**PREDIMED STUDY: SUMMARY AND DIETARY INTERVENTION**

**Summary**

The PREDIMED study is a parallel group, multi-center, randomized, single-blinded trial aimed at assessing the effects on the risk of major cardiovascular events of two intensive behavioral counseling and nutrition education interventions in comparison with a control group. Both intervention groups are assigned a traditional MeDiet. In one of these two groups we supplement the diet with EVOO (1 liter/week) and the other with 30 g/d of nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds). The third arm of randomization is the control group, whose participants do not receive education on the MeDiet, but are given advice on how to follow a low-fat diet. We are recruiting men (age: 55 to 80 years) and women (age: 60 to 80 years) with either diabetes or three or more major cardiovascular risk factors. All participants are free of cardiovascular disease at baseline. Study participants are randomized to three equally sized groups. They will be followed-up for clinical outcomes during a median time longer than four years by the primary care physicians who recruited them for the study. The primary endpoint will be a composite outcome of cardiovascular events (cardiovascular death, myocardial infarction, and stroke). A first evaluation study of the 3-month intervention has been carried out.

**Design**

Parallel group, multi-center, randomized trial aimed at assessing the effects on the incidence of major cardiovascular events of two intensive behavioral counseling and nutrition education interventions in comparison with a control group. The Institutional Review Board (IRB) of the Hospital Clinic (Barcelona, Spain) accredited by the US Department of Health and Human Services (DHHS) update for Federalwide Assurance for the Protection of Human Subjects for International (Non-US) Institutions # 00000738 approved the study protocol. The trial has been registered in Current Controlled Trials (London) and assigned a provisional number (CCT NAPN-13481).

**Outcomes**

Primary outcomes: composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Secondary outcomes: death of any cause and incidence of angina leading to a revascularization procedure, heart failure, diabetes mellitus, cancer, dementia, and other degenerative disorders.

**Other outcomes:** changes in blood pressure, body weight, adiposity measures, blood sugar, lipid profile, markers of inflammation, and other intermediate markers of cardiovascular risk.

**Follow-up**

Participants recruited in 2003 will be followed for up to 6+ years and will have the longest follow-up. Participants entering the study after December 2005 will be followed only for 4 years, thus having the shortest follow-up. Consequently, we expect a median follow-up longer than 4 years.

**DIETARY INTERVENTION**

The PREDIMED dietitians are directly responsible for the dietary intervention. All PREDIMED dietitians are registered dietitians, trained and certified to deliver the PREDIMED intervention protocol. Before the implementation of the protocol, training consisted of approximately 24 hours of initial theoretical and practical group discussion with experts in nutrition education and discussion in between 3 to 5 conference calls to review and improve the protocol. These calls are continued bimonthly throughout the study. During the calls each dietitian discusses her practice sessions with the team, and together the group identifies problems and solutions in protocol implementation. Feedback and discussion also occur among the dietitians and the center coordinators, and between center coordinators and the Data Manager, especially after data from PFQ and objective biochemical measurements (in a random sample of participants) of compliance are analyzed.

Control group: After screening visit 2, participants randomized to the Control group have an interview with a PREDIMED dietitian. This interview includes: a) a simplified assessment of adherence to the MeDiet (14-item questionnaire). b) Brief personal recommendations to follow a low-fat diet (AHA guidelines). For total fat intake these recommendations are in some way opposite to those given to the participants in the 2 MeDiet intervention groups. c) A leaflet with written recommendations to follow a low-fat diet is given. No further visits are scheduled for the Control group until the 1-year follow-up evaluation.

Mediterranean diet groups:

**Individual multiethnic interview with a PREDIMED dietitian.** After screening visit 2, participants randomized to either of the two MeDiet intervention groups have a face-to-face interview with the dietitian. This interview includes:

a) The 14-item questionnaire of adherence to the MeDiet.

b) Personal individual recommendations for changes to be introduced in the participant's diet in order to achieve a personalized goal. The dietitian provides a comprehensive number of reasons to adopt a MeDiet, highlighting the advantages of following this diet, rather than the risks of not adhering to it, and transmitting a positive message with stress on the particular benefits for diabetic patients and for those at high cardiovascular risk. The dietitian personalizes the message by adapting it to the patient’s clinical condition, preferences, and beliefs. The training of the PREDIMED dietitians emphasized the holistic approach to lifestyle change in order to tailor the intervention to nutritional assessment and individual needs, and encourage adherence to the MeDiet. A contracting procedure is used and a negotiated change in diet is the targeted goal, working with the subject to determine what he or she considers an attainable goal. The focus can be on reducing portion change, portion size changes, or dietary changes in cooking methods.

Accomplishments in the previous months, even if minor, are considered as support to provide further empowerment and self-reward. The usefulness and effectiveness of this approach has been shown in an even larger randomized trial currently conducted in the US that is aimed instead to reduce fat intake (Mossavar-Rahmani, 2004; Patten, 2003).

Importantly, caution is taken to make sure that participants with diabetes, overweight/obesity, and/or hyperlipidemia may not receive contradictory dietary advice from other health professionals external to the PREDIMED trial. Because unsaturated fats like those contained in olive oil and nuts are still perceived as fattening by some nutrition experts, it is particularly important to allay the fear of an eventual weight gain that might have both the person who is on a weight-management program and his/her nutritionist. A leaflet with written information about the main food components and cooking habits of the MeDiet, together with recommendations on the desired frequency of intake of specific foods, is given.

Participants assigned to the MedDiet group receive an additional leaflet on health benefits, use, and conservation of olive oil, while those in the MedDiet+Nuts are given a leaflet with similar information regarding nuts, with emphasis on the three nut types used in the trial.

d) The participant is scheduled for a group session in the next 1-2 weeks. The visit ends with an agreement to participate in the group session.

group sessions: The PREDIMED dietitian runs the sessions. No more than 20 participants may attend. Separated sessions are organized for each intervention group (MeDiet or MeDiet+Nuts). The group session includes:

a) An introductory talk by the dietitian to remind the participant to follow the 14-item score.

b) Clarification of possible doubts about face-to-face counseling or written material.

c) The following written material is given to each participant and discussed with them:

- Description of 4-5 foods typical of the MeDiet and adapted to the season of the year.
- A quantitative 1-week buying list of food items, according to the season of the year.
- The cooking recipes for cuisine practices according to the suggested menus.
- The cooking recipes for cuisine practices according to the suggested menus.

- A leaflet for each participant and discussed with them:

  - Description of 4-5 foods typical of the MeDiet and adapted to the season of the year.
  - A quantitative 1-week buying list of food items, according to the season of the year.
  - The cooking recipes for cuisine practices according to the suggested menus.
  - The cooking recipes for cuisine practices according to the suggested menus.

- The needed amount of either olive oil (1 liter = 1 liter/week for 15 weeks) or sachets of walnuts, hazelnuts, and almonds (1,350 g walnuts = 15 gits; 675 g hazelnuts = 7.5 gits, and 675 g almonds = 7.5 gits, aliquot for 90 days) are provided to participants, together with instructions about their use and conservation.

e) The contact ends with an agreement to participate in the next visit (in the next 3 months).

For the MedDiet-Nuts group we offer participants three kinds of nuts: walnuts, hazelnuts, and almonds, instead of providing only one type of nut, because we have received funding from the nut industry to provide the three of them. As stronger evidence may support that ALA-rich walnuts can offer special advantages in cardiovascular prevention, we are supplying a higher amount of walnuts.

Follow-up visits and reiteration of individual and group sessions:

The individual and group visits are repeated every 3 months with the same contents. Each visit includes three steps: assessment, intervention, and future directions.

**Description of intervention diets**

Our main focus is to change the dietary pattern instead of focusing in changes in macronutrients. Total fat intake for the 2 intervention groups is ad libitum (a high fat intake is allowed, as long as most fat is derived from vegetable sources, particularly olive oil or nuts). There is also no specific energy restriction. Total energy intake should be adapted to participant's weight, age, and requirements, and the dietitians tailor the advice to his/her individual needs. The two intervention diets will strongly differ from the diet recommended to the Control group in relevant macronutrients, mainly ALA present in walnuts and polyphenols in EVOO, together with flavonoids, other polyphenols, and sterols present in nuts and EVOO.

The general guidelines to follow the MedDiet that PREDIMED dietitians provide to participants in the intervention groups include the following positive recommendations:

a) abundant use of olive oil for cooking and dressing dishes; b) consumption of >=2 daily servings of vegetables (at least one of them as fresh vegetables in a salad), without counting garnishing; c) >=3 daily servings of fresh fruits (including natural juices); d) >=3 weekly servings of legumes; e) <=5 weekly servings of fish or seafood (at least one serving of fatty fish); f) >=3 weekly servings of nuts or seeds; g) select white meats (poultry without skin or rabbit) instead of red meats or processed meats (burgers, sausages); h) cook regularly (at least twice a week) with tomato, garlic and onion adding or not other aromatic herbs, and dress vegetables, pasta, rice and other dishes with tomato, garlic and onion adding or not other aromatic herbs. This sauce is made by slowly simmering the minced ingredients with abundant olive oil. Negative recommendations are also given to eliminate or limit the consumption of cream, butter, margarine, cold meat, paté, duck, carbonated and/or sugared beverages, pastries, industrial bakery products.
Online Supporting Material: Supplementary Material 1 (English)

products (such as cakes, donuts or cookies), industrial desserts (puddings, custard), french fries or potato chips, and out-of-home pre cooked cakes and sweets. The dietitians insist that two main meals per day should be eaten (seated at a table, lasting more than 20 minutes); for usual drinkers, the main source of alcohol should be wine (maximum 300 ml, 1-3 glasses of wine per day). If wine intake is usual, a recommendation to drink a glass of wine per day (bigger for men, 150 cc, than for women, 100 cc) during meals is given. Limited consumption (<1 serving per week) is advised for cured ham, red meat (after removing all the visible fat), chocolate (only black chocolate, with more than 50% cocoa), cured or fatty cheeses.

Menu development Most of the studies that have examined the Mediterranean diet have been conducted under relatively controlled conditions, with most foods and dishes given to a reduced sample of participants by the research team. The PREDIMED trial represents a further step to obtain more relevant information for public health use, because the nutritional intervention is undertaken in free-living persons, who receive information, motivation, support and empowerment to modify their food habits in a real-life context, i.e. they continue to buy their foods and cook their meals. Such an intervention provides a realistic scenario that may be easily applied to public health policies. However, since palatability of meals is extremely important to ensure compliance, menus and recipes with these characteristics for the two intervention diets have been developed. Menus are designed to meet the nutrient targets. They are provided to the participants and they may learn to prepare the menus using the recipes and the information given by the dietitian.

Food supply and distribution A 15-liter supply of EVOO rich in polyphenols (®Hojiblanca, Spain) is provided every 3 months to each participant in the MedDiet group. Similarly, every 3 months a supply of 1,350-g walnuts (®California Walnut Commission, Sacramento, Cal), 675-g almonds (®Borges SA, Reus, Spain), and 675 g hazelnuts (®La Morella Nuts, Reus, Spain) is provided to each participant assigned to the MedDiet+Nuts group. Participants at each site pick up olive oil and nut allowances at the time of the 3-month group visit. Individualized methods of food delivery have been devised for occasions in which participants need to have their 3-month session rescheduled. Provisions have been made to improve participants’ compliance in the 2 Med Diet groups. The olive oil allowance (1 liter/week) takes into account the needs of the whole family. Also, additional 1000 g packs of mixed nuts are provided for each family unit every 3 months. The three nut industry companies are committed to supply for free the nuts used in the study until its termination. The Hojiblanca Company has agreed to supply the olive oil for free during the year 2005, and our agreement with the company has to be renewed every year. We also have approached the International Olive Oil Council as a second option for additional supply of olive oil. None of the investigators has any conflict of interest with these food companies, and there is a complete freedom to publish the findings of the study.

Adherence promotion Efforts to promote adherence began at the earliest stages of the study. During screening and orientation, participants are repeatedly provided with information about key features of the study and with the concept of MedDiet. At the first screening visit, the attitude towards dietary change is assessed in the eligibility questionnaire. Individuals must be willing to change their diets otherwise they are excluded. The dietitian-led motivational and education intervention includes both individual and group sessions every 3 months. Additional written material is provided. Furthermore, the free distribution and supply of key food items ensures a high adherence to the intended diets during the trial. Acceptance of the intervention protocol is increased because no specific caloric restriction is imposed and participants are allowed an ad libitum fat intake, if it comes from olive oil, nuts, other plant-sources or fatty fish. However, after randomization, every effort is made to promote adherence. In many instances, these efforts are tailored to the specific needs of the participant (e.g. food items delivered to home or work). These procedures are very effective as evidenced by the high rates of adherence and follow-up in the pilot study.

Compliance assessment The 3-month and yearly-administered FFQ will provide information about compliance and attainment by participants of the nutrients targets. Although the FFQ that we are using has been previously validated in Spain, we are conducting a sub-study to validate and calibrate it again.

At any rate, the information extracted from the FFQ will only provide a subjective assessment of compliance. To obtain also an objective evaluation, we measured biological markers of compliance in a random subset of participants from the three arms of trial. In a random sample of participants a blood sample and urine aliquots are used to blindly ascertain the following markers of compliance: a) plasma fatty acid composition (specifically oleic and ALA, which are reliable indicators of MUFA and walnut consumption, respectively); b) urinary tyrosol and hydroxytyrosol (EVOO); c) urinary resveratrol and ethanol (wine and other alcoholic beverages). To relate these measurements to the time of intake, participants are asked the time spent since they last consumed the specific foods when blood and urine samples are taken.

English version of the Spanish written material MEDITERRANEAN DIET INTRODUCTION Countries on the Mediterranean coast are well known not only for their low rates of heart diseases and various types of cancer, but also for their low death rates owing to these causes and long life expectancy, i.e. they enjoy enviable health. It is believed that this is due, among other factors, to the traditional eating habits of the peoples who live in the Mediterranean area. This notion has led nutritionists and doctors, as well as agricultural producers, the media and wide segments of the population to set their sights on the so-called "Mediterranean Diet". Three staple foods are regarded as typical of Mediterranean cuisine: olive oil, cereals (wheat) and wine, although, in terms of nutrition, there are many other outstanding foodstuffs: fresh fruit, greens and vegetable, nuts, other cereals (rice), pulses, a fairly high level of fish consumption as opposed to meat and small quantities of dairy products. These foods are prepared or dressed using olive oil and in most cases seasoned with garlic, parsley, aromatic herbs and spices. Often these foodstuffs are accompanied by moderate amounts of wine.

There are other characteristics of the Mediterranean diet that complement meals and no doubt contribute to the beneficial effect on health: the diet includes attractive and tasty dishes, carefully prepared to be shared among friends and family sat around a table and followed by relaxing table-talk and, though less frequent, the possibility of a siesta, all of which alleviates daily stress.

RECOMMENDATIONS FOR FOLLOWING A MEDITERRANEAN DIET

- Use olive oil for cooking and dressing foodstuffs
- Consume 2 or more portions of greens or vegetables a day (at least 1 raw, e.g. salad)
- Eat three or more pieces of fruit a day (including natural fruit juices)
- Eat pulses at least 3 times a week
- Eat fish or seafood at least 3 times a week (at least 1 blue fish)
- Eat nuts and or seeds at least 3 times a week
- Eat more white meats (skinless fowl and/or rabbit) than red meats, sausages or other processed meats (hamburgers, sausages, meatballs)
- Garnish pasta, rice and vegetable dishes with lightly fried tomato, garlic and onion or leeks at least twice a week
- Limit the consumption of the following foods and drinks to at least once a week:
  - Cream, butter or margarine
  - Sweetened drinks (soft drinks)
  - Confectionery, industrial bakery products, crisps (chips) or similar products and pre-cooked dishes or foods.
**PREDIMED Study**  
**Mediterranean diet+Virgin Olive Oil group**

**VIRGIN OLIVE OIL**

Olive oil is the foundation stone of the Mediterranean diet, regarded as one of the healthiest in the world. The cultivation of olive trees began some 6,000 years ago and became widespread throughout the Mediterranean basin following Greek and Roman colonisations.

**Health properties**

Certainly, the most typical characteristic of the diet in Mediterranean countries is a high consumption of olive oil. It is used in cooking and for dressing crop-based foods, such as vegetables and pulses, in order to heighten their flavour and facilitate consumption. It, therefore, plays an important role in promoting the healthy properties of a diet rich in vegetable food content. Furthermore, olive oil itself is considered to be a very healthy fat, and especially if it is virgin olive oil. Apart from being more natural, virgin olive oil is more beneficial as it conserves all the healthy components of olives, among them vitamin E and other powerful antioxidants which are largely lost during the refining process.

The main fat component of olive oil is oleic acid which contributes to reducing cholesterol counts. Olive oil contains very few saturated fatty acids and no cholesterol. It is, therefore, recommended to help control cholesterol. Moreover, historical evidence exists to show that populations of the Mediterranean area that use olive oil as their main cooking fat suffer from fewer chronic and degenerative diseases, such as heart diseases (angina and heart attacks), of the brain (cerebral thrombosis and dementia), diabetes and various types of cancer, than the populations of Northern Europe that usually use other fats, such asland, butter or margarines. Additional there is no evidence to suggest that the habitual consumption of olive oil causes an increase in weight or a predisposition to obesity.

Various studies have also been carried out on people with diabetes that indicate that a diet with virgin olive oil helps to control diabetes and is much more pleasant than a diet low in all types of fat, which is what is usually recommended to diabetics, but is very difficult to follow.

Apart from the historical scientific evidence to recommend the use of olive oil as a cooking fat, it should be noted that the type of fat it contains make it more resistant to heat than seed-based oils. Olive oil can be reused in frying without altering its beneficial properties, and is, therefore, the oil most recommended for this type of cooking.

**Conservation and use of olive oil**

Oils should be stored away from direct sunlight at a temperature of between 15º and 20ºC, so avoiding excessive heat that would particularly affect their gastronomic qualities. The best way of conserving the properties of oil is to use opaque or coloured containers.

From the culinary point of view, oil is recommended both in its natural state and in the preparation of foods that have to be submitted to high temperatures, provided that this does not exceed 210ºC, the moment when oil begins to give off smoke.

**PREDIMED Study**  
**Mediterranean Diet + Nuts group**

**NUTS**

Nuts have been eaten since ancient times. Together with cereals (wheat), vegetables, fruit, pulses and olive oil, they constitute one of the main ingredients of the Mediterranean diet and contribute their beneficial properties to our health. Indeed, various studies undertaken on large groups of populations have shown that people who eat nuts daily in their normal diet have only half the heart problems (angina, heart attacks or death as a result) than those who hardly ever eat nuts. It has also been observed that there is a lesser risk of becoming diabetic when nuts are frequently consumed. Moreover, it has been shown that people who consume more nuts are slimmer and do not get as fat over the years as those who hardly ever eat them.

Nuts contain many nutritional substances that are good for our health: unsaturated fats, vegetable proteins, fibre, vitamin E, A and folic acid, antioxidant compounds and minerals such as calcium, magnesium, phosphorus and zinc.

Despite their high fat content (and, therefore calories), there is no evidence to show that habitual consumption leads to increase in body weight. This is largely due to the fact that they make you feel full so removing the desire to eat other high calorie foods. In general, when you eat nuts, your appetite for foods rich in saturated fats (bad fats) and sugar, such as confectionery products and enriched dairy products, is reduced. For this reason, and because nut fat is of the unsaturated type ("good" fat), their habitual consumption has the effect of reducing cholesterol counts.

**WALNUTS**

Walnuts differ from other nuts in that they are very rich in omega 6 and omega 3 type unsaturated fats. Moreover, the antioxidants they contain are among the most powerful in the plant world. It should be mentioned that, like omega 3 in fish, nut fats possess important beneficial properties for general health and the heart in particular.

**ALMONDS**

Almonds form part of many traditional desserts and sweats of Arabic origin, such as nougat. Currently, Spain is the second largest producer and consumer of almonds in the world, after the United States. As with hazelnuts and olive oil, almonds are rich in oleic acid. They differ from other nuts in that they contain more fibre, vitamin E, calcium and magnesium.

**HAZELNUTS**

Hazelnuts, another widely consumed nut in Spain, are very rich in oleic acid. Furthermore, they are nuts that provide a large amount of folic acid, a vitamin very important for regulating the metabolism, a lack of which can lead to thrombosis and an acceleration of degenerative processes such as arteriosclerosis and senile dementia.

During the study, walnuts, almonds and hazelnuts must be eaten daily. The recommended quantity per day is:

- 15 g. of walnuts (approximately 3 units)
- 7.5 g. of almonds (approximately 6 units)
- 7.5 g. of hazelnuts (approximately 8 units)

The amount of nuts in the bags provided should last for 15 days. It is important that the entire content contents of the bags be consumed in 15 days. If you forget to take them one day, double the ration the following day.

It is preferable to store the nuts (especially the walnuts) in the fridge. If this is not possible, store them in a dry and dark place, closing the bags with a peg or something similar.

Nuts must always been eaten raw and with their skin, as heat can destroy their healthy properties and the skin is rich in vitamins and antioxidants. They can be eaten alone (as an appetizer, at tea-time or as a dessert), or mixed with food, e.g. salads, fruit, yoghurt, bread, etc. They can be eaten all at once or at intervals throughout the day.

If you are a habitual consumer of nuts, you may eat more, including any foodstuff made of nuts, such as nougat. You have to calculate the quantity of nuts you consume, so you should not share them with friends or family.
PROTECT YOU AND YOUR FAMILY’S HEARTS BY SERVING LOW FAT FOODS

Bread, pasta, rice, fruit, vegetables, salads and pulses form part of a healthy diet. Prepare them in a healthy way for you and your family’s hearts. Help your family to eat less fat.

BUY LOW FAT FOODS

Bread, Cereals and pasta, Rice, Potatoes, Fruit and vegetables, Beans, lentils and chickpeas, Skimmed milk and other skimmed dairy products, Low fat and skimmed soft cheeses, White fish and seafood, Skinless chicken or turkey. Cuts of low fat meat instead of meat with high fat content (like streaky bacon, beef, lamb…).

COOK WITH LESS FAT

. Avoid oil, butter or oil-based dressings
. Dress dishes with the minimum amount of oil
. Use simple preparations such as boiling, baking, and grilling. Avoid stews, sautés, hotpots, fried, lightly fried and battered foods.
. Put a minimum amount of oil in the frying pan, just enough to prevent the ingredients from sticking
. Cook without adding sausages, streaky bacon or butter.

REMOVE THE FAT

. Do not spread bread with butter, oil or other fats. Remove visible fat before cooking meat. Drain away the fat given off by meat during cooking. Allow the meat stock to cool so as to remove the layer of fat before reheating it

WHICH FOODS CONTAIN MOST FAT AND WHICH SHOULD YOU NOT EAT?

. Oils, Butter and margarine, Cream, creamy fillings and ice creams, Lard, Sausages and fatty meats, Nuts, Fried foods, Sauces and mayonnaise, Precooked foods, Sunflower seeds, crisps and other packaged snacks.