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Modified Mediterranean diet and survival after myocardial infarction: the EPIC-Elderly study

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Abstract Mediterranean diet is associated with lower incidence of coronary heart disease, and two randomised trials indicated that it improves prognosis of coronary patients. These trials, however, relied on a total of 100 deaths and evaluated designer diets in the clinical context. We have evaluated the association of adherence to the modified Mediterranean diet, in which unsaturates were substituted for monounsaturates, with survival among elderly with previous myocardial infarction within the European Prospective Investigation into Cancer and nutrition (EPIC) study. As of December 2003, after a median follow-up of 6.7 years, 2671 EPIC participants from nine countries were 60 years or older and had prevalent myocardial infarction but no stroke or cancer at enrolment,

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complete information on dietary intakes and important covariates and known survival status. Adherence to the modified Mediterranean diet was assessed through a 10-unit-scale. Mortality ratio in relation to modified Mediterranean diet was estimated through Cox regression controlling for possible confounding. Increased adherence to modified Mediterranean diet by two units was associated with 18% lower overall mortality rate (95% confidence interval 7–27%, fixed effects model). There was no significant heterogeneity by sex, age at enrolment, or country, although the association tended to be less evident among northern Europeans. Associations between food groups contributing to the modified Mediterranean diet and mortality were generally weak. A diet inspired by the Mediterranean pattern that can be easily adopted by Western populations is associated with substantial reduction of total mortality of coronary patients in the community.

Keywords Mediterranean diet · Survival · Elderly · Myocardial infarction

Abbreviations

EPIC	European Investigation into Cancer and nutrition
NA	Not Applicable
ACE	Angiotensin-Converting Enzyme

Introduction

Ancel Keys and his colleagues [1] were the first to provide evidence that Mediterranean diet conveyed protection against coronary heart disease on the basis of mostly ecological evidence. Since 1995, the association of Mediterranean diet with coronary mortality and total mortality has been examined in several cohort studies and the results were generally consistent in pointing to a beneficial effect of this diet [2–8]. In these studies the Mediterranean diet was operationalised through simple scores that capture the essential characteristics of this dietary pattern. Because the underlying pathobiological processes in coronary heart disease are likely to be similar before and after the occurrence of the first non-fatal coronary events, the Mediterranean diet has been evaluated as a potentially useful adjunct in the management of coronary patients.

Two major randomized controlled trials reported that dietary regiments reflecting, or inspired by, the Mediterranean diet sharply improve the prognosis of coronary patients [9–11]. The Lyon study [9, 10] has been criticized [12] because the baseline diet was only assessed in the experimental group whereas nutrient intake in the control group was only assessed at the conclusion of the study. Moreover, dietary data were reported for only a minority of randomised subjects whereas the numbers of observed endpoints were generally low. The Singh study on the other hand has been criticized for the possible violations of the integrity of the data [13, 14]. These major studies have used designer diets emphasizing α-linolenic acid in clinical contexts. Recently, it was reported that adherence to Mediterranean diet is associated with significantly better prognosis of subjects who participated in a population-based cohort study in Greece and who at enrolment reported that they had medically diagnosed coronary heart

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disease [15]. That study was undertaken within the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC).

Our intention in the present paper was to see whether a Mediterranean dietary pattern is inversely associated with fatality among European elders with coronary infarct. We have thus evaluated the association of a Mediterranean-inspired diet [8] with long-term mortality of subjects who have survived coronary heart attack(s), volunteered to participate in the European-wide EPIC study and were 60 years or older at enrolment (EPIC-Elderly).

Methods

Recruitment

The European Prospective Investigation into Cancer and Nutrition is a multi-centre, prospective cohort study with the purpose of investigating the role of biological, dietary, lifestyle, and environmental factors in the etiology of cancer and other chronic diseases. Between 1992 and 2000, a total of 519 978, apparently healthy volunteers were recruited in 23 centres from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the UK). Sample selection criteria and methodology for the EPIC study have been reported in detail elsewhere [16]. The study protocol has been approved by ethical committees at all the participating centres. All participants signed informed consent forms before enrolment. All procedures have been in line with the Helsinki declaration for human rights.

Data for 100 442 participants, who were 60 years or older at recruitment were included in the EPIC-Elderly project. EPIC-Elderly was aimed at identifying the dietary patterns across European elders and examining their association with mortality. Subjects from all EPIC countries are included in the EPIC-Elderly database with the exception of Norway, the cohort of which is relatively young (all of the Norwegians in the EPIC cohort were younger than 60 years at enrolment).

Data on diet

Information on foods and beverages consumed during the year preceding enrolment was collected with the use of instruments that had been developed and validated within each center [17]. The assessment tools included self- or interviewer-administered food frequency or quantitative dietary questionnaires, as well as, in some centres, an additional 7- or 14- day record on meals consumed.

Nutrient intakes were calculated with the use of food composition databases specific to each country [18]. For the analysis, 14 inclusive food groups and nutrients were considered: potatoes, vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, fish and seafood, eggs, sugar and confectionary, non-alcoholic beverages, monounsaturated lipids, polyunsaturated lipids and saturated lipids. There is no overlap among the different food groups except for type of lipids. For each participant, g day^{-1} of intake of each of the indicated foods or nutrients as well as total energy intake (in kJ day^{-1}), were calculated. Alcohol consumption was expressed in grams of ethanol per day.

Modified Mediterranean diet scale

A scale indicating the degree of adherence to the Mediterranean diet has been constructed by Trichopoulou and colleagues [2], and has been subsequently revised [5, 8]. Values of zero or one were assigned to each of nine indicated components using as cut-offs the overall sex specific medians among the study participants who did not report at enrolment that they had been diagnosed with coronary heart disease, stroke or any form of cancer. Specifically, persons whose consumption of presumed beneficial components (vegetables, legumes, fruits and nuts, cereal, fish) was below the median consumption were assigned a value of zero, whereas for individuals with consumptions above the median a value of one was given. In contrast, persons with, below the median consumption of presumed detrimental components (meat and dairy products) were assigned a value of one and a value of zero otherwise. For ethanol, a value of one was given to men consuming quantities of ethanol from 10 g day^{-1} to less than 50 g day^{-1} and 0 otherwise, whereas for women the corresponding cut-offs were 5 g and 25 g day^{-1}—cut-off values for ethanol were chosen on the basis of the reported U-shape association of alcohol intake with coronary mortality [19, 20]. For lipid intake, the ratio of unsaturates (sum of monounsaturates and polyunsaturates) to saturates was constructed, higher values presumed to be beneficial. Thus, although there are nine components in the Mediterranean diet, the total modified Mediterranean diet score (estimated as the sum of the above indicated 0 s and 1 s) has a 10-point range , taking values from zero (none of the components takes the value of 1, minimal adherence) to nine (maximal adherence).

Lifestyle and medical variables

Data on a number of lifestyle and health variables were also recorded with the use of a pre-coded questionnaire which included occupational and leisure time physical activities, educational achievement, history of illnesses and history of smoking. For leisure, time spent on each of a number of activities (in hours per week) was multiplied by an energy cost coefficient to convert hours/week in kJ [21]; all products were then summed to produce a score of daily physical activity at leisure expressed in sex- and centre-specific tertiles.

Anthropometric measurements (height, weight, waist and hip circumference) were taken in all EPIC centres using similar, standardized procedures except for France and Oxford. In the latter centres self-reported values were recorded instead, with actual measurements being obtained for a fraction of the participants. Body mass index was calculated as the ratio of weight in kilograms divided by the square of the height in meters—for participants with self reported weight and height these values were used in the respective calculations.

Regarding medical history, participants were asked whether they had been diagnosed by a medical doctor with myocardial infarction, angina pectoris without myocardial infarction, cancer, stroke or diabetes mellitus. All individuals were also asked whether they were taking drugs for hypertension and/or hypercholesterolaemia.

Follow-up

Information on vital status of EPIC participants is obtained by population mortality registries (most centres), or by active follow-up (France, Germany, Greece). As of December 2003, from the initial 100 442 participants of the EPIC-Elderly cohort with reasonable energy intakes (those in the top and bottom 1% of the ratio of energy intake to estimated energy requirement were excluded), 6090 reported, at enrolment, a previous diagnosis of coronary heart disease (myocardial infarction and/or angina pectoris), with or without diabetes mellitus but no stroke or cancer. For 6 of the 6090 participants, vital status or date of death had not been ascertained. In addition, for 877 of the 6090 study participants, information was missing for one or more of the sociodemographic, medical, dietary, somatometric, lifestyle or medication variables used in the present investigation. From the remaining 5207 coronary participants with or without diabetes mellitus but no stroke or cancer, for which vital status had been ascertained and for which all the required information was available, the 2671 participants who reported at enrolment a previous diagnosis of myocardial infarction with or without angina pectoris, were considered in this study, whereas the remaining 2536 individuals with reported angina pectoris but no infarction were also excluded from further analysis.

Statistical analysis

All analyses were performed using the STATA statistical software. Descriptive statistical analysis was performed through cross tabulations. Dietary variables, as well as, energy intake were presented as means and standard deviations.

Among the study participants with reported medical diagnosis of myocardial infarction at enrolment, the association between the studied food groups or nutrients and mortality, as well as between the modified Mediterranean diet score and mortality (fatality) was assessed through proportional hazards models, always adjusting for sex (males, females) and age (60–64, 65–69, ≥ 70, categorically). In addition, adjustment was done for treatment for hypertension (yes, no), treatment for hypercholesterolaemia (yes, no), diabetes mellitus at enrolment (yes, no), educational achievement (none/primary school, technical school, secondary school, university degree, categorically), smoking status (never, former, 1–10 cigarettes per day, 11–20 cigarettes per day, 21–30 cigarettes per day, ≥31 cigarettes per day, ordered), body mass index (quintiles, ordered), waist to hip ratio (quintiles, ordered), physical activity at current work at enrolment (retired or sedentary occupation, non-sedentary occupation, categorically), physical activity score at leisure (in centre and sex specific tertiles, categorically) and total energy intake (quintiles, ordered). Eggs, potatoes and sugar and confectionary are not part of the modified Mediterranean diet but, in analyses which investigated the impact of the modified Mediterranean diet score on mortality, they were controlled for as continuous variables, to accommodate possible confounding by these nutritional variables.

In all proportional hazards (Cox) regression models, length of follow-up was the primary time variable and death from any cause was the focal outcome event. Subjects who were alive as of the date of last follow-up or were lost from follow-up were considered as censored. The proportionality assumption was checked with the log-log plots. Separate proportional hazard models were used for overall and for country-specific analyses as well as for analyses excluding subjects who died within the first six months of follow up or the Greek subjects. Models were stratified by country and, for the country specific analyses, by centre.

Results

In comparison to participants in the EPIC-Elderly cohort who had at enrolment no prevalent cardiovascular disease or cancer, those with prevalent myocardial infarction and also no stroke or cancer, had a mortality ratio, adjusted for

Table 1 Distribution of 2671 EPIC-Elderly participants with previous myocardial infarction at enrolment by country, sex and age at enrolment

Country	Males, *n*				Females, *n*			
	60–64	65–69	≥70	Total	60–64	65–69	≥70	Total
Denmark	314	18	0	332	96	5	0	101
France[a]	NA	NA	NA	NA	55	34	0	89
Germany	267	30	0	297	77	10	1	88
Greece	61	97	87	245	21	27	32	80
Italy	59	4	1	64	22	5	3	30
Netherlands	19	1	0	20	68	74	0	142
Spain	33	5	0	38	13	2	0	15
Sweden	219	104	100	423	60	33	39	132
UK	112	135	167	414	33	49	79	161
Total	1084	394	355	1833	445	239	154	838

NA: Not applicable

[a] Cohort containing only women

age and sex, of 2.56 (95% confidence interval 2.33–2.83). All subsequent analyses relied exclusively on 2671 EPIC-Elderly participants who, at enrolment, reported medically confirmed myocardial infarction with or without angina pectoris, but no prevalent cancer or stroke. Table 1 shows the distribution of these participants by country, sex and age at enrolment. In the French cohort only women were recruited. Most elderly with prevalent myocardial infarction were 60–64 years at enrolment but there are considerable differences among cohorts with respect to mean age at enrolment (with the UK and Greek EPIC-Elderly cohorts being older than the corresponding cohorts from the other countries). Among the 2671 participants with prevalent myocardial infarction 786 (29%) reported that they had also angina pectoris.

Survival status at the end of a median follow-up period of 6.7 years (range from 0.008 years, a study participant who died 3 days after enrolment, to 11.27 years) was ascertained for the 2671 study participants. Table 2 shows accumulated person-years, deaths and death rates standardized for age (using as standard the overall study population of the 2671 EPIC-Elderly participants) by baseline sociodemographic, somatometric and selected lifestyle and medical variables. The mortality patterns in this table are largely in line with expectations even though the data are not mutually adjusted except for age. Thus, mortality is higher among men than among women, it increases with age, it is higher among smokers than among non smokers, it declines with educational advancement, it is higher among those with higher waist-to-hip ratio (particularly among men), tends to decline with increasing level of physical activity and it is lowest among consumers of modest quantities of alcoholic beverages. With respect to body mass index the data do not conform to prediction possibly because this is a survivor cohort and because this variable should be judged in conjunction with waist-to-hip ratio. Concurrent prevalence of diabetes mellitus, hypertension or hyperlipidaemia increase mortality of subjects with previous myocardial infarction but only among men.

Table 3 shows the distribution of 2671 participants with diagnosed myocardial infarction at enrolment and of deaths among them during the follow-up period, by sex and major categories of the modified Mediterranean diet score. The distribution of subjects according to the score differs among countries, with participants from Greece, Italy and Spain being over-represented in its highest category. In the UK the modified Mediterranean diet score tends to be also relatively high because one of the component cohorts in this country is composed of vegetarians. In these crude data, un-stratified cumulative mortality across the three categories of increasing modified Mediterranean diet score is 0.23, 0.24, 0.13 among men and 0.14, 0.12 and 0.09 among women.

Table 4 shows the mean daily intakes and associated standard deviations of 11 food groups (in g day^{-1}), of lipids by major type (also in g day^{-1}), of important ratios of lipid intake, and of total energy intake (in kJ day^{-1}) among the study participants with myocardial infarction at enrolment. Table 4 also shows mortality ratios per increments in the intake of the indicated dietary variables approximately equal to the average of the standard deviations among males and females. Mortality rate ratios are not mutually adjusted but they are adjusted for all the non-nutritional variables shown in Table 2, as well as, for country, sex, alcohol intake and total energy intake, except where energy intake is evaluated (last line of Table 4) when there is really no point in also adjusting for energy intake. Most of the generally weak associations in Table 4 are expected although only the associations of cereals (inverse), fruits and nuts (inverse), the ratio of monounsaturated to saturated lipids

Table 2 Number of deaths from any cause, accumulated person years and age-adjusted death rates among 2671 EPIC-Elderly participants with myocardial infarction at enrolment by sex, age, sociodemographic, anthropometric and selected lifestyle and medical variables

Variable	Males			Females		
	Deaths, *n*	Accumulated person years	Age adjusted death rates[a] (per 1000 person years)	Deaths, *n*	Accumulated person years	Age adjusted death rates[a] (per 1000 person years)
Age						
60–<65	188	7144.6	26.3	38	3218.4	11.8
65–<70	75	2407.0	31.2	31	1724.0	18.0
≥70	105	1880.7	55.8	30	908.3	33.0
Smoking status						
Never	49	2355.5	20.6	40	3031.0	11.2
Former	232	7345.6	31.2	39	2051.4	17.6
Current	87	1731.2	52.3	20	768.3	23.6
Educational achievement						
None or primary school	200	5415.3	36.5	54	2903.7	18.1
Technical school	79	2737.5	28.7	18	1267.9	14.0
Secondary school	29	1112.8	25.1	13	913.1	14.7
University degree	60	2166.7	30.6	14	766.0	16.8
Body mass index (kg/m^2)						
≤25	106	2643.9	39.1	42	2094.0	19.7
>25–<30	180	6285.5	28.6	29	2303.0	12.2
≥30	82	2502.8	32.5	28	1453.7	19.9
Waist to hip ratio[b]						
≤0.90	64	2035.8	30.1	75	5071.4	14.5
>0.90–<0.95	97	3254.8	29.9	17	508.9	33.2
≥0.95	207	6141.7	33.9	7	270.4	32.4
Physical activity at work						
Retired or sedentary occupation	321	9690.0	32.2	95	5311.8	17.2
Non sedentary occupation	47	1742.3	20.4	4	538.9	5.3
Physical activity at leisure[c]						
First third (low)	108	3178.7	33.9	43	1956.7	22.3
Second third	123	3616.2	34.4	36	1723.2	20.4
Last third (high)	137	4637.4	29.5	20	2170.8	9.3
Alcohol intake (g/day)						
Low[d]	198	5853.8	32.1	72	3811.9	18.6
Moderate	141	4937.6	29.6	24	1730.0	13.9
High[e]	29	640.9	47.8	3	308.8	33.0
Diabetes mellitus						
Absent	305	10 219.2	29.6	85	4950.9	16.7
Present	63	1213.0	53.7	14	899.8	16.5
Drugs for hypertension (at enrolment)						
No	256	8139.0	30.6	63	3871.8	15.7
Yes	112	3293.3	34.5	36	1978.9	18.5
Drugs for hyperlipidaemia (at enrolment)						
No	314	9695.4	31.6	92	5248.3	17.0
Yes	54	1736.8	44.1	7	602.4	15.4

[a] With direct adjustment, using study population (combined men and women) as standard, except for age

[b] Values for some participants were imputed from a linear regression model, with weight and height as independent variables and waist to hip ratio as dependent variable

[c] Sex and centre specific tertiles of scores for physical activity at leisure time

[d] Men < 10 g; women < 5 g

[e] Men > 50 g; women > 25 g

Table 3 Distribution of 2671 EPIC-Elderly participants with myocardial infarction at enrolment and of 467 deaths by sex, country and score in the modified Mediterranean diet scale

Country	Males (deaths, *n*/participants, *n*)				Females (deaths, *n*/participants, *n*)			
	Modified Mediterranean diet score				Modified Mediterranean diet score			
	0–3	4–5	6–9	Total	0–3	4–5	6–9	Total
Denmark	43/151	33/124	9/57	85/332	6/36	6/50	1/15	13/101
France[a]	NA	NA	NA	NA	1/15	0/41	1/33	2/89
Germany	16/106	29/144	5/47	50/297	4/56	1/24	0/8	5/88
Greece	0/0	14/51	16/194	30/245	0/2	2/23	5/55	7/80
Italy	1/2	1/19	3/43	5/64	1/7	0/10	0/13	1/30
Netherlands	4/11	2/9	0/0	6/20	16/106	5/32	0/4	21/142
Spain	0/3	1/9	9/26	10/38	0/0	0/7	0/8	0/15
Sweden	35/201	31/177	3/45	69/423	9/72	5/47	0/13	14/132
UK	24/63	58/168	31/183	113/414	9/37	17/75	10/49	36/161
Total	123/537	169/701	76/595	368/1833	46/331	36/309	17/198	99/838

NA Not applicable

[a] Cohort containing only women

Table 4 Mean and Standard Deviation of daily intake of food groups and associated mortality ratios (95% confidence intervals) for the chosen increments

Food group intake (g/day)	Males, *n*		Females, *n*			
	Mean (g/day)	Standard Deviation (g/day)	Mean (g/day)	Standard Deviation (g/day)	Chosen increment[a] (g/day)	Mortality rate ratio[b] (95% confidence interval)
Potatoes	127.6	95.3	92.9	60.7	78	1.03 (0.94–1.12)
Vegetables	210.3	159.3	209.0	140.6	150	0.99 (0.86–1.13)
Legumes	11.1	17.5	9.7	14.5	16	0.97 (0.87–1.08)
Fruits and nuts	233.5	188.7	252.3	172.8	181	0.88 (0.78–0.99)
Dairy products	340.6	251.4	354.3	235.0	243	1.10 (1.00–1.21)
Cereals	218.6	111.0	176.2	96.3	104	0.85 (0.77–0.95)
Meat	113.8	63.6	87.2	50.8	57	1.04 (0.95–1.14)
Fish	42.8	36.0	35.2	34.7	35	1.02 (0.92–1.13)
Eggs	13.9	15.4	13.3	14.2	15	1.05 (0.96–1.15)
Confectionery	40.3	36.3	32.6	28.6	32	1.01 (0.92–1.11)
Non-alcoholic beverages	1143.4	734.8	1263.6	789.6	762	1.10 (0.97–1.25)
Monounsaturated lipids (all sources)	31.2	13.3	25.1	11.6	12	1.02 (0.89–1.17)
Polyunsaturated lipids (all sources)	14.7	6.5	12.7	5.7	6	1.04 (0.94–1.15)
Saturated lipids (all sources)	30.3	13.2	25.8	11.1	12	1.12 (1.00–1.25)
Ratio of monounsaturated lipids to saturated lipids	1.1	0.5	1.0	0.4	0.5	0.79 (0.64–0.97)
Ratio of unsaturated lipids to saturated lipids	1.6	0.6	1.6	0.5	0.6	0.89 (0.77–1.03)
Energy intake in kJ	9083.1	2469.7	7501.5	2135.1	2302	1.01 (0.92–1.10)

[a] An arbitrarily-chosen number around the average of the within sex standard deviation

[b] Stratified by country and adjusted for sex (males, females), age (60–64 years, 65–69 years, ≥70 years), diagnosis of diabetes mellitus at baseline (yes, no), previous treatment for hypertension (yes, no), previous treatment for hypercholesterolemia (yes, no), waist to hip ratio (in ordered quintiles), body mass index (in ordered quintiles), educational achievement (none/primary school, technical school, secondary school, university degree), smoking status (never, former and 4 categories of current smoker: 1–10 cigarettes per day, 11–20 cigarettes per day, 21–30 cigarettes per day, ≥31 cigarettes per day, ordered), physical activity at current work (retired or sedentary occupation, non sedentary occupation), physical activity score at leisure (in centre and sex specific tertiles, categorically), alcohol intake (low, moderate, high as defined in Table 2, categorically) and total energy intake (in ordered quintiles) except for energy intake. Not mutually adjusted

Table 5 Mortality ratios and 95% confidence intervals associated with a 2-unit increment in modified Mediterranean diet score

Over all countries[b]	Crude		Age- and sex- adjusted		Fully adjusted [a]	
	Mortality ratio	95% Confidence Interval	Mortality ratio	95% Confidence Interval	Mortality ratio	95% Confidence Interval
Fixed	0.78	(0.69–0.88)	0.77	(0.68–0.87)	0.82	(0.73–0.93)
Random	0.77*	(0.68–0.87)	0.77 **	(0.68–0.87)	0.81***	(0.70–0.95)
Analyses by country[c]						
Denmark (2 centres)	0.78	(0.61–1.00)	0.79	(0.62–1.01)	0.95	(0.72–1.24)
France (4 centres)	0.41	(0.06–2.72)	0.46	(0.07–2.99)	0.54 [d]	(0.22–1.31)
Germany (2 centres)	0.97	(0.68–1.38)	0.86	(0.59–1.25)	0.92	(0.62–1.37)
Greece (1 centre)	0.41	(0.23–0.72)	0.37	(0.20–0.68)	0.44	(0.22–0.87)
Italy (5 centres)	0.53	(0.18–1.54)	0.42	(0.11–1.52)	0.54[d]	(0.22–1.31)
Netherlands (2 centres)	0.77	(0.42–1.40)	0.77	(0.43–1.40)	0.67	(0.35–1.30)
Spain (5 centres)	0.93	(0.34–2.55)	1.07	(0.38–3.00)	0.54 [d]	(0.22–1.31)
Sweden (2 centres)	0.86	(0.65–1.13)	0.86	(0.65–1.14)	0.93	(0.69–1.25)
UK (2 centres)	0.74	(0.61–0.90)	0.76	(0.62–0.92)	0.74	(0.60–0.91)

[a] Adjusted for sex (males, females), age (60–64 years, 65–69 years, ≥70 years), diagnosis of diabetes mellitus at baseline (yes, no), previous treatment for hypertension (yes, no), previous treatment for hypercholesterolemia (yes, no), waist to hip ratio (in ordered quintiles), body mass index (in ordered quintiles), educational achievement (none/primary school, technical school, secondary school, university degree), smoking status (never, former and 4 categories of current smoker: 1–10 cigarettes per day, 11–20 cigarettes per day, 21–30 cigarettes per day, ≥31 cigarettes per day, considered as an ordered variable), physical activity at current work (retired or sedentary occupation, non sedentary occupation), physical activity score at leisure (in centre and sex specific tertiles, categorically), consumption of potatoes (continuously), consumption of eggs (continuously), consumption of sugar and confectionary and total energy intake (in ordered quintiles)

[b] Stratified by country

[c] Stratified by centre within country, fixed models

[d] Estimated through the fully adjusted Cox regression model, stratified by centre within country with data from Italy, France and Spain combined due to the small number of deaths in these countries (6, 2 and 10 respectively) *P-value for heterogeneity = 0.414

** P-value for heterogeneity = 0.433

*** P-value for heterogeneity = 0.298

(inverse), saturated lipids (positive) and dairy products (positive) with mortality are statistically significant.

Table 5 shows adjusted mortality ratios associated with a two-unit increment in the modified Mediterranean diet score, overall and by country. Cox regression (fixed and random effects) models stratified by country were used to assess the overall associations of the modified Mediterranean diet score with mortality, whereas in analyses by country stratification by center and fixed effect models were used. France, Italy and Spain were combined for the fully adjusted analysis (last column of Table 5) due to the very small number of deaths in the indicated countries, most of which have occurred among those who, at enrolment, were between 60 and 65 years old. Increased adherence to modified Mediterranean diet by two units among persons with prevalent myocardial infarction at enrolment is associated with a significant 18% reduction of mortality in fixed effects model or 19% reduction of mortality in random effects model. No statistically significant evidence of heterogeneity exists among countries in the association of the modified Mediterranean diet score with overall mortality, although the association is apparently weaker in Denmark, Germany and Sweden. Moreover there was no significant evidence of heterogeneity by sex ($P = 0.34$) or age at enrolment ($P = 0.66$). Controlling for exact age at enrolment as well as for the other variables indicated in Table 5 mortality ratios (95% confidence intervals) were: for the 1529 participants who were 60–64 years old at enrolment, 0.88 (0.73–1.05), for the 633 who were 65–69 years old, 0.80 (0.61–1.04) and for the 509 who were 70 years or older at recruitment 0.75 (0.59–0.95).

Exclusion of 21 deaths that occurred during the first 6 months of follow-up had little effect on the point estimates of the mortality ratio. Thus, point estimate for the fully adjusted mortality ratio in the fixed effects model declined from 0.82 to 0.80 (95% confidence interval 0.71–0.91) whereas in the random effects model the point estimate for the fully adjusted mortality ratio declined from 0.81 to 0.79 (95% confidence interval 0.67–0.93). We have also run the fixed and random effects models after exclusion of both deaths during the first 6 months and data from Greece in order to rule out the possibility that the overall point estimate for the mortality ratio was driven by the very low mortality ratio that was estimated for the Greek cohort (mortality ratio = 0.44). The point estimate for the mortality ratio associated with an increase by two-units of the modified Mediterranean Diet Score was 0.82 (95% confidence interval 0.73–0.94) for the fixed and 0.81 (95% confidence interval 0.71–0.93) for the random effects model.

Drugs routinely taken by survivors from a myocardial infarction may be related to prognosis but in order to act as confounding variables they should also be related to the modified Mediterranean diet score. We did not have coded information on drugs used in all centers but we have explored whether such relations exist in the centre where the strongest association between the score and mortality was evident, that is the Greek centre. No significant difference in the mean value of the modified Mediterranean diet score was evident between users and non users of any of the 10 most frequently used medications with the exception of glibenclamide an anti-diabetic drug the takers of which had mean score 5.57 whereas the non takers had a mean score of 6.35. Controlling for glibenclamide for the Greek data had no effect in the point estimate or the confidence intervals in Table 5.

Discussion

We have studied a large sample of individuals, living in 9 European countries, who, at enrolment, were 60 years of age or older, had reported that they had been diagnosed as having had myocardial infarction but no cancer or stroke and were prospectively followed-up for a mean period of 6.7 years. We have restricted the analyses to European volunteers who, at enrolment were 60 years old or more for two reasons: Firstly, the association of Mediterranean diet with mortality has been more evident among older than among younger persons [5], possibly because cumulative effects of diet are necessary for the manifestation of beneficial or detrimental effects, or because younger persons are more receptive to contemporary changes in dietary patterns (more extreme misclassification). Secondly, there are published data relying on the EPIC-Elderly cohort assessing the association of modified Mediterranean diet with mortality among participants 60 years old or more at enrolment [8] and these data could be, and have been used for comparative purposes, as indicated below.

During a total of 17,283 person years, 467 deaths occurred corresponding to an age and sex adjusted mortality ratio of slightly more than 2.5-fold. Closer adherence to a modified Mediterranean diet, relying on plant foods and unsaturated lipids was associated with a statistically significant reduction of overall mortality. The lack of distinction between low-fat and whole dairy, as well as, between whole-grain and refined cereals is a data-imposed limitation in the definition of the Mediterranean diet score but this is likely to lead to underestimation of the real effect. Our results were generally more evident in the South compared to North Europe probably because in the former southern countries the modified Mediterranean diet closely approximates the Mediterranean diet due to the high consumption of olive oil. No statistically significant evidence of heterogeneity was evident among countries with respect to the association of the modified Mediterranean diet with overall mortality. As also noted in other studies in which the association of a nutritional score with a health outcome was found to be more discriminatory than each of its components [5], advantages of an a-priori score are that it captures the extremes of the nutritional exposures of interest, pre-empts mutual nutritional confounding without facing colinearity problems and captures possible synergistic effects among the nutritional variables [22, 23].

Given the continuous nature of the pathobiological processes in coronary heart disease it is not inappropriate to integrate the evidence concerning the relation of variable forms of Mediterranean diet with occurrence of the disease among apparently healthy individuals [1, 5–7] with that concerning the relation of this diet with the prognosis of coronary heart disease [9–11, 15]. In fact, since coronary mortality is a large fraction of total mortality, studies evaluating the association of various forms of Mediterranean diet with total mortality are also relevant [2–5, 7, 8]. The overall evidence is quite consistent in pointing to Mediterranean diet as an important tool for both the prevention and the management of coronary heart disease.

Nevertheless, a number of questions remain. Is the Mediterranean diet equally important for the prevention of coronary heart disease as for the management of it? Is α-linolenic acid the central beneficial component of the Mediterranean diet as proposed by the authors of a major randomised trial [9, 10] or can alternative variants of the Mediterranean diet (that is, any diet with high intake of fruits, vegetables, nuts, legumes, fish, and a good unsaturated/saturated ratio but in which olive oil is not present), convey similar protection? If the latter is true, does the general nutritional environment within which choices are made (e.g. Greece vs. Sweden) matter? Finally, how do the results of randomised dietary interventions compare with those of observational studies evaluating the Mediterranean diet in relation to prognosis of coronary heart disease?

With respect to the first question there is a possible comparison of the effectiveness of the modified Mediterranean diet in reducing total mortality and mortality among coronary patients. In the EPIC-Elderly study a modified Mediterranean diet, identical to that evaluated in the present paper, was evaluated in relation to overall survival of study participants who, at enrolment, were free from coronary heart disease (as well as cancer and stroke) [8]. In that study, a two-unit increment in the modified Mediterranean diet score was associated with an 8% reduction in total mortality [8]. In the present study the reduction of mortality among coronary patients was 18% but the mortality background was twice as high as that of persons without coronary heart disease (the mortality ratio of coronary patients in comparison to apparently healthy individuals was, as indicated earlier 2.54). Thus, it appears that the association between Mediterranean diet and risk of death is about 5 times stronger, in absolute terms, among coronary patients than among apparently healthy individuals ((2.5x0.18) vs. 0.08).

With respect to the second and third questions, there seems to be a general agreement that α-linolenic acid is important for the prevention of coronary deaths [9, 10, 24] but our results indicate that diets freely chosen by the general population can approach the Mediterranean optimum without specific emphasis to α-linolenic acids rich foods provided that the nutritional milieu and the food culture are conducive to the intake of a Mediterranean diet (contrast in Tables 3 and 5 the Mediterranean to the northern European countries). In this context it should be recognised that there are many potentially beneficial dimensions in the Mediterranean diet including its ability to reduce endothelial dysfunction and vascular inflammation [25, 26].

To address the fourth question we have compared the results of the two randomised trials [9–11] with those of our observational study. Randomised trials are methodologically superior but they suffer unavoidably from small numbers. Thus, total deaths in the study by de Lorgeril and colleagues [9, 10] were 38 and in the study by Singh and colleagues [11] 62 whereas in our study total deaths were 467. The inherent instability of estimates relying on small numbers emerges when the results in the first report of de Lorgeril and colleagues [9] are compared with those in his final report [10]: all cause mortality ratio was estimated at 0.30 in the first study but at 0.44 in the second one. In the Singh et al study a crude mortality ratio of 0.63 was derived by simple division of total deaths in the two arms. These estimates from the randomised trials (0.44 and 0.63) could be compared with the mortality ratio in our study associated with a four-unit increment in the modified Mediterranean diet score ($0.82^2 = 0.67$). This is because our estimates in Table 5 are anchored to an increment of two units whereas the contrasted diets in each of the two trials are likely to differ by more than two units in our 10-unit scale and the differences are probably closer to four units.

Thus, we can infer that the Mediterranean diet can be followed by the general population in any country but more easily in the Mediterranean countries and that closer adherence to it by, say by four units in our 10-unit scale can reduce the risk of death overall, among patients with a previous coronary infarct by 33%. This reduction of mortality is at least twice as large in absolute terms as the reduction of overall mortality among apparently healthy individuals so that variants of Mediterranean diet should be considered as generally useful but particularly so among persons who have suffered and survived a coronary infarct. It would have been interesting to analyze mortality by cause, but this information is processed later and was not available at the time of analysis.

Advantages of our investigation are its large sample size, and its reliance on naturally consumed diets assessed through validated food frequency questionnaires. Disadvantages are the lack of medical documentation of the self-reported coronary infarct, although misclassification of diagnosis is likely to be small for such a serious condition and to have been non-differential with respect to diet. In certain instances the reported myocardial infarcts may have been a “false-positive” report, but this could only have led to underestimation of the true association, since modified Mediterranean diet appears more strongly related to survival among patients with infarcts than among patients without coronary heart disease [8]. The cut-offs and increments did not rely on gender-specific distributions and nutritional habits of the studied population but, even arbitrary but reasonable values are unlikely to introduce systematic bias in the results. Time between occurrence of coronary infarct and enrolment in the study could be an effect modifier of the reported associations but our results are still valid in that they reflect the weighted effect of the modified Mediterranean diet on survival.

Information of coronary-specific medication (beta blockers, calcium blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, etc.) was not available in all centres. It is theoretically possible that adherence to treatment could be associated with adherence to at least some of the components of the Mediterranean diet, but we found no empirical data to document the strength of this possible association. The association, however, is unlikely to be of a size sufficient to introduce substantial confounding [27, 28]. Indeed, controlling for the only drug that was significantly, albeit weekly, with Mediterranean diet score in one of the centres, had no effect on the association of the score with mortality among participants in that centre. Finally, our study was observational, lacking the inherent methodological strength of randomisation, an unavoidable consequence of the focus on realistic diets rather than medicalized dietary regimes.

In conclusion, our findings indicate that variants of Mediterranean diet can be recommended as an important complement in the pharmaceutical and surgical management of coronary heart disease, possible conveying a considerable degree of benefit.

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