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Empirically-derived food patterns and the risk of total mortality and cardiovascular events in the PREDIMED study

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ABSTRACT

Background and aims: There is little evidence on *post hoc*- derived dietary patterns (DP) and all-cause mortality in Southern-European populations. Furthermore, the potential effect modification of a DP by a nutritional intervention has not been sufficiently assessed. We assessed the association between *a posteriori* defined baseline major DP and total mortality or cardiovascular events within each of the three arms of a large primary prevention trial (PREDIMED) where participants were randomized to two active interventions with Mediterranean-type diets or to a control group (allocated to a low-fat diet).

Design: We followed-up 7216 participants for a median of 4.3 years. A validated 137-item food-frequency questionnaire was administered. Baseline DP were ascertained through factor analysis based on 34 predefined groups. Cox regression models were used to estimate multivariable-adjusted hazard ratios (HR) for cardiovascular disease (CVD) or mortality across quartiles of DP within each of the three arms of the trial.

Results: We identified two major baseline DP: the first DP was rich in red and processed meats, alcohol, refined grains and whole dairy products and was labeled Western Dietary Pattern (WDP). The second DP corresponded to a "Mediterranean-type" dietary pattern (MDP). During follow-up, 328 participants died. After controlling for potential confounders, higher baseline adherence to the MDP was associated with lower risk of CVD (adjusted HR for fourth vs. first quartile: 0.52; 95% CI (Confidence Interval): 0.36, 0.74; p-trend <0.001) and all-cause mortality (adjusted HR: 0.53; 95% CI: 0.38, 0.75; p-trend <0.001), regardless of the allocated arm of the trial. An increasing mortality rate was found across increasing quartiles of the WDP in the control group (allocated to a low-fat diet), though the linear trend was not statistically significant (p=0.098).

CONCLUSIONS: Higher adherence to an empirically-derived MDP at baseline was associated with a reduced risk of CVD and mortality in the PREDIMED trial regardless of the

* CVD: Cardiovascular Disease, DP:Dietary Pattern, EVOO: Extra Virgin Olive Oil, FFQ: Food Frequency Questionnaire, IPW: Inverse Probability Weighting, MeDiet:Mediterranean Diet, MDP: Mediterranean Dietary Pattern, WDP: Western Dietary Pattern.

allocated arm. The WDP was not associated with higher risk of mortality or cardiovascular events.

INTRODUCTION

The main causes of death in developed countries are cancer and cardiovascular disease (CVD)*, chronic conditions in which prevention by lifestyle, particularly a healthy diet, plays an important role.

In the context of overall dietary patterns (DP), many epidemiological studies have examined the health benefits of an *a priori* defined Mediterranean diet (MeDiet) and found consistent evidence that individuals who better adhere to this DP have a healthier ageing and a longer life span [1, 2].

In the last decade there has been growing interest in assessing the relationships between diet and disease through the study of whole DP instead of focusing on single nutrients or foods [3]. The approach consisting in collecting food data and using them afterwards to identify the DP actually followed by the study subjects is known as the *a posteriori* approach (post hoc). It detects DP empirically derived from available data using principal component analysis or factor analysis [4-6]. Though several studies have assessed the relationship between *a posteriori* DP and various health outcomes [7], including all-cause mortality [7-10], there is little evidence on *post hoc* DP and mortality in Southern European populations [11]. An interesting issue that has not been explored is whether the adverse effects of a DP can be modified by a nutritional intervention. We evaluated the association between *a posteriori* defined major DP and CVD incidence or total mortality in each of the three arms of a large randomized trial testing an intervention with a Mediterranean-type diets for the primary prevention of CVD (the PREDIMED study). Participants in the PREDIMED trial were randomized to two active interventions with Mediterranean-type diets or to a control group (allocated to a low-fat diet). We assessed whether this intervention was able to modify the association between baseline DP and two outcomes: all-cause mortality and the risk of cardiovascular events.

METHODS

Subjects

The PREDIMED (PREvención con DIeta MEDiterránea) trial (ISRCTN35739639) is a multicenter, randomized, controlled, parallel group, primary prevention trial conducted in Spain to assess the effects of MeDiet on major cardiovascular events. The study protocol has been published elsewhere [12, 13] and full details are available at www.predimed.es. Between October 2003 and June 2009 we recruited 7,447 high-risk participants and randomly assigned them to one of three dietary interventions: two MeDiets supplemented with either extra virgin olive oil (EVOO) or mixed nuts and a control group (low-fat diet). Participants in the two MeDiet groups received either extra-virgin olive oil (to consume 50 g/d) or mixed nuts per day (15 g/d walnuts, 7.5 g/d hazelnuts, and 7.5 g/d almonds) at no cost. They received instructions directed to upscale the traditional MeDiet 14-item score, including 1) the use of olive oil for cooking and dressing; 2) increased consumption of vegetables, nuts, and fish products; 3) consumption of white meat instead of red or processed meat; 4) preparation of home-made sauce by simmering tomato, garlic, onion and aromatic herbs with olive oil to dress vegetables, pasta, rice and other dishes; and 5) for alcohol drinkers, to follow a moderate pattern of red wine consumption. Participants allocated to the control group received small nonfood gifts and were advised to reduce all types of fat and were given written recommendations according to American Heart Association guidelines. No total calorie restriction was advised, nor was physical activity promoted in any of the three groups. The primary endpoint for the main trial was a composite of cardiovascular events. Total mortality was also used as a secondary outcome. All participants provided written informed consent to a protocol approved by the institutional review boards of the recruiting centers.

Eligible participants were community-dwelling men aged 55-80 years and women aged 60-80 years without previous CVD who fulfilled at least one of the following criteria: type-2 diabetes or 3 or more cardiovascular risk factors, namely smoking, hypertension, dyslipidemia, overweight (BMI ≥ 25 kg/m^2) or a family history of premature CVD. For the present study we excluded 231 participants, 79 of them because their baseline food-frequency questionnaires (FFQ) were missing and 152 who displayed out-of-range total energy intake (<500 or >3500 kcal/d in women or <800 or >4000 kcal/d in men) [14]. Consequently, the final sample size included 7,216 participants.

Dietary assessment

Data on dietary intake were collected at baseline with a semi-quantitative 137-item validated FFQ [15]. For each item, a typical portion size was included, and consumption frequencies were registered in 9 categories that ranged from "never or almost never" to "≥ 6 times/day". Daily food consumption was estimated by multiplying the portion size of each food item by its consumption frequency. Energy and nutrient intake were derived using a computer program based on available information in Spanish food composition tables.

Assessment of non- dietary variables

Several questionnaires were used at baseline examination to collect sociodemographic data, lifestyle variables, history of illnesses, and medication use. A validated questionnaire [16] was used to collect information on physical activity.

Ascertainment of mortality

During follow-up dietitians delivered the nutritional intervention with quarterly individual visits and quarterly group sessions [13]. The questionnaires and examinations carried out at baseline were repeatedly administered every year to all participants. Besides, once a year a team of medical doctors reviewed medical records to collect information on the main outcomes, both in primary care centers and hospitals. Also, yearly inquiries were made of the

National Death Index. Considering all the sources of information, we are reasonably confident that ascertainment of mortality outcomes was complete. When a death was identified using any of these primary sources, medical records were requested where the patient had been cared for and submitted to the end-point adjudication committee for assignment of the cause of death. This committee was blinded with respect to the intervention group and the food habits of participants.

Statistical analyses

The 137 food items included in the FFQ were grouped into 34 predefined food categories. A principal component analysis was applied to these 34 categories in order to identify a reduced number of factors that could explain the maximum proportion of the variance from the original groups. Food groups with absolute loading >0.29 were considered relevant components of the identified patterns (**Table 1**).

The score for each participant was calculated by summing up the consumption of each food group weighted by each factor score obtained in the factor analysis. The resulting quantitative scores were categorized into quartiles. The Scree plot and the criteria of eigenvalues >2 were used to select factors. We selected 2 factors that accounted for 13% of the total variance.

Baseline characteristics and nutritional habits of participants according to their quartiles of adherence to both selected factors (dietary patterns) were analyzed (tables 2 and 3) and p values for linear trend tests were calculated for each variable. Nutritional variables were log-transformed to calculate the p values for linear trend.

We used Cox regression models with length of follow-up since randomization for the trial as the primary time variable. The exposure time was calculated as the time elapsed between recruitment and the date of death for deceased participants, the last study visit, or the last recorded clinical event of participants still alive. Hazard ratios (HR) with 95% confidence intervals (CI) for the three upper quartiles compared to the lowest quartile of each DP were calculated. In multivariable model 1, potential confounders included as covariates were sex, age (continuous), intervention group and recruitment center. We constructed a second model (multivariable model 2) that also included as covariates smoking status (never, former or current smoker), baseline BMI (kg/m^2, continuous), physical activity during leisure time (METs min/day, continuous), baseline self-reported hypertension, hypercholesterolemia, diabetes, history of previous depression and educational level (three categories). We conducted analyses stratified by each of the three arms of the trial. We repeated the main analyses adjusting also for total energy intake (kcal/day, continuous). Tests of linear trend across successive quartiles of adherence to each of the two food patterns were calculated.

In order to assess the effects of the intervention across the quartiles of baseline adherence to each DP, a new variable was created combining the joint exposure to the quartile of adherence to the studied DP and the intervention. This cross-classification was conducted with the aim of assessing whether the intervention was able to modify the association between baseline adherence to DP and the risk of death or cardiovascular events. We used inverse probability weighting (IPW) not only to control for baseline confounding but also to estimate the absolute risks according to the joint classification of participants in 12 groups by both quartile of the dietary pattern and intervention arm allocated in the trial [17]. To calculate the weights we used as predictors baseline values of age, sex, smoking habit, BMI, physical activity, hypertension, hypercholesterolemia, diabetes, educational level and history of depression. This method allows analyzing observational studies (the effects of baseline adherence to DP in our case) in a way similar to a randomized trial, under the assumption that all relevant confounders are included in the computation of weights. We estimated the absolute risks of mortality (or cardiovascular events) for each combined category of the DP (quartiles) and the intervention group (3 categories), using the weighted pseudo-population obtained with the IPW procedure. Relative risks were also calculated for upper quartiles of each DP using as reference the first quartile of the DP, within each intervention group and the p for linear trend was calculated.

We used STATA version 12.0 (StataCorp) for all analyses.

RESULTS

The mean (± SD) age of the 7,216 participants was 67.0 (6.2) y. Participants were followed-up for an average of 4.3 y. During this period 328 deaths were recorded; the mean age at death was 73.8 (6.9).

Factor analysis revealed two major DP. Absolute factor loadings >0.29 for each DP are presented in **Table 1**. The first factor was characterized by a high consumption of high fat processed meats and red meats, alcohol, refined grains, canned fish, whole-fat dairy products, sauces, eggs, processed meals, commercial bakery and chocolates, whereas consumption of low-fat dairy products was inversely loaded. We labeled it as "Western Dietary Pattern (WDP)".

The second factor was loaded with vegetables, EVOO, walnuts, oily fish and canned fish, fruits, other nuts, whole-wheat bread, white fish and low fat dairy products. In addition, it was defined by a low consumption (negative loadings) of refined grains and of other olive oils different from EVOO. We labeled this second factor as Mediterranean-type dietary pattern (MDP).

The baseline characteristics of participants by quartiles of the WDP and the MDP are shown in **Tables 2** and **3** respectively. Subjects with a higher adherence to the WDP were more likely to be men, current smokers and were more physically active. They also showed higher total energy intake and significantly higher intakes of fat, except for monounsaturated fatty acids, and also greater consumption of most food groups with the exception of vegetables and

Table 1. Factor loadings for the two major dietary patterns in the PREDIMED study

	Western Dietary Pattern	Mediterranean dietary pattern
High fat processed meat	0.55	
Alcohol	0.45	
Red meat	0.45	
Refined grains	0.40	-0.30
Canned fish/Seafood	0.38	0.38
Sauces	0.33	
Processed meal	0.32	
Whole dairy products	0.31	
Eggs	0.30	
Commercial bakery	0.29	
Chocolates	0.29	
Low fat dairy products	-0.33	0.29
Olive oil (not extra-virgin)		-0.39
White fish		0.33
Whole grain bread		0.35
Nuts (not walnut)		0.36
Fruit		0.36
Oily fish		0.39
Walnuts		0.40
Extra-virgin olive oil		0.47
Vegetables		0.51

Table 2. Baseline characteristics of the 7216 participants according to quartiles of adherence to Western Dietary Pattern (WDP)

	WDP1 (n=1804)	WDP2 (n=1804)	WDP3 (n=1804)	WDP4 (n=1804)	p for trend
Men (%)	23.0	33.0	47.5	67.0	<0.001
Smoking status					
Former smokers (%)	16.4	20.4	27.0	34.5	<0.001
Current smokers (%)	7.1	10.7	15.0	22.7	<0.001
Diabetes (%)	55.7	49.0	45.2	44.5	<0.001
Hypertension (%)	84.0	84.1	82.9	79.9	<0.001
Age (y)	68.2±6.0	67.4±6.1	66.7±6.1	65.8±6.3	<0.001
Weight (kg)	74.3±11.2	75.4±12.0	77.4±12.0	80.0±11.8	0.006
BMI (kg/m^2)	30.2±4.0	29.9±3.9	29.9±3.8	29.8±3.6	<0.001
Physical activity during leisure time (METs-min/day)	210.2±223.5	210.4±205.6	242.9±253.7	260.8±264.2	<0.001
Total energy intake (kcal/d)	1839.3±444.5	2053.8±394.2	2294.2±389.2	2757.4±462.4	<0.001
Carbohydrate intake (% total energy)	43.1±7.2	42.4±7.0	41.3±6.9	40.3±7.0	<0.001
Protein intake (% total energy)	17.8±3.1	16.9±2.6	16.3±2.5	15.4±2.4	<0.001
Fat intake (% total energy)	38.3±7.5	39.0±6.7	39.7±6.5	39.8±6.3	<0.001
Monounsaturated fatty acid intake (% total energy)	19.5±5.2	19.5±4.6	19.6±4.3	19.4±4.0	0.339
Polyunsaturated fatty acid intake (% total energy)	5.9±2.1	6.2±2.0	6.4±2.1	6.4±2.0	<0.001
Saturated fatty acid intake (% total energy)	9.3±2.1	9.7±2.1	10.2±2.1	10.7±2.3	<0.001
Alcohol intake (g/d)	2.2±5.2	4.6±7.7	8.8±11.9	17.7±20.6	<0.001
Vegetables (g/d)	336.3±157.3	335.0±145.1	329.1±142.5	335.8±143.3	0.927
Fruits (g/d)	365.0±202.9	369.7±200.9	371.1±199.4	367.7±202.7	0.355
Whole-fat dairy products (g/d)	42.3±76.6	78.0±126.4	110.8±152.5	163.8±192.2	<0.001
Low-fat dairy products (g/d)	390.5±239.6	300.0±221.0	243.8±206.5	189.9±202.1	<0.001

Eggs (g/d)	15.9±9.9	18.8±9.8	21.1±9.7	24.3±12.9	<0.001
Red meat (g/d)	30.8±24.4	43.3±28.9	55.2±33.3	72.2±45.2	<0.001
White fish (g/d)	46.4±33.3	44.6±28.9	43.1±26.4	42.0±31.0	<0.001
Oily fish (g/d)	22.3±21.5	24.5±20.9	24.8±20.2	27.0±22.0	<0.001
Other fish and seafood (g/d)	18.4±16.1	25.8±18.9	31.3±21.7	41.1±30.7	<0.001
High-fat processed meat (g/d)	1.8±3.4	4.5±5.9	7.5±8.7	16.2±16.8	<0.001
Processed meals (g/d)	0.5±1.2	0.9±1.8	1.9±2.3	2.5±4.1	<0.001
Refined grains (g/day)	62.7±60.4	104.0±76.1	126.4±86.3	160.5±103.7	<0.001
Whole bread (g/d)	55.3±77.2	24.5±52.9	18.7±46.2	12.5±38.6	<0.001
Chocolates (g/d)	2.1±4.6	3.9±7.6	5.3±8.1	9.4±15.1	<0.001
Commercial bakery (g/d)	3.1±7.1	5.9±10.5	9.0±14.6	14.1±20.9	<0.001
Sauces (g/d)	0.9±1.5	1.4±2.0	2.0±2.7	3.2±3.9	<0.001
Extra-virgin olive oil (g/d)	16.8±21.1	19.7±22.6	22.2±23.4	25.7±24.5	<0.001
Other olive oils (g/d)	19.7±20.3	17.9±19.1	17.7±20.3	16.5±20.6	0.224
Nuts (g/d)	7.1±11.3	5.4±8.3	11.1±14.2	13.3±16.1	<0.001

Table 3. Baseline characteristics of the 7216 participants according to quartiles of adherence to Mediterranean Dietary Pattern (MDP)

	MDP1 (n=1804)	MDP2 (n=1804)	MDP3 (n=1804)	MDP4 (n=1804)	p for trend
Men (%)	46.0	42.0	41.0	40.5	<0.001
Smoking status					
Former smokers (%)	22.8	24.5	24.8	26.3	0.242
Current smokers (%)	17.0	15.5	11.6	11.5	<0.001
Diabetes (%)	50.0	47.1	48.8	48.7	0.728
Hypertension (%)	83.1	83.4	81.3	83.0	0.540
Age (y)	67.6±6.4	67.4±6.1	66.9±6.0	66.3±6.2	<0.001
Weight (kg)	76.8±12.1	76.8±12.1	76.3±11.7	76.5±12.2	0.007
BMI (kg/m^2)	30.2±3.7	30.0±3.8	29.9±3.9	29.8±4.0	0.001
Physical activity during leisure time (METs-min/week)	211.2±219.4	224.7±247.9	235.0±225.2	253.2±258.9	<0.001
Total energy intake (kcal/d)	2156.1±575.9	2122.2±5239	2189.7±487.5	2476.6±510.9	<0.001
Carbohydrate intake (% total energy)	43.2±7.5	42.2±7.0	41.2±6.7	40.5±6.9	<0.001
Protein intake (% total energy)	15.4±2.6	16.6±2.7	17.1±2.8	17.3±2.8	<0.001
Fat intake (% total energy)	38.7±7.1	38.6±6.6	39.4±6.6	40.2±6.7	<0.001
Monounsaturated fatty acid intake (% total energy)	19.3±4.8	19.2±4.4	19.6±4.5	19.9±4.5	<0.001
Polyunsaturated fatty acid intake (% total energy)	5.9±2.2	5.9±1.8	6.2±1.9	6.8±2.1	<0.001
Saturated fatty acid intake (% total energy)	10.3±2.4	10.0±2.2	9.9±2.1	9.6±2.1	<0.001
Alcohol intake (g/d)	9.2±16.1	8.3±13.7	8.1±13.8	7.7±12.4	0.001
Vegetables (g/d)	254.1±101.2	300.4±107.9	345.5±121.2	436.6±178.9	<0.001
Fruits (g/d)	285.2±156.5	340.0±171.1	385.8±197.8	462.6±229.3	<0.001
Whole-fat dairy products (g/d)	159.9±199.6	94.4±141.6	72.5±112.1	68.2±110.2	<0.001
Low-fat dairy products (g/d)	186.9±196.0	270.6±215.5	312.1±231.2	354.5±241.1	<0.001

Eggs (g/d)	19.6±11.7	19.5±10.8	19.8±10.1	21.1±11.6	<0.001
Red meat (g/d)	53.2±40.3	50.5±34.6	49.2±35.7	48.6±36.7	<0.001
White fish (g/d)	33.0±24.7	41.0±25.8	46.0±26.3	56.1±37.0	<0.001
Oily fish (g/d)	16.1±14.1	21.5±18.0	25.9±20.3	35.1±26.0	<0.001
Other fish and seafood (g/d)	19.2±16.5	25.4±19.6	30.4±21.9	41.6±30.0	<0.001
High-fat processed meat (g/d)	8.4±13.3	8.0±11.1	7.0±10.3	6.7±10.7	<0.001
Processed meals (g/d)	1.6±3.4	1.3±2.6	1.1±2.3	1.1±2.2	0.010
Refined grains (g/day)	153.2±102.4	121.1±89.4	97.2±75.7	82.2±74.6	<0.001
Whole bread (g/d)	6.3±22.7	17.4±41.6	29.9±55.2	57.2±82.1	<0.001
Chocolates (g/d)	4.3±8.3	4.2±7.8	5.0±10.2	7.2±12.8	<0.001
Commercial bakery (g/d)	10.0±18.7	7.7±14.1	7.5±13.6	6.9±12.0	<0.001
Sauces (g/d)	1.9±2.55	1.9±2.7	1.8±2.8	1.9±3.2	0.213
Extra-virgin olive oil (g/d)	6.5±13.6	16.3±20.2	25.3±22.7	36.3±23.6	<0.001
Other olive oils (g/d)	30.0±20.5	20.0±19.4	13.6±18.2	8.2±15.1	<0.001
Nuts (g/d)	4.1±6.3	7.1±8.9	10.3±11.7	18.9±19.1	<0.001

fruit. They had a statistically significant lower consumption of white fish, whole bread, and low-fat dairy products. Participants with a higher score for the MDP were more likely to be women, non-smokers and more physically active. They presented a reduced intake of carbohydrate, and higher intake of protein and fat, specifically mono- and poly-unsaturated fat.

Table 4 shows the hazard ratios (HR) for all-cause mortality according to baseline adherence to both DP in the whole PREDIMED cohort. After adjustment for sex, age, intervention group and recruitment center (model 1), there was no significant association between the upper quartile of WDP and death (HR 1.07; 95% CI: 0.77,1.50). Model 2, including additional confounders, showed similar results (HR 1.04; 95% CI: 0.74,1.47).

However, adherence to the empirically-derived MDP did show an inverse association that was statistically significant for the linear trend (p<0.001) and suggested strong risk reductions in the two upper quartiles, with HR 0.74 (95% CI: 0.54,0.99) for the third versus the first quartile and HR 0.53 (95% CI: 0.38, 0.75) for the fourth versus the first quartile (all in model 2).

When we assessed the association between empirically derived DP and cardiovascular events (myocardial infarction, stroke or cardiovascular death, i.e. the primary end-point of the main trial) no significant association was found between the WDP and the risk of cardiovascular events (HR for the upper versus the lowest quartile: 1.00; 95% CI: 0.70,1.43; adjusted for sex, age, intervention group and recruitment center) (**table 5**). Model 2, including additional confounders, showed similar results (HR 1.05; 95% CI: 0.73,1.51).

In contrast, a decreased risk of cardiovascular events was observed among subjects classified in the third and fourth baseline quartiles of the empirically-derived MDP (HR 0.60; 95% CI: 0.42, 0.81 and HR 0.52; 95%CI: 0.36, 0.74; respectively in model 1 and 2). Results were similar

Table 4. Hazard ratios for total mortality according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together (n= 7216)

Western dietary pattern	**Q1**	**Q2**	**Q3**	**Q4**	
	n= 1804	**n= 1804**	**n= 1804**	**n=1804**	**p for trend**
Overall mortality (n)	71	69	86	102	
Person-years	7635	7605	7805	8034	
Men (%)	23.0	33.0	47.5	67.0	<0.001
Age (y)	68.2±6.0	67.4±6.1	66.7±6.1	65.8±6.3	<0.001
Multivariable model[1]	1(ref)	0.94 (0.67-1.32)	1.09 (0.78-1.51)	1.07 (0.77-1.50)	0.53
Multivariable model[2]	1(ref)	0.93 (0.66-1.30)	1.05 (0.75-1.46)	1.04 (0.74-1.47)	0.65
Mediterranean dietary	**Q1**	**Q2**	**Q3**	**Q4**	
Pattern	**n= 1804**	**n= 1804**	**n= 1804**	**n= 1804**	**p for trend**
Overall mortality (n)	115	85	73	55	
Person-years	7882	7613	7619	7963	
Men (%)	46.0	42.0	41.0	40.5	<0.001
Age (y)	67.6±6.4	67.4±6.1	66.9±6.0	66.3±6.2	<0.001
Multivariable model[1]	1(ref)	0.80 (0.60-1.06)	0.70 (0.52-0.95)**	0.51 (0.36-0.71)**	<0.001
Multivariable model[2]	1(ref)	0.82 (0.62-1.10)	0.74 (0.54-0.99)**	0.53 (0.38-0.75)**	<0.001

[1]Adjusted for sex, age, recruitment center and interventional group.
[2]Adjusted for sex, age, recruitment center and interventional group, smoking status (never smoker, former smoker and current smoker), baseline body mass index, physical activity during leisure time, self-reported hypertension, self-reported depression, self-reported diabetes, self-reported hypercholesterolemia and education level (three categories)
*p<0.05 ** p<0.001

Table 5. Hazard Ratios for primary cardiovascular event according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together (n= 7216)

Western dietary pattern	**Q1**	**Q2**	**Q3**	**Q4**	
	n= 1804	**n= 1804**	**n= 1804**	**n= 1804**	**p for trend**
Primary cardiovascular event (n)	67	61	65	84	
Person-years	7627	7590	7799	8024	
Men (%)	23.0	33.0	47.5	67.0	<0.001
Age (y)	68.2±6.0	67.4±6.1	66.7±6.1	65.8±6.3	<0.001
Multivariable model[1]	1 (ref)	0.95 (0.67-1.35)	0.94 (0.66-1.35)	1.00 (0.70-1.43)	0.93
Multivariable model[2]	1 (ref)	0.96 (0.68-1.38)	0.97 (0.68-1.39)	1.05 (0.73-1.51)	0.73
Mediterranean dietary	**Q1**	**Q2**	**Q3**	**Q4**	
Pattern	**n= 1804**	**n= 1804**	**n= 1804**	**n= 1804**	**p for trend**
Primary cardiovascular event (n)	104	70	54	49	
Person-years	7881	7599	7610	7950	
Men (%)	46.0	42.0	41.0	40.5	<0.001
Age (y)	67.6±6.4	67.4±6.1	66.9±6.0	66.3±6.2	<0.001
Multivariable model[1]	1(ref)	0.75 (0.55-1.02)	0.58 (0.41-0.81)**	0.50 (0.35-0.71)**	<0.001
Multivariable model[2]	1(ref)	0.76 (0.56-1.04)	0.60 (0.42-0.83)**	0.52 (0.36-0.74)**	<0.001

[1]Adjusted for sex, age, recruitment center and interventional group.
[2]Adjusted for sex, age, recruitment center and interventional group, smoking status (never smoker, former smoker and current smoker), baseline [2]Adjusted for sex, age, recruitment center and interventional group, smoking status (never smoker, former smoker and current smoker), baseline body mass index, physical activity during leisure time, self-reported hypertension, self-reported depression, self-reported diabetes, self-reported hypercholesterolemia and education level (three categories)
*p<0.05 ** p<0.001

in both multivariable models (P for trend <0.001), suggesting an inverse association between baseline adherence to the MDP and the risk of major cardiovascular events.

To further analyze the association between empirically derived DP and cardiovascular events we repeated the analysis using each time as outcome each of the three components of the primary end-point of the trial, namely acute myocardial infarction, stroke and cardiovascular death (Table 6). For each of these analyses participants with the other 2 end-points were excluded. We observed that the MDP was inversely and strongly associated with the risk of myocardial infarction and also with the risk of cardiovascular death (fourth quartile vs first quartile: HR 0.52 ; 95% CI: 0.36, 0.74 and HR 0.37 ; 95%CI: 0.18, 0.76; respectively for each outcome in both adjusted models 2). Moreover, we found that higher baseline WDP adherence was significantly associated with a higher risk of cardiovascular death (p for linear trend = 0.033 in the multiple-adjusted model).

Table 6. a) Hazard Ratios for acute myocardial infarction according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together

Western dietary pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Acute Myocardial Infarction (n)	24	23	26	30	
Person-years	7508	7482	7662	7846	
Multivariable model[1]	1 (ref)	0.96 (0.54-1.72)	0.94 (0.52-1.68)	0.83 (0.46-1.50)	0.50
Multivariable model[2]	1 (ref)	0.97 (0.54-1.74)	0.96 (0.53-1.72)	0.85 (0.47-1.56)	0.58

Mediterranean dietary Pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Acute Myocardial Infarctation (n)	42	22	22	17	
Person-years	7675	7450	7517	7857	
Multivariable model[1]	1(ref)	0.57 (0.34-0.96)*	0.55 (0.32-0.93)*	0.38 (0.21-0.68)*	0.001
Multivariable model[2]	1(ref)	0.59 (0.35-1.00)	0.58 (0.34-0.97)*	0.41 (0.23-0.75)*	0.003

b) Hazard Ratios for stroke according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together

Western dietary pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Stroke (n)	37	33	31	34	
Person-years	7551	7520	7676	7856	
Multivariable model[1]	1 (ref)	0.99 (0.61-1.59)	0.91 (0.55-1.50)	0.94 (0.57-1.57)	0.78
Multivariable model[2]	1 (ref)	1.03 (0.63-1.66)	0.98 (0.59-1.63)	1.05 (0.62-1.77)	0.89

Mediterranean dietary Pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Stroke (n)	48	34	27	26	
Person-years	7688	7492	7526	7897	
Multivariable model[1]	1(ref)	0.81 (0.52-1.26)	0.67 (0.41-1.08)	0.66 (0.40-1.10)	0.073
Multivariable model[2]	1(ref)	0.81 (0.52-1.26)	0.66 (0.41-1.08)	0.68 (0.41-1.13)	0.086

c) Hazard Ratios for cardiovascular death according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together

Western dietary pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Cardiovascular death (n)	14	14	20	33	
Person-years	7493	7467	7649	7872	
Multivariable model[1]	1 (ref)	1.03 (0.48-2.19)	1.41 (0.69-2.85)	1.90 (0.95-3.77)	0.031
Multivariable model[2]	1 (ref)	1.03 (0.48-2.19)	1.37 (0.67-2.81)	1.91 (0.95-3.86)	0.033

Mediterranean dietary Pattern	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
Cardiovascular death (n)	32	23	15	11	
Persons-years	7670	7472	7482	7857	
Multivariable model[1]	1(ref)	0.80 (0.47-1.38)	0.53 (0.28-0.99)*	0.36 (0.18-0.73)*	0.002
Multivariable model[2]	1(ref)	0.84 (0.48-1.45)	0.56 (0.30-1.05)	0.37 (0.18-0.75)*	0.003

[1]Adjusted for sex, age, recruitment center and interventional group.
[2]Adjusted for sex, age, recruitment center and interventional group, smoking status (never smoker, former smoker and current smoker), baseline [2]Adjusted for sex, age, recruitment center and interventional group, smoking status (never smoker, former smoker and current smoker), baseline body mass index, physical activity during leisure time, self-reported hypertension, self-reported depression, self-reported diabetes, self-reported hypercholesterolemia and education level (three categories)
*p<0.05 ** p<0.001

In order to assess the potential effect modification by the nutritional intervention we obtained the absolute risks of death or cardiovascular events for each of the 12 groups formed by the joint combination according to the nutritional intervention (3 levels) and the baseline adherence to DP (quartiles). We used inverse probability weighting in this analysis to avoid confounding and obtain exchangeable groups.

Figure 1a displays the absolute overall risk of all-cause death (rate/1000 person-year) for each category made by the cross-classification according to quartiles of baseline adherence to the WDP and to the 3 randomized arms of the trial (the 2 intervention groups and the control group). Although statistically non-significant (p for trend=0.098), a suggestion for a trend of higher total mortality with higher quartiles of the WDP was present only in the control group, but not in the two active intervention groups. The highest absolute risk of death was observed in participants who were in the highest quartile of baseline adherence to the WDP and did not receive the intervention with MeDiet (i.e. they were allocated to the control group).

Likewise, **figure 1b** shows that regardless of the intervention group, better baseline adherence to the MDP seemed to be associated with lower absolute risks for overall mortality in the three groups, being the inverse dose-response trend statistically significant in the control and in the PREDIMED active intervention group supplemented with EVOO (p for trend=0.012 and 0.027 respectively).

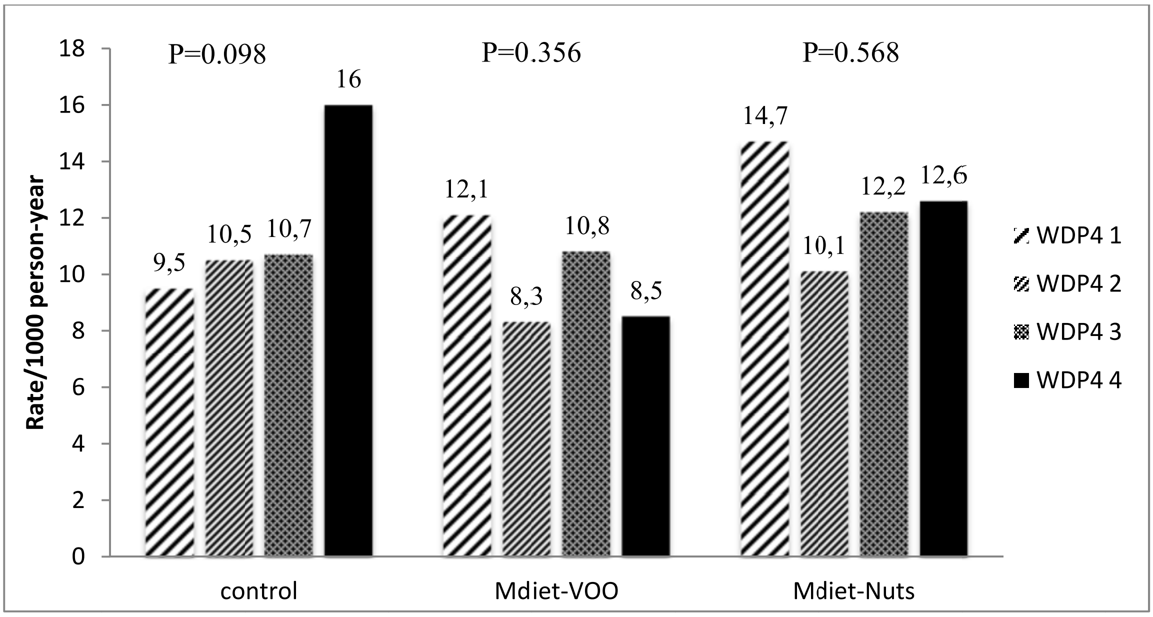

Figure 1a)

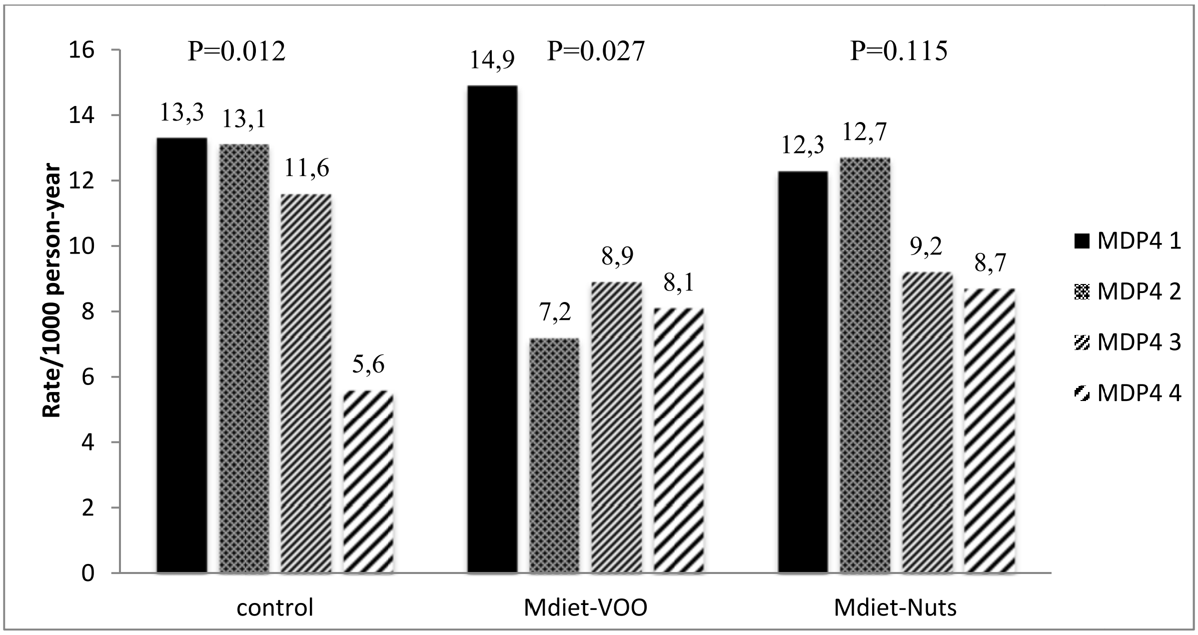

Figure 1b)

Figure 2a shows the absolute all-cause mortality risk (rate/1000 person-year) for each category built according to the joint classification by quartiles of WDP and allocated intervention arm in the trial. No statistically significant interactions were found.

Finally, **figure 2b** represents the cardiovascular risk according to the joint classification by both baseline adherence to the empirically-derived MDP and the allocated intervention arm. These absolute rates might suggest that, even in absence of the PREDIMED nutritional intervention (i.e., in the control group), the inverse association between baseline adherence to MDP and cardiovascular events was clearly apparent. Interestingly, the lowest absolute rates of cardiovascular events were observed in both intervention groups for the 2 upper quartiles of adherence to the baseline MDP (in the group supplemented with nuts) and for the fourth quartile (in the group supplemented with EVOO). The inverse dose-response trend between baseline adherence to the MDP and cardiovascular events remained significant within both intervention groups (p for trend=0.013 for EVOO and 0.007 for nuts).

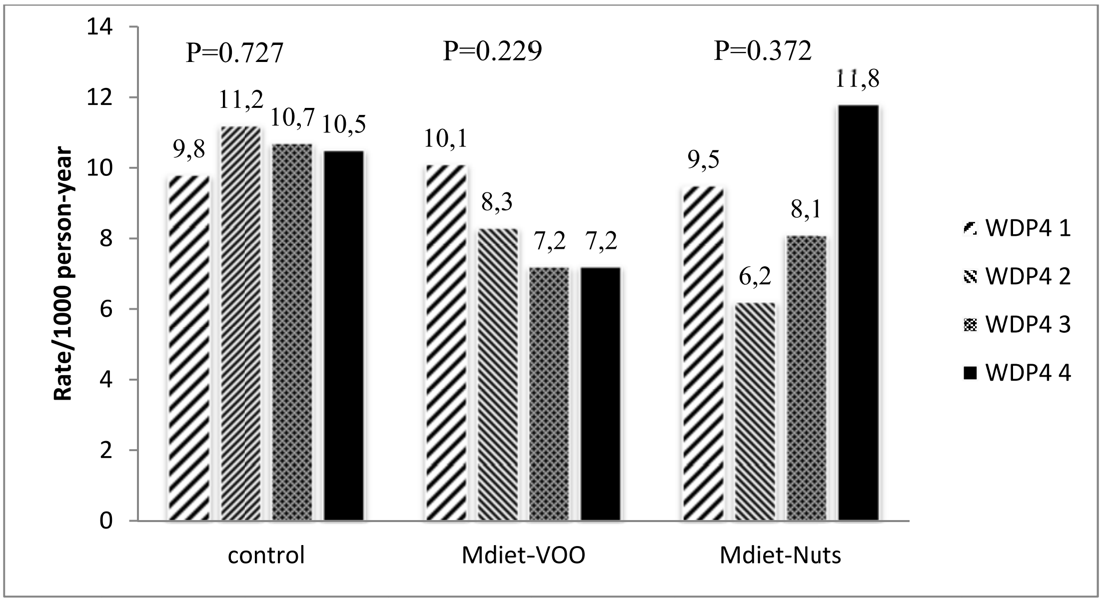

Figure 2 a)

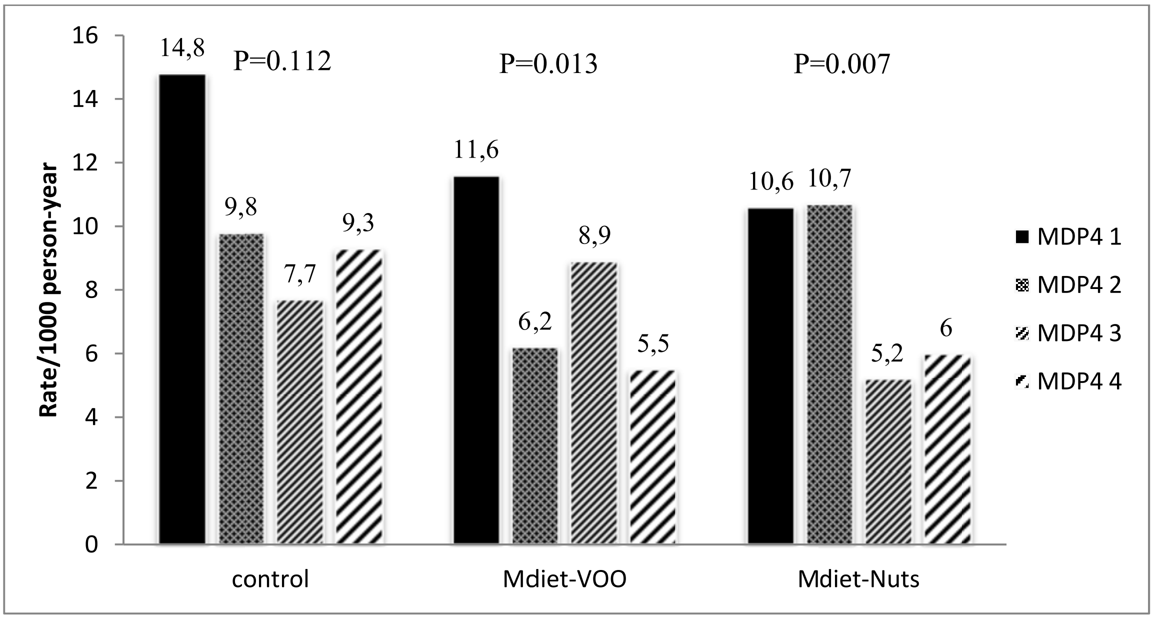

Figure 2 b)

To deepen into the combined effects of baseline DP and intervention on overall mortality or cardiovascular events, we assessed the potential interactions between both factors. When the two intervention groups with MeDiet were merged together, we found a p-value=0.054 for the interaction between the highest quartile of WDP and the MeDiet intervention in the analysis of all-cause death. However, the likelihood ratio test assessing the overall effect modification was not statistically significant (3 degrees of freedom, p=0.27)

DISCUSSION

Using factor analysis, we investigated the association between baseline adherence to empirically-derived DP (i.e. post hoc patterns) and all-cause mortality or major cardiovascular events in a cohort of older Spanish subjects at high risk of CVD who underwent a nutritional intervention in the PREDIMED trial [18, 19]. Two DP were identified: WDP and MDP (table 1). The results showed that a closer baseline adherence to the MDP was associated with a statistically significant 47% reduction in all-cause mortality along the follow-up period. An inverse association of similar magnitude was also observed between the baseline adherence to the MDP and cardiovascular events. These inverse associations between baseline adherence to the MDP and overall mortality or cardiovascular events were always present, in a low or high magnitude, regardless of the allocated intervention group. However, the intervention with the MeDiet, supplemented with EVOO or nuts, in conjunction with a good baseline conformity with a MDP led to the lowest absolute cardiovascular risk. On the other hand, although no significant results were found, a (non-significant) suggestion for a detrimental association of the WDP with a higher risk of all-cause death was present in the control group. Interestingly, when specific cardiovascular events were separately analyzed, an association of the WDP with a higher risk of cardiovascular death was found. Both findings suggest a detrimental effect of WDP leading to a higher mortality risk.

An interesting point of our study is that we were able to assess the combined effects on hard clinical end-points of both the baseline adherence to empirically-derived DP and of a dietary intervention. We observed that in the control group the differences between the highest and lowest quartiles of both the WDP and the MDP appeared to be more apparent, especially when mortality was analyzed. Control group subjects in the highest quartile of baseline adherence to MDP exhibited a 42% relative reduction in their mortality risk compared to their counterparts in the lowest quartile.

The present findings assume that the baseline DP might be a good proxy for lifetime dietary exposures. In this line of thought, lifetime exposure can be more important to prevent premature mortality than to follow a supplemented MeDiet or a low-fat diet for only 4 to 5 years. However, we were not able to demonstrate a potential interaction between a high baseline adherence to WDP and the intervention with MeDiet (both active intervention groups merged together versus control), though the p value approached the limit of statistical significance (p=0.054).

Few studies have examined the association between a healthy DP using factor analysis and the risk of death in high-risk elderly populations [8, 19]. Our results agree with previous reports from the Mediterranean area [8] and non-Mediterranean countries [19], where a MDP was not always identified. In the same context, there are few studies analyzing empirically derived DP and CVD [8, 20], and they also found that in Mediterranean areas, better adherence to a MDP was associated with lower CVD risk.

Our results are also consistent with previous studies that have reported inverse associations between an *a priori* defined MDP (or a DP similar to this traditional diet) and total mortality [19, 21, 22]. In relation to CVD, there are several studies analyzing the effects of a priori defined MDP, that found a cardio-protective effect of this DP [23, 24]. However, different country-specific DP have been described in Mediterranean populations and these results should be interpreted with caution.

Regarding the Spanish context, a recent study in a large cohort found that higher adherence to an empirically derived MDP in adults was associated with a reduction in the risk of all-cause mortality [6].Several explanations can account for the inverse association observed between better baseline adherence to a MDP and mortality. First, the MDP has been shown to have a beneficial effect on the incidence and prevalence of several diseases [25]. Second, plant-based foods are protective and plant-based DP may decrease disease risk, whereas diets high in animal foods may be more likely to increase the risk of mortality [26]. In fact, participants in the upper baseline quartiles of MDP followed a diet rich in plant based foods and poor in animal foods, and had the lowest risk of mortality. Third, the available evidence about olive oil, suggests that it plays a role in the prevention of coronary heart disease, and cancer, and may influence survival [1, 2, 21, 22, 25] . Besides, olive oil and particularly EVOO improves the lipid profile and has potent antioxidant and anti- inflammatory properties [27, 28] .

Though we found a WDP associated with higher cardiovascular mortality, the absence of association between WDP and all-cause mortality was unexpected. Several mechanisms might also be proposed to explain this absence of association. A suggested explanation is that the "WDP" described in the U.S.[7] and the "WDP" in our study are not entirely equivalent and may not produce the same potential adverse effects on health and longevity. Thus, the consumption of foods known to be associated with lower mortality, such as fish and seafood and alcohol in moderation [29], was included in the so-called WDP in our cohort. Besides, it is possible that residual confounding may have affected our results.

Our study has several strengths, including the opportunity to assess the combined effects of the baseline diet and the dietary intervention, the large sample size, the Mediterranean setting, the prolonged follow-up, the sub-studies conducted to validate the questionnaire [30], and the objective, blinded and comprehensive ascertainment of events and close follow-up of participants.

There are also limitations to our study. First, the results cannot be generalized to younger and/or healthier individuals from other geographical locations. Second, there is an inherent difficulty to change dietary habits in elderly subjects. Third, even though we adjusted the data for the main known risk factors for mortality or CVD, residual confounding cannot be completely excluded. Fourth, there is a potential for measurement error in the FFQ, which provides only subjective information in comparison with the use of objective markers of food intake. Fifth, the number of observed deaths was small. Despite this last limitation, which is associated with lower statistical power, we found a significant inverse association between the MDP and total mortality. Finally, the method used to define DP (factor analysis) involves several questionable decisions that must be taken into account (e.g. the definition and categorization of predefined food groups). Nevertheless, our results are in line with those of other studies using similar factor analyses to define DP.

In conclusion, in a population of Spanish Mediterranean individuals at high cardiovascular risk participating in a nutritional intervention trial, a greater baseline adherence to a MDP was associated with a substantial reduction in CVD and overall mortality after follow-up for ≈5 y. Further research is required to confirm the present findings in other Mediterranean and non-Mediterranean settings, especially to better observe if the MeDiet could be able to reduce the detrimental effect of a baseline WDP on cardiovascular or overall mortality risk.

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Authors Contribution

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Analysis and Interpretation of the Data: MA Martínez-González, C Razquin, I Zazpe.

Critical revision of the article for important intellectual content and final approval of the article: all authors.

Statistical expertise: M.A. Martinez-Gonzalez and E.Toledo.

All authors have read and approved the final manuscript.

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Figure and table legends

Table 1. Factor loadings for the two major dietary patterns in the PREDIMED study

Table 2. Baseline characteristics of the 7216 participants according to quartiles of adherence to Western Dietary Pattern (WDP)

Table 3. Baseline characteristics of the 7216 participants according to quartiles of adherence to Mediterranean Dietary Pattern (MDP)

Table 4. Hazard ratios for total mortality according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together (n= 7216)

Table 5. Hazard Ratios for primary cardiovascular event according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together (n= 7216)

Table 6. a) Hazard Ratios for acute myocardial infarction according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together.

b) Hazard Ratios for stroke according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together.

c) Hazard Ratios for cardiovascular death according to quartiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern in the PREDIMED study with the three intervention groups considered together.

Figure 1. Absolute risks[1] for overall mortality according to the quartiles of baseline adherence to WDP (a) or MDP (b) and to the randomly allocated arm of the trial (intervention groups or control group).

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[1] Absolute risks were adjusted for potential confounders using inverse probability weighting.

MDP:Mediterranean Dietary Pattern, WDP: Western Dietary Pattern.

Figure 2. Absolute risks[2] for cardiovascular events according to the quartiles of baseline adherence to WDP (a) or MDP (b) and and to the randomly allocated arm of the trial (intervention groups or control group)..

MDP:Mediterranean Dietary Pattern, WDP: Western Dietary Pattern.

[2] Absolute risks were adjusted for potential confounders using inverse probability weighting.

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