

Primary prevention of cardiovascular disease with a Mediterranean diet: The PREDIMED study

The Predimed study is a large randomized trial aimed to assess the effects of the Mediterranean diet in the primary prevention of chronic diseases. It was launched in 2003 and for almost five years 7,447 volunteers with a high cardiovascular risk have participated to help more than 90 researchers to determine if the Mediterranean diet supplemented with extra virgin olive oil or nuts prevents the occurrence of cardiovascular disease, compared to a low fat diet. The final results were recently published and showed that the Mediterranean diet can reduce the risk of cardiovascular disease by 30%. In addition, it provided evidence on the benefit of the Mediterranean diet in the prevention of various chronic diseases, such as diabetes, cancer, hypertension and neurodegenerative diseases. The results support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease.

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INTRODUCTION

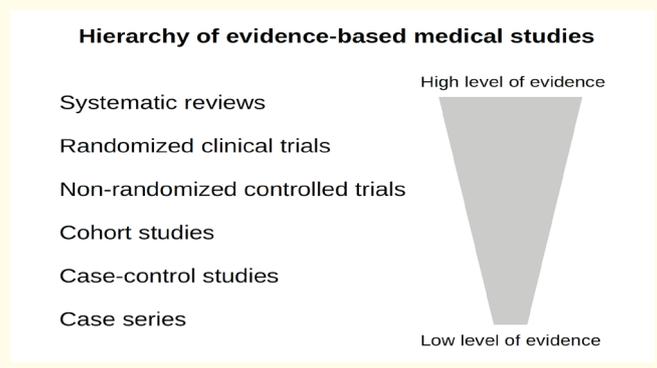
The final results of the Predimed (PREvention with Mediterranean Diet) study were recently published in the New England Journal of Medicine and have concluded that among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil (VOO) or nuts reduced the incidence of major cardiovascular events⁽¹⁾. While for the general public and some scientists the beneficial effects on health of the Mediterranean diet had already been demonstrated, this is actually the first time that the preventive effects of the Mediterranean diet has been demonstrated with a high level of evidence.

In the Seven Countries Study, Ancel Keys and his colleagues were the first to recognize the beneficial effects of the Mediterranean dietary pattern⁽²⁾. They observed that people living in the isle of Crete, in Greece, tended to live longer compared to subjects living in other countries and they had lower rates of heart disease and some cancers. However, they were unsuccessful to demonstrate that a Mediterranean-type diet could improve health, since possible contributors, like obesity rates, physical activity, genetic variants were not assessed.

Over the past four decades, observational studies had conclusions similar to those of Keys and his coworkers. However, in the era of evidence-based medicine, nutritional recommendations to the public should be based on the highest level of evidence and this is only given by meta-analyses of large-scale randomized clinical trials (Figure 1). Before 2003, when the Predimed study was launched, no study of these characteristics had been performed to evaluate the preventive features of the Mediterranean Diet. The closest trial was the Lyon diet Heart Study⁽³⁾, which aimed to assess secondary prevention variables with a modified Mediterranean diet (enriched with alpha-linolenic acid, from vegetable sources, but

with little olive oil content) compared to the usual diet. The results of this study in patients who had suffered a myocardial infarction showed a marked reduction in morbidity and mortality from coronary heart disease in the group of modified Mediterranean diet. Furthermore, nutrition experts had expressed their discrepancies because of the high-fat content of Mediterranean dietary patterns

Figure 1: Hierarchy of evidence-based medical studies.



(up to >40% of total energy intake), which is in conflict with the usual recommendation to follow a low-fat diet in order to avoid overweight/obesity and to prevent coronary heart disease⁽⁴⁻⁶⁾.

Therefore, the lack of sufficient evidence led a group of researchers to begin in October 2003, the recruitment of participants for a primary prevention, randomized, multicenter, parallel group study trial, in order to definitely assess the cardiovascular benefits of the Mediterranean diet and its main components (ie, VOO). Yet, the final goal of Predimed study was to obtain the highest level of scientific evidence in order to allow recommendations to the general public

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to help to reduce cardiovascular risk factors, reduce the incidence and delay the onset of cardiovascular events and eventually reduce cardiovascular morbidity and mortality and extend life expectancy of patients with a high cardiovascular risk.

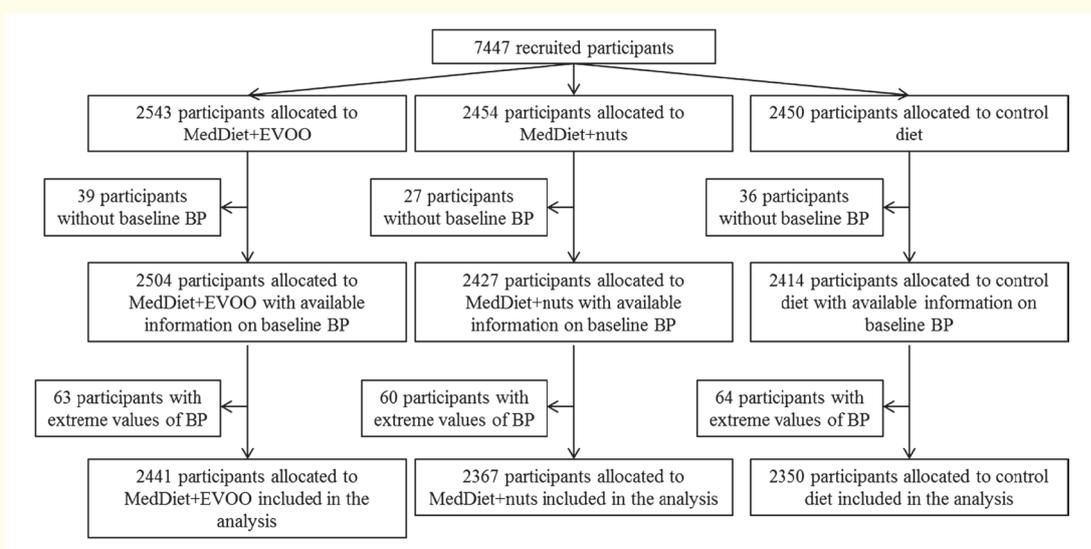
DESIGN AND RECRUITMENT

The study was conducted in Spain for cost-effective reasons and because non-Mediterranean populations are not yet prepared to adopt a Mediterranean diet in a short period of time. The study finally involved 7447 volunteers with a high cardiovascular risk (Figure 2). To participate in the study, volunteers had to be men between 55 and 80 years and women aged 60 to 80 who had been diagnosed of type-2 diabetes mellitus or who met three of the following criteria: smoking, hypertension, elevated LDL-cholesterol level, low HDL-cholesterol level, overweight or obesity, or a family history of premature coronary heart disease. These volunteers were randomized into three dietary groups. Two groups received recommendations for a Mediterranean-style diet, which was supplemented with VOO (approximately 1 liter per week) or nuts (30 g of mixed nuts -walnuts, hazelnuts and almonds- per day) and the third group received recommendations to follow a low-fat diet. Dietary recommendations were given by a group of dietitians quarterly and the adherence to the Mediterranean diet was

assessed by a 14-item dietary screener^[7,8]. A leaflet with written information about the main food components and cooking habits of the Mediterranean Diet, together with recommendations on the desired frequency of intake of specific foods, was given to each participant. Participants assigned to the Mediterranean Diet groups received an additional leaflet with information on health benefits, use, and conservation of VOO or the three nut types used in the trial. Since, in the PREDIMED trial, the nutritional intervention was undertaken in free-living persons, they needed to receive information, motivation, support and empowerment to modify their food habits in a real-life context. This implied that menus and recipes needed to be developed for the two intervention diets and they are provided to the participants so they may learn to prepare the menus using the recipes and the information given by the dietitians. Compliance with these recommendations was assessed by food-frequency questionnaires and by measuring urinary hydroxytyrosol concentrations (for VOO) and plasma alpha-linolenic acid concentrations (for nuts). Volunteers were followed-up for a median of 4.8 years.

It is understandable that this monumental work needed a great deal of organization and the involvement of more than 90 researchers, clinicians, dietitians, lab technicians, etc, who belonged to 18 research centers and hospitals across Spain,

Figure 2: Flowchart of participants in the PREDIMED trial. Published under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), on Toledo et al. BMC Med. 2013;11:207.



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including data management and statistical units. The trial also included external advisors from the Columbia University College of Physicians and Surgeons, the Harvard School of Public Health, Loma Linda University and the Spanish branch of the EPIC Study, who were in charge of reviewing the implementation of the protocol and to monitor the progress.

THE FIRST RESULTS OBTAINED

A pilot study of the Predimed trial was published in 2006^[20]. It included the first 772 participants (339 males and 433 females, mean age 67 ± 6 years) who completed an intervention period of 3 months. For all three groups of intervention, changes in diet, blood pressure, blood sugar, insulin sensitivity (not participating in diabetes), lipid profile and serum biomarkers of major inflammation were assessed. Although the follow-up time was short and insufficient to assess primary cardiovascular events (heart, attack, stroke or death from cardiovascular causes), all intermediate markers of vascular risk measured (blood pressure, blood sugar, insulin resistance, lipid profile and inflammatory markers) showed favorable results in both groups of Mediterranean diet compared to the control group. It was important to note that body weight was maintained despite vegetable fat intake was increased in the two groups of Mediterranean Diet, avoiding the risk of enhanced adiposity in this group. Therefore, in this first phase of the PREDIMED trial it was concluded that an intervention designed to encourage a Mediterranean dietary pattern supplemented with VOO or nuts produces an improvement in cardiovascular risk factors after 3 months of intervention.

In this pilot study, an increase of 76.5% was observed in the alpha-linolenic acid intake in the Mediterranean Diet+Nuts group, which was especially relevant given that there are abundant epidemiological evidence of cardioprotective effect of intake of n-3 PUFA^[9-11]. Also, significant reductions were observed for inflammation markers like soluble intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and interleukin-6 in the two groups of Mediterranean Diet^[21]. The results of numerous epidemiological studies have shown that a (high) plasma concentration of ICAM-1 could be a predictor of future cardiovascular events^[12-15] and the development of clinical diabetes^[16]. It is noteworthy that the concentration of reactive-protein C, which can also predict future cardiovascular

complications^[12,17], decreased only in the Mediterranean Diet+VOO group^[18]. Another substudy of the Predimed trial, including 372 participants, observed a reduction in markers of oxidative stress (circulating oxidized LDL) after 3 months of intervention in both Mediterranean diet groups compared to the low-fat group^[19].

After one year of follow-up and 1224 participants, modifications of dietary patterns^[20], as wells as reduced prevalence of metabolic syndrome in the Mediterranean diet supplemented with nuts group^[21] were observed, which supported the feasibility of the trial. Additionally, a reduction in the incidence of type-2 diabetes by 50% by both Mediterranean diets compared to the control diet was found^[21]. Among people with metabolic syndrome, the Mediterranean Diet reduced oxidative damage to DNA, measured as 8-oxo-7,8-dihydro-2'-deoxyguanosine, after 1-year intervention^[22]. The Mediterranean diet enriched with nuts was responsible for a decrease of atherogenic pattern of lipoprotein subfractions^[23]. Indeed, participants allocated to this group had lower concentrations of medium-small and very small LDL, decreased LDL particle number and an increase of large LDL concentrations. While the Mediterranean diet + nuts had a beneficial effect on LDL profile, the Mediterranean diet+VOO influenced VLDL. In this latter group, VLDL-cholesterol and VLDL-triglycerides content, as wells as the triglyceride to apolipoprotein B ratio in VLDL, were reduced, which was associated to the triglyceride lowering effect of the Mediterranean diet^[24].

FINAL RESULTS

The results obtained during the first year of the trial were certainly promising. The plethora of data that is being collected from the study is leading to an enormous amount of results that have been published in the last years and that will continue being published in the following ones. Among the most remarkable results, a reduction of 52% in the incidence of type-2 diabetes was observed after a median of 4 years of intervention in a subgroup of 418 participants, together with improved hazard ratios of diabetes, in the Mediterranean diets supplemented with VOO or nuts groups compared with the control group^[25]. In another subgroup (n=187), the Mediterranean diet rich in VOO, was associated with higher levels of plasma antioxidant capacity^[26]. Contrarily, the Mediterranean diet was unable to improve the progression of subclinical carotid atherosclerosis, measured as the carotid intima-media thickness,

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after one year of intervention^[27]. Regarding blood pressure, both the traditional Mediterranean diet and the low-fat diet exerted beneficial effects. However, after 4-year follow-up, lower values of diastolic blood pressure were found in the two groups promoting the Mediterranean diet than in the control group.

Nevertheless, the most stunning results were those published in the New England Journal of Medicine in April 2013^[1]. After a median follow-up period of 4.8 years a total of 288 primary-outcome events occurred: 96 in the group assigned to a Mediterranean diet with VOO (3.8%), 83 in the group assigned to a Mediterranean diet with nuts (3.4%), and 109 in the control group (4.4%). Although no effect on all-cause mortality was apparent, the unadjusted hazard ratios for stroke were 0.70 (95% confidence interval [CI], 0.53 to 0.91) for the Mediterranean diet with VOO and 0.70 (95% CI, 0.53 to 0.94) for the Mediterranean diet with nuts as compared with the control diet (P=0.015), indicating a 30% of lower risk.

The beneficial results of the study were associated with different components of the Mediterranean diet. For instance, polyphenols in VOO were associated with lower blood pressure levels^[28] and better cognitive function^[29]. Fiber intake was related to reductions in classical and novel cardiovascular risk factors like body weight, waist circumference, blood pressure, glucose, total cholesterol levels and CRP^[30]. Cholesterol lowering was also attributed to sterol intake, since in contrast to variations in saturated fat, cholesterol or fiber intake, which were unrelated to LDL-cholesterol changes, serum sitosterol-to-cholesterol ratios was correlated inversely to LDL-cholesterol changes^[31]. Magnesium intake was inversely associated with cardiovascular, cancer, and all-cause mortality, with a 34% lower mortality risk of those in the highest tertile of magnesium intake, compared with lower consumers^[32]. Even alcohol consumption showed favorable effects in these high cardiovascular risk individuals. Moderate alcohol intake (5-15 g/day) was significantly associated with lower risk of incident depression, although heavy drinkers seemed to be at higher risk^[33]. However, it is noteworthy that alpha-linolenic acid, which had been taken as a marker of nut intake and was a protagonist of the Lyon Diet Heart Study^[3], has not been directly associated to any particular effect so far.

CRITICISMS

Despite the impressive results reported by the Predimed study, an editorial of the NEJM^[34], expressed some criticisms about the design and results of the trial. In the editorial, Appel and Van Horn considered that the control group did not actually achieve a low fat intake and consumed a variant of the Mediterranean diet, since the percentage of energy intake in this group was only 4 percentage points lower than the Mediterranean-Diet groups (37% vs 41%). In fact, the most striking differences between the randomized groups resulted from the supplemental foods (VOO and nuts), not the dietary advice, which led to modest between-group differences (as compared with the control group) in legume and fish

consumption and no major differences in intake of other nutrients and food groups. Additionally, the reduction in cardiovascular disease was most evident for stroke, an outcome that is exceedingly dependent on blood pressure. Reduction of blood pressure was observed in the pilot study^[7] and probably contributed to observed reductions in cardiovascular disease. However, the effects of the interventions on known blood-pressure determinants (i.e., weight and dietary sodium and potassium intake) are unknown.

According to Appel and Van Horn^[34], the PREDIMED trial is neither a pure test of a Mediterranean-style diet nor a pure test of VOO and nuts and interpretation of the PREDIMED trial is similar in complexity to that of the Lyon Diet Heart Study^[3]. Mediterranean-style diet was already recommended by policymakers^[6] on the basis of an extensive body of evidence from observational studies. What the Predimed adds is, specifically, in the context of a Mediterranean-style diet, that increased consumption of mixed nuts or substitution of regular olive oil with VOO has beneficial effects on cardiovascular disease. Still, for these authors there are unanswered questions: Will the benefits of VOO and mixed nuts accrue to persons consuming other diets? Does high consumption of VOO and mixed nuts lead to weight gain? Can the benefits of VOO and mixed nuts occur at lower doses? Answers will be looked for.

Other criticisms include that the low-fat group's protocol was changed during the trial and that the low risk reduction margins may have been accounted for in the baseline differences between the groups including sex, obesity, use of diuretics, and use of oral hypoglycemics^[35].

CONCLUSIONS

The Mediterranean Diet has been regarded as a healthy dietary pattern for decades but there was a lack of high-level evidence studies to support its benefits. Therefore, it was imperative that a randomized controlled trial with a high number of participants was carried out. The Predimed study involved 7447 subject with a high cardiovascular risk, who were given recommendations to follow a Mediterranean-style diet or a low-fat diet and were followed for almost 5 years. The intervention with the traditional Mediterranean diet supplemented with VOO or nuts reduced by 30% the incidence of major cardiovascular complications (death from cause cardiovascular, myocardial infarction and stroke), providing the first order scientific evidence of the efficacy of traditional Mediterranean Diet in primary prevention of cardiovascular disease.

Despite the criticisms, the Predimed study has become the greatest study on the healthy benefits of the Mediterranean Diet. Now, it remains to be elucidated whether is the whole pattern the responsible for the protection or the intake of VOO or nuts is sufficient. Also, it should be investigated if the Mediterranean Diet is also protective in healthy persons. The Predimed study has set the starting point.

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 Lieu : Clermont-Ferrand, France
 Site : <http://www.chu-clermontferrand.fr/>

4th European Lipidomic Meeting**22-24 septembre 2014**

Organisateur : Medical University Graz
 Lieu : Graz, Autriche
 Site : http://massspec.uni-graz.at/ELM_2014/index.php

**BENEFIQ 2014 : Intl on Health
Ingredients****23-25 septembre 2014**

Organisateur : INAF
 Lieu : Québec, Canada
 Site : <http://www.benefiq.ca/eng/>

**2nd Intl Workshop on Molecular
Medicine of Sphingolipides****12-17 octobre 2014**

Organisateur ISN
 Lieu : Kloster Banz, Autriche
 Site : <http://www.sphingolipids2014.com/>

**Journée SFEL : Omega 3
Longues Chaînes****17 octobre 2014**

Organisateur : SFEL (Société Française
d'Etude sur les Lipides)
 Lieu : Paris, France
 Site : <http://www.sfel.asso.fr/>

**SIAL 2014 : Salon International
de l'Agroalimentaire****19-23 octobre 2014**

Organisateur : SIAL
 Lieu : Paris, France
 Site : <http://www.sialparis.fr/>

**5th European Workshop on Lipid
Mediators****23-24 octobre 2014**

Organisateur : Faculty of Pharmacy
 Lieu : Istanbul, Turquie
 Site : <http://workshop-lipid.eu/>

**Congrès International de
Nutrition 2014****9-12 novembre 2014**

Organisateur : Public Health Nutrition
 Lieu : Las Palmas, Canaries
 Site : <http://www.nutrition2014.org/>

**GLN : Cholestérol, ami ou
ennemi****18 novembre 2014**

Organisateur : GLN (Groupe Lipides
Nutrition)
 Lieu : Paris, France
 Site : <http://lipides-et-nutrition.net/journees-gln-conferences/>

**Journée Scientifique : Congrès
Nutrition et Cancer****29 novembre 2014**

Organisateur : Cerden
 Lieu : Bruxelles, Belgique
 Site : <http://www.cerden.be/Formations/journ%C3%A9es-scientifique>

**2nd World Congress of Clinical
Lipidology****5-7 décembre 2014**

Organisateur : Clinical Lipidology
 Lieu : Vienne, Autriche
 Site <http://clinical-lipidology.com/>

**Journées Francophones de
Nutrition****10-12 décembre 2014**

Organisateur : SFNEP
 Lieu : Bruxelles, France
 Site : <http://www.lesjfn.fr/>



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