to be associated with higher adiponectin concentrations in

both studies[117,118]. These observations have yet to be confirmed in intervention studies.

Mediterranean diet and endothelial function. Several studies have examined the effects of a Mediterranean-type dietary intervention on intermediate end points such as endothelial function. An increase in flow-mediated dilatation has been reported, suggesting an improvement in endothelial function in men with hypercholesterolaemia[119]. This effect is likely to be a result of increased antioxidant intake; in an examination of the postprandial effects of components of the Mediterranean diet on endothelial function a meal containing olive oil as a fat source was found to reduce brachial artery flow-mediated vasodilation by 31%, but this decrease was shown to be reduced by the concomitant administration of vitamins C and E (71%) or balsamic vinegar and salad (65%)[120]. Similarly, a meal containing a combination of olive oil rich in antioxidants (green compared with refined) and red wine (compared with white wine) was found to improve flow-mediated dilatation in healthy volunteers, with the low antioxidant versions of these foods having no effect[121].

In the intervention study in patients with metabolic syndrome described earlier endothelial function (defined as a score describing blood pressure and platelet aggregation response to L-arginine infusion) was also found to be improved in the intervention group after 2 years ($P<0{\cdot}001$)[115].

Mediterranean diet and metabolic syndrome. As described earlier for inflammation and endothelial function, in a trial of 180 patients with the metabolic syndrome in which patients were randomised to a standard diet or a Mediterranean-diet it was shown that after adoption of a Mediterranean diet for 2 years only forty of the patients randomised to the Mediterranean diet arm still fulfilled criteria for the metabolic syndrome compared with seventy-eight patients in the control group ($P<0{\cdot}001$)[115]. Dietary analysis of the study has shown that the patients following the Mediterranean diet had a greater fibre, PUFA and MUFA and complex carbohydrate intake, a lower *n*-6:*n*-3 fatty acid intake and lower intakes of energy, saturated fat and cholesterol. Total fruit, vegetable, nut, wholegrain and olive oil consumption was also found to be higher in the intervention group.

The PREDIMED investigation has undertaken an interim analysis after 1 year on a subset of the participants who were older and at high risk of CVD[122]. At baseline approximately >61% fulfilled criteria for metabolic syndrome. It was found that the Mediterranean diet supplemented with nuts but not the same diet supplemented with olive oil reduced the prevalence of metabolic syndrome at 1 year by 13·7%.

Mediterranean diet and diabetes. The Seguimiento Universidad de Navarra project, a prospective cohort study (*n* 13 380) of graduates of the University of Navarra, registered nurses in Spain and other university graduates, has reported that adherence to a Mediterranean diet is associated with a reduced risk of development of diabetes (incidence rate ratios adjusted for age and gender compared with those with low adherence scores were 0·41 (95% CI 0·19, 0·87) for those with moderate adherence and 0·17 (95% CI 0·04, 0·75) for those with high adherence)[123]. One potential mechanism suggested by the authors relates to evidence that extra virgin olive oil may protect against insulin resistance. Patients on Mediterranean diet interventions have been found to have reduced plasma glucose[48,115,124] and homeostatic model assessment score (insulin resistance)[115].

Mediterranean diet and lipids. In the Medi-RIVAGE Study the effects of either a Mediterranean-type diet or a low-fat diet for 3 months on cardiovascular risk factors were evaluated in >200 French volunteers with moderate risk for CVD[125]. The volunteers were advised to adopt either a Mediterranean-type diet or a low-fat diet similar to that of the American Heart Association. Neither of the groups complied completely with the diets, but changes were found in clinical and biological markers, including total cholesterol and TAG, in both intervention groups. The observed lowering of plasma cholesterol was reported to indicate a potential 9% reduction in cardiovascular risk in the low-fat diet group compared with 15% in the Mediterranean diet group[125]. Other intervention studies have also demonstrated a beneficial lipid-altering effect[126,127], including HDL-raising effects[48,115].

Mediterranean diet and body weight and blood pressure. Intervention studies have demonstrated an effect of the Mediterranean diet on BMI in some[115,126], but not all[48] studies. In a study of different weight-loss diets a restricted-energy Mediterranean diet was found to produce a greater weight loss than a low-fat restricted-energy diet, and also to have beneficial effects on glycaemic control[124].

Mediterranean diet interventions have also been shown to reduce blood pressure[48,115], and adherence to the Mediterranean diet has recently been shown in a longitudinal study to be related to reduced age-related changes in blood pressure[128].

Antioxidant effects of Mediterranean diet. A number of studies have examined the association between adherence to the Mediterranean diet, as an antioxidant-rich diet, and various biomarkers of oxidative stress. An examination of reduced:oxidised glutathione in a twin study has shown an association with the Mediterranean diet that is not confounded by genetic or shared environmental factors[129]. An association between Mediterranean diet adherence and both total antioxidant capacity and oxidised LDL-cholesterol concentrations has been shown in the ATTICA Study[130]. These associations from observational studies have been confirmed by an analysis of PREDIMED intervention data after 3 months, in which both oxidised LDL levels and malondialdehyde concentrations in mononuclear cells were found to be decreased in the two Mediterranean diet interventions, although effects on serum glutathione peroxidase activity were not observed[131].

Public health considerations and the need for further research

There is therefore increasing evidence from epidemiological and intervention studies about the benefits of the Mediterranean diet on CHD. However, there are a number of important areas in which further research must be carried out.

A need for further intervention trials and epidemiological studies? The results of the Lyon Diet Heart Study[63], if replicated in other populations, could provide a substantially enhanced method of reducing the morbidity and mortality associated with CHD. A recent systematic review calls for further studies investigating dietary patterns, including the Mediterranean dietary pattern, in cohort studies and randomised controlled trials[18], and ultimately these dietary patterns will have to be tested in the primary and secondary prevention settings.

It is important to remember, however, that since the Lyon Diet Heart Study was carried out, the pharmacological management of patients post MI has also changed substantially, with widespread use of statins, angiotensin-converting enzyme inhibitors, β-blockers and aspirin, and it remains unclear whether the impact of dietary change is likely to be maintained in this different pharmacological milieu. A repeat of the Lyon Diet Heart Study, therefore, assumes even greater importance.

The difficulties faced by researchers when trying to design randomised trials to study the effects of diet and/or lifestyle on clinical outcomes have been highlighted and the importance of epidemiological investigations and studies that use intermediate end points have been emphasised[132]. For observational studies the recommendation is for large studies with repeated comprehensive dietary assessments, coupled where possible with biochemical assays of nutrients, as these assays will define dietary intakes with greater accuracy and permit better quantification of intake of nutrients and foods.

A crucial consideration in observational epidemiology is how the effects of diet can be separated from other lifestyle choices such as exercise, social class and cultural differences, and it is not certain that adjustment for known confounders really does take account of these interactions. For example, it has been suggested that the effect of the Mediterranean diet may be explained by potential geographic, social and other cultural differences among target populations[68], including attitudes to food and to the diet–health link[133]. The ultimate proof of causality needs to come from randomised controlled trials and the possibility of residual confounding constantly acknowledged in observational epidemiological studies. Recent studies have looked at overall lifestyle patterns, rather than just dietary patterns. These studies have included some method of assessment of diet quality, smoking, alcohol consumption, physical activity and BMI and have demonstrated strong associations with cardiovascular, cancer and total mortality[134–138], and therefore the development of a lifestyle score that encompasses adherence to the Mediterranean diet may be a useful tool in future epidemiological studies.

Mediterranean diet pattern and non-Mediterranean populations. Most of the observational studies and one intervention study with clinical end points have been carried out in Mediterranean or European populations, although the association with mortality has been confirmed in an American population[49]. It has been suggested that the Mediterranean diet may be difficult to adopt in other populations because of differences in cultural and environmental conditions[33], and it has been suggested that the Lyon Diet Heart Study may be difficult to replicate in northern European populations[139]. It has been recognised that new dietary habits need to be financially and gastronomically acceptable and practically feasible for patients (and their relatives)[63].

A number of studies have sought to determine whether the Mediterranean diet is transferable to other populations. A study in Germany has investigated whether it is theoretically possible to incorporate some characteristics of the Mediterranean diet into the German food pattern by comparing the food consumption data of four Mediterranean countries with that of Germany. Results show that Germans eat fewer vegetables, cereals and pulses and more animal products, but that availability of food is such that components of the Mediterranean diet could be incorporated into German food patterns[140].

Two studies have examined a Mediterranean diet intervention in clinical populations. It was shown that dietary advice to adopt a Mediterranean diet in patients post MI leads to increases in Mediterranean diet score of about three units at both 6 months and 12 months[141]. Three different methods of delivering dietary advice were tested, including behavioural counselling, but it was shown that dietary change is achieved regardless of the method of advice delivery used. Increases in total fruit, vegetable and legume consumption and an improvement in the MUFA : SFA intake have been achieved in patients with rheumatoid arthritis in Glasgow assigned to a Mediterranean diet intervention[142].

Changing dietary patterns worldwide. These interventions occur against a background of globalisation and convergence of dietary patterns towards a typical Western diet, and this situation is not just a problem for Mediterranean countries, as outlined earlier[143]. Less-developed countries are tending to adopt more-energy-dense diets rich in animal products and fast-food consumption[143,144]. Public health policy options range from measures to raise awareness of the health benefits of the Mediterranean diet or other healthy dietary patterns, through changing relative food prices in favour of such diets, to taxing individuals who do not follow such diets and are therefore more prone to develop chronic disease with associated healthcare costs[144].

Factors determining adherence to a Mediterranean diet. At present, little work has been carried out to determine what factors are associated with adherence to a Mediterranean diet and how public health messages can best be promoted. The PREDIMED investigation has shown that a 1-year behavioural intervention comprising both group and individual sessions by dietitians in conjunction with the provision of certain key foods of the Mediterranean diet results in improved dietary habits of the participants at high risk of CVD[69], and a similar effect of dietary advice has been shown for patients with CHD[141]. Whether such interventions would be effective for the general population remains to be determined, although it has been shown among university students that women are more compliant with the Mediterranean diet pattern than men, that younger participants (both male and female) are less likely to comply and that those who are more physically active are more likely to follow a Mediterranean diet pattern[145].

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Current dietetic advice for secondary prevention of CHD. UK dietetic guidelines on the dietary advice that should be given in the secondary prevention of CVD state that every individual who has CHD should be advised to reduce saturated fats and replace them with unsaturated fats and individuals who have had an MI should be advised to increase marine *n*-3 fat intake (an update from the British Dietetic Association (R Vine and A Mead on behalf of the UK Heart Health and Thoracic Dietitians Specialist Group of the British Dietetic Association, unpublished results) confirms this advice as a recommendation to consume at least two large servings of oily fish weekly) and also be given 'Mediterranean' dietary advice (advice to increase *n*-3 fats, fruit and vegetables and fresh foods and to reduce saturated fats and processed foods)[146]. These recommendations largely concur with those given by the National Institute for Health and Clinical Excellence for cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of CVD[147].

Conclusion

It is clear that diet is associated with the development of CHD. The incidence of CHD is lower in southern European countries than in northern European countries and it is thought that this position may, at least partly, be a result of diet. Numerous studies have shown that the Mediterranean diet appears to protect against CHD, and this finding has been confirmed by meta-analysis. However, it is uncertain whether the benefits of the Mediterranean diet are transferable to other non-Mediterranean populations, although encouragingly a recent small US-based Mediterranean-style diet randomised controlled trial in survivors of a first MI indicates that this transfer may be possible[148]. Another uncertainty is whether the effects of the Mediterranean diet, as demonstrated in the Lyon Diet Heart Study, will still be feasible in light of the changes in pharmacological therapy seen in patients with CHD since the study was conducted. Further work needs to be carried out to answer this question, and if such an effect is confirmed consideration needs to be given to the best methods to effectively deliver this public health message worldwide.

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