

# A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study<sup>1–4</sup>

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## ABSTRACT

**Background:** Vegetarian diets have been associated with reduced mortality. Because a pure vegetarian diet might not easily be embraced by many individuals, consuming preferentially plant-derived foods would be a more easily understood message. A provegetarian food pattern (FP) emphasizing preference for plant-derived foods might reduce all-cause mortality.

**Objective:** The objective was to identify the association between an a priori–defined provegetarian FP and all-cause mortality.

**Design:** We followed 7216 participants (57% women; mean age: 67 y) at high cardiovascular risk for a median of 4.8 y. A validated 137-item semiquantitative food-frequency questionnaire was administered at baseline and yearly thereafter. Fruit, vegetables, nuts, cereals, legumes, olive oil, and potatoes were positively weighted. Added animal fats, eggs, fish, dairy products, and meats or meat products were negatively weighted. Energy-adjusted quintiles were used to assign points to build the provegetarian FP (range: 12–60 points). Deaths were confirmed by review of medical records and the National Death Index.

**Results:** There were 323 deaths during the follow-up period (76 from cardiovascular causes, 130 from cancer, 117 for noncancer, noncardiovascular causes). Higher baseline conformity with the provegetarian FP was associated with lower mortality (multivariable-adjusted HR for  $\geq 40$  compared with  $< 30$  points: 0.59; 95% CI: 0.40, 0.88). Similar results were found with the use of updated information on diet (RR: 0.59; 95% CI: 0.39, 0.89).

**Conclusions:** Among omnivorous subjects at high cardiovascular risk, better conformity with an FP that emphasized plant-derived foods was associated with a reduced risk of all-cause mortality. This trial was registered at [www.controlled-trials.com](http://www.controlled-trials.com) as ISRCTN35739639. *Am J Clin Nutr* 2014;100(suppl):320S–8S.

## INTRODUCTION

Food patterns (FPs)<sup>5</sup> that are based on plant-derived foods are purportedly healthier than those in which meat, especially red and processed meat, are the main sources of macronutrients (1–6). Specifically, an FP characterized by very low intakes of meat and processed meat (7, 8) appears to be associated with greater longevity and lower cardiometabolic risk (9). When most foods are derived from vegetable sources (ie, a vegetarian diet is adopted), health benefits are apparent. Thus, coronary artery disease (CAD) mortality was reported to be significantly lower by 24% among vegetarians compared with nonvegetarians in a collaborative re-

analysis of 5 prospective studies (10). Subsequently, a meta-analysis of 7 cohort studies confirmed a lower cardiovascular mortality in vegetarians, but inconsistent results for the association between vegetarian diets and death from any cause were found (11). More recently, a 5-y follow-up of the Adventist Health Study 2 cohort showed an overall association of vegetarian dietary patterns with lower mortality (12). Most available comparisons between vegetarians and nonvegetarians relied on a single measurement of diet at baseline, but dietary patterns may change over time and the length of exposure to vegetarianism may account for heterogeneity between results from different cohorts (10, 13, 14). In a pooled analysis of 5 cohort studies, vegetarian diets were inversely associated with CAD mortality, but when vegetarians were subdivided according to whether or not they had followed their current diet for  $\geq 5$  y, the cardiovascular benefits were confined only to those who had been vegetarian for  $> 5$  y (15).

Given that in most cultures the proportion of true vegetarians is low, it would be interesting to examine whether moderate or intermediate approaches to a predominantly plant-based FP relate

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to lower mortality. To our knowledge, previous investigations on the relation between a priori-defined FPs and mortality have included both vegetable- and animal-derived foods as positive items in the score used to build the hypothesized healthy FP (16). In this context, an FP that positively weighs vegetable-derived foods and negatively weighs animal-derived foods can be conceptualized as a progressive and gentle approach to vegetarianism (ie, a “pro-vegetarian” FP) that incorporates a range of progressively increasing proportions of plant-derived foods and concomitant reductions in animal-derived foods. We hypothesized that such a provegetarian FP would relate to improved survival. Confirmation of this hypothesis might have a good translational impact, because the recommendation to preferentially consume foods from plant sources instead of foods from animal sources would be an easily understandable message for health promotion. We assessed this association between an a priori, hypothesis-oriented provegetarian FP and all-cause mortality in a Mediterranean cohort of elderly subjects at high cardiovascular risk.

## SUBJECTS AND METHODS

### Design

The design, objectives, and methods of the Prevención con Dieta Mediterránea (PREDIMED) study have been reported elsewhere (17, 18). Briefly, the PREDIMED study is a parallel-group, multicenter, randomized clinical trial designed to test the effects of 2 Mediterranean-type diets (MedDiets) on cardiovascular disease compared with a control (low-fat) diet ([www.predimed.es](http://www.predimed.es)). PREDIMED investigators are listed in the Supplemental Appendix under “Supplemental data” in the online issue.

Participants were drawn from primary care health centers and centrally randomly assigned in a 1:1:1 ratio to 1 of 3 different dietary patterns: a MedDiet supplemented with extra-virgin olive oil, a MedDiet supplemented with nuts, or a control diet. Primary

care physicians were not informed of the allocation of participants. The methods for the dietary intervention of the PREDIMED trial have been described previously (18). Participants received quarterly individual and group sessions, and those allocated to the MedDiets received free provisions of either extra-virgin olive oil or tree nuts throughout the study, which lasted a median of 4.8 y. The institutional review board of Hospital Clinic de Barcelona (Barcelona, Spain) approved the study protocol on July 2002. In the present study we analyzed the trial as an observational prospective cohort with repeated dietary measurements. The trial was registered at [www.controlled-trials.com](http://www.controlled-trials.com) as ISRCTN35739639.

### Subjects

Participants were men aged 55–80 y or women aged 60–80 y with no previously documented cardiovascular disease but at high cardiovascular risk. They had either type 2 diabetes or  $\geq 3$  major cardiovascular risk factors at baseline, including current smoking, hypertension ( $\geq 140/90$  mm Hg or treatment with antihypertensive agents), high LDL cholesterol  $> 160$  mg/dL, low HDL cholesterol ( $< 40$  mg/dL), overweight/obesity [BMI (in  $\text{kg}/\text{m}^2$ )  $\geq 25$ ], or a family history of premature CAD. Exclusion criteria were history of cardiovascular disease (ie, a previous medical diagnosis of CAD, stroke, or peripheral arterial disease), any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, low predicted likelihood of changing dietary habits according to the stages-of-change model, or illiteracy (17).

Primary care physicians reviewed the clinical histories of potential candidates, which were drawn from computer-based records of each participating center, and selected those subjects who apparently met eligibility criteria. They then invited suitable candidates by telephone to attend a screening visit where eligibility criteria were reassessed in a face-to-face interview. We recruited 7447 participants between October 2003 and June 2009. All participants provided written informed consent. We excluded 231 subjects who were outside the predefined range for baseline total caloric intake (500–3500 kcal/d for women and 800–4000 kcal/d for men), thus leaving 7216 subjects available to be included in the final analyses. The steering committee of the PREDIMED monitored the progress of the trial, which was supervised by an external data and safety monitoring board.

### Dietary assessment

Registered dietitians obtained dietary information on each participant in face-to-face interviews. Food pictures or food models to facilitate the estimation of serving sizes were not used in the interviews. At baseline and yearly thereafter dietitians collected a previously and repeatedly validated 137-item food-frequency questionnaire (FFQ) (19–21). Spanish food composition tables were used to derive nutrient composition and to estimate total energy intake.

The foods included in the provegetarian FP are shown in **Table 1**. Briefly, to build the provegetarian FP, we adjusted the consumption (g/d) of 7 food groups from plant origin (fruit, vegetables, nuts, cereals, legumes, olive oil, and potatoes) and 5 food groups from animal origin (added animal fats, eggs, fish, dairy products, and meats and meat products) for total energy intake

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<sup>5</sup>Abbreviations used: CAD, coronary artery disease; FFQ, food-frequency questionnaire; FP, food pattern; MedDiet, Mediterranean-type diet; PREDIMED, Prevención con Dieta Mediterránea.

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**TABLE 1**  
Scoring criteria for the provegetarian food pattern<sup>1</sup>

Component	Included foods
Vegetable food groups, by quintile <sup>2</sup>	
1. Vegetables	Carrot, Swiss chard, cauliflower, lettuce, tomatoes, green beans, eggplant, peppers, asparagus, spinach, other fresh vegetables
2. Fruit	Citrus, banana, apple, pear, strawberry, peach, cherry, fig, melon, watermelon, grapes, kiwi, canned fruit
3. Legumes	Lentils, chickpeas, beans, peas
4. Cereals	White bread, whole-grain bread, cold breakfast cereal, rice, pasta
5. Potatoes	Potato chips, French fries, boiled potatoes
6. Nuts	Almonds, peanuts, hazelnuts, pistachios, pine nuts, walnuts
7. Olive oil	Common (refined) olive oil, extra-virgin olive oil, olive pomace oil
Animal food groups, by reverse quintile <sup>3</sup>	
8. Meats/meat products	Beef, pork, lamb, rabbit, liver, chicken, turkey, cooked ham, Parma ham, mortadella, salami, foie gras, spicy pork sausage, bacon, cured meats, hamburger, hot dog
9. Animal fats for cooking or as a spread	Butter, lard
10. Eggs	Eggs
11. Fish and other seafood	White fish, dark-meat fish, salad or smoked fish, clams, mussels, shrimp, squid
12. Dairy products	Whole milk, skim or low-fat milk, condensed milk, cream, milk shake, yogurt, custard, cheese, ice cream

<sup>1</sup> The overall provegetarian pattern was built by summing both components with a potential range of 12–60.

<sup>2</sup> The consumption (g/d) of each food group was transformed into energy-adjusted quintiles by using the residuals method (1 = first quintile, 2 = second quintile, 3 = third quintile, 4 = fourth quintile, 5 = fifth quintile). The sum of quintile values across the 7 food groups gave a potential range of 7–35.

<sup>3</sup> Consumption (g/d) was transformed into energy-adjusted quintiles (residuals), and the quintile values were reversed (1 = fifth quintile, 2 = fourth quintile, 3 = third quintile, 4 = second quintile, 5 = first quintile). The sum of reverse quintile values across the 5 food groups had a potential range of 5–25.

by using the residual method separately for men and women. The energy-adjusted estimates (residuals) were ranked according to their sex-specific quintiles. The quintile values for animal products were reversed (assigning a value of 5 for the first quintile, 4 for the second quintile, and successively until the value of 1 was assigned to the fifth quintile). To obtain the provegetarian FP, quintile values of plant foods and reverse quintile values of animal foods were summed; thus, the final scores could range from 12 (lowest adherence) to 60 (highest adherence). We classified adherence to the provegetarian FP in 5 categories (cutoffs): very low (<30), low (30–34), moderate (35–39), high (40–44), and very high (>44) adherence. Because few deaths occurred in the category of very high adherence to the provegetarian diet, we merged the 2 upper categories for the multivariable analyses. We chose to use these specific round cutoffs instead of quintiles because the groups thus built are more meaningful per se and could be more easily used for future comparisons with similar studies. This is in line with current recommendations given in epidemiology about procedures to categorize continuous variables (22). However, we also show the results of an alternative analysis that used quintiles of the provegetarian FP.

For the sensitivity analysis, we built a similar FP but used absolute cutoffs for each of the 12 food groups with goals expressed as servings per day or servings per week (ie, normative or absolute cutoffs) instead of using energy-adjusted quintiles of consumption of each food group (23, 24). However, the same food groups as in the quintile-based assessment were considered and the score assigned 1 point for each of the 12 goals that was met (consumption of each item at or above the limit for plant foods and below the limit for animal foods). We set the cutoffs taking into account the number of servings per day or servings per week recommended in a 14-item score of adherence to the MedDiet used in the PREDIMED study (24, 25). The cutoffs for each food group (in servings) were as follows: vegetables ( $\geq 2$ /d), fruit ( $\geq 3$ /d), cereals ( $\geq 2$ /d), potatoes ( $\geq 1$ /d), legumes ( $\geq 3$ /wk), olive oil ( $\geq 4$  tablespoons/d), nuts ( $\geq 3$ /wk), dairy products

( $\leq 1$ /d), meat ( $\leq 3$ /wk), fish ( $\leq 3$ /wk), eggs ( $\leq 3$ /wk), and butter or lard ( $\leq 3$ /wk). In these analyses, we did not compute residuals from regressions on energy intake; instead, we adjusted only for confounding by total energy intake by introducing it as a covariate in the standard multivariable models.

### Covariate assessment

All measurements were taken at baseline and yearly thereafter by using the same procedures. Information was collected with specific questionnaires and from the subjects' medical history. Information on medication use, sociodemographic variables, lifestyle, health conditions, and medical diagnoses was obtained according to standardized protocols and review of medical records. Physical activity was evaluated by using the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (26, 27). Weight, height, and waist circumference were measured by trained nurses with the use of standardized procedures. The waist-to-height ratio was calculated as waist circumference divided by height, both in centimeters (25). Blood pressure was measured by trained nurses with the use of a validated semiautomatic oscillometer in triplicate (Omron HEM-705CP). The presence of type 2 diabetes at baseline was assessed by American Diabetes Association criteria at the time of the study's inception (2003): namely, fasting plasma glucose  $\geq 7.0$  mmol/L or 2-h plasma glucose  $\geq 11.1$  mmol/L after a 75-g oral-glucose load. A second test that used the same criteria was required for confirmation.

### Ascertainment of deaths

Outcomes were adjudicated by the End-Point Adjudication Committee, chaired by a cardiologist and including 3 general practitioners, 1 endocrinologist, and 1 medical epidemiologist. The panel members were blinded to the intervention group and to the repeated dietary assessments. This committee centrally ascertained

deaths from clinical registers on the basis of clinical records and death certificates listing an International Classification of Diseases code corresponding to any fatality. We used the *International Classification of Diseases* (10th revision) to classify deaths resulting from cancer (codes C00–D48) and cardiovascular disease (codes R00–R09, R55, R57, and R96). The clinical records of all participants were reviewed regardless of their continuation in the trial. Linkage to the National Death Index served to gather additional information on fatal events.

### Statistical analyses

To appraise the degree of overlap between the provegetarian FP and the MedDiet (according to the PREDIMED 14-point score) (24, 25), we used their cross-classification in quintiles and the Pearson's correlation coefficient between these 2 dietary indexes.

Time-to-event data were analyzed by using the Kaplan-Meier method. The time of the event was defined as the number of days from recruitment to the last visit or death as determined by the adjudicator. Cox proportional hazards analyses were conducted to assess the association of the provegetarian FP with total mortality, with stratification for center. After a crude analysis, we fitted a model adjusted for sex and age. In a subsequent model we additionally adjusted for major risk factors of death by using baseline values of covariates. Robust SEs were used.

To take advantage of the yearly dietary measurements, we updated the calculation of the provegetarian FP for each participant every year from baseline to death from the repeated FFQs. We replaced missing values in each follow-up FFQ with the cumulative averages obtained in the preceding visit. To use all of the available longitudinal data and to analyze the association

**TABLE 2**

Baseline characteristics of participants according to categories of the provegetarian food pattern: the PREDIMED trial, 2003–2010<sup>1</sup>

	Provegetarian food pattern category					P <sup>2</sup>
	Very low: <30	Low: 30–34	Moderate: 35–39	High: 40–44	Very high: >44	
<i>n</i>	669	2055	2761	1423	308	
Sex, male (%)	43.5	41.8	43.0	41.7	45.8	0.61
Age (y)	66.4 ± 6.2 <sup>3</sup>	67.0 ± 6.2	67.0 ± 6.2	67.3 ± 6.0	67.6 ± 6.4	0.01
Primary or lower education (%)	72.8	77.5	78.7	78.6	76.0	0.02
Hypertension [ <i>n</i> (%)]	82.4	82.4	83.0	83.0	82.1	0.97
High blood cholesterol [ <i>n</i> (%)]	67.6	69.3	71.6	77.7	82.5	<0.001
Diabetes [ <i>n</i> (%)]	52.5	51.6	49.5	43.2	37.7	<0.001
BMI (kg/m <sup>2</sup> )	30.4 ± 3.9	30.1 ± 3.9	30.0 ± 3.8	29.8 ± 3.8	29.4 ± 3.8	<0.001
Smoking [ <i>n</i> (%)]						
Current smoker	17.5	14.7	13.8	12.0	11.0	0.03
Former smoker	22.6	23.8	24.8	26.3	24.7	
Alcohol intake (g/d)	9.5 ± 15.6	8.1 ± 13.7	8.2 ± 13.7	8.2 ± 14.3	9.4 ± 14.8	0.11
Physical activity (MET-min/d)	209 ± 221	221 ± 233	235 ± 245	240 ± 222	272 ± 308	<0.001
Vegetables (g/d)	254 ± 111	294 ± 126	343 ± 149	388 ± 149	442 ± 148	<0.001
Fruit (g/d)	267 ± 158	319 ± 182	376 ± 192	432 ± 210	555 ± 220	<0.001
Legumes (g/d)	15 ± 11	18 ± 13	21 ± 14	25 ± 13	28 ± 13	<0.001
Cereals (g/d)	105 ± 64	129 ± 77	144 ± 83	164 ± 89	205 ± 100	<0.001
Potatoes (g/d)	58 ± 41	72 ± 43	85 ± 49	96 ± 53	113 ± 48	<0.001
Nuts (g/d)	4.4 ± 8.5	7.2 ± 11	10 ± 13	14 ± 15	22 ± 20	<0.001
Olive oil (g/d)	32 ± 16	36 ± 17	40 ± 18	43 ± 17	47 ± 17	<0.001
Meats/meat products (g/d)	160 ± 62	141 ± 55	129 ± 55	113 ± 51	105 ± 53	<0.001
Animal fats for cooking or as a spread (g/d)	1.3 ± 2.9	0.6 ± 2.4	0.4 ± 2.0	0.2 ± 1.5	0.1 ± 0.8	<0.001
Eggs (g/d)	25 ± 12	23 ± 11	20 ± 11	16 ± 10	15 ± 10	<0.001
Fish and other seafood (g/d)	113 ± 49	105 ± 57	96 ± 47	92 ± 45	90 ± 47	<0.001
Dairy products (g/d)	495 ± 229	419 ± 219	371 ± 215	314 ± 200	259 ± 179	<0.001
Intake						
Total energy (kcal/d)	2144 ± 539	2147 ± 521	2236 ± 536	2336 ± 552	2568 ± 533	<0.001
Carbohydrate (% of energy)	38.0 ± 6.8	40.5 ± 7.0	42.0 ± 6.8	44.0 ± 6.9	46.3 ± 6.7	<0.001
Protein (% of energy)	18.5 ± 3.2	17.5 ± 2.8	16.4 ± 2.5	15.3 ± 2.2	14.4 ± 1.9	<0.001
Total fat (% of energy)	40.6 ± 6.5	39.6 ± 6.7	39.2 ± 6.8	38.4 ± 6.9	36.9 ± 6.3	<0.001
MUFAs (% of energy)	19.4 ± 4.1	19.5 ± 4.5	19.6 ± 4.7	19.5 ± 4.7	18.7 ± 4.2	0.03
SFAs (% of energy)	11.7 ± 2.4	10.5 ± 2.2	9.8 ± 2.0	9.1 ± 2.0	8.1 ± 1.7	<0.001
PUFAs (% of energy)	5.8 ± 2.0	6.1 ± 2.1	6.3 ± 2.1	6.5 ± 1.9	6.8 ± 2.0	<0.001
Vitamin C (mg/d)	155 ± 63	176 ± 79	203 ± 84	231 ± 95	278 ± 100	<0.001
Vitamin D (μg/d)	6.0 ± 3.6	6.0 ± 3.9	5.7 ± 3.4	5.7 ± 3.4	5.8 ± 3.5	0.002
Iron from heme sources (mg/d)	4.6 ± 1.8	4.0 ± 1.4	3.7 ± 1.4	3.3 ± 1.2	3.1 ± 1.3	<0.001
Folate (μg/d)	326 ± 90	364 ± 102	406 ± 117	451 ± 129	525 ± 127	<0.001
Dietary fiber (g/d)	19 ± 6	22 ± 7	26 ± 8	30 ± 9	36 ± 10	<0.001

<sup>1</sup> MET-min, metabolic equivalent task minutes; PREDIMED, Prevención con Dieta Mediterránea.

<sup>2</sup> Comparisons of characteristics across categories of the provegetarian food pattern were performed by using 1-factor ANOVA for quantitative variables or chi-square tests for categorical variables.

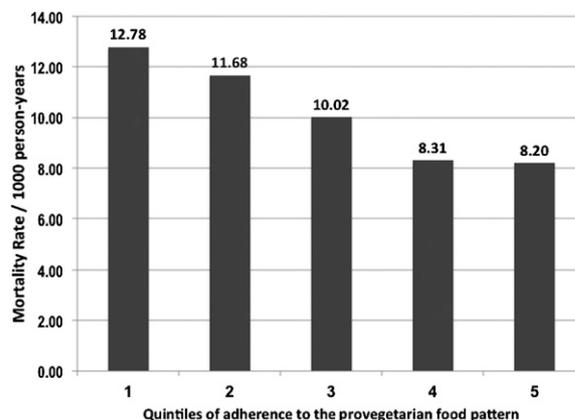
<sup>3</sup> Mean ± SD (all such values).

between the provegetarian FP and mortality at all time points simultaneously, we used generalized estimating equations in Stata 12.1 (StataCorp). We assumed a binomial distribution with logistic models and the unstructured matrix as the working correlation structure. As a further approach to the usual diet of many lactoovovegetarians we repeated the analyses including the baseline consumption of dairy products and eggs as favorable items instead of adverse items in the score.

## RESULTS

Older participants and those with lower educational levels, high blood cholesterol at baseline, and who were more physically active showed better adherence to the provegetarian FP, whereas participants with diabetes, current smokers, and those with a higher BMI showed lesser adherence. No significant differences in adherence to this FP were found for sex, baseline hypertension, or alcohol intake (Table 2). As expected, the consumption of the 7 plant-derived food groups increased monotonically across increasing categories of the provegetarian FP, whereas the consumption of the 5 food groups from animal sources monotonically decreased ( $P < 0.001$  for all) (Table 2). The most striking differences were observed for the consumption of nuts (which included all tree nuts and peanuts). The intakes of total energy, carbohydrate, polyunsaturated fat, and vitamin C, folate, and fiber were greater in the groups with better adherence to the provegetarian FP. Conversely, the intakes of protein, total fat, saturated fat, and heme iron were inversely associated with adherence to this FP. Although significant, only minimal differences were observed for mono-unsaturated fat and vitamin D intakes across categories of adherence to the provegetarian FP (Table 2).

The correlation coefficient between the 2 scores assessing the provegetarian FP was 0.66 (95% CI: 0.64, 0.67). The cross-classification of both scores in 3 categories (<35, 35–39, and  $\geq 40$  for the quintile-based score; and <4, 4, and  $>4$  for the serving-based score) classified 57.5% of subjects in the same category, and only 4.8% were misclassified in extremely opposed categories. The cross-classification in approximate quintiles of both scores placed 79.7% of subjects in the same or adjacent quintile, and only 4.2% were misclassified  $>2$  quintiles apart. On the contrary, no large degree of overlap between the provegetarian FP and the MedDiet was found. Only 24.3% of participants were classified in the same quintile of both patterns,



**FIGURE 1.** Absolute risk of death across baseline quintiles of the provegetarian food pattern: the Prevención con Dieta Mediterránea trial, 2003–2010. Quintile score limits were as follows for quintiles 1–5: <33, 33–35, 36–37, 38–40,  $>40$ , respectively.

and the Pearson's correlation coefficient between these 2 dietary indexes was only 0.23 (95% CI: 0.21, 0.25).

During follow-up (median: 4.8 y; IQR: 2.8–5.8 y), 323 deaths (76 from cardiovascular causes, 130 from cancer, and 117 from other causes) occurred among 31,078 person-years. The crude absolute rates of death decreased monotonically across successive quintiles of the provegetarian FP (Figure 1). Death rates decreased from 14.9/1000 person-years among participants with low adherence (score  $<30$ ) to 8.7/1000 person-years among those with high adherence ( $>40$ ) (Table 3). The significance of the inverse linear trend in the crude Cox model stratified by center ( $P = 0.014$ ) strengthened after sex and age were adjusted for ( $P = 0.003$ ). The fully adjusted HRs (95% CIs) for categories of low, moderate, or high/very high adherence compared with the very low (reference) adherence category were 0.71 (0.50, 1.02), 0.68 (0.48, 0.96), and 0.59 (0.40, 0.88), respectively, with a significant inverse linear trend ( $P = 0.027$ ) (Table 3). When we separated high and very high adherence categories, only 9 deaths were observed in the latter category ( $>44$  points). For this group, the HRs (95% CIs) were as follows: crude, 0.46 (0.22, 0.95); age- and sex-adjusted, 0.38 (0.18, 0.79); and multivariable-adjusted, 0.44 (0.21, 0.92).

When we positively weighed eggs and dairy products and added them to the positive part of the score together with plant-based

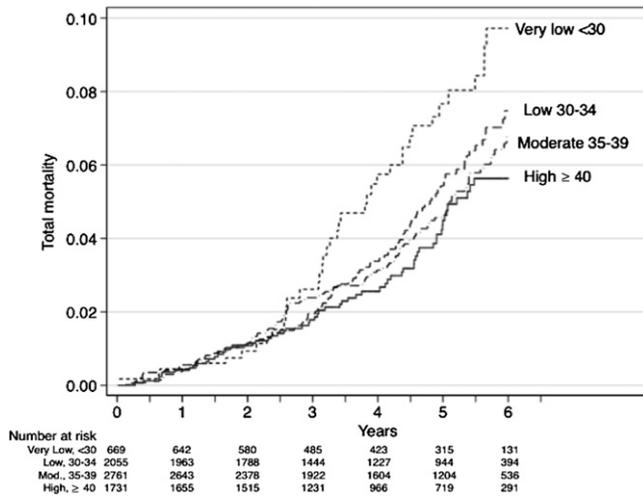
**TABLE 3**

HRs (95% CIs) of death according to baseline categories of the provegetarian food pattern: the PREDIMED trial, 2003–2010<sup>1</sup>

	Provegetarian food pattern category				P-trend
	Very low: $<30$	Low: 30–34	Moderate: 35–39	High/very high: $\geq 40$	
<i>n</i>	669	2055	2761	1731	
No. of deaths	44	97	118	64	
Persons-years of follow-up	2951	8926	11,830	7371	
Absolute death rate ( $\times 10^{-3}$ )	14.9 (10.9, 20.0)	10.9 (8.82, 13.2)	9.97 (8.26, 11.9)	8.68 (6.69, 11.1)	
Crude HR	1 (ref)	0.73 (0.51, 1.04)	0.67 (0.47, 0.96)	0.58 (0.40, 0.86)	0.014
Age- and sex-adjusted HR	1 (ref)	0.69 (0.48, 0.99)	0.62 (0.44, 0.88)	0.52 (0.35, 0.78)	0.003
Multivariable-adjusted HR <sup>2</sup>	1 (ref)	0.71 (0.50, 1.02)	0.68 (0.48, 0.96)	0.59 (0.40, 0.88)	0.027

<sup>1</sup> All estimates were stratified by center. PREDIMED, Prevención con Dieta Mediterránea; ref, reference.

<sup>2</sup> Adjusted for sex, age, intervention group, smoking (5 categories: never smoker; former smoker,  $>5$  y; former smoker,  $\leq 5$  y; current smoker,  $\leq 20$  cigarettes/d; current smoker,  $>20$  cigarettes/d), leisure-time physical activity, total energy intake, educational level (3 categories), and alcohol consumption. Robust SEs were used.



**FIGURE 2.** Cumulative hazards of death across categories of the provegetarian food pattern: the Prevención con Dieta Mediterránea trial, 2003–2010. Mod., moderate.

foods, the age- and sex-adjusted HRs of death from any cause (95% CIs) were 1 (reference), 0.83 (0.56, 1.23), 0.75 (0.51, 1.09), and 0.52 (0.33, 0.80) for <30, 30–34, 35–39, and ≥40 points, respectively. This inverse association remained significant after further adjustment for other covariates. Therefore, the alternative inclusion of eggs and dairy products in the score did not attenuate the potential benefits associated with better adherence to this food pattern.

When we restricted the analysis to cardiovascular deaths, the multivariable-adjusted HRs (95% CIs) for 30–34, 35–39 and ≥40 points of adherence to the provegetarian FP were 0.48 (0.24, 0.99), 0.44 (0.22, 0.90), and 0.47 (0.21, 1.04), respectively, and showed strong inverse associations (*P*-trend = 0.039). Inverse but nonsignificant associations were found for cancer deaths, with HRs (95% CIs) of 0.95 (0.56, 1.62), 0.67 (0.38, 1.17), and 0.66 (0.35, 1.24), respectively. Nonsignificant inverse associations were also found for deaths from noncancer, noncardiovascular causes, with point estimates of 0.71 (0.37, 1.36), 0.98 (0.53, 1.81), and 0.70 (0.34, 1.46) for 30–34, 35–39 and ≥40 points of adherence, respectively. When the provegetarian FP was categorized into 4 groups (with cutoffs at 30, 35, and 40, as shown in Table 3), the Kaplan-Meier curves started to diverge after 2.5–3 y of follow-up (Figure 2). When we used quintiles instead of the previous cutoffs for grouping participants

according to their adherence to the provegetarian FP, the results consistently showed an inverse association (Table 4 and Figure 1).

A significant inverse association was also found when we used generalized estimating equations to take into account all available longitudinal data with updated yearly dietary information and analyzed the association between the provegetarian FP and mortality at all time points simultaneously (Table 5). Significant differences were found between participants in the category of high/very high adherence (>40 points) compared with those with low adherence (<30 points). The fully adjusted RR for this comparison was 0.59 (95% CI: 0.39, 0.89) with a significant inverse linear trend test (Table 5). In updated analyses, only 7 deaths were observed in the category of very high adherence (>44 points). For subjects in this category, the age- and sex-adjusted RR was 0.43 (95% CI: 0.19, 0.95), and the point estimate did not materially change after further adjustment.

As expected, when we additionally adjusted the models for putative mediators such as BMI, waist-to-height ratio, diabetes, hypertension, hyperlipidemia, and the use of medication for these conditions, the inverse associations between either the baseline provegetarian FP (including only plant foods) or the yearly updated score and mortality were attenuated (~3–4% upward change in the point estimates for the HR in the 3 upper categories; data not shown). However the results remained significant and clinically relevant.

A similar provegetarian FP that used servings per day or servings per week (ie, normative or absolute cutoffs (23, 24) as goals instead of energy-adjusted quintiles of consumption) was constructed for sensitivity analysis (Table 6). Because this score assigned 1 point to each of the 12 goals that was met, the possible range was 0–12 points. The fully adjusted HRs in this sensitivity analysis were 0.85 (95% CI: 0.65, 1.11) for moderate baseline adherence (4 goals met) and 0.70 (95% CI: 0.51, 0.95) for high adherence (>4 goals met), with a significant inverse linear trend (*P* = 0.003).

**DISCUSSION**

In a prospective cohort of >7000 elderly participants at high cardiovascular risk, we found that the preference for plant-derived foods in the customary diet was associated with reduced mortality from any cause during a 4.8-y follow-up compared with preferential selection of foods from animal sources. Our findings were robust in sensitivity analyses that used alternative

**TABLE 4**  
HRs (95% CIs) of death according to quintiles of the provegetarian food pattern: the PREDIMED trial, 2003–2010<sup>1</sup>

	Provegetarian food pattern					<i>P</i> -trend
	Q1: <33	Q2: 33–35	Q3: 36–37	Q4: 38–40	Q5: >40	
<i>n</i>	1721	1592	1165	1425	1313	
No. of deaths	96	80	51	50	46	
Persons-years of follow-up	7511	6851	5091	6018	5607	
Absolute death rate (× 10 <sup>-3</sup> )	12.8 (10.4, 15.6)	11.7 (9.3, 14.5)	10.0 (7.5, 13.2)	8.3 (6.2, 10.9)	8.2 (6.0, 10.9)	
Crude HR	1 (ref)	0.91 (0.68, 1.23)	0.78 (0.56, 1.10)	0.66 (0.47, 0.93)	0.65 (0.46, 0.92)	0.002
Age- and sex-adjusted HR	1 (ref)	0.89 (0.66, 1.20)	0.75 (0.53, 1.05)	0.65 (0.46, 0.91)	0.61 (0.43, 0.87)	<0.001
Multivariable-adjusted HR <sup>2</sup>	1 (ref)	0.98 (0.72, 1.32)	0.81 (0.57, 1.14)	0.70 (0.49, 0.99)	0.66 (0.46, 0.96)	0.006

<sup>1</sup> All estimates were stratified by center. PREDIMED, Prevención con Dieta Mediterránea; Q, quintile; ref, reference.

<sup>2</sup> Adjusted for sex, age, intervention group, smoking (5 categories: never smoker; former smoker, >5 y; former smoker, ≤5 y; current smoker, ≤20 cigarettes/d; current smoker, >20 cigarettes/d), leisure-time physical activity, total energy intake, educational level (3 categories), and alcohol consumption. Robust SEs were used.

**TABLE 5**

Generalized estimating equations for RRs (95% CIs) of death according to the provegetarian food pattern: the PREDIMED trial, 2003–2010<sup>1</sup>

	Yearly updated provegetarian food pattern <sup>2</sup>				<i>P</i> -trend
	Very low: <30	Low: 30–34	Moderate: 35–39	High/very high: ≥40	
<i>n</i>	669	2055	2761	1731	
No. of deaths	42	96	125	60	
Crude HR	1 (ref)	0.78 (0.54, 1.12)	0.81 (0.57, 1.14)	0.60 (0.40, 0.88)	0.021
Age- and sex-adjusted HR	1 (ref)	0.77 (0.54, 1.10)	0.80 (0.57, 1.13)	0.60 (0.41, 0.89)	0.027
Multivariable-adjusted HR <sup>3</sup>	1 (ref)	0.76 (0.53, 1.10)	0.79 (0.55, 1.13)	0.59 (0.39, 0.89)	0.028

<sup>1</sup> PREDIMED, Prevención con Dieta Mediterránea; ref, reference.

<sup>2</sup> Updated every year by using repeated measurements of diet.

<sup>3</sup> Adjusted for sex, age, intervention group, smoking (5 categories), leisure-time physical activity, total energy intake, educational level (3 categories), and alcohol consumption. Robust SEs were used.

definitions for an FP with preference for plant-based foods and remained significant on updating the dietary assessment with the use of yearly diet measurements. The present results support a relative reduction in the risk of death from any cause of ≥30% associated with only a modest decrease in the consumption of animal foods together with compensatory increases in plant-based foods. This modest change is realistic, affordable, and achievable because it represents the observed FP in a sizable proportion of our cohort. The provegetarian FP does not mean a radical shift to the exclusive consumption of plant foods but a more gradual and gentle approach. All of these reasons increase the translational potential of our results into health and nutrition policies.

We acknowledge limitations in our study. The Mediterranean cohort studied was elderly and at high risk of cardiovascular disease, which limits the generalizability of our findings to younger and/or healthier individuals. Also, the score used to determine conformity with the -provegetarian diet may lack accuracy because of measurement errors inherent to dietary assessment tools.

We also acknowledge that not every plant food is a good choice for a healthy diet. In fact, refined cereals and potatoes have been inconsistently associated with higher cardiometabolic risks (28–32), and 79% of the cereals and grains consumed by our participants were refined, especially white bread, which is abundantly consumed in Spain and accounted for a large fraction of the cereal group (41%). There is also evidence to support the healthy aspects of fish consumption (placed as a negative food in our score), but

the existing literature does not support a consistent inverse association between fish consumption and all-cause mortality (33–35). Our aim was to examine whether encouraging the consumption of all plant-derived foods while discouraging the consumption of all animal foods could signal a lower risk of all-cause mortality. Under this rationale, it seems logical to include frequently consumed plant foods such as potatoes or cereals, regardless of whether they are refined or not, as positive components of the provegetarian FP while excluding fish because of its animal origin. However, the differences in fish consumption between extreme categories of the provegetarian FP were small (Table 2).

The positive trend observed for the association between the provegetarian FP and high blood cholesterol at baseline (Table 2) may seem somewhat surprising. However, it is possible that participants' knowledge of their high blood cholesterol had prompted them to accomplish dietary changes toward a provegetarian FP, and a merely cross-sectional association where reverse causality bias cannot be excluded is shown in Table 2. The higher energy intake (Table 2) among participants with better adherence to the provegetarian FP also may seem surprising, but it could be explained by their higher energy expenditure in leisure-time physical activity (also shown in Table 2), because exercise-induced increases in energy requirements are typically compensated by increases in total energy intake (36, 37).

Strengths of our study include its large sample size, the sufficient length of follow-up, the yearly repeated assessment of diet

**TABLE 6**

HRs (95% CIs) of death according to adherence to a score based on absolute servings of plant-derived foods (positive) and animal-derived foods (negative): the PREDIMED trial, 2003–2010<sup>1</sup>

	Adherence to the absolute serving-based index			<i>P</i> -trend
	Low: <4	Moderate: 4	High: >4	
<i>n</i>	3763	1904	1549	
No. of deaths/person-years	184/15,964	81/8303	58/6811	
Crude HR	1 (ref)	0.83 (0.64, 1.08)	0.70 (0.52, 0.95)	0.005
Age-, energy-, and sex-adjusted HR	1 (ref)	0.82 (0.63, 1.07)	0.66 (0.48, 0.90)	0.001
Multivariable-adjusted HR <sup>2</sup>	1 (ref)	0.85 (0.65, 1.11)	0.70 (0.51, 0.95)	0.003

<sup>1</sup> All estimates were stratified by center. Scores were assigned as follows—1 point for each of 7 positively weighted items (servings): vegetables (≥2/d), fruit (≥3/d), cereals (≥2/d), potatoes (≥1/d), legumes (≥3/wk), olive oil (≥4 table-spoons/d), and nuts (≥3/wk); and 1 point for each of 5 negatively weighted items (servings): dairy products (≤1/d), meat (≤3/wk), fish (≤3/wk), eggs (≤3/wk), and butter or lard (≤3/wk). Potential range: 0 (minimum) to 12 points. PREDIMED, Prevención con Dieta Mediterránea; ref, reference.

<sup>2</sup> Adjusted for sex, age, smoking (5 categories), intervention group, leisure-time physical activity, total energy intake, educational level, and alcohol consumption. Robust SEs were used.

during follow-up, the use of a clinically meaningful outcome (all-cause mortality), the repeated validation studies of the FFQ (19–21) including the use of biomarkers showing that this FFQ is able to correctly classify participants according to their food intake (38, 39), and the robustness of our findings under different sensitivity analyses. Another strength of our study is that the assessment of FPs is attractive from a physiopathologic perspective because it captures the way food is eaten and because the different constituents of the component foods of an FP are likely to synergistically interact (40–43) to reduce the risk of death from chronic diseases (28, 40, 43–45). The assessment of the overall diet by using the approach of a previously defined FP (ie, a priori or hypothesis-oriented patterns), rather than appraising only single nutrients or foods, avoids reductive fallacies and has intuitive appeal for many reasons (16). Those reductive fallacies tend to emphasize the role of individual nutrients in pathophysiologic mechanisms of disease, but given the complex etiology and the many processes involved in the genesis of chronic diseases, the idea of attributing to few nutrients the ability to modify disease risk seems unrealistic (40, 46). In this line of thought, the assessment of FPs has acquired an emerging role in nutritional epidemiology. People do not eat isolated nutrients, they eat foods and consume them in particular patterns (41, 44, 47–50). In this context, a plant-based FP that emphasizes abundant intake and a variety of biologically active phytochemicals is likely to have a strong potential to reduce chronic disease risk (42, 43).

Many observational studies have consistently reported that FPs that are rich in phytochemicals and low in meat or other animal products [the MedDiet, the Dietary Approaches to Stop Hypertension diet, the Prudent dietary pattern, or the alternative Healthy Eating Index] are associated with reduced risks of chronic degenerative diseases, whereas opposite food patterns, rich in animal foods and poor in plant-based foods (typically called Western or westernized diets), are associated with higher risks (2, 3, 32, 45, 51–57). Thus, our observation of an inverse association between adherence to a provegetarian FP and overall mortality concurs with available evidence from previous epidemiologic studies.

The MedDiet is also consistently associated with improved survival (53, 58) and represents a food pattern rich in plant-derived foods. But differences between both dietary patterns do exist. These differences are related to the contrasting roles given in the provegetarian FP and in the MedDiet (24, 52, 59) to alcohol and to some food groups (fish, potatoes, or cereals). In fact, no large degree of overlap was found in our study between the present provegetarian score and the traditional MedDiet.

Our results are consistent with previous reports of a detrimental effect on total mortality of a high consumption of animal foods, especially red meat and processed meat (7, 8, 60). They also concur with reports of a survival advantage of vegetarians compared with nonvegetarians, although results of studies are less consistent (10–15, 60). In the European Prospective Investigation into Cancer and Nutrition–Elderly study, a plant-based FP was identified with the use of principal components analysis. That post hoc pattern (although it excluded potatoes) resembled our a priori–built provegetarian pattern, and it also was associated with lower overall mortality, with a 1-SD increment corresponding to a significant 14% reduction in all-cause mortality (28).

Similar to the present results, many prior studies found stronger inverse associations between adherence to plant-rich FPs

and cardiovascular mortality than with other causes of death (2, 3, 11, 45, 49, 57, 59–61). However, the breakdown into different causes of death limits the statistical power of our analyses. In any case, the point estimates of the HRs for the 3 categories of higher adherence were always <1 for both cancer and non-cancer and noncardiovascular causes of death.

In summary, we provide evidence to support that the simple advice to increase the consumption of plant-derived foods with compensatory reductions in the consumption of foods from animal sources confers a survival advantage to older subjects at high cardiovascular risk.

Steering committee members are as follows: R Estruch, MA Martínez-González, J Salas-Salvadó, E Ros, D Corella, and M Fito. End-Point Adjudication Committee members are as follows: F Aros (chair), M Aldamiz, A Alonso, J Berjon, L Forga, J Gallego, MA Garcia Layana, A Larrauri, J Portu, J Timiraus, and M Serrano-Martinez.

The authors' responsibilities were as follows—MAM-G and AS-T: conception and design; MAM-G: writing of the first draft and statistical expertise; and MAM-G, AS-T, JS-S, LS-M, and RE: analysis and interpretation of the data. All authors critically revised the manuscript for important intellectual content and approved the final manuscript. ER and JS-S have consulted for and received grants from the California Walnut Commission and the International Nut Council, respectively. None of the other authors had a conflict of interest to report.

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