



EDITORIAL

The PREDIMED study

ESTUDIO PREDIMED

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Prospective studies have shown that greater adherence to plant-based dietary patterns is associated with reduced cardiovascular disease (CVD) rates.¹ However, causal inference from epidemiologic studies is uncertain due to residual confounding and other sources of bias. To obtain the highest level of scientific evidence, randomized clinical trials (RCTs) using food patterns and assessing clinical end-points are warranted. One food pattern reputed for its beneficial health effects is the Mediterranean diet (MeDiet), characterized by abundant use of olive oil; high consumption of fruit, vegetables, legumes, cereals, and nuts; regular but moderate intake of wine (especially red wine) with meals; moderate consumption of fish, seafood, fermented dairy products (yogurt and cheese), poultry and eggs; and low consumption of red and processed meats and sweets.²

There is a strong evidence from epidemiologic studies indicating that increasing compliance with the MeDiet is associated with reduced fatal and non-fatal CVD and all-cause mortality, as well as reduced incidence of cancer and neurodegenerative diseases.³ A prior RCT, the Lyon Diet Heart study, conducted in survivors of a myocardial infarction, tested a MeDiet enriched with alpha-linolenic acid, but not olive oil, versus a control diet and observed a strong protection against recurrent infarction.⁴ The PREDIMED (PREvención con Dieta MEDiterránea) study was a primary prevention RCT designed to test the hypothesis

that the MeDiet would be superior to a low-fat diet for CVD protection.⁵

PREDIMED is a multicenter, randomized, nutritional intervention trial for the primary prevention of CVD with MeDiet. The study was carried out in Spain from 2003 to 2011 and was funded exclusively by Instituto de Salud Carlos III, while food industries donated the key foods used in the study. Candidates were selected from primary care facilities affiliated with 11 recruiting sites and were at high risk for CVD, but had no clinical disease at enrolment. Criteria for recruitment were age 55–80 years and the presence of diabetes or ≥ 3 risk factors (smoking, overweight or obesity, hypertension, dyslipidemia, and family history of early-onset CVD). Participants were randomized into one of three interventions: MeDiet supplemented with extra-virgin olive oil (EVOO), MeDiet supplemented with nuts, and control diet (advice to follow a low-fat diet). Registered dietitians delivered the PREDIMED intervention at quarterly individual visits and group sessions in which participants were instructed to follow the allocated diet. In the group sessions, participants received written material with information on key Mediterranean foods and seasonal shopping lists, menus and recipes for one week. Those randomized into the corresponding MeDiet groups were given free allocations of EVOO (1 L per week, including a minimum of 50 mL/day for participants and the rest for family needs) or mixed nuts (30 g/day: 15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts plus extra allocations for the family); participants in the control diet group received non-food gifts. As we wished to test the

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effects of the nutrition intervention alone, the diets were energy-unrestricted and increased physical activity was not promoted.

Dietitians used a specific tool to both evaluate actual adherence to the MeDiet and set goals for future adherence: a validated 14-point MeDiet score.⁶ Further information was collected yearly on lifestyle, habitual food consumption with a validated food frequency questionnaire covering 137 foods, physical activity, health status, and medication changes. Anthropometric and blood pressure measurements and an ECG were taken yearly. Fasting blood and spot urine were obtained and serum, plasma and DNA samples were saved. Objective biomarkers of adherence to the supplemental foods (urinary hydroxytyrosol as marker of EVOO consumption and plasma α -linolenic acid as marker of walnut consumption) were determined in random samples.

The primary end-point was incident CVD (an aggregate of non-fatal myocardial infarction, non-fatal stroke, and CVD death).⁵ Secondary outcomes include total mortality, diabetes, metabolic syndrome, peripheral arterial disease, atrial fibrillation, neurodegenerative diseases and major cancers. An event adjudication committee, whose members were blinded to group allocation, was responsible for event ascertainment. A total of 7447 candidates were randomized into the three intervention groups. The mean age of participants was 67 years and the mean BMI was 30 kg/m², close to one-half had diabetes, two-thirds had dyslipidemia, and 4 out of 5 had hypertension. After 4.8 years, 288 major cardiovascular events occurred: 96 in the MeDiet + EVOO group (3.8%), 83 in the MeDiet + nuts group (3.4%), and 109 in the control group (4.5%). The respective rates of the primary end point were 8.1, 8.0, and 11.2 per 1000 person-years. The unadjusted hazard ratios were 0.70 (95% CI, 0.53–0.91) for the MeDiet + EVOO and 0.70 (CI, 0.53–0.94) for the MeDiet + nuts. Disease risk reductions were similar across subgroups of sex, age, and cardiovascular risk factors. Stroke was the predominant CVD in this cohort and was significantly reduced by the MeDiets. Hence, the PREDIMED study demonstrated for the first time with a randomized design that an enriched MeDiet is useful in the primary prevention of CVD in individuals at high risk.

Regarding other cardiovascular outcomes, the MeDiet intervention also reduced the risk of peripheral arterial disease⁷ and atrial fibrillation,⁸ although the antiarrhythmic effect (38% protection) in this post hoc analysis was limited to the MeDiet enriched with EVOO. Three further PREDIMED studies provide mechanistic evidence for protection against CVD. Results of the first 772 participants after intervention for 3 months showed improved blood pressure, insulin sensitivity, lipid profile, and circulating inflammatory molecules with the two MeDiet interventions versus the control diet.⁹ In another sub-cohort, the MeDiet reduced 24-hour ambulatory blood pressure, the gold standard for blood pressure assessment, compared to the control diet.¹⁰ The changes of nearly –4 mm Hg for mean systolic blood pressure and –2 mm Hg for mean diastolic blood pressure were remarkable given that most participants were hypertensive and received standard anti-hypertensive medications. Finally, in a carotid ultrasound study at 2 years, participants allocated the MeDiet plus nuts showed plaque regression and those in the MeDiet plus olive oil arm showed delayed progression

of atherosclerotic lesions, compared with progression in the control group.¹¹

As secondary endpoints of the PREDIMED study, we also assessed diabetes incidence and metabolic syndrome (MetS) status. These are important topics, as there was no information on whether dietary changes alone, without weight loss or exercise, might prevent these conditions. The final results on incident diabetes in the 3541 participants without diabetes at baseline after follow-up for 4.1 years also showed protection from the MeDiets. There were 273 cases of new-onset diabetes (80 in the MeDiet + EVOO group, 92 in the MeDiet + nuts group, and 101 in the control group). After multivariable adjustment, hazard ratios for diabetes were 0.60 (0.43–0.85) for MeDiet + EVOO and 0.82 (0.61–1.10) for MeDiet + nuts in comparison with the control group.¹² The results extend those of prior observational studies showing that lifestyle interventions, and specifically the MeDiet, can reduce the incidence of diabetes in persons at high risk,¹³ but here the beneficial effect was mainly due to diet alone, without other lifestyle changes. Regarding MetS, the results of the full PREDIMED cohort after 4.8 years of follow-up showed that participants with MetS at baseline ($n=3392$) who were allocated to the two MeDiets had a 32% higher rate of reversion of the syndrome compared to those in the control diet group, and this beneficial effect was driven mainly by reduced waist circumference.¹⁴ Of note, even though the PREDIMED MeDiets were rich in fat, which accounted for a mean 42% of daily energy, participants did not gain weight or abdominal adiposity, attesting to the healthfulness of high-fat dietary patterns based on vegetable fat.¹⁵

Among non-CVD outcomes in the PREDIMED cohort, two deserve to be mentioned. Although based on a few incident cases, the MeDiet with EVOO was associated with reduced breast cancer rates in women.¹⁶ In a subcohort of participants who underwent sequential cognitive tests, the two MeDiets were associated with improved cognition compared to the control diet after nearly 4 years of follow-up.¹⁷ Thus, the MeDiet appears to have pleiotropic effects, affecting multiple pathways leading to protection from cardiometabolic disorders, cancer and brain dysfunction. CVD protection by the MeDiet can be explained by a beneficial impact on classical and emergent cardiovascular risk factors, as well as nutrigenomic effects, such as the demonstration that the MeDiet reduced the adverse effect of the *TCF7L2* rs7903146 (C>T) polymorphism on cardiovascular risk factors (fasting glucose and lipids) and stroke incidence.¹⁸ The richness in powerful phenolic antioxidants of the MeDiet and the supplemental foods given in PREDIMED also contributes to their health effects.¹⁹

There are several limitations to the study.⁵ First, the control group received a lower intensity intervention for the first 3 years of the trial, but this was corrected before the recruitment was completed and the final results were similar regardless of the differences in intensity of the intervention. Second, there were more losses to follow-up in the control group than in the MeDiet groups. However, dropouts had a worse cardiovascular risk profile at baseline, which would induce a bias toward a benefit for the control group, hence it does not contribute to explain the findings. Also, the lower retention rate in the group allocated to a low-fat diet reflects both the inherent difficulty to adhere to a low-fat diet on the long term and the fact that no foods

were provided for free. Third, in spite of intensive counsel to reduce all dietary fat, participants in the control group did not really achieve a low-fat diet. Thus, median total fat intake as a percentage of energy decreased after 5 years from 40.0% to 37.4% in the control group. Likely reasons are that participants were older adults belonging to a Mediterranean culture in which olive oil is used abundantly in the kitchen and at the table; low-fat foods have a poor palatability that hinders long-term compliance, and use of olive oil permits abundant intake of cooked vegetables and salads, hence recommending to increase vegetable consumption while limiting olive oil made little sense to participants in the control diet group. Still, we cannot say that the PREDIMED control diet was low fat, only lower in fat than the MeDiet, which was nearly 42% fat as percentage of energy. Finally, the results were obtained in an older Mediterranean population at high cardiovascular risk, which limits the generalizability of the findings. Precisely the impact that the PREDIMED study has had in the international nutrition community is prompting researchers and official institutions in several non-Mediterranean countries to develop PREDIMED-like studies in other populations.

In conclusion, PREDIMED is a landmark RCT of nutrition intervention that has demonstrated for the first time that the traditional MeDiet protects against CVD and its risk factors. Important teachings are as follows. First, the results show that a high-unsaturated fat dietary pattern is better for cardiovascular health than a lower fat diet. Second, the PREDIMED MeDiets showed a protective effect in older persons at high risk for CVD, most of whom were being treated with antidiabetic, hypolipidemic, and/or antihypertensive drugs, then it can be said that the MeDiet was effective to control part of the residual risk observed after standard cardiologic treatment. Third, given the age of PREDIMED participants, the results show that it is never too late to change dietary habits to improve cardiovascular health. Last, the supplemented foods given to participants at no cost were instrumental to promote good adherence to the overall MeDiet pattern. Thus, part of the study's success might be attributed to EVOO and nuts, unsaturated fatty acid- and antioxidant-rich foods that, in spite of their high fat content, did not promote weight gain. Importantly, the 30% CVD risk reduction shown with the MeDiet in PREDIMED is of similar magnitude to that reported in statin trials, albeit it is obtained at no cost for the health system. PREDIMED is providing first class scientific evidence of the power of food to influence cardiovascular and other health outcomes.

The PREDIMED investigators, together with several other Spanish nutrition research groups, have launched a new and ambitious study as continuation of PREDIMED, the PREDIMED-PLUS trial.²⁰ This new randomized controlled trial has been designed to test the hypothesis that a behavioral intervention consisting of a calorie-restricted MeDiet in conjunction with increased physical activity leading to sustained weight loss will reduce CVD in comparison with usual care in older overweight or obese individuals fulfilling criteria for the MetS. Here participants in the two treatment arms (active intervention and control) receive free supplemental extra-virgin olive oil and mixed nuts like in PREDIMED, albeit at lower doses, the purpose being to go a step further than PREDIMED, namely, using the same diet that we know reduces CVD risk but testing the effect of additional lifestyle

intervention aimed at weight loss. The trial is ongoing and has recently completed recruitment of 6000 participants, the predefined target for this 6-year trial, in 23 sites throughout Spain. Hopefully the results of PREDIMED-PLUS will prove it to be another landmark clinical trial and again help shape nutrition policy worldwide.

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Conflict of interest

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References

1. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity. A comprehensive review. *Circulation*. 2016;33:187-225.
2. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr*. 2011;14(12A):2274-84.
3. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr*. 2010;92:1189-92.
4. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779-85.
5. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a

- Mediterranean diet. *N Engl J Med*. 2013;368(14):1279–90. Erratum in: *N Engl J Med*. 2014;370(9):886.
6. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A short screener is valid for assessing Mediterranean Diet adherence among older Spanish men and women. *J Nutr*. 2011;141:1140–5.
 7. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Mediterranean diet inversely associated with peripheral artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311:415–7.
 8. Martínez-González MÁ, Toledo E, Arós F, Fiol M, Corella D, Salas-Salvadó J, et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation*. 2014;130:18–26.
 9. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors. *Ann Intern Med*. 2006;145:1–11.
 10. Doménech M, Roman P, Lapetra J, García de la Corte FJ, Sala-Vila A, de la Torre R, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. *Hypertension*. 2014;64:69–76.
 11. Sala-Vila A, Romero-Mamani ES, Gilabert R, Núñez I, de la Torre R, Corella D, et al. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet. A sub-study of the PREDIMED trial. *Arterioscler Thromb Vasc Biol*. 2014;34:439–45.
 12. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas M-I, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;160:1–10.
 13. Salas-Salvadó J, Martínez-González MA, Bulló M, Ros E. The role of diet in the prevention of type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2011;21:B32–48.
 14. Babio N, Toledo E, Estruch R, Ros E, Martínez-González MA, Castañer O, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *CMAJ*. 2014;186:E649–57.
 15. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:666–76.
 16. Toledo E, Salas-Salvadó J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. *JAMA Intern Med*. 2015;175:1752–60.
 17. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med*. 2015;175:1094–103.
 18. Corella D, Carrasco P, Sorlí JV, Estruch R, Rico-Sanz J, Martínez-González MÁ, et al. Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. *Diabetes Care*. 2013;36:3803–11.
 19. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, Martínez-González MA, López-Sabater MC, Covas MI, et al. Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial. *BMC Med*. 2014;12:77.
 20. www.predimedplus.com Accessed 25.11.16.