

Adherence to the Mediterranean diet reduces mortality in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)

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(Received 14 January 2011 – Revised 14 March 2011 – Accepted 14 March 2011 – First published online 17 May 2011)

Abstract

Epidemiological studies show that adherence to a Mediterranean diet (MD) increases longevity; however, few studies are restricted to Mediterranean populations or explore the effect of a MD pattern that directly incorporates olive oil. Therefore the relationship between adherence to the MD and mortality was studied within the the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). The EPIC-Spain analysis included 40 622 participants (37.7% males) aged 29–69 years who were recruited from five Spanish regions in 1992–1996. During a mean follow-up of 13.4 years, 1855 deaths were documented: 913 from cancer, 399 from CVD, 425 from other causes and 118 from unknown causes of death. Risk of all-cause and cause-specific mortality was assessed according to the level of adherence to a relative MD (rMED) score, measured using an 18-unit scale incorporating nine selected dietary components. A high compared with a low rMED score was associated with a significant reduction in mortality from all causes (hazard ratio (HR) 0.79; 95% CI 0.69, 0.91), from CVD (HR 0.66; 95% CI 0.49, 0.89), but not from overall cancer (HR 0.92; 95% CI 0.75, 1.12). A 2-unit increase in rMED score was associated with a 6% ($P < 0.001$) decreased risk of all-cause mortality. A high olive oil intake and moderate alcohol consumption contributed most to this association. In this Spanish cohort, following an olive oil-rich MD was related to a significant reduction in all-cause mortality, and reduced the risk of mortality from CVD. These results support the important role that the MD pattern has on reducing mortality in Mediterranean countries.

Key words: Mediterranean diet; Morality; EPIC-Spain; Cohort studies

The Mediterranean diet (MD) encompasses the traditional dietary patterns found in the olive-growing regions of the Mediterranean basin in the 1960s⁽¹⁾, and is globally recognised

as a healthy dietary model⁽²⁾ and an intangible cultural heritage of humanity by the United Nations Educational, Scientific and Cultural Organization (UNESCO)⁽³⁾. The traditional

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-Spain, Spanish cohort of EPIC; HR, hazard ratio; MD, Mediterranean diet; rMED, relative Mediterranean diet.

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MD pattern is characterised by the daily use of olive oil, an abundance of plant foods such as fruit and vegetables, nuts and seeds, cereals and legumes, the consumption of fish and seafood especially in coastal regions, moderate-to-low intake of dairy products mostly from fresh cheese and yoghurt, moderate alcohol mostly in the form of wine, and a less frequent consumption of meat and meat products⁽⁴⁾.

Numerous epidemiological studies have explored the health benefits of the MD and evidence consistently shows that individuals who adhere to the MD have healthier ageing and a longer life span^(5–8). This is related, in part, to its role in preventing major chronic diseases such as CVD, certain cancers, type 2 diabetes and also some neurodegenerative diseases, as supported by findings from observational studies^(6,9). Furthermore, randomised controlled dietary trials have shown that the MD reduces incidence of type 2 diabetes⁽¹⁰⁾, the metabolic syndrome^(11,12) and CVD risk factors^(13,14). The MD's favourable fatty acid profile, high fibre content, wide variety of antioxidants and phytochemicals, other still unidentified biologically active compounds and their synergistic interactions can explain some of its beneficial effects on health⁽⁵⁾.

Over a decade ago the key elements of the MD were grouped into an *a priori* MD score⁽¹⁵⁾, to reflect the level of adherence to this dietary pattern. Various versions of this and other MD scores are now widely used to study the relationship between the MD pattern and different health parameters⁽¹⁶⁾. Prospective studies have shown that following the MD is associated with a decrease in overall mortality^(17–20) and a meta-analysis of cohort studies calculated that a 2-unit increase in MD score reduced the risk of mortality by 8%⁽⁹⁾. A Mediterranean-like diet has also been reported to have a beneficial effect on mortality in countries outside the Mediterranean basin^(17,21,22).

Results from an elderly cohort within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, which included subjects aged 60 years or more from nine European countries, showed that a 2-unit increase in MD score was related to a 7% reduction in mortality⁽¹⁹⁾. However, this association was not significant in six out of nine of these countries, including Spain and Italy. This may have been due to a lack of statistical power, as relatively few deaths had accrued at this time in these Mediterranean cohorts. In contrast, a previous study set in Greece observed a 14% reduction in total mortality for every 2-unit increase in MD score⁽²³⁾.

Therefore, whether the MD can reduce mortality to a similar extent in other Mediterranean populations still remains unclear. Furthermore, studies using *a priori* MD scores to assess the impact of the MD on mortality commonly include the MUFA:SFA ratio^(9,16) and do not directly incorporate olive oil intake, the hallmark of the MD. In previous research within the Spanish cohort of EPIC (EPIC-Spain), a high intake of fresh fruit, root vegetables and fruiting vegetables decreased the risk of mortality⁽²⁴⁾. Therefore, we aimed to investigate the relationship between the entire MD pattern and all-cause and cause-specific mortality in the EPIC-Spain cohort.

Experimental methods

Study design and population

EPIC is a large multi-centre prospective cohort study conducted across ten European countries and designed to study the role of dietary, lifestyle, environmental and genetic factors in the development of cancer and other chronic diseases. The full methodological details have been published previously^(25,26). The present study includes participants from EPIC-Spain; 41 438 healthy volunteers (15 632 men) aged 29–69 years old, recruited between 1992 and 1996 from three regions in the north (Asturias, Gipuzkoa and Navarra) and two regions in the south (Granada and Murcia). Participants were recruited from different social sectors and from both urban and rural areas (with a participation rate from 55 to 89% between centres). The majority of volunteers were active blood donors (75%), and to a lesser extent industrial workers, civil servants or the general population. At recruitment participants gave their informed consent and the present study was approved by the Medical Ethical Committee of Bellvitge Hospital.

Cohort follow-up and mortality ascertainment

Follow-up for all-cause mortality began in 1992–93 and for this analysis was completed between December 2006 and June 2009, varying by centre. Date and underlying cause of death were obtained through record linkage with the Spanish National Statistics Institute (Instituto Nacional de Estadística; INE), which centralises this information from regional mortality registries. Cause of death was coded using International Classification of Diseases (ICD)-9 until 1999 and ICD-10 from 1999 to 2008; coding I00–I99 for CVD and C00–C99 for cancer. All other causes of death, including codes D1–D48 for *in situ*/benign/uncertain or unknown behaviour neoplasm (*n* 24), were grouped into 'other causes'. Participants with implausible dietary values, the lowest and highest 1% of the ratio of total energy intake:energy requirement, were excluded from this analysis (816 participants including fifty-six deaths). Therefore, the final study population included 40 622 participants.

Dietary and lifestyle data collection

Participants were interviewed in person to collect information on usual food intake over the previous year by means of a computerised version of a validated dietary history questionnaire, used across all centres^(27,28). In a pilot study to evaluate the relative validity and reproducibility of the dietary history questionnaire, the Pearson correlation coefficients between the mean daily intake of food groups used in the relative MD (rMED) score based on the twelve 24 h diet recalls and the second dietary history, ranged from 0.29 to 0.90⁽²⁷⁾. Dietary information obtained from the diet history questionnaire was used to calculate ethanol intake (g/d) derived from alcoholic beverages and total energy intake (kJ/d), which was estimated using food composition tables⁽²⁹⁾. An interviewer-administered lifestyle questionnaire was used to

collect information on sociodemographic and lifestyle factors, including history of tobacco consumption, physical activity and reproductive indicators in women. Detailed information on medical history was collected at recruitment, including self-reported medication use and history of diseases such as diabetes, cancer and CVD. Anthropometrics (waist and hip circumference, weight and height) were measured at recruitment using standardised procedures.

The relative Mediterranean diet score

The rMED score, as previously applied in EPIC studies⁽³⁰⁾, was used to estimate the level of adherence to the MD. It consists of an 18-point linear scale that incorporates nine selected components of the MD. Each component (apart from alcohol) is calculated as a function of energy density (g per 8368 kJ per d (g per 2000 kcal/d)), using the nutrient density model⁽³¹⁾, and then divided into tertiles of intakes. For the six components presumed to fit the MD, fruit (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (fresh or frozen), olive oil and cereals, a score of 0 to 2 was assigned to the first, second and third tertile of intake. For the two components presumed to not fit the MD, total meat and dairy products, the scoring is reversed so that 2 points are assigned to the lowest tertile. Alcohol was scored dichotomously, as in previous EPIC studies⁽¹⁵⁾, assigning 2 points for moderate consumers (5–25 g/d for women and 10–50 g/d for men) and 0 for participants outside these sex-specific ranges. An rMED score ranging from 0 to 18 was obtained by summing the points from each component, whereby 0 represented the lowest adherence to the MD pattern and 18 represented highest adherence. The rMED score was analysed as a continuous variable (per 2-unit increase) and as a categorical variable (low adherence, 0–6 units; medium adherence, 7–10 units; high adherence, 11–18 units).

Statistical analysis

STATA statistical software version 10 (StataCorp LP, College Station, TX, USA) was used for all analyses. The association between non-nutritional covariates and the rMED score was assessed by frequency distributions and χ^2 tests for categorical variables and by means, standard deviations and the Kruskal–Wallis rank sum test for continuous variables. Cox proportional hazards regression models were used to test the association between the rMED score (as a categorical and continuous variable) and all-cause mortality. Age was the primary time variable; entry time was defined as age at recruitment and exit time was defined as age at death (for cases) or last complete follow-up (for at-risk participants), depending on which occurred first. All models were stratified by centre, age at EPIC study entry and sex, and adjusted for BMI (quintiles), waist circumference (continuous), education level (none, primary, secondary, technical training, university or unspecified), validated physical activity index⁽³²⁾ (inactive, moderately inactive, moderately active and active) based on a cross-tabulation of physical activity at work and during leisure-time, smoking status (never, former, current smoker of < 20 cigarettes/d,

current smoker of ≥ 20 cigarettes/d and non-specified smoking status or cigarettes/d) and energy intake (continuous). Trend tests were obtained by scoring the rMED categories in a continuous scale from 1 to 3. Two-sided *P* values less than 0.05 were considered statistically significant.

A competing risk approach⁽³³⁾ was implemented to assess the association between the MD and cause-specific mortality (CVD, cancer and other), and to test if the association between the MD and mortality differed depending on the causes of death. The Cox models were stratified by type of outcome, which allows for different associations between each risk factor and the relative hazard of each outcome, under the proportional hazard assumption. This method is based on data augmentation, as each subject needs to be assigned a separate observation for each mortality outcome. In order to compare the hazard ratios (HR) for the different causes of mortality, we first assumed different associations between the main exposure variable (the rMED score) and the covariates for each outcome, using interaction terms. This full model, with different associations between the exposure variable and covariates for each mortality outcome, was successively compared with reduced models with the same associations between these variables, using the log-likelihood ratio tests. The estimates and CI were obtained after using robust standard errors on the reduced model⁽³⁴⁾.

Plausible effect modification by sex, age at recruitment (< 55 years and ≥ 55 years), BMI (< 25, 25–30, ≥ 30 kg/m²), waist circumference (below and above the National Cholesterol Education Program-Adult Treatment Panel III cut-offs of 102 cm for men and 88 cm for women⁽³⁵⁾) and smoking status (never, former, current) were explored by modelling interaction terms between each of these separate variables and the rMED score, and tested using the log-likelihood ratio test. In addition, risk of all-cause mortality in relation to categories of the rMED score was examined in analyses stratified by these cohort subgroups.

HR were calculated for each separate component of the rMED score, using the first tertile as the reference category, and mutually adjusting for the other components in the rMED score and the covariates mentioned previously. The relative importance of each of the rMED components on mortality was also assessed⁽²³⁾. Each component was alternately subtracted from the original rMED score (i.e. score without fruit or without olive oil), while adjusting for the component excluded to control for potential confounding. This reduced the rMED score from 0–18 to 0–16, so to maintain comparability with the original range the logarithms of the HR were multiplied by 17/19 (and then expressed as a 2-unit increase) before exponentiating them.

Sensitivity analyses were carried out by additional adjustment for alcohol intake, which is associated with mortality and CHD in this cohort⁽³⁶⁾, and for the presence of diabetes, hyperlipidaemia or hypertension. Additional models were also created excluding participants with chronic diseases at recruitment (CVD (*n* 9011), diabetes mellitus (*n* 2034) and/or cancer (*n* 524)), the first 2-years of follow-up (81 149 person years, including 109 cases), and mis-reporters of energy intake defined using Goldberg cut-offs (*n* 13 795)⁽³⁷⁾.

Finally, the main Cox analyses were repeated using the original MD score constructed by Trichopoulou⁽²⁰⁾, for ease of comparison with previous results.

Results

The cohort of 40 622 subjects was followed-up for a mean of 13.4 years, during which time 1855 deaths were recorded (Table 1); 399 from CVD, 913 from cancer and 425 from other causes (118 subjects had missing information on cause of death). The mean rMED score was 8.6 (SD 2.7) overall and was highest in Granada and Murcia and lowest in Asturias.

The distribution of the baseline characteristics of the subjects according to level of adherence to the rMED is shown in Table 2. Subjects with the highest category of rMED score were older, had a higher BMI but lower energy intake ($P < 0.001$) and lower total fat and saturated fat intakes. Females, current smokers and heavy alcohol drinkers were more likely to have lower rMED scores ($P < 0.001$).

The multivariate HR (unadjusted and fully adjusted) for the association between the rMED score and all-cause and cause-specific mortality are presented in Table 3. A high compared with a low rMED score was associated with a significant 21 (95% CI 9, 31) % reduction in all-cause mortality and every 2-unit increase in rMED score was associated with a 6 (95% CI 3, 10) % decrease in mortality. In cause-specific mortality analyses, a high compared with a low rMED score was associated with a significant reduction in mortality from other causes (HR 0.71; 95% CI 0.54, 0.94) and mortality from CVD (HR 0.66; 95% CI 0.49, 0.89). A 2-unit increase in rMED score reduced the risk of CVD mortality by 16% ($P = 0.02$) in females and by 11% in males ($P = 0.01$) (data not shown).

A high compared with a low rMED score was not significantly associated with death from overall cancer (HR 0.92; 95% CI 0.75, 1.12). However, in secondary analyses including only cancers with greater evidence of being causally related to dietary factors⁽³⁸⁾ (oesophageal, stomach, intestinal, colorectal and other digestive organ cancers, pancreatic, breast and prostate cancer) (570 cases), the rMED score was associated with a borderline reduction in risk of death (HR 0.79; 95% CI 0.61, 1.01; $P = 0.056$ for high *v.* low score). However, the competing risk analysis showed that there was no evidence of a

significant difference in the association between the rMED score and each of the major causes of death (P for interaction = 0.129).

There was no evidence that sex modified the association between the rMED score and all-cause mortality (even though the association between the rMED score was only significant in men; Table 4), or between the rMED score and cause-specific mortality (data not shown). Hence, the main analyses are presented globally. Although the effect estimates varied in analyses stratified by age group, smoking status, BMI and waist circumference, there was no evidence of interaction with the rMED score (Table 4).

The mutually adjusted HR of mortality according to tertile of intake for the individual components of the rMED score are presented in Table 5. The majority of the Mediterranean components on their own were not significantly associated with mortality. However, a high intake of olive oil and moderate intake of alcohol were associated with a significant decreased risk of mortality, by 15% ($P = 0.006$) and 11% ($P = 0.029$), respectively. The negative association between moderate alcohol intake and mortality was significant in men (HR 0.87; $P = 0.033$) but not in women (HR 0.97; $P = 0.767$) (data not shown). As high intakes of alcohol are known to be detrimental to health, we also analysed the association between mortality and intake of alcohol separately for low intakes (less than 5 g/d for women or 10 g/d for men) and high intakes (more than 25 g/d for women or 50 g/d for men). Compared with moderate alcohol intake, high alcohol intake significantly increased risk of mortality by 17% ($P = 0.034$), while low intake was not associated with mortality (HR 1.06; $P = 0.148$). We also assessed the risk of mortality for intake above *v.* below the sex-specific median of MUFA:SFA ratio (HR 1.03; 95% CI 0.93, 1.15), for comparison with previous articles, even though it was not within the rMED score.

After alternately subtracting each of the nine components from the rMED score, the magnitude of the decrease in risk of mortality was generally reduced, but remained significant (Fig. 1). Fig. 1 also confirms the predominant weight that olive oil, alcohol and cereals contribute to the association between mortality and a 2-unit increase in rMED score, because alternate exclusion of these three dietary components

Table 1. Distribution of participants, all-cause and cause-specific mortality and Mediterranean diet adherence in the five centres of the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)

EPIC-Spain centre	Cohort sample	Person-years	Mortality by cause				rMED score†		
			Total*	Total: % male	CVD	Cancer	Other	Mean	SD
Asturias	8374	112 024	338	58	73	200	65	7.8	2.5
Granada	7725	108 408	368	40	76	142	70	9.0	2.6
Murcia	8348	110 054	323	56	70	142	82	9.1	2.7
Navarra	7924	109 314	389	71	77	210	93	8.1	2.7
Gipuzkoa	8251	103 266	437	73	103	219	115	8.7	2.7
Total	40 622	543 066	1855	60	399	913	425	8.6	2.7

rMED, relative Mediterranean diet.

* Cause of death is undefined for 118 cases.

† The rMED score ranges from 0 (lowest adherence) to 18 (highest adherence) and includes nine components: vegetables, legumes, fruit and nuts, cereals, fresh fish and seafood, olive oil, alcohol, meat and dairy products (from EPIC-Spain dietary questionnaire data).

Table 2. Baseline characteristics of the 40 622 participants in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) according to level of adherence to the relative Mediterranean diet (rMED)

	All cohort (n 40 622)		rMED score*					
	n	%	Low (n 9294)		Medium (n 21 549)		High (n 9779)	
Sociodemographic and lifestyle characteristics†	n	%	n	%	n	%	n	%
Sex, male	15 324	37.7	2941	31.6	7946	36.8	4437	45.0
Age at enrolment (years)								
Mean	49.3		48.2		49.3		50.2	
SD	8.0		8.0		8.0		8.0	
BMI (kg/m ²)								
Mean	28.3		28.1		28.3		28.4	
SD	4.2		4.4		4.2		4.2	
Waist circumference‡								
Men < 102 cm, women < 88 cm	23 400	57.6	5446	58.6	12 365	57.4	5589	57.1
Men ≥ 102 cm, women ≥ 88 cm	17 222	42.4	3848	41.4	9184	42.6	4190	42.9
Educational level								
No formal education	12 372	30.5	2700	29.1	6640	30.8	3032	31.0
Primary school	15 687	38.6	3871	41.7	8321	38.6	3495	35.7
Secondary school	2628	6.5	657	7.1	1365	6.3	606	6.2
Technical or professional training	3347	8.2	732	7.9	1749	8.1	866	8.9
University degree	4677	11.5	981	10.6	2501	11.6	1195	12.2
Not specified§	1911	4.7	353	3.8	973	4.5	585	6.0
Physical activity								
Active	4363	10.7	876	9.4	2277	10.6	1210	12.4
Moderately active	7133	17.6	1504	16.2	3846	17.9	1783	18.2
Moderately inactive	13 509	33.3	3257	35.0	7138	33.1	3114	31.8
Inactive	15 617	38.4	3657	39.4	8288	38.5	3672	37.6
Smoking status								
Never	22 538	55.5	5121	55.1	12 160	56.4	5257	53.8
Former	7183	17.7	1368	14.7	3730	17.3	2085	21.3
Current (< 20 cigarettes/d)	5541	13.6	1335	14.4	2920	13.6	1286	13.2
Current (≥ 20 cigarettes/d)	3838	9.5	1141	12.3	1941	9.0	756	7.7
Not specified§	1522	3.8	329	3.7	798	3.7	395	4.0
Alcohol intake								
0 g/d	15 303	37.7	4185	45.0	8385	38.9	2733	28.0
< 10 g/d	10 686	26.3	2502	26.9	5735	26.6	2449	25.0
≥ 10 and < 20 g/d	4374	10.8	395	4.3	2060	9.6	1919	19.6
≥ 20 and < 40 g/d	4806	11.8	648	7.0	2407	11.2	1751	17.9
≥ 40 g/d	5453	13.4	1564	16.8	2962	13.7	927	9.5
Energy intake (kJ/d)								
Mean	8903		9225		8862		8690	
SD	2780.7		2958.5		2797.8		2530.1	
Carbohydrate intake (g/4184 kJ per d)								
Median	103.7		100.6		103.5		107.0	
SD	17.7		18.8		17.6		16.1	
Protein intake (g/4184 kJ per d)								
Median	47.9		48.0		48.1		47.3	
SD	7.8		8.5		7.8		6.5	
Total fat intake (g/4184 kJ per d)								
Median	39.5		40.9		39.5		38.2	
SD	6.6		7.0		6.6		6.0	
MUFA intake (g/4184 kJ per d)								
Median	17.4		16.4		17.4		18.4	
SD	4.2		4.0		4.3		4.0	
SFA intake (g/4184 kJ per d)								
Median	12.0		13.9		12.0		10.4	
SD	3.5		3.8		3.3		2.8	
PUFA intake (g/4184 kJ per d)								
Median	5.5		6.1		5.6		5.3	
SD	2.7		3.0		2.8		2.2	
MUFA:SFA ratio								
Median	1.4		1.17		1.4		1.8	
SD	0.49		0.4		0.4		0.5	

* rMED low score, 0–6; medium score, 7–10; high score, 11–18.

† All comparisons between rMED groups and tests for trend were statistically significant ($P < 0.001$; χ^2 for categorical variables or the Kruskal–Wallis rank sum test for continuous variables), except for waist circumference ($P = 0.082$).

‡ National Cholesterol Education Program's Adult Treatment Panel III cut-offs.

§ Not specified refers to subjects with missing information on smoking status or number of cigarettes smoked per d.

Table 3. Association between adherence to the relative Mediterranean diet (rMED) and all-cause and cause-specific mortality in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)

(Hazard ratios (HR) and 95 % confidence intervals)

Mortality cause†	rMED score: categorical*						<i>P</i> for trend	rMED score: continuous		
	Low (<i>n</i> 9294)		Medium (<i>n</i> 21 549)		High (<i>n</i> 9779)			2-Unit increase		
	HR	95 % CI	HR	95 % CI	HR	95 % CI		HR	95 % CI	<i>P</i>
All-cause deaths (<i>n</i>)		431		967		457			1855	
Unadjusted HR‡	1	Reference	0.84	0.75, 0.95	0.74	0.65, 0.85	<0.001	0.92	0.89, 0.95	<0.001
Multivariate HR§	1	Reference	0.88	0.79, 0.99	0.79	0.69, 0.91	0.001	0.94	0.90, 0.97	<0.001
CVD deaths (<i>n</i>)		92		213		94			399	
Unadjusted HR‡	1	Reference	0.84	0.65, 1.08	0.67	0.50, 0.90	0.007	0.88	0.82, 0.95	0.001
Multivariate HR§	1	Reference	0.84	0.66, 1.09	0.66	0.49, 0.89	0.006	0.88	0.81, 0.95	<0.001
Cancer deaths (<i>n</i>)		204		486		223			913	
Unadjusted HR‡	1	Reference	0.95	0.80, 1.12	0.85	0.70, 1.04	0.108	0.96	0.92, 1.01	0.135
Multivariate HR§	1	Reference	0.99	0.84, 1.18	0.92	0.75, 1.12	0.414	0.98	0.93, 1.03	0.510
Other deaths (<i>n</i>)		110		207		108			425	
Unadjusted HR‡	1	Reference	0.68	0.54, 0.87	0.66	0.50, 0.86	0.004	0.88	0.82, 0.95	0.001
Multivariate HR§	1	Reference	0.72	0.57, 0.91	0.71	0.54, 0.94	0.022	0.90	0.84, 0.97	0.008

* rMED low score, 0–6; medium score, 7–10; high score, 11–18.

† Cause-specific analysis excludes 118 cases with no information on cause of death.

‡ Cox proportional hazards regression analysis stratified by centre, age and sex.

§ Adjusted for BMI, waist circumference, education level, physical activity, smoking status and intensity and total energy intake.

from the score resulted in the greatest percentage reduction in effect (–27.7, –18.5 and –15.4%, respectively).

The negative association between mortality and the rMED score was similar in the sensitivity analyses (Table 6), where additional adjustments were made for alcohol intake and the presence of diabetes, hypertension or hyperlipidaemia or a

history of CVD, cancer or diabetes at recruitment or after the exclusion of the first 2 years of follow up and mis-reporters of energy intake. The exclusion of subjects with chronic diseases at recruitment (cancer, CVD or diabetes) resulted in a minimal attenuation of the association (HR 0.95; 95 % CI 0.91, 1.00; for a 2-unit increase in rMED score).

Table 4. Association between adherence to the relative Mediterranean diet (rMED) and mortality in the population subgroups in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)

(Hazard ratios (HR) and 95 % confidence intervals)

Cohort subgroup	Cases (<i>n</i>)	Person-years	rMED score: categorical*						<i>P</i> for trend	<i>P</i> for interaction
			Low		Medium		High			
			HR†	95 % CI	HR†	95 % CI	HR†	95 % CI		
Sex										
Male	1121	203 038	1	Reference	0.88	0.75, 1.02	0.76	0.63, 0.90	0.002	
Female	734	340 028	1	Reference	0.89	0.75, 1.06	0.85	0.68, 1.06	0.152	0.512
Age at recruitment										
< 55 years	819	399 653	1	Reference	0.95	0.80, 1.12	0.93	0.76, 1.14	0.492	
> 55 years	1036	143 413	1	Reference	0.83	0.71, 0.97	0.70	0.58, 0.84	<0.001	0.312
Smoking status‡										
Never	791	302 650	1	Reference	0.85	0.71, 1.01	0.73	0.59, 0.91	0.005	
Former	382	95 893	1	Reference	0.93	0.69, 1.23	0.89	0.64, 1.22	0.468	
Current	682	144 217	1	Reference	0.94	0.78, 1.14	0.83	0.66, 1.04	0.113	0.775
BMI										
< 25 kg/m ²	307	118 872	1	Reference	0.90	0.67, 1.20	0.87	0.60, 1.25	0.435	
25–29 kg/m ²	852	260 963	1	Reference	0.81	0.68, 0.96	0.77	0.63, 0.94	0.016	
≥ 30 kg/m ²	696	163 231	1	Reference	0.94	0.78, 1.14	0.79	0.63, 1.00	0.048	0.455
Waist circumference§										
Men < 102 cm, women < 88 cm	900	312 902	1	Reference	0.78	0.66, 0.93	0.78	0.65, 0.95	0.018	
Men ≥ 102 cm, women ≥ 88 cm	955	230 164	1	Reference	0.99	0.84, 1.17	0.81	0.66, 0.99	0.032	0.062

* rMED low score, 0–6; medium score, 7–10; high score, 11–18.

† Cox proportional hazards regression analysis: stratified by centre, age and sex and adjusted for BMI, waist circumference, education level, physical activity, smoking status and intensity and total energy intake.

‡ Stratified models of smoking status exclude twenty-two non-cases with unknown smoking status. Former smokers additionally adjusted for duration of smoking and current smokers additionally adjusted for number of cigarettes smoked per d.

§ Waist circumference cut-offs correspond to the National Cholesterol Education Program's Adult Treatment Panel III criteria.

Table 5. Mortality risk according to tertile intake of each component of the relative Mediterranean diet (rMED) in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) (Mutually adjusted hazard ratios (HR) and 95% confidence intervals)

rMED score component	Tertile (g/8368 kJ (2000 kcal) per d)	Total (n 40 622)			P for trend
		Cases (n 1855)	HR*	95% CI	
Vegetables	< 164.3	687	1	Reference	0.736
	164.3 to < 282.2	592	0.95	0.84, 1.06	
	≥ 282.2	576	1.02	0.90, 1.16	
Fruit and nuts	< 204.4	695	1	Reference	0.250
	204.4 to < 380.0	584	0.91	0.81, 1.02	
	≥ 380.0	576	0.93	0.82, 1.06	
Legumes	< 32.1	611	1	Reference	0.972
	32.1 to < 56.0	548	0.92	0.82, 1.03	
	≥ 56.0	696	1.00	0.89, 1.12	
Fish and seafood	< 35.2	562	1	Reference	0.896
	35.2 to < 64.1	634	1.13	1.00, 1.27	
	≥ 64.1	659	1.02	0.90, 1.15	
Cereals	< 151.8	614	1	Reference	0.132
	151.8 to < 214.0	604	0.92	0.82, 1.03	
	≥ 214.0	637	0.91	0.81, 1.03	
Olive oil	< 13.7	710	1	Reference	0.006
	13.7 to < 24.7	578	0.93	0.83, 1.04	
	≥ 24.7	567	0.85	0.75, 0.96	
Alcohol†	Outside range	1287	1	Reference	0.029
	Inside range	568	0.89	0.80, 0.99	
Dairy	< 198.5	712	1	Reference	0.176
	198.5 to < 352.0	568	1.02	0.90, 1.14	
	≥ 352.0	575	1.08	0.95, 1.24	
Meat	< 96.9	625	1	Reference	0.233
	96.9 to < 136.6	574	0.95	0.85, 1.07	
	≥ 136.6	656	1.08	0.96, 1.22	

* Cox proportional hazards regression analysis: stratified by centre, age and sex and adjusted for BMI, waist circumference, education level, physical activity, smoking status and intensity, total energy intake and mutually adjusted for all rMED score components in the Table.

† Alcohol expressed as g/ethanol per d, not as a function of energy density: Inside range for males: ≥ 10 g to < 50 g, and for females: ≥ 5 g to < 25 g.

Finally, we repeated the analysis with the original MD score developed by Trichopoulou *et al.*⁽²⁰⁾ and found that a high *v.* a low MD score was associated with a 17 (95% CI 5, 27) % reduction in mortality.

Discussion

The role of a Mediterranean dietary pattern on all-cause and cause-specific mortality was assessed within the Spanish adult population. The present results show that high adherence to the MD was related to a significant 21% reduction in all-cause mortality and a 34% reduction in CVD. The beneficial effect of the MD on mortality seemed to be predominantly due to the abundance of olive oil and moderate alcohol intake within this dietary pattern.

The present results are in line with previous findings, where high adherence to a MD was associated with a reduction in mortality by 21% in men and by 20% in women in the USA⁽¹⁷⁾, and by 17%⁽¹⁹⁾ and 25%⁽³⁹⁾ in two elderly European cohorts. Findings from prospective studies in Sweden⁽²¹⁾, Denmark⁽⁴⁰⁾ and even Australia⁽⁴¹⁾ also support the protective effect of a Mediterranean-like diet on risk of dying. Nevertheless, it is also of interest to explore this relationship within exclusively Mediterranean populations, as this is where the closest conformity to a genuine MD is found (including a

habitual and high intake of olive oil), and where the greatest benefits would be presumed to be seen. To date this had only been studied in the Greek population⁽²³⁾, where a 2-unit increase in a 9-unit MD score was associated with a 14% decreased risk of dying. This was comparable with the association observed in our Spanish population, where an increase in the rMED score of a similar proportion (4-unit increase due to a 18-unit scale) was associated with a 12% decreased risk of dying. However, direct comparison of results between studies should be made with caution, considering that the variations in the magnitude of the association are likely to be influenced by many factors besides the study population. One such factor is variation in the MD score due to inclusion of different MD components (i.e. MUFA:SFA ratio instead of olive oil) or the use of energy density of intakes and tertiles as cut-offs instead of sex-specific medians.

In cause-specific mortality analyses it was clear that the MD was beneficial for mortality from CVD. This finding has been reported by several other studies⁽⁹⁾ and the cardioprotective role of the MD is now well documented^(9,42) and mechanisms that mediate this effect are increasingly understood^(12,13,42,43). In previous studies on the MD and cause-specific mortality, the greatest benefit of the MD was consistently seen in mortality from CVD^(17,20,39), in particular from CHD^(20,39).

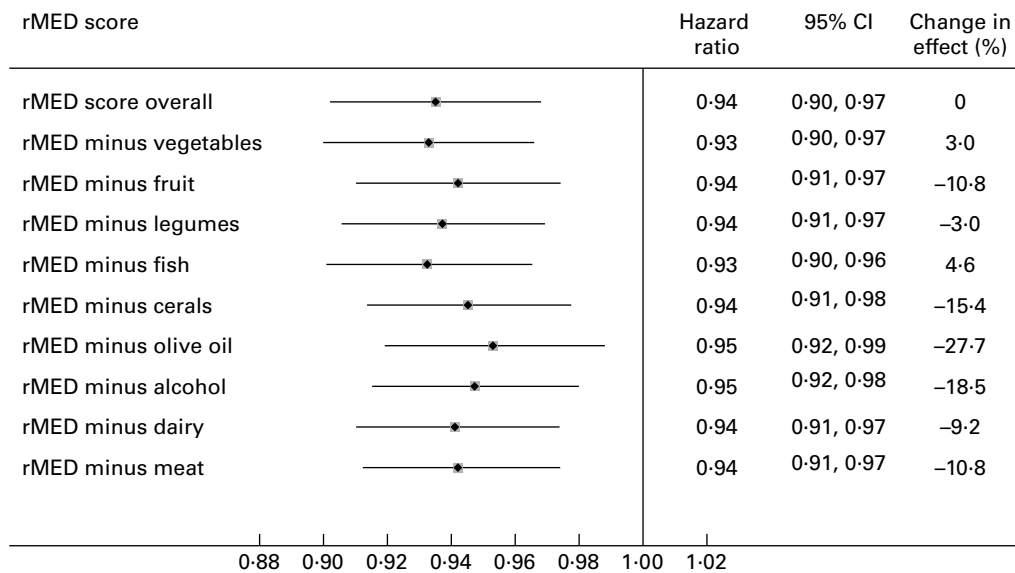


Fig. 1. Association between mortality and a 2-unit increase in the relative Mediterranean diet (rMED) score while alternately subtracting each component.

It is also worth noting that there was an important negative association for death from other causes, which has also been reported previously^(17,39). In the present study this category includes death from other types of chronic diseases, respiratory disorders and other diseases and infections, as well as external causes. It is likely that a broad spectrum of nutritional attributes of the MD^(2,5,7,44), such as its rich source of varied antioxidants, favourable lipid profile, high fibre content and abundance of phytochemicals, could help prevent or improve the prognosis or response to treatment of a wide range of illnesses^(6,45), thereby reducing mortality.

The MD did not appear to reduce mortality from cancer when all cancers were analysed together, a finding common to other studies^(21,39), although not all^(17,20). This is not unexpected considering cancer risk factors vary greatly depending on the cancer site⁽³⁸⁾, and cancer is often described as a constellation of many different diseases, some much less dietary related. Along these lines, we found that there was a stronger borderline significant association between the MD and the more dietary related cancers. This is consistent with evidence

from previous studies that have observed that the MD is related to a reduced risk of stomach, colorectal, breast and upper aerodigestive tract cancers⁽⁴⁶⁾.

The protective effect of the MD on mortality appeared to be predominantly driven by high olive oil and moderate alcohol intake. In terms of olive oil, there was a notable 15% decreased mortality for subjects whose consumption of olive oil was in the highest tertile. Although a previous study in EPIC-Greece found that an increment of 20 g olive oil per d did not significantly reduce mortality, regular olive oil consumption has been shown to decrease mortality in survivors of a myocardial infarction⁽⁴⁷⁾ and reduce the likelihood of having a first acute myocardial infarction⁽⁴⁸⁾. Olive oil is particularly renowned for its cardioprotective properties^(44,49), in line with results from EPIC-Spain where the top tertile of olive oil intake was related to a 18% reduction in CHD incidence⁽³⁰⁾. In addition, the Italian EPICOR Study (Italian cardiovascular section of EPIC) found that the top quartile of olive oil consumption was associated with a 44% reduction in CHD risk in women⁽⁵⁰⁾.

Table 6. Sensitivity analyses for the association between mortality and each 2-unit increase in the relative Mediterranean diet (rMED) in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)

(Hazard ratios (HR) and 95% confidence intervals)

Characteristics	Cases (n)	At risk (n)	rMED score*: continuous		
			HR	95% CI	P
			2-Unit increase		
Additional adjusting by:					
Alcohol intake†	1855	38 767	0.94	0.91, 0.98	0.001
Diabetes, hypertension and hyperlipidaemia or medication for such disorders	1855	38 767	0.93	0.90, 0.97	<0.001
Excluding:					
First 2 years of follow-up	1746	38 767	0.93	0.90, 0.97	<0.001
Subjects with chronic diseases at baseline (cancer, CVD, diabetes)	1068	29 060	0.95	0.91, 1.00	0.035
Mis-reporters of energy according to Goldberg classification ⁽³⁷⁾	1206	25 621	0.94	0.90, 0.98	0.007

* rMED score uses tertiles as cut-offs for nine components (energy density (g/8368 kJ per d)) of: vegetables, legumes, fruit (including nuts and seeds), cereals, fish and seafood, olive oil, alcohol, meat and dairy products. rMED low score, 0–6; medium score, 7–10, high score, 11–18.

† Alcohol intake categorised as: 0 g/d; < 10 g/d; ≥ 10 and < 20 g/d; ≥ 20 and < 40 g/d; ≥ 40 g/d.

Moderate alcohol consumption also contributed considerably to the protective effect of the MD pattern on mortality, and when its effect was analysed separately a moderate compared with a low or high alcohol intake was associated with an 11% decreased risk of dying. Moderate alcohol intake is associated with a decreased risk of mortality, mainly from CHD⁽⁵¹⁾. Accordingly, alcohol was inversely associated with the incidence of CHD in a previous study within this cohort⁽³⁶⁾, and a study assessing the relative importance of each of the MD components on total mortality in Greece showed that moderate alcohol consumption contributed most within the MD score⁽²³⁾. In secondary analyses we found that high alcohol intake significantly increased risk of mortality compared with moderate intake, which is in line with evidence showing that high alcohol intake is detrimental to health, and is a risk factor for some cancers⁽³⁸⁾. However, a low intake of alcohol was not associated with mortality. Nevertheless, the low intake group can be difficult to interpret, as it contains never drinkers, low drinkers and also heavy drinkers who have stopped drinking for health reasons. Despite this, a possible limitation of the rMED score is that equal weight is given to low and high alcohol intake (assigning 0 points to each), even though their effect on health is distinct⁽⁵¹⁾. In future analyses it may be more appropriate to differentiate the scoring of abstainers or low alcohol drinkers from heavy drinkers.

In the present study the highest *v.* the lowest tertile of intake of fruit and vegetables was not associated with mortality. However, in a previous study in this cohort⁽²⁴⁾, the highest *v.* the lowest quartile of fresh fruit, root vegetables and fruiting vegetables were all associated with a significant reduction in overall mortality, suggesting that a significant protective effect for some components might only be seen when comparing more extreme levels of intake or subgroups of these food groups.

Although it is useful to understand the relative importance of each of the components of the MD and the possible biological mechanisms involved, it is important to highlight that no one component was wholly responsible for the observed association. The overall Mediterranean dietary pattern conferred the greatest benefit, as this combines the health effects of many food groups and the biological interactions that take place between them⁽¹⁶⁾. This is also one of the advantages of using dietary indices such as the rMED score to study the effect of this dietary pattern on health outcomes. Other strengths of the present study include its prospective design with a long follow-up period and sufficient number of deaths to enable stratification by cause of death and by cohort subgroups. In addition, a large number of plausible confounders and effect modifiers were taken into account in the analyses.

There are some study limitations that deserve discussion. Reverse causality may exist, as subjects with CVD or cancer or with early symptoms of these diseases may have already altered their diet or lifestyle as a consequence. However, adjusting for the presence of diabetes, hypertension or hyperlipidaemia or excluding cases diagnosed during the first 2 years of follow-up or subjects with CVD, cancer or diabetes

at baseline, did not notably alter the association. Another limitation is from dietary measurement error; however, a validated interviewer-administered diet history questionnaire was used, which has fewer measurement errors than FFQ⁽⁵²⁾, and also covered over 600 food and recipe items^(27,28). Reporting bias is a potential limitation, and is especially prevalent in obese individuals who commonly report implausibly low energy intakes⁽⁵³⁾. Therefore, we applied more stringent criteria using Goldberg cut-offs⁽³⁷⁾ to identify subjects with implausible dietary intakes. However, when these subjects were excluded in sensitivity analyses the association between the MD and mortality did not change. Since close adherence to the MD was linked to a generally healthier lifestyle (i.e. doing more physical activity and giving up smoking) and also to a higher education level, there could be residual confounding from lifestyle characteristics or certain medication use (i.e. aspirin) that was not ascertained, or from variables adjusted for but measured imprecisely. However, since the key known confounders were taken into account, we assume this could only have a minimal impact on the results.

This large prospective study supports the important role that an olive oil-rich MD plays on reducing mortality in Mediterranean populations, and the extent of the beneficial effect is in line with previous research in Mediterranean countries. The present results also confirm that the MD is associated with a significant and substantial reduction in CVD mortality and has beneficial effects on selected cancers that are potentially more diet related. These health benefits underscore the MD's importance as a cultural heritage of humanity.

Acknowledgements

The present study was supported by the European Commission (DG-SANCO), the International Agency for Research on Cancer (IARC), the Health Research Funds (FIS) of the Spanish Ministry of Health (grant no. Exp P10710130) from the 'Instituto de Salud Carlos III'; the Spanish Regional Governments of Andalucía, Asturias, Basque Country, Murcia (no. 6236) and Navarra and the Catalan Institute of Oncology, and Red Temática de Investigación Cooperativa en Cáncer (RTICC) (grant no. C03/10, R06/0020).

All authors have contributed towards the different phases of manuscript preparation (the study design, interpretation of the results and drafting of the manuscript or revising it critically for important intellectual content) and also approved the final submitted version. In particular, G. B. was responsible for the statistical analysis and N. T. for the competing risk analysis. G. B. was also responsible for drafting the manuscript and C. A. G. is the guarantor.

All authors declare that there are no conflicts of interest in relation to this article.

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