EDITORIALS

Did the PREDIMED Trial Test a Mediterranean Diet?

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The U.S. Dietary Guidelines recommend healthy dietary patterns — specifically, the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean-style diets.[1] A persuasive body of evidence from observational studies has documented that Mediterranean-style diets are associated with a substantially reduced risk of cardiovascular disease.[2] Mediterranean diets are not a single dietary pattern, but they do have common features — an emphasis on vegetables, fruits, beans, nuts, seeds, breads, unrefined grains, and olive oil (but not necessarily extra-virgin olive oil); inclusion of fish and wine; and minimal intake of meats and full-fat dairy products.[3] Such diets are rich in total, monounsaturated, and polyunsaturated fat and are lower in saturated fat.

In this issue of the *Journal*, Estruch and colleagues document that provision of extra-virgin olive oil or mixed nuts, in the context of a Mediterranean-style diet, substantially reduced the occurrence of cardiovascular disease.[4] In brief, the Prevención con Dieta Mediterránea (PREDIMED) trial, conducted in Spain, randomly assigned 7447 persons at high risk for cardiovascular disease to one of three groups: participants who received advice on a Mediterranean diet and provision of extra-virgin olive oil, those who received advice on a Mediterranean diet and provision of mixed nuts, and those who received advice to reduce dietary fat (control diet). Extra-virgin olive oil is rich in polyphenols and monounsaturated fat, and mixed nuts are rich in polyphenols, monounsaturated fat, and polyunsaturated fat, including alpha-linolenic acid.

The primary end point was a composite of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). Interim analyses prompted early termination of the trial. As compared with the control group, the two groups that received advice on a Mediterranean diet reduced the risk of cardiovascular disease by approximately 30%. For any therapy, including drug therapy, this magnitude of benefit is impressive; for a dietary intervention, such results are truly remarkable. Still, results might be exaggerated because early termination of trials tends to spuriously inflate estimated benefit.[5]

Central to the interpretation of the results of the PREDIMED trial is an understanding of achieved dietary changes. Despite advice to lower fat intake and limit consumption of olive oil and nuts, the control group did not achieve a low fat intake. Indeed, the control group appeared to consume a variant of the Mediterranean diet. At the end of the trial, total fat was 37% of energy intake in the control group and 41% of energy intake in the other two groups; saturated-fat intake was low and similar in the three groups, approximately 9% of energy intake. In the group receiving extra-virgin olive oil, the additional 4 percentage points in energy intake from fat resulted mostly from increased monounsaturated-fat intake. In the group receiving mixed nuts, the additional 4 percentage points resulted from increases of approximately 2 percentage points in both monounsaturated and polyunsaturated fat.

The most striking differences between the randomized groups resulted from the supplemental foods, 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. The amount of extra-virgin olive oil and nuts provided to participants and their households was substantial (1 liter of extra-virgin olive oil per week and 30 g of mixed nuts per day). At the end of follow-up, the average energy intake from

olive oil was 22.0% in the group receiving extra-virgin olive oil (vs. 16.4% in the control group); the average energy intake from nuts was 8.2% in the group receiving mixed nuts (vs. 1.6% in the control group). Those in the group receiving extra-virgin olive oil modestly decreased consumption of regular olive oil but replaced it with even greater amounts of extra-virgin olive oil.

The reduction in cardiovascular disease was most evident for stroke, an outcome that is exceedingly dependent on blood pressure. This result is concordant with those of observational studies, which have shown that Mediterranean-style diets and olive oil are associated with reduced risk of stroke.[6-8] Previously, the PREDIMED investigators reported that, at 3 months after randomization, the group receiving extra-virgin olive oil and the group receiving mixed nuts had substantially lowered blood pressure.[9] Indeed, reductions in blood pressure 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.

The impressive results of the PREDIMED trial confirm that changes in diet can have powerful, beneficial effects. But what are its policy implications? The PREDIMED trial is neither a pure test of a Mediterranean-style diet nor a pure test of extra-virgin olive oil and nuts. Interpretation of the PREDIMED trial is similar in complexity to that of the Lyon Diet Heart Study, which tested provision of a margarine rich in alpha-linolenic acid, coupled with brief advice to consume a Mediterranean diet.[10]

Policymakers[1] already recommend consumption of a Mediterranean-style diet on the basis of a persuasive body of evidence from observational studies. Our sense is that the policy implications of the PREDIMED trial relate primarily to the supplemental foods. Specifically, in the context of a Mediterranean-style diet, increased consumption of mixed nuts or substitution of regular olive oil with extra-virgin olive oil has beneficial effects on cardiovascular disease.

Still, there are many unanswered questions. Will the benefits of extra-virgin olive oil and mixed nuts accrue to persons consuming other diets? Does high consumption of extra-virgin olive oil and mixed nuts lead to weight gain? Can the benefits of extra-virgin olive oil and mixed nuts occur at lower doses?

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Efficiently Killing a Sugar-Coated Yeast

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With the inclusion in this issue of the *Journal* of the study by Day et al. on the treatment of cryptococcal meningitis,[1] the *Journal* has provided the medical community with a trilogy of studies for the understanding of combination therapy with amphotericin B and flucytosine for cryptococcal