The Mediterranean Diet and Cardiovascular Epidemiology
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The Mediterranean diet was first considered to be a low-saturated fat diet that conveyed protection against coronary heart disease by lowering plasma total cholesterol levels. Later, the emphasis shifted away from the low-saturated-fat content of this diet toward its high content of olive oil and its overall constellation of characteristics. Moreover, there is now evidence that the Mediterranean diet benefits not only the risk for coronary heart disease but also cancer occurrence, total mortality, and longevity.

Key words: cancer, cholesterol, coronary heart disease, Mediterranean diet, olive oil

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THE MEDITERRANEAN DIET: DEFINITION AND SCORING

First considered by Ancel Keys1 to be a low-saturated fat diet that protected against coronary disease by lowering the total cholesterol level in the plasma, this diet was eventually appreciated less for what it did not contain and more for what it did contain: olive oil.2-7 It is now recognized that this diet is also beneficial in the prevention of cancer8-10 and in promoting longevity.5,11 The traditional Mediterranean diet is characterized by a high intake of vegetables, legumes, fruits and nuts, and unrefined cereals, a high intake of olive oil but a low intake of saturated lipids, a moderately high intake of fish, a low-to-moderate intake of dairy products (mostly in the form of cheese or yogurt), a low intake of meat and poultry, and (if accepted by religion and social norms), a moderate intake of ethanol, primarily in the form of wine and generally during meals.5,11 In several studies, this diet has been operationalized by using an a priori score based on study- and gender-specific median values. The use of an a priori score is intuitively appealing because it captures the extremes of the exposure of interest (degree of adherence to the Mediterranean diet), bypasses nutritional confounding by incorporating possible nutritional confounders in the score, integrates possible effect modification among nutritional variables through the same process and, in contrast to a posteriori scores, does not tend to be biased.12-14

THE MEDITERRANEAN DIET AND CARDIOVASCULAR RISK: EPIDEMIOLOGICAL EVIDENCE

The epidemiological evidence concerning the relationship between the Mediterranean diet and coronary heart disease risk can be divided into three categories: ecological, analytical, and interventional. The ecological evidence is as a good as this type of evidence can be.1,15 Analytical observational studies have been of both cohort6,11,16,17,18 and case-control design.19,20 Cohort studies relied on cardiovascular mortality or total mortality, whereas case-control studies were mainly based on non-fatal coronary events. It should be realized, however, that it has not been possible to establish which elements in the Mediterranean diet are crucial for the beneficial effects. The Lyon Heart Study, a randomized clinical trial on the secondary prevention of coronary heart disease,21 has been very useful, but did not strictly refer to the traditional Mediterranean diet. In the sections below, we discuss some recent data regarding the benefits of the
Mediterranean diet on cardiovascular diseases and/or some of the associated risk factors.

The EPIC-Greece Cohort Study

The enrollment of participants in the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC) took place between 1994 and 1999. A total of 28,572 participants, 20 to 86 years old, were recruited from all regions of Greece. From an extensive food frequency questionnaire, 14 all-inclusive food groups or nutrients were considered: potatoes, vegetables, legumes, fruits and nuts, dairy products, cereals, meat, fish, eggs, monounsaturated lipids (mainly olive oil), polyunsaturated lipids (vegetable-seed oils), saturated lipids and margarines, sugar and sweets, and non-alcoholic beverages. For each participant, intake of each of the indicated groups in grams per day and total energy intake were calculated.11

A scale indicating the degree of adherence to the traditional Mediterranean diet was constructed by Trichopoulou et al.6,11 A value of 0 or 1 was assigned to each of nine components with the use of the sex-specific median as the cutoff. For beneficial components (vegetables, legumes, fruits and nuts, cereal, and fish), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat and poultry and dairy products, which are rarely nonfat or low-fat in Greece), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g/d and to women who consumed between 15 and 25 g/d. The ratio of monounsaturated lipids to saturated lipids was used as a measure of fat intake. Thus, the total Mediterranean diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

All participants whose vital status was ascertained by active follow-up until July 2002 were included, but those with diagnoses of coronary heart disease or cancer at enrollment (prevalent cases) were excluded from the analysis; a total of 22,043 participants were included. Cox models were used to assess the association between the studied food groups and mortality, as well as between the Mediterranean diet score and mortality. The models were adjusted for all recorded potential confounding variables.

A two-point increment in the Mediterranean diet score was associated with a significant reduction in total mortality. The association with the Mediterranean diet score was stronger for mortality from coronary heart disease than for mortality from other diseases, including cancer (Table 1). The inverse association between the Mediterranean diet score and total or coronary mortality was evident irrespective of sex, smoking status, level of education, body-mass index, waist-to-hip ratio, and level of physical activity.

A reduction in total and coronary mortality in relation to the Mediterranean diet score was apparent even though no strong associations with mortality were evident for each of the components of the Mediterranean diet score. Several explanations for this finding are possible. Individual components may have small effects that emerge only when the components are integrated into a simple, essentially additive score. There may also be biologic interactions between different components of the Mediterranean diet. In analyses focusing on individual components, effects are examined against the background of average risk associated with other nutritional components, whereas an inclusive dietary score assesses the extremes of cumulative exposure (from 0 to 9) in the absence of other major nutritional effects.11,14

These results are compatible with those of the Lyon Heart Study through the use of variants of the Mediterranean diet.21 The magnitude of the reduction in mortality associated with greater adherence to a Mediterranean diet is also compatible with the reported advantage of Mediterranean populations over North American and northern European populations with respect to coronary heart disease risk.

Reduction in the Risk of a First Acute Myocardial Infarction

The aim of another study conducted in Spain20,22 was to assess the potential role of olive oil for the

<p>| Table 1. Hazard Ratios for Death Associated with a Two-Point Increment in the Mediterranean Diet Score in a Greek General Population Sample |
|-----------------|-----------------|-----------------|------------------|</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Deaths/ No. of Participants</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>275/22,043</td>
<td>0.74 (0.65–0.86)</td>
</tr>
<tr>
<td>Death from coronary heart disease</td>
<td>54/22,043</td>
<td>0.68 (0.50–0.94)</td>
</tr>
</tbody>
</table>

From Trichopoulou et al., 2003.11 Adapted with permission.
primary prevention of coronary heart disease and to quantify the reduction in the risk of a first acute myocardial infarction that can be provided by a high dietary olive oil intake. For this purpose, the authors used a case–control design (171 cases of myocardial infarction and 171 age-, gender- and hospital-matched controls) and assessed the protection against coronary heart disease afforded by a Mediterranean diet. Cases were defined as male or female subjects, under 80 years old, survivors of a first acute myocardial infarction admitted to one of the three tertiary hospitals of Pamplona (Spain) within the periods October 1999 to June 2000 or October 2000 to February 2001. Patients had to fulfill the criteria for definite acute myocardial infarction of the MONICA project (two or more electrocardiograms showing specific changes, probable changes plus abnormal cardiac enzymes, or typical symptoms plus abnormal enzymes). A previous history of angina pectoris, a previous diagnosis of coronary heart disease, or other prior diagnosis of major cardiovascular disease were exclusion criteria.

A control subject of the same age (5-year bands), gender, and hospital was matched to each case. Eligible controls were patients admitted to the surgical, trauma, or urology wards of the same hospital during the same month that matched cases for diseases believed to be unrelated to diet.

A Mediterranean diet score was derived from six food items that were considered protective: 1) olive oil, 2) fiber, 3) fruits, 4) vegetables, 5) fish, and 6) alcohol. For each of these six factors, each participant was assigned a score of 1 to 5 corresponding to his/her quintile of intake. The investigators also inversely ranked the quintile score for two other elements assumed to be harmful: 7) meat/meat products and 8) some carbohydrate-rich items with high glycemic load (white bread and other items). The eight quintile values for each participant were then added. It was found that the higher the score, the lower the odds ratio (OR) of myocardial infarction. A significant linear trend was apparent after adjustment for the main cardiovascular risk factors. For each additional point in the score (observed range: 9–38) the OR (95% confidence interval, CI) was 0.92 (0.86–0.98). These data support the hypothesis that a Mediterranean diet, which emphasizes olive oil, fiber, fruits, vegetables, fish and moderate alcohol intake and reduces meat/meat products, can be an effective means of reducing the risk of coronary heart disease.20 In this case-control study, the exposure to the upper quintile of energy-adjusted olive oil (median intake, 54 g/d) was associated with a substantially reduced risk (OR = 0.18; 95% CI: 0.06–0.63) after adjustment for dietary and non-dietary confounders.22

PREDIMED

As indicated above, a Mediterranean-type diet has been widely considered to be a model of healthy eating despite the concern from some nutrition experts about its relatively high fat content (up to or exceeding 40% of total energy intake), which is in conflict with the conventional recommendation to follow a low-fat diet in order to avoid overweight/obesity and to prevent coronary heart disease.23,24 Adherence to a Mediterranean diet was associated with lower coronary mortality in a cohort study11 and in a relatively small trial with patients after a myocardial infarction,21 but no large primary prevention trial with clinical events as the endpoint has been performed.

The potential cardiovascular preventive effect of Mediterranean diet in the face of the huge and increasing global burden of cardiovascular disease makes the resolution of this dilemma a priority for public health. Other important reasons to thoroughly assess the effect of dietary guidelines based on the Mediterranean diet include: a) the long tradition of following Mediterranean diets without any harm in southern Europe, where life expectancy is high5; b) the low incidence of coronary heart disease in these countries despite having similar or even higher levels of classical risk factors compared with the US population25; c) the diversity of mechanistic and epidemiological observations of beneficial effects on cardiovascular health of the consumption of key components of the Mediterranean diet, such as monounsaturated lipids, extra-virgin olive oil, or nuts; and d) the higher palatability, acceptance, and compliance with Mediterranean diet compared with low-fat diets.26

The presumed anti-atherogenic properties of olive oil have been mainly attributed to its high content of oleic acid. However, in recent years, converging evidence indicates that polyphenols only present in extra-virgin olive oil significantly contribute to these benefits. The concentration of phytochemicals in oils is influenced by the oil extraction procedure utilized. Extra-virgin olive oil is obtained from the first pressing of the ripe fruit and has a high content of antioxidants (tocopherols, polyphenols, flavonoids) and sterols. Lower-quality olive oils (refined olive oils) lose nearly all of this antioxidant capacity because they are refined by physical and chemical procedures (and are mostly colorless and aroma free), although their fatty acid composition is close to that of extra-virgin olive oil.

Extra-virgin olive oil polyphenolic derivatives (hydroxytyrosol, tyrosol, and their secoiridoid derivatives) have shown strong antioxidant and anti-inflammatory activity both in vitro and in vivo. The Lyon Diet Heart Study found a 50% to 70% relative reduction in the risk of mortality or a second event when patients who had
suffered a myocardial infarction were assigned to an experimental diet rich in bread, vegetables, fish, and fruit and low in red meat (replaced with poultry). Butter and cream were replaced with a special margarine rich in alpha-linolenic acid (ALA). This study using the so-called “Mediterranean diet” included patients who had already experienced a clinical event, so it was a secondary prevention trial and its results may therefore not be extrapolated to issue dietary guidelines for primary prevention. Additionally, major aspects of the design and methods of this trial have been criticized. It was designed to provide the experimental group with a high amount of ALA; however, no special consideration was given to olive oil, which is the major source of dietary fat in Mediterranean countries or to the special relevance of extra-virgin olive oil as an important source of polyphenols. On the other hand, no protective effect for olive oil was observed in the Greek EPIC cohort described above, thus raising the issue of whether the large amount of fat provided by olive oil in fact affords protection against coronary heart disease.

In the Lyon Diet Heart Study, the assessment of true dietary patterns and nutrient intakes at baseline and at the end of the study were reported for only a subset of participants (30% of the control group and 50% of the experimental group). In addition, no biochemical verification of dietary compliance was done. Thus, the diet followed by most participants completing the trial is not known. A third major issue was that only 12.9% of energy intake was provided by monounsaturated lipids in the group assigned to the Mediterranean diet. Additional concerns about the Lyon trial are related to the low number of observed endpoints (44 and 14 in the control and intervention group, respectively), the improbably large reduction in relative risk in spite of not observing changes in some of the classical risk factors, and the fact that the trial was stopped very early (after 27 months of follow-up).

In this era of evidence-based medicine, nutritional recommendations should be based on large-scale, randomized intervention studies in which clinically relevant (“hard”) endpoints are evaluated. However, no randomized, controlled trial has ever been conducted to assess to what extent a Mediterranean diet offers greater benefits than a traditional low-fat diet in the primary prevention of cardiovascular events. In October 2003, we started the recruitment of participants for such a primary prevention trial in Spain, the PREDIMED (PREvención con Dieta MEDiterránea) Study. The PREDIMED study was the first large trial to randomize high-risk patients to follow a traditional Mediterranean diet with extra virgin olive oil for primary cardiovascular prevention. The PREDIMED trial was designed to overcome previous limitations and to provide results with the best quality of evidence.

The PREDIMED study is a parallel group, multicenter, randomized, single-blinded trial aimed at assessing the effects of two intensive behavioral counseling and nutrition education interventions compared with a control group on the risk of major cardiovascular events. Both intervention groups were assigned a traditional Mediterranean diet. In one of these groups, the traditional Mediterranean diet was supplemented with nuts, and participants randomized to this group received a free supply of 30 g/d of nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds). In the other group, the Mediterranean diet was supplemented with extra-virgin olive oil. The third arm of randomization was the control group, whose participants did not receive education on the Mediterranean diet, but were given advice on how to follow a low-fat diet. Men (age: 55 to 80 years) and women (age: 60 to 80 years) with either diabetes or three or more major cardiovascular risk factors (smoking, high blood pressure, high LDL cholesterol, low HDL cholesterol, overweight or obesity, or family history of premature coronary heart disease) were recruited. All participants were free of cardiovascular disease at baseline and were randomized to three equally sized groups (3500 in each of the three groups). They are being followed up for clinical outcomes during a median time of four years by the primary care physicians who recruited them for the study. The primary endpoint will be a composite outcome of cardiovascular events, including any of the following: cardiovascular death, myocardial infarction, coronary revascularization procedures, and ischemic stroke.

The recruitment for the pilot phase of the study started between October and November 2003 in eight field centers and in January 2004 in the remaining two field centers. After 3 months, 800 participants were assessed for compliance with dietary advice and changes in intermediate biological markers of cardiovascular risk. A summary of preliminary data obtained from the first 632 participants of the PREDIMED trial was examined, focusing on the results obtained for the intervention group of the extra-virgin olive oil group in comparison with the control group (low-fat diet). Three months after randomization, changes in diet, serum lipids, blood pressure, inflammatory markers, and oxidative stress markers were assessed.

Changes in Diet Assessed with a Food-Frequency Questionnaire

The main changes observed were an increase of 111% in the consumption of extra-virgin olive oil in the first group assigned to Mediterranean diet. These
changes convincingly show that participants were compliant with the intervention. Extra-virgin olive oil consumption also increased in the group who were assigned to consume nuts. Statistically significant increments in the consumption of legumes were seen in all three groups, but were greater in the two intervention groups. The overall food pattern was also favorably modified in both intervention groups, with reductions in pastries and meat, whereas fruit consumption significantly increased. Regarding nutrients, statistically significant changes in the expected direction were observed. They were not impressive, but of moderate magnitude compared with changes in foods or food groups. However, these changes can be considered to be important when taking into account what can be expected after a single individual contact and a single group intervention in a trial that includes only free-living people.

The 3-month macronutrient profile of the Mediterranean diet group showed a decrease in saturated fatty acids, but no increase in monounsaturated lipids. Replacement of monounsaturated lipids from meat with monounsaturated lipids from extra-virgin olive oil probably occurred, because changes in the consumption of these two food items were highly significant and in opposite directions. Moreover, participants in this group almost exclusively consumed extra-virgin olive oil and no other types of olive oil, thus ensuring a high intake of polyphenols. For many participants in this group, the major change was to start using extra-virgin olive oil instead of other liquid oils. The minimal intervention in the control group (a leaflet recommending a low-fat diet from the American Heart Association) did not change the overall fat intake, although saturated fatty acid consumption decreased and a modest increase in fiber intake was also observed. After 3 months, the control group still showed a nutritional profile that did not deviate much from the traditional Mediterranean diet.

Changes in Diet Objectively Assessed with Biological Markers of Compliance

Samples from 10% of the participants in each group were extracted to objectively assess compliance through changes in plasma fatty acid composition and in urinary tyrosol and hydroxytyrosol. In spite of the small sample size, changes were statistically significant for the relevant biomarkers, and these results confirmed that the changes were in the expected direction.

Changes in Cardiovascular Risk Factors after Three Months

Statistically significant improvements were observed for systolic and diastolic blood pressure in the extra-virgin olive oil group compared with the control group. HDL cholesterol significantly increased in the intervention group. In addition, statistically significant reductions were observed for soluble intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in the group consuming extra-virgin olive oil compared with the controls. These findings compare favorably with previous observational studies assessing differences in ICAM-1 and VCAM-1 according to n-3 fatty acid intake (7%–8% reduction), and also with previous trials using either long-chain n-3 fatty acids (no effect), fish oils (–12% for ICAM-1 and –20% for VCAM-1, but only among older subjects), linseed oil (–18.7% in VCAM-1 but no change in ICAM-1), or alpha-tocopherol (–11% in ICAM-1). These results are therefore important in support of the effectiveness of the dietary intervention and the rationale of the PREDIMED trial.

THE MEDITERRANEAN DIET AND INSULIN RESISTANCE: THE PIZARRA STUDY

The relationship between type of dietary fatty acid and degree of insulin resistance was evaluated in a study in Pizarra, Spain. The study included all subjects between the ages of 18 and 65 years in Pizarra, an urban town (population 6600) 30 km from Malaga in Andalusia, southern Spain. Participants were identified by number from the municipal register, which contains a list of all the inhabitants of the town, together with their address and date of birth. Of these, 1226 people were randomly selected using a random number table. All participants were requested by mail to attend their local health center to undergo a medical examination. A second letter giving another appointment was sent to anybody not attending their first appointment, and all those still not attending were visited at home to ascertain the reason. People who were institutionalized for whatever reason, pregnant women, and those with a severe medical problem or psychological disorder were excluded. Final participation was 78.5%, and the final sample distribution by age and sex was not significantly different from the total population distribution.

All participants were interviewed and underwent a physical examination according to standard procedures. All of the examinations were performed by the same investigators and dietitians. Standardized measurements were taken of weight, height, body-mass index (in kg/m²), blood pressure, waist and abdominal circumferences, waist-to-hip ratio, and sagittal diameter. The blood pressure was measured twice with a mercury sphygmomanometer with an interval of 5 minutes between measurements. An oral glucose tolerance test was given to 1020 persons, and blood samples were taken at baseline and 120 minutes after the oral-glucose-tolerance
test; the serum was stored at –70°C until further study. Insulin resistance was estimated by homeostasis model assessment.

During the course of the interviews about dietary habits that were conducted in the homes of a random subset of 538 subjects, a sample was taken of the oil being used. To avoid the oil’s being swapped for newer oil before the sampling, the family was not told of the intention to request a sample of their oil until the time of the investigator’s visit. All participants authorized the collection of these samples of oil from their kitchens. The strength of the association between variables was measured by calculating the OR from logistic models, and the relationships were measured by linear correlation coefficients.

Insulin resistance was significantly lower in people who used olive oil compared with those who used sunflower oil or a mixture. Statistical significance remained in the group of people with normal oral glucose tolerance test after adjusting for obesity. In the whole sample, insulin resistance correlated negatively with the concentration of oleic acid \( (r = -0.11; P = 0.02) \) and positively with that of linoleic acid \( (r = 0.10; P = 0.02) \) from the cooking oil. In subjects with normal glucose, insulin resistance was correlated negatively with oleic acid from cooking oil \( (r = -0.17; P = 0.004) \) and from plasma phospholipids \( (r = -0.11; P = 0.01) \), and positively with the concentration of linoleic acid in cooking oil \( (r = 0.18; P = 0.004) \) and plasma phospholipids \( (r = 0.12; P = 0.005) \). The risk of having raised insulin resistance was significantly lower in people who consumed olive oil, either alone \( (OR = 0.50) \) or mixed \( (OR = 0.52) \), compared with those who consumed only sunflower oil.

In this study, no association was found between the intake of oleic acid, the composition of oleic acid in plasma phospholipids, and peripheral insulin action. The findings are consistent with the notion that adherence to a Mediterranean diet may benefit insulin sensitivity, and therefore decrease cardiovascular disease risk.

**SUMMARY**

In conclusion, there is considerable evidence that diet has an important role in cardiovascular epidemiology, and that an optimal diet for cardiovascular health has an extensive overlapping with the traditional Mediterranean diet. It has not yet been established which are the particular components or interactive processes in the Mediterranean diet that are responsible for its apparent health effects. There is evidence, however, that olive oil has beneficial properties and there is strong evidence that it is not possible to consume the large quantities of vegetables and legumes that Mediterraneans do in the absence of olive oil.

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