Special Article

Evaluating and adapting the Mediterranean diet for non-Mediterranean populations - a critical appraisal

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Abstract

This review discusses the limitations of current techniques for evaluating the Mediterranean diet in non-Mediterranean populations, and how differences between the eating and lifestyle habits of these two populations may influence

the implementation of a Mediterranean diet in non-Mediterranean populations. Food groups may vary significantly between Mediterranean and non-Mediterranean populations due to the precise foods within the food group and due to aspects of food production and preparation. Examples include MUFA in relation to its source (meat versus olive oil), vegetables in relation to the amount consumed and how they are prepared, alcohol in terms of its pattern of intake and source (wine versus other sources), and the nature of meat and dairy produce. Lifestyle factors such as meal patterns and exposure to sunlight may also act as confounding factors when assessing the overall benefits of a Mediterranean diet. Improving Mediterranean diet scores and measuring plasma nutrient levels may help mitigate the effects of these confounders. These considerations may have important health implications when implementing a Mediterranean diet in non-Mediterranean populations.

Introduction

Despite the multiple forms of the Mediterranean diet (Med diet) that have arisen as a consequence of the diverse food habits across the region, nutritionists have nevertheless established a model Med diet. This model Med diet is characterised by a large quantity and diversity of plant-derived foods (whole grain cereals, raw and cooked vegetables, fresh and dry fruits, legumes and nuts), fish, a moderate intake of meat and dairy produce (both preferably from goats and sheep), olive oil as added fat, and a moderate intake of wine during meals. [1,2] This dietary pattern typically represented the food habits of Southern Italy and Greece (especially Crete) around the 1970s. These countries were part of the "Seven Countries Study", which was the first study to demonstrate the health benefits of a Med diet with regard to all-cause mortality, and especially cardiovascular mortality, when comparing a traditional Med diet with diets from the US and North European countries. [3] Later, the health effects of the Med diet were studied within a single population by classifying the subjects into groups according to their adherence to a Med diet, [4] and by evaluating their disease risk relative to how far their food habits were from the traditional Med diet. [5] Both of these studies were conducted within Mediterranean populations and used *a priori* dietary patterns that were based on the main characteristics of the Med diet.

Subsequently, it was proposed to apply Med diet scores to non-Mediterranean populations. However, there are a number of differences between the eating and lifestyle habits of Mediterranean and non-Mediterranean populations that make using the original Med diet scores either impossible (for example, when the Med diet score includes olive oil, since only a few populations in the world use olive oil), or misleading (for example if the foods of the score have different compositions in Mediterranean and non-Mediterranean countries). This latter point could potentially influence the evaluation of the effectiveness of a Med diet for non-Mediterranean populations. Analysing the results of various studies that have applied a Med diet score (either the original one, or a derived or modified score), it is possible to pinpoint those features of the Med diet that appear most stringent. This is important because of the interest in using a Med diet in non-

Mediterranean populations to manage coronary heart disease (CHD) and other chronic diseases. [6,7]

This review discusses some of the differences between the eating and lifestyle habits of Mediterranean and non-Mediterranean populations that could potentially impact on the health benefits of a Med diet. We address three main issues:

1. Are the *a priori* Med diet scores that have been constructed from literature data or dietary assessment obtained in Mediterranean populations appropriate for evaluating adherence to a Med diet and its health effects in non-Mediterranean countries?
2. Are there factors associated with a Med diet in Mediterranean countries but not present in non-Mediterranean countries that may affect the health benefits obtained from a Med diet (eg differences in lifestyle and meal structure)?
3. Could differences in the types and varieties of foods consumed and their methods of preparation also play a role?

These issues will be illustrated by comparing the western diet, and especially the UK diet, with the diet in Mediterranean countries.

Dietary assessments of adherence to a Med diet

A priori dietary patterns

By the 1990s, nutritional epidemiology had foreseen the limits of using an assessment system based on nutrient intake. The ability to understand the relationship between food and health was restricted because of incomplete food composition tables and because of the difficulty in ascertaining the specificity of a given nutrient, or even a given food, to an observed health effect. It became evident that a holistic approach should be used in nutritional epidemiology, [8,9] and this especially applied to the Med diet, a dietary pattern whose beneficial effects were becoming widely acknowledged. [10] Several Med diet scores were therefore designed. [5,11,12] Only the Med diet scores of Trichopoulou et al, referred to here as MDS, will be discussed here because it is the one most widely used, and also because it has been modified to fit various populations.

In the original MDS, the authors took advantage of the food consumption pattern of an elderly Greek population who had maintained a traditional Med diet up until the 1990s. [5] A nutritional survey of this population provided a quantitative assessment of the characteristic foods of the Med diet. A point scale was established to assess the degree of adherence to the traditional Med diet. The authors arbitrarily decided that the median sex-specific value of the consumption of nine selected characteristic components of the Med diet would be the cut-off determining adherence. A value of 0 or 1 was assigned for each of the five presumed beneficial food groups ie vegetables, legumes, fruits and nuts, cereals and fish. A value of 0 was assigned if consumption was below the median, and a value of 1 was assigned if consumption was above the median. It was decided to replace olive oil with the ratio of monounsaturated fatty acids (MUFAs) to saturated fatty acids (SFAs) because Ancel Keys had established that this ratio was the main factor contributing to the low cardiovascular disease (CVD) mortality. [3] Thus a value of 1 was assigned to individuals with a MUFA:SFA ratio at or above the median observed in the population, and a value of 0 for a ratio less than the median. For dairy products, and meat and meat products (whose consumption is typically low or moderate in the Med diet), a value of 0 was assigned for consumption at or above the median, and a value of 1 was assigned for consumption below the median. With regard to the moderate intake of ethanol in the Med diet, a value of 1 was assigned to men consuming between 10 g and < 50 g per day and to women consuming between 5 g and < 25 g per day. Thus, the final MDS ranged from 0 (minimal adherence) to 9 (maximal adherence).

This pattern was perfectly adapted to the Greek population and conformed with previous results on the benefits of a Med diet on mortality. [5] It was therefore proposed to apply it to other populations, e.g. populations in the EPIC study. However, a few modifications were necessary in order to adapt the MDS to other European populations. The score for the EPIC study had two major adaptations [13]:

(1) In the original score, the major source of MUFAs is olive oil and the high MUFA:SFA ratio reflects a high consumption of olive oil and a low consumption of animal products. Because relatively few people in Northern

Europe use olive oil, it was necessary to modify the score using another marker for vegetable oil consumption. Hence the MUFA:SFA ratio became unsaturated fat:SFA. This had two consequences. Firstly, it did not take into consideration substances in the non-saponifiable fraction of olive oil (especially the triterpene squalene and the phenolic compounds hydroxytyrosol and oleocanthal), many of which have antioxidant and anti-inflammatory actions and are potentially beneficial against chronic degenerative diseases, and hence mortality. Secondly, MUFAs are, to a large extent, markers of olive oil in the original MDS since it was applied to a population mainly consuming olive oil for cooking and as a salad dressing. But when applied to Northern European populations, MUFAs reflect, to a large extent, the consumption of animal fat, and it has been demonstrated that these MUFAs are associated with CVD [14] and breast cancer, [15] as further discussed by Gerber and Richardson. [16] It is interesting to note that in an "*a posteriori*" adaptation of the MDS, olive oil replaced the ratio MUFA:SFA. [17]

(2) A significant difference between Greek and North European populations is in their intake of plant-derived foods. Retaining the Greek level of consumption would have resulted in the majority of North European people scoring 0 for vegetables and legumes. Hence, it was decided to use as a cut-off the median of the consumption of the nine components of the MDS in each population. Under these conditions, the value of the cut-off differed markedly among the EPIC populations. For example, the median Greek consumption of vegetables (excluding potatoes) in the EPIC study was 500g/d for men and 550 g/d for women, [5] whereas the median values for all populations of the EPIC study were 157g/day for men and 184 g/d for women. [13] As might be anticipated, such a modified MDS was not associated with a reduced mortality risk in the North

European populations analysed. [13] The *a posteriori* adaptation of the MDS of Sofi et al proposed absolute values for food consumption to be reached in order to describe adherence to a Med diet. [17] These values were derived from a segmented regression analysis of each food consumption of the MDS and overall mortality of the Greek EPIC cohort. The "change-point" on the segment provided for the food cut-off to be used in the MDS. Thus for vegetables the "change-point" is >500 g, very close to what could be deduced from the literature, and the amount that is generally proposed in public health recommendations.

Several other modified Med diet scores have subsequently been proposed. In the US, Fung and colleagues excluded potato products from the vegetable group, separated fruit and nuts into two groups, eliminated the dairy group because low-fat milk is predominantly used in the US, included whole-grain products only, included only red and processed meats in the meat group, and allocated 1 point for alcohol intake between 5 and 15 g/d. [18] It was called the alternate MDS (aMDS) and was not associated with overall post-menopausal breast cancer risk, but only in sub-classes of this disease. In 2010, another modification was developed and applied to the EPIC cohorts. [19] Each component (apart from alcohol) was calculated as a function of energy density (g/1000 Kcal/d) and was then divided into tertiles of intake. A score of 0, 1 or 2 was assigned to the first, second, and third tertiles of intake for the five components presumed to fit the Med diet, namely fruit (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (fresh or frozen, excluding fish products and preserved fish), and cereals. The scoring was inverted for the two components presumed not to fit the Med diet, namely total meat and dairy produce. This scoring recognized the importance of olive oil: 0 was assigned to non-consumers, 1 for subjects consuming below the median (calculated only within olive oil consumers), and 2 for subjects consuming equal or above this median. Alcohol was assigned either 2 for moderate consumers (range: 5–25 g/d for women and 10–50 g/d for men) or 0 for subjects outside (above or below) the sex-specific range. This modification was called the relative Med diet (rMED). The rMED scores were then grouped into low (0–6), medium (7–10), and high (11–18). This score compensated for the difference in food consumption among the cohorts by using energy density and took into consideration the specificity of olive oil. The results are not shown by cohorts, but the overall results showed a risk reduction for gastric adenocarcinoma of 33% with increasing adherence to the rMED.

Correlating and confounding factors associated with a Med diet

It has been shown that the order of courses in a meal and the pattern of meals through the day are strong characteristics of a Med diet. [20] Lunch is the main meal, providing not only the required energy but also a sufficient quantity of plant-derived nutrients, ie fibre, micronutrients and phytochemicals. In addition, besides the expected typical food intake, sharing of meals with family or colleagues and an absence of snacking were found to be major features in Sardinia, where there is high adherence to a traditional Med diet, compared with Malta, where many traditional features have been lost. [20] Although these different factors might play an additional role to food components in preserving health, they are not currently assessed in dietary questionnaires and hence cannot be controlled for by statistical techniques.

Several other factors may be reduced or absent in the lifestyles of people living in non-Mediterranean countries. A healthy energy balance derived from physical activity was an intrinsic part of the Med diet in Mediterranean populations following a traditional lifestyle. Also, taking a siesta - still current in some Mediterranean countries - has been associated with a lower risk of CVD, [21] but this is rarely considered in epidemiological studies. Another potentially confounding factor in relation to several chronic degenerative disorders is the possible protective effects conferred by vitamin D. [22,23] Because of more intense sunlight, the UV-induced synthesis of vitamin D will supplement nutritional intake to a greater extent for many people in Mediterranean countries, compared to more northerly countries.

Comparison between foods and their preparation methods in Mediterranean and non-Mediterranean countries

The precise composition of a food and how it is produced and prepared can differ significantly between Mediterranean and non-Mediterranean countries. These differences may impact on the overall health benefits of a Med diet in non-Mediterranean countries.

Olive oil

The major difference between northern and Mediterranean countries in relation to olive oil is simply whether or not it is consumed, and this has been discussed earlier. However, the quality of olive oil and its culinary use may also be important with regard to its health benefits. Although MUFA content does not vary significantly between different qualities of olive oil, olive oil also contains a "non-saponifiable" fraction comprising various triterpenes (mostly squalene), phytosterols (mostly β-sitosterol), tocopherols (mostly vitamin E) and phenolics, and these may vary between various types of olive oil and be influenced by culinary practices. Levels of squalene, a putative protective factor against breast cancer, [24] phytosterols and tocopherols are reduced with increasing refinement of virgin olive oil. In addition, phenolics are only present in significant quantities in virgin olive oil and so their health benefits will be lost when non-virgin olive oils are consumed. Potentially important phenolics in virgin olive oil include lignans, which are associated with reduced breast cancer risk,[25,26] hydroxytyrosol, which has cardioprotective and anticancer activity in experimental systems, [27] and the anti-inflammatory substance oleocanthal. Frying with virgin olive oil reduces the phenolic content, [28] and this highlights the potentially important role that consumption of raw virgin olive oil may play in the Med diet.

Vegetables

Populations in Mediterranean and non-Mediterranean countries can have quite different preferences for types of vegetables and their preparation methods, and this may influence health outcomes in relation to vegetable consumption. [29] Dutch university students were reported to prefer "Brussels sprouts, green peas and carrots often with apple sauce" whereas Greek students chose "mostly fresh salads of tomatoes, cucumber, cabbage, rocket, radishes, spinach and lettuce with olive oil, vinegar or balsamic vinegar and herbs, or green vegetables in baked pies (spinach pie, leak pie, etc.)". [30] Salads were found to be consumed several times a week in an analysis of the traditional Cretan Med diet. [31] In EPIC cohorts from northern countries, consumption of raw vegetables as a proportion of total vegetable consumption was reported to be lower compared to their southern counterparts. [32] This was particularly striking for UK men who consumed only half as much raw vegetables as cooked vegetables, whereas the proportions of raw and cooked vegetables were fairly similar in Mediterranean countries. Data from the UK Living Costs and Food Survey indicate that the main purchased fresh vegetables in the UK in 2010 included cabbages, brussel sprouts, cauliflower, salad leaves, carrots, alliums and tomatoes. [33]

These wide variations in preferred types of vegetables may have a significant impact on phytochemical intake and hence on any correlated disease risk. The low consumption of dark green leafy vegetables (eg broccoli, spinach, kale) in the UK [32] is noteworthy since these represent a major dietary source of vitamins C and K, folate, β-carotene, lutein + zeaxanthin and flavones. [34] Garlic consumption, common in Mediterranean countries, is low in the UK, and the WCRF/AICR 2007 report considered it "probable" that garlic consumption contributes to protective effects against stomach and colorectal cancers. [35] Differences in the phytochemical content between different varieties of the same vegetable can be substantial. For example, flavonol content of lettuce varieties ranged from 0.5 µg/g fresh weight for iceberg lettuce - a variety commonly purchased in North European countries - to 207 µg/g fresh weight for the Italian variety lollo rosso. [36] Dietary flavonol intake is linked to a decreased risk of CVD, including stroke. [37] Of course, low consumption of one vegetable may be compensated for by consumption of another vegetable containing the same beneficial nutrients, and moreover many phytochemicals present in vegetables are also found in fruits. Thus, a mixed and diverse diet can help ensure an optimum intake of a wide range of healthy phytochemicals. The potential importance of a varied diet was highlighted in an EPIC study which showed that diversity of fruit and vegetables consumption was associated with a decreased risk of lung cancer, an effect over and above the inverse association with quantity. [38] It is noteworthy that a traditional Med diet includes a particularly wide diversity of fruits and vegetables.

Preparation method can influence both nutrient levels and nutrient bioavailability. Consumption of raw vegetables preserves heat labile nutrients such as vitamins A and C and folates that otherwise can be lost when vegetables are cooked. Also, using an oil-based dressing - olive oil is traditional in Mediterranean countries - was shown to increase the bioavailability of carotenoids from salad ingredients. [39] Breaking down the food matrix by cooking or pureeing can also increase the bioavailability of carotenoids.[40] The common practice in North European countries of boiling a single type of vegetable and discarding the cooking water can result in significant nutrient loss due to leaching of water soluble nutrients such as folates and glucosinolates into the cooking water. [41,42] This practice is less common in Mediterranean countries, where soups and stews are preferred, and since these cooking methods retain the cooking medium, there is no loss of water soluble nutrients. Frying vegetables can lead to significant losses of fat soluble nutrients such as carotenoids, probably into the cooking fat, [43] but this practice is not very common in the Med diet. On the other hand when the entire contents of the pan are consumed, for example in Mediterranean stews, the overall nutritional value of the dish will not be compromised.

The emphasis in a traditional Med diet is for seasonal, field-grown vegetables, whereas for a North European market "Mediterranean" vegetables are frequently grown under glass. This latter cultivation practice reduces UV-B exposure due to the limited light absorbing properties of glass. It is also often accompanied by increased fertiliser use. Both of these factors can have adverse effects on phytochemical production, although this appears to depend both on the type of vegetable and the specific phytochemical. [44]

In conclusion, the nutritional benefits that different populations receive from consuming vegetables may vary widely, and is not accounted for by simply determining absolute levels of consumption.

Fruits and Nuts

Total fruit consumption in the UK is low compared to Mediterranean countries, and across Europe there is a North South gradient for total consumption. [32] Apples, bananas and citrus fruits together accounted for about two-thirds of all fresh fruit purchased in 2010 by UK households, and processed fruits and fruit products (excluding fruit juices) accounted for a third of total fruit purchases. [33] Consumption of summer fruits popular in Mediterranean countries - such as pomegranates, figs, grapes and "orange fruits" (eg apricots, peaches, nectarines, cantaloupe melons) - is relatively low in the UK.

When eaten raw, many fruits are a good source of vitamin C. By contrast, the relative amounts of various phytochemicals can vary widely: citrus fruits are good sources of flavanones and flavones, berries are rich in anthocyanins and flavan-3-ols, and Mediterranean "orange" fruits are important sources of α-carotene and β-carotene. Due to the difficulty for epidemiological studies to identify the effects of individual nutrients within a diet, it is unclear if the particular nutrient content of a specific fruit affects health outcomes. However, Chong et al concluded that there was some limited evidence that fruits rich in flavonols, anthocyanins and procyanindins, such as pomegranate, purple grapes and berries, are more effective at reducing CVD risk. [45]

Fruit is a typical way to end a meal in Mediterranean countries. At the end of a meal there is a rise in pro-oxidant and pro-inflammatory processes and this is linked to increased cardiovascular damage. Postprandial hyperlipidaemia and hyperglycaemia are also risk factors for a number of metabolic disorders including type 2 diabetes, CVD and metabolic syndrome. Some studies have shown that consumption of phenolic-rich fruits during the postprandial phase increases the antioxidant capacity of the blood[46] Hence consuming fruit at the end of a meal is a prudent strategy for healthy eating.

In conclusion, consumption of a wide range of fruits is advisable, especially if phytochemical intake from vegetables is limited. Eating fruit, rather than a pastry, at the end of a meal not only reduces calorie intake but fruit phenolics may also help counteract oxidative stress and other pathological events during the postprandial phase.

An analysis of nut consumption in the EPIC study found that cohorts from central European countries (North of France, Germany, Netherlands, UK) and Mediterranean countries (South of France, Greece, Italy, Spain) had similar overall levels of consumption. [47] However, a higher proportion of peanuts relative to tree nuts (mainly walnuts, almonds and hazelnuts) were consumed in the central European countries. For example in the UK, peanuts and tree nuts constituted 40.4% and 36.4% respectively of total nuts and seeds consumed, whereas in Spain these figures were 26.8% and 54.9% respectively.

All types of nuts have been shown to reduce the risk of CHD, although only very limited data is available for peanuts. [48] Nuts have hypocholesterolaemic effects, and a number of intervention studies have demonstrated that nuts lower both

LDL-cholesterol and the ratio of LDL-cholesterol to HDL-cholesterol. [48] Participants of the PREDIMED study (a multi-centre intervention study) who consumed nuts as part of a Med diet had a statistically significant reduction ($p < 0.05$) in LDL-cholesterol and the LDL/HDL-cholesterol ratio. [49] The cardioprotective effects of nuts may be related to their relatively high proportion of unsaturated fatty acids such as MUFA and linoleic acid. [50] The hypocholesterolaemic effects of nuts may also, in part, be related to their quite high phytosterol content. Pistachio nuts - a common aperitif nut in Mediterranean countries - have the highest phytosterol content of all nuts (279 mg/100 g), and oil- and dry-roasted peanuts and peanut butter also contain moderate levels of phytosterols (135 mg/100 g in oil-roasted peanuts). [51] Tree nuts, which constitute a higher proportion of nuts in Mediterranean countries, have additional nutrients including: a high vitamin E content in almonds,[52] high levels of α-linolenic acid in walnuts,[50] and, when eaten with their skins, high levels of phenolic antioxidants.[53]

In conclusion, although there is good evidence that tree nuts have hypocholesterolaemic properties, there is currently no strong evidence for hypocholesterolaemic properties for peanuts. Moreover, high levels of salt in many peanut products preclude high intake, especially in subjects with high blood pressure, and peanuts are also relatively high in saturated fat including palmitic acid.

Cereals

It is difficult to appropriately assess the effects of cereals from a nutritional questionnaire, since cereals can be refined or whole grain, salted or sweetened, all factors that strongly influence health. In one MDS where neither sweetened cereals nor bread from fast-food were scored for, it was still not possible to clearly evaluate the effects of cereals. [11] Whole grain cereals are very likely to be a better marker for health benefits, but this evaluation can only be applied when whole grain cereals are consumed by a high percentage of the subjects under study. [54] Another approach is to score refined cereals negatively. [55]

Legumes

Legume consumption excluding peas and green beans (ie pulses) showed a gradient of consumption in cohorts from the EPIC study, with higher levels of consumption in southern countries and lower levels in northern countries. [32] As well as quantitative differences, the preferred types of legumes in these two regions also differs. Commonly consumed legumes in Mediterranean countries include chickpeas, lentils and fava (broad) beans, although there are national differences eg chickpea consumption is high in Spain and intake of fava beans is high in Egypt. In the UK, chickpeas, fava beans and lentils are mainly consumed by ethnic minorities, and the major types of legumes in the UK diet are canned "baked beans in sauce" and garden peas. [33]

Legume consumption is associated with a decreased risk of CHD and CVD, [56] and consumption of various legumes, including baked beans (which are made from haricot beans),[57] has been found in a recent meta-analysis to lower cholesterol levels.[58] Legumes have excellent nutritional value and were ranked as an important source in the US diet for fibre, phytosterols, folate, vitamin B6, flavonols, favan-3-ols and various minerals.[34] Both fibre and phytosterols may be linked to the hypocholesterolaemic effects of legumes.[59] In relation to the UK diet, garden peas contain 134 mg/100 g phytosterols,[60] which is comparable to amounts found in other pulses, and haricot beans are a good source of fibre. This suggests that legumes commonly consumed in the UK may have some of the cardioprotective effects of the pulses more commonly associated with a Med diet.[29]

Fish

There is good evidence that fish consumption lowers the risk of cardiovascular mortality.[61] The most important bioactive nutrients in fish are generally considered to be the n-3 LC-PUFAs EPA and docosahexaenoic acid (DHA). A recent systematic review concluded that marine n-3 LC-PUFAs are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.[62] There is less evidence for a role of LC-PUFAs in the prevention of cancer.[63]

Levels of n-3 LC-PUFAs are considerably higher in oily fish than white fish. Since there is variability in the relative proportions of oily and non-oily fish between countries, measuring total fish intake may not reflect the intake of n-3 LC-PUFAs for a given population. The relative amounts of oily and non-oily fish does not follow a north south gradient since consumption of "very fatty fish", defined by Welch et al as including herrings, kippers and mackerel, is high in Scandinavian countries. [64] By contrast, the proportion of these types of fish consumed in the UK is relatively low, and so in the UK total fish consumption will be associated with a proportionally lower intake of n-3 LC-PUFAs from fish than is the case in some other countries.

A wide range of factors including the fish's food source influence the LC-PUFA content of oily fish, and this is particularly important when considering farmed fish, an increasingly important dietary source. Farmed salmon is a major source of n-3 PUFAs in the UK diet. Salmon, like other salt-water fish, has only a limited capacity to synthesise LC-PUFAs and instead obtains LC-PUFAs from its feed. When fed fish oils, farmed salmon are an excellent source of LC-PUFAs, but there are increasing environmental and commercial pressure on fish farmers to use non-marine sources of oils. This practice can drastically reduce DHA levels. For example, levels of 17 g DHA/100 g total fatty acids were determined in salmon that were fed fish oils, whereas levels of 5 g DHA/100 g total fatty acids were found in salmon fed plant oils. [65] Feeding fish oils during the last few months before marketing the fish is one technique that can restore EPA and DHA to fish fed a diet that has been predominantly vegetable-based. [66] Hence, the food supply of farmed fish is an important consideration when assessing the health benefits of oily fish.

Pan frying with olive oil is one of the most popular ways of preparing fish in Mediterranean countries and fish fried in virgin olive oil has been found to absorb significant quantities of antioxidant phenolics, terpenic acids and vitamin E from the oil. [67] Hence, there may be incidental benefits of frying fish in olive oil. On the other hand, there can also be an exchange of fatty acids between those in the fish with those in the frying oil. N-3 fatty acids in sardines fell between 2-3 fold when they were fried in either sunflower oil or olive oil and there was a rise in n-6 fatty acids. [68]

In conclusion, the type of fish, its diet, and how it is prepared contribute to its nutritional content, and these factors may vary significantly between Mediterranean and non-Mediterranean countries.

Dairy produce

The preferred types of dairy produce consumed in many Mediterranean countries are significantly different to those consumed in non-Mediterranean countries. In most Mediterranean countries, Spain being the main exception, proportionally less milk and milk beverages and more cheese and yogurt are consumed than in North European countries. [69] Significantly, a large number of the cheeses in Mediterranean countries are made from sheep's milk (eg Roquefort and *tomme* from the Pays Basque region of Southern France, *manchego* from Spain, and *feta* from Greece) and goat's milk (such as the wide range of *chevres* from Southern France). By contrast, the main dairy produce in

Northern Europe is cow's milk and cow's milk cheese such as "cheddar type" hard cheese in the UK.

Although cheeses made from goat and sheep milk have a similar total saturated fat content as cheeses made from cow milk, the composition of the saturated fats is different since goat and sheep milk are richer in medium chain fatty acids (MCFAs) ie <12 carbon atoms (<12C). These MCFAs include caproic acid (C6:0), caprylic (C8:0) and capric (C10:0) (the names are derived from the Latin *caper* for a goat) (Table 1). [70] For example, fresh goat cheese with 40% fat comprises 15% <12C FAs whereas these FAs only constitute 7% in a comparable cow's milk cheese. Similarly, the fat content of Roquefort cheese comprises 15% <12C FAs and 23% palmitic acid. By comparison, a cow's milk fatty cheese comprises 33% palmitic acid (16C), the most atherogenic SFA. [71] MCFAs are non-atherogenic, and are directly oxidised in the liver thus reducing their accumulation in adipose tissue. Some epidemiological evidence supporting the beneficial effects of MCFAs came from the Nurses' Health Study (a prospective cohort study including more than 80,000 US females) which showed that in contrast to LCFAs, intake of MCFAs was not significantly associated with the risk of CHD. [72]

The composition of milk is influenced by the animal's diet and this can have beneficial effects. Goats and sheep are more likely than cows to be raised on natural pasture. Pasture is rich in ALA and gives rise to higher levels of ALA in the animal's lipids which can be desaturated to EPA, an n-3 LC-PUFA with anti-inflammatory properties.

High consumption of dairy produce was considered to be detrimental in the MDS devised by Trichopoulou and colleagues. This is because the dairy produce was rarely low-fat and longer chain SFAs have detrimental effect on cholesterol levels. There is now a trend in many countries towards low-fat dairy produce. In the UK, weekly purchases of whole milk have steadily decreased year on year (2655 ml/week in 1974 down to 352 ml/week in 2010) with a concomitant rise in the purchase of skimmed milk (mostly semi-skimmed). [33] Similarly, milk consumption in the US is mostly low-fat. However, not all saturated fats are harmful. Myristic acid (14C), present in the milk of ruminants, is necessary for the myristoylation of several functional proteins, [73] and it is not atherogenic when the exogenous source is ≤ 2% of the total energy intake. Also, the natural *trans*-FA *trans*-palmitoleic acid (cis-16:1 n-7), levels of which correlate strongly with whole fat dairy consumption, was shown to be associated with lower metabolic risk factors. [74] These observations question the relevance of the low-fat milk recommendations in many countries.

Meat

A recent meta-analysis concluded that red meat consumption is associated with a small increase in the risk for colorectal cancer, [75] although other analyses have concluded that because of possible confounding the current evidence for such an association is weak. [76] It has been suggested that the pro-carcinogenic effects of haem iron, a putative carcinogen in red meat, can be suppressed by various dietary constituents such as chlorophyll, calcium and antioxidant vitamins (C and

E), [77,78] although the possible relevance of these interactions in relation to the Med diet is not known. Marinating, a technique traditionally used in Mediterranean cuisine to tenderise cheap cuts, may also potentially have beneficial health effects. Cooking meat at high temperatures, such as frying and grilling, generates carcinogenic heterocyclic aromatic amines (HA), and marinades that contain virgin olive oil, onions, garlic, herbs or red wine have high antioxidant capacity and have been shown to inhibit HA formation. [79-81]

The geographical characteristics of the Mediterranean favour small livestock with specialised feeding habits: sheep and goats can take advantage of the hilly landscape and of Mediterranean grazing, whereas pigs prefer open wild spaces such as in holm-oak forest. Because the pasture of Mediterranean animals used to produce dairy and meat is richer in PUFAs than that of the equivalent animal given animal feeds, their FA profile is healthier. This is especially true for pigs running in open spaces in Corsica and Sardinia - their meat is leaner, and their fat consists of 40 to 50% MUFA. Together with the higher content of LA, this results in less SFA in the fat composition (Table 2). [71,82]

Other foods

A number of other foods not generally scored for in MDS may have important health benefits for a Med diet. These include herbs (also taken as herbal teas), wild greens, and pumpkin, sunflower and other types of seeds. Local consumption of these can be high, and many are very rich sources of phytochemicals (for example, pumpkin seeds contain high levels of phytosterols) and other nutrients. [2]

Notable by their absence in a traditional Med diet are modern fast foods and sugar-sweetened drinks. [20] Fast foods can be a major source of salt and trans fats - both well-known risk factors for CVD, and both fast foods and sugar-sweetened drinks are positively associated with long-term weight gain. [83] An evaluation of fast foods and sugar-sweetened drinks is only rarely included in MDS. In one such study from rural Lebanon it was found that when food consumption deviated from a traditional Med diet by including refined cereals and pastries and sugar-sweetened drinks, there was an increase in obesity and visceral adiposity. [55]

Alcohol

Moderate alcohol consumption (defined as men consuming 10g to < 50g per day and women consuming 5g to < 25 g per day) is assumed to be beneficial in MDS [5]. This is most strongly linked to a reduced risk of CVD. The most compelling mechanism to explain the cardioprotective effects of moderate alcohol consumption is the increase in levels of HDL-cholesterol; beneficial effects on the vasculature may also be involved.

A number of studies from non-Mediterranean countries have shown that even moderate alcohol consumption increases the risk of cancer at some sites, such as the breast. [84,85] By contrast, a Med diet reduces overall cancer risk, and there is no evidence from specific analysis of the alcohol component that moderate levels of consumption in the context of a Med diet increases cancer risk. [86] One important factor that might contribute to these disparities between Mediterranean and non-Mediterranean countries with regard to the risk of cancer with moderate alcohol consumption is drinking pattern. [87] Whereas the custom in Mediterranean countries is to drink in moderation with a meal, drinking outside mealtimes and binge drinking are more prevalent in North European countries. [88,89] Drinking with a meal slows the rate of absorption of alcohol from the gut whereas drinking on an empty stomach raises absorption rates, and may increase blood alcohol concentrations to levels that saturate alcohol metabolic pathways resulting in the production of carcinogenic metabolites. Dietary folates may also possibly influence the cancer risks of drinking. Some studies, [90] but not all, [84] have shown that folates reduce the cancer-associated effects of moderate alcohol consumption. It is noteworthy that the Med diet has particularly high levels of folate consumption, and there is a good correlation between folate consumption and adherence to a Med diet. [91]

Alcohol consumption in Mediterranean countries is typically associated with wine, mostly red which is drunk with a meal, whereas beer and spirits are consumed in greater quantities in some non-Mediterranean countries. [88] There is some evidence that over and above the effects of alcohol, phenolics that occur in red wine may have specific cardioprotective effects. Distinguishing between the effects of alcohol and phenols in wine can be undertaken using dealcoholised wine. For example, dealcoholised red wine retained the ability of complete wine to modulated leucocyte adhesion molecules, important inflammatory biomarkers related to atherosclerosis in subjects at high risk of CVD. [92] Studies also suggest that drinking wine with a meal may confer additional cardioprotective effects. [93] A large number of studies have shown that dealcoholised wine increases postprandial total antioxidant capacity and reduces postprandial rises in oxidised LDL-cholesterol, an important risk factor for CVD. [46,94,95]

In summary, drinking moderate amounts of red wine with a meal may have superior health benefits compared to other types of drinking, and this is not assessed when measuring consumption of alcohol in MDS. Hence, factors not monitored in MDS - such as drinking pattern, other dietary constituents and type of alcohol - are important factors to consider when weighing up the risks and benefits associated with moderate alcohol consumption.

Discussion

In the traditional concept of the Med diet, there are various food habits and lifestyle aspects that may be absent in non-Mediterranean populations. We have described how the *a priori* MDS first described by Trichopoulou and colleagues in 2003 therefore needed to be adapted for specific populations; but in effect it is no longer Mediterranean since there are a number of nutritional characteristics which are different from the typical Mediterranean diet. Determining if these adaptations influence health outcomes is important when applying a Med diet to populations in non-Mediterranean countries. One lifestyle factor that may be important is physical activity, and in fact this is generally taken into consideration in questionnaires. But for others, such as meal structure, the organisation of meals during the day, conviviality, and taking a siesta, it would be necessary to extend the scope of questionnaires undertaken as part of evaluating the MDS. Although more time consuming, information on the source of meat and dairy products would also be helpful by assessing the importance of specific categories of SFA, and the level of PUFAs. This could be supported with biomarker measurements of fatty acids and other nutrients. [11] Another biological measurement of interest is vitamin D status.

It became evident during the early development of MDS that the first MDS, originally developed for a Mediterranean population, would have to be adapted for non-Mediterranean populations in order to take into consideration the genuine eating habits of non-Mediterranean populations. [19,54,55] In fact, taking a nutritional survey *a posteriori* in order to identify dietary patterns is the best way to reveal the healthiest type of diet among the eating habits of this population. These patterns could then be compared to the original Med diet, and differences between the two patterns can be identified. Using this approach to adapting the MDS, some important features have been identified. For example, the rMed-score [19] and the new *a posteriori* MDS [17] identified the importance of taking olive oil consumption into account, and for the latter the necessity of considering an absolute amount of food in relation to its beneficial effect.

Measuring plasma levels of selected nutrients that are specific to a unique source or class of food (e.g. LC n-3 PUFA and fish) may offer a more precise way than Food Frequency Questionnaires of assessing the role of specific nutrients for the health benefits of the traditional Med diet. When applying the Med diet in non-Mediterranean populations, particularly relevant nutrients are those linked with health whose levels are likely to be influenced by culinary and lifestyle factors that vary significantly between Mediterranean and non-Mediterranean populations. One candidate nutrient is folate, since dietary intake of folate is associated with a reduced risk of a range of chronic disorders such as colon cancer. [96] Folate levels in foods are influenced by culinary practices: it is water soluble and heat labile and boiling results in leaching of folate into cooking water. [41] Moreover, folate levels vary widely between vegetables since it occurs mainly in green leafy vegetables and so will not be specifically assessed by quantifying total vegetable intake. Hence, folate plasma levels may not necessarily be reflected in MDS.

Sufficient plasma levels of other nutrients that are linked to adherence to a Med diet may also be important in order for non-Mediterraneans to achieve the full benefits of a traditional Med diet. Gerber et al. found a significant correlation between plasma levels of α-tocopherol, β-carotene, EPA and DHA with the Med diet quality index, especially when these nutrients were combined in a composite index, thus establishing that plasma values of these nutrients correlated with good adherence to a Med diet. [11] Subjects in Northern Spain with higher Med diet adherence, as measured by two dietary indexes, had significantly higher plasma concentrations of β-carotene, folates, vitamin C, α-tocopherol and HDL cholesterol.[91] Carotenoids may also be useful biomarkers because of their association with risk of cancer at certain sites and because food preparation can influence bioavailability. However, correlating plasma concentrations of a particular nutrient with disease reduction is not straightforward since food plants contain many nutrients that are consumed at the same time e.g. most of the fruit and vegetables containing carotenoids contain also lignans.

Conclusions

Although there is extensive epidemiological evidence supporting the health benefits of a Mediterranean diet, this is mostly derived from Mediterranean diet scores that do not fully take into consideration the many potentially confounding factors between Mediterranean and non-Mediterranean populations. We have identified a number of factors that may confound the assessment of the health benefits of a Med diet in Mediterranean countries, both because of the nature of the food itself and also due to aspects of food production and preparation. Lifestyle factors such as meal patterns and exposure to sunlight may also act as confounders. Improving Mediterranean diet scores and measuring plasma nutrient levels may help mitigate the effects of these confounders. Taking into consideration these confounders may have important health implications when implementing a Mediterranean diet in non-Mediterranean populations.

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Table 1 Medium chain fatty acid content of sheep, goat and cow milk[70]

Fatty acid	Fatty acid composition (% total)		
	Sheep	Goat	Cow
Caproic C6:0	2.9	2.4	1.6
Caprylic C8:0	2.6	2.7	1.3
Capric C10:0	7.8	10.0	3.0
Total	13.3	15.1	5.9

Table 2 Fat composition of various meats (based on [71,82])

Meat	Fatty acids (% total fat)				
	Saturated fatty acids	Monounsaturated fatty acids	Total polyunsaturated fatty acids	Linoleic acid	Alpha-linolenic acid
Lamb	52.1	40.5	5.8	5.0	0.8
Pork	43.2	47.6	9.2	8.6	0.6
Beef	56.4	40.3	3.2	2.5	0.7