Adherence to a Mediterranean Diet and Survival in a Greek Population

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ABSTRACT

BACKGROUND

Adherence to a Mediterranean diet may improve longevity, but relevant data are limited.

METHODS

We conducted a population-based, prospective investigation involving 22,043 adults in Greece who completed an extensive, validated, food-frequency questionnaire at base line. Adherence to the traditional Mediterranean diet was assessed by a 10-point Mediterranean-diet scale that incorporated the salient characteristics of this diet (range of scores, 0 to 9, with higher scores indicating greater adherence). We used proportional-hazards regression to assess the relation between adherence to the Mediterranean diet and total mortality, as well as mortality due to coronary heart disease and mortality due to cancer, with adjustment for age, sex, body-mass index, physical-activity level, and other potential confounders.

RESULTS

During a median of 44 months of follow-up, there were 275 deaths. A higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality (adjusted hazard ratio for death associated with a two-point increment in the Mediterranean-diet score, 0.75 [95 percent confidence interval, 0.64 to 0.87]). An inverse association with greater adherence to this diet was evident for both death due to coronary heart disease (adjusted hazard ratio, 0.67 [95 percent confidence interval, 0.47 to 0.94]) and death due to cancer (adjusted hazard ratio, 0.76 [95 percent confidence interval, 0.59 to 0.98]). Associations between individual food groups contributing to the Mediterranean-diet score and total mortality were generally not significant.

CONCLUSIONS

Greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.

MANY STUDIES HAVE EVALUATED THE associations between food groups, foods, or nutrients and chronic diseases, and a consensus about the role of nutritional factors in the etiology of these diseases has gradually emerged.[1,2] During the past 10 years, several groups of investigators have attempted to identify dietary patterns associated with increased longevity.[3-14] Because these studies have used data that were collected for other purposes, they have usually not included general populations or have not had sufficient information to control for energy intake or physical activity, two variables that are crucial in studies of diet.[15] Also, rather than using an a priori approach, which builds on previous knowledge concerning the health effects of various dietary constituents, studies of associations between diet and disease outcomes[9,13,16-21] have tended to use a posteriori techniques,[22] with dietary patterns ascertained through methods based on observed correlations among dietary variables.[23]

The traditional Mediterranean diet is characterized by a high intake of vegetables, legumes, fruits and nuts, and cereals (that in the past were largely unrefined), and a high intake of olive oil but a low intake of saturated lipids, a moderately high intake of fish (depending on the proximity of the sea), a low-to-moderate intake of dairy products (and then mostly in the form of cheese or yogurt), a low intake of meat and poultry, and a regular but moderate intake of ethanol, primarily in the form of wine and generally during meals.[24] Ecologic evidence suggesting beneficial health effects of the Mediterranean diet has emerged from the classic studies of Keys.[25] Trichopoulou et al.[6] have quantified adherence to the Mediterranean diet in terms of a nine-point scale. This group[6] and others[8,10,12] have used minor variants of this scale and have reported inverse associations between the score and total mortality among elderly persons in small studies, each including fewer than 400 subjects. We investigated the relation of the Mediterranean dietary pattern and the Mediterranean-diet score with overall mortality in a large sample of the general Greek population.

METHODS

RECRUITMENT AND APPROVAL

The enrollment of participants in the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC) took place between 1994 and 1999. A total of 28,572 participants, 20 to 86 years old, were recruited from all regions of Greece. EPIC is conducted in 22 research centers in 10 European countries and is coordinated by the International Agency for Research on Cancer, with the purpose of investigating the role of biologic, dietary, lifestyle, and environmental factors in the etiology of cancer and other chronic diseases.[26-28] All procedures were in accordance with the Helsinki Declaration, all participants provided written informed consent, and the study protocol was approved by the ethics committees at the International Agency for Research on Cancer and the University of Athens Medical School.

DATA ON DIET

Usual dietary intake during the year preceding enrollment was assessed with the use of a semiquantitative food-frequency questionnaire including approximately 150 foods and beverages commonly consumed in Greece. The questionnaire was administered in person by specially trained interviewers and has been validated.[29,30] For each of the items, respondents were asked to report their frequency of consumption and portion size, with the latter being calculated on the basis of information provided on household units and 76 photographs of usual portion sizes. Responses to these questions were checked for completeness and used in the estimation of nutrient intake. Standard portion sizes were used for the estimation of consumed quantities,[29,31] and nutrient intakes were calculated with the use of a food-composition data base that had been modified to accommodate the particularities of the Greek diet.[31,32]

Eventually, 14 all-inclusive food groups or nutrients were considered: potatoes, vegetables, legumes, fruits and nuts, dairy products, cereals, meat, fish, eggs, monounsaturated lipids (mainly olive oil), polyunsaturated lipids (vegetable-seed oils), saturated lipids and margarines, sugar and sweets, and nonalcoholic beverages. For each participant, intake of each of the indicated groups in grams per day and total energy intake were calculated.[30]

ENERGY EXPENDITURE

A section of the lifestyle questionnaire addressed the frequency and duration of participation in occupational and leisure-time physical activities.[33] An energy-expenditure index was computed by assigning a multiple of the resting metabolic rate[34] to each activity (a metabolic equivalent [MET] value). Time spent on each of the above activities was multiplied by the MET value of the activity, and all MET-hour products were summed to produce an estimate of

Table 1. Mediterranean-Diet Score, Other Base-Line Characteristics, and Mortality among 22,043 Study Participants.*

Variable	Mediterranean-Diet Score of 0–3 (N=6848)		Mediterranean-Diet Score of 4–5 (N=9488)		Mediterranean-Diet Score of 6–9 (N=5707)		Sex- and Age-Adjusted Rate of Death per 1000 Person-Yr†	Sex- and Age-Adjusted Hazard Ratios for Death (95% CI)‡	Multivariate Hazard Ratio for Death (95% CI)§
	no. (%)	no. of deaths/ no. of person-yr	no. (%)	no. of deaths/ no. of person-yr	no. (%)	no. of deaths/ no. of person-yr			
Sex									
Male	2457 (36)	74/8869	3808 (40)	61/13,974	2630 (46)	44/9774	5.59	1.00	1.00
Female	4391 (64)	45/16,115	5680 (60)	34/20,986	3077 (54)	17/11,421	1.95	0.35 (0.27–0.45)	0.39 (0.25–0.60)
Age									
<55 Yr	3777 (55)	16/13,834	5513 (58)	13/20,199	3355 (59)	17/12,467	0.97	1.00	1.00
55–64 Yr	1473 (22)	23/5314	2146 (23)	20/7872	1410 (25)	12/5170	3.11	3.34 (2.25–4.95)	3.30 (2.18–4.98)
≥65 Yr	1598 (23)	80/5836	1829 (19)	62/6889	942 (17)	32/3558	10.70	11.40 (8.25–15.87)	10.14 (6.91–14.88)
Education									
≤5 Yr	1513 (22)	50/5531	1750 (18)	44/6554	893 (16)	17/3406	3.83	1.00	1.00
≥6 Yr	5335 (78)	69/19,453	7738 (82)	51/28,406	4814 (84)	44/17,789	3.00	0.72 (0.55–0.93)	0.71 (0.54–0.92)
Height									
<161.3 cm	3756 (55)	60/13,767	4775 (50)	41/17,744	2534 (44)	21/9501	3.47	1.00	1.00
≥161.3 cm	3092 (45)	59/11,217	4713 (50)	54/17,216	3173 (56)	40/11,694	3.39	1.03 (0.74–1.43)	1.01 (0.73–1.41)
Body-mass index									
<28.06	3387 (49)	55/12,305	4769 (50)	41/17,465	2834 (50)	26/10,408	3.31	1.00	1.00
≥28.06	3461 (51)	64/12,679	4719 (50)	54/17,495	2873 (50)	35/10,787	3.44	1.03 (0.81–1.32)	1.05 (0.82–1.34)
Waist-to-hip ratio									
<0.87	3708 (54)	37/13,595	4739 (50)	22/17,382	2558 (45)	11/9407	3.23	1.00	1.00
≥0.87	3140 (46)	82/11,389	4749 (50)	73/17,578	3149 (55)	50/11,788	3.41	1.09 (0.77–1.53)	1.05 (0.74–1.49)
Level of physical activity									
<35.01 MET-hr/day	3770 (55)	94/13,733	4707 (50)	67/17,379	2575 (45)	35/9538	3.73	1.00	1.00
≥35.01 MET-hr/day	3078 (45)	25/11,251	4781 (50)	28/17,581	3132 (55)	26/11,657	2.60	0.71 (0.54–0.94)	0.72 (0.55–0.94)
Ethanol intake									
<10 g/day	5766 (84)	99/21,046	6971 (73)	60/25,716	3433 (60)	31/12,742	3.58	1.00	1.00
10 to <30 g/day	639 (9)	8/2322	1697 (18)	21/6178	1649 (29)	21/6057	2.42	0.74 (0.53–1.03)	0.73 (0.52–1.01)
≥30 g/day	443 (6)	12/1616	820 (9)	14/3066	625 (11)	9/2396	2.27	0.92 (0.63–1.35)	0.86 (0.58–1.27)
Smoking status									
Never smoked	3905 (57)	58/14,290	5143 (54)	43/19,075	2860 (50)	20/10,729	2.53	1.00	1.00
Former smoker	1039 (15)	27/3705	1706 (18)	27/6180	1203 (21)	18/4362	2.49	1.22 (0.87–1.72)	1.27 (0.90–1.79)
Current smoker	1904 (28)	34/6989	2639 (28)	25/9705	1644 (29)	23/6104	3.93	1.75 (1.26–2.44)	1.83 (1.30–2.57)

* The cutoff points for height, body-mass index (the weight in kilograms divided by the square of the height in meters), waist-to-hip ratio, and level of physical activity were the median values for those variables. The Mediterranean-diet score ranges from 0 to 9, with higher scores indicating greater adherence to the Mediterranean diet. Details are presented in the Methods section. CI denotes confidence interval, and MET metabolic equivalents.
† Rates were directly adjusted, with the use of the study population as the standard.
‡ Ratios were adjusted for sex and age, with the use of Cox regression.
§ Ratios were adjusted mutually but not for Mediterranean-diet score, with the use of Cox regression.

daily physical activity, indicating the amount of energy expended per kilogram of body weight during an average day. Anthropometric measurements and demographic and lifestyle characteristics were also recorded with the use of standardized procedures.

MEDITERRANEAN-DIET SCALE

A scale indicating the degree of adherence to the traditional Mediterranean diet was constructed by Trichopoulou et al.[6] and revised to include fish intake.[35] A value of 0 or 1 was assigned to each of nine

Table 2. Daily Dietary Intake of Several Food Groups in Relation to Mediterranean-Diet Score.

Dietary Variable	Men				Women			
	All	Diet Score of 0–3 (N=2457)	Diet Score of 4–5 (N=3808)	Diet Score of 6–9 (N=2630)	All	Diet Score of 0–3 (N=4391)	Diet Score of 4–5 (N=5680)	Diet Score of 6–9 (N=3077)
		number (percent)				*number (percent)*		
Vegetables								
Median (g/day)	549.9				499.6			
≥Median		452 (18)	1892 (50)	2104 (80)		893 (20)	3094 (54)	2587 (84)
<Median		2005 (82)	1916 (50)	526 (20)		3498 (80)	2586 (46)	490 (16)
Legumes								
Median (g/day)	9.1				6.7			
≥Median		569 (23)	1920 (50)	1996 (76)		1110 (25)	3136 (55)	2436 (79)
<Median		1888 (77)	1888 (50)	634 (24)		3281 (75)	2544 (45)	641 (21)
Fruits and nuts								
Median (g/day)	362.5				356.3			
≥Median		572 (23)	1885 (50)	1991 (76)		1141 (26)	3015 (53)	2418 (79)
<Median		1885 (77)	1923 (50)	639 (24)		3250 (74)	2665 (47)	659 (21)
Dairy products								
Median (g/day)	196.7				191.1			
≥Median		1684 (69)	1920 (50)	844 (32)		2891 (66)	2712 (48)	971 (32)
<Median		773 (31)	1888 (50)	1786 (68)		1500 (34)	2968 (52)	2106 (68)
Cereals*								
Median (g/day)	177.7				139.7			
≥Median		874 (36)	1914 (50)	1660 (63)		1548 (35)	2992 (53)	2034 (66)
<Median		1583 (64)	1894 (50)	970 (37)		2843 (65)	2688 (47)	1043 (34)
Meat								
Median (g/day)	120.8				89.8			
≥Median		1370 (56)	1980 (52)	1098 (42)		2500 (57)	2855 (50)	1219 (40)
<Median		1087 (44)	1828 (48)	1532 (58)		1891 (43)	2825 (50)	1858 (60)
Fish								
Median (g/day)	23.7				18.8			
≥Median		494 (20)	1906 (50)	2062 (78)		1101 (25)	3000 (53)	2473 (80)
<Median		1963 (80)	1902 (50)	568 (22)		3290 (75)	2680 (47)	604 (20)
Olive oil								
Median (g/day)	45.5				38.7			
≥Median		574 (23)	1841 (48)	2033 (77)		1128 (26)	2963 (52)	2483 (81)
<Median		1883 (77)	1967 (52)	597 (23)		3263 (74)	2717 (48)	594 (19)
Potatoes								
Median (g/day)	88.7				65.8			
≥Median		1022 (42)	1943 (51)	1483 (56)		1870 (43)	2929 (52)	1776 (58)
<Median		1435 (58)	1865 (49)	1147 (44)		2521 (57)	2751 (48)	1301 (42)
Eggs								
Median (g/day)	16.3				14.1			
≥Median		1209 (49)	1911 (50)	1328 (50)		2126 (48)	2888 (51)	1560 (51)
<Median		1248 (51)	1897 (50)	1302 (50)		2265 (52)	2792 (49)	1517 (49)

indicated components with the use of the sex-specific median as the cutoff. For beneficial components (vegetables, legumes, fruits and nuts, cereal, and fish), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, poultry, and dairy products, which are rarely nonfat or low-fat in Greece), persons whose consumption was below the median were assigned a value of 1, and persons whose consumption was at or above the median

Table 2. (Continued.)

Dietary Variable		Men				Women		
	All	Diet Score of 0–3 (N=2457)	Diet Score of 4–5 (N=3808)	Diet Score of 6–9 (N=2630)	All	Diet Score of 0–3 (N=4391)	Diet Score of 4–5 (N=5680)	Diet Score of 6–9 (N=3077)
		number (percent)				*number (percent)*		
Sweets								
Median (g/day)	22.8				20.1			
≥Median		1243 (51)	1893 (50)	1312 (50)		2166 (49)	2847 (50)	1561 (51)
<Median		1214 (49)	1915 (50)	1318 (50)		2225 (51)	2833 (50)	1516 (49)
Nonalcoholic beverages (including juices)								
Median (g/day)	337.5				250.5			
≥Median		1221 (50)	1917 (50)	1310 (50)		2051 (47)	2874 (51)	1649 (54)
<Median		1236 (50)	1891 (50)	1320 (50)		2340 (53)	2806 (49)	1428 (46)
Monounsaturated lipids								
Median (g/day)	55.9				46.5			
≥Median		733 (30)	1885 (50)	1830 (70)		1356 (31)	2957 (52)	2261 (73)
<Median		1724 (70)	1923 (50)	800 (30)		3035 (69)	2723 (48)	816 (27)
Saturated lipids								
Median	33.1				27.0			
≥Median		1232 (50)	1936 (51)	1280 (49)		2182 (50)	2862 (50)	1530 (50)
<Median		1225 (50)	1872 (49)	1350 (51)		2209 (50)	2818 (50)	1547 (50)
Polyunsaturated lipids								
Median (g/day)	15.0				12.6			
≥Median		1070 (44)	1868 (49)	1510 (57)		1916 (44)	2813 (50)	1845 (60)
<Median		1387 (56)	1940 (51)	1120 (43)		2475 (56)	2867 (50)	1232 (40)
Percentage energy from saturated lipids								
Median	12.6				13.0			
≥Median		1736 (71)	1925 (51)	787 (30)		3078 (70)	2682 (47)	814 (26)
<Median		721 (29)	1883 (49)	1843 (70)		1313 (30)	2998 (53)	2263 (74)
Ratio of monounsaturated lipids to saturated lipids								
Median	1.7				1.7			
≥Median		392 (16)	1882 (49)	2174 (83)		836 (19)	3105 (55)	2633 (86)
<Median		2065 (84)	1926 (51)	456 (17)		3555 (81)	2575 (45)	444 (14)
Energy intake								
Median (kJ/day)†	9851.4				7794.6			
≥Median		887 (36)	1913 (50)	1648 (63)		1605 (37)	2943 (52)	2026 (66)
<Median		1570 (64)	1895 (50)	982 (37)		2786 (63)	2737 (48)	1051 (34)

* Cereals included flour, cereal flakes, starches, pasta, rice, other grain, bread, crisp bread, rusks, breakfast cereals, biscuits, dough, pastry, and other cereal products.
† To convert values for energy intake to kilocalories, divide by 4.184.

were assigned a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g per day and to women who consumed between 5 and 25 g per day. Finally, for fat intake, we used the ratio of monounsaturated lipids to saturated lipids, rather than the ratio of polyunsaturated to saturated lipids, because in Greece, monounsaturated lipids are used in much higher quantities than polyunsaturated lipids. Thus, the total Mediterranean-diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

PARTICIPANTS AND FOLLOW-UP
Results were available for 25,917 participants whose vital status was ascertained by active follow-up until

July 2002 and for whom complete information on dietary, lifestyle, and anthropometric variables was available. For 832 other study participants, information was missing for one or more of the dietary, anthropometric, or lifestyle variables; and for an additional 1823 participants, who lived in remote areas of Greece, vital status had not been ascertained as of July 2002. A total of 3874 of the 25,917 study participants with complete data were excluded because of diagnoses of coronary heart disease (in 1512 participants), diabetes mellitus (in 1989 participants), or cancer (in 529 participants) at enrollment; 156 of these participants had more than one of these conditions. Thus 22,043 participants were included in the analyses.

The median duration of follow-up was 3.7 years (44 months), with a range of 1 month (for a participant who died) to 96 months. The date and cause of death for all participants who died were obtained from death certificates and other official sources, and trained physicians coded the cause of death according to the *International Classification of Diseases, 9th Revision.*[36] Those who adjudicated the outcomes were blinded to the diet score. We investigated mortality from all causes, mortality from coronary heart disease, and mortality from cancer.

STATISTICAL ANALYSIS

All analyses were performed with the use of SAS statistical software.[37] Frequency distributions were used for descriptive purposes. Medians and means plus standard deviations were used for dietary variables, including energy intake. Survival data were modeled through Cox proportional-hazards regression. The Cox models were used to assess the association between the studied food groups and mortality, as well as between the Mediterranean-diet score and mortality. The models were adjusted for sex, age (<35 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, or ≥65 years), smoking status (never smoked; former smoker; and five categories of current smoker: 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, 21 to 30 cigarettes per day, 31 to 40 cigarettes per day; and 41 or more cigarettes per day), years of education (≤5, 6 to 11, 12, or ≥13), and ordered quintiles of body-mass index (the weight in kilograms divided by the square of the height in meters), the ratio of the waist circumference to the hip circumference (waist-to-hip ratio), and energy-expenditure score. All dietary analyses were also adjusted for energy intake (in ordered quintiles)[38]; consumption of eggs and potatoes, which are not part of the Mediterranean-diet score, was controlled for (as a continuous variable) whenever the effect of the score was evaluated. Separate analyses were performed for total mortality, mortality from cancer, and mortality from coronary heart disease.

RESULTS

STUDY PARTICIPANTS

During the follow-up period, 81,139 person-years were accrued, and 275 deaths occurred. The mean base-line body-mass index was 28.1 for men and 28.8 for women. The distribution of base-line characteristics and deaths according to Mediterranean-diet score is shown in Table 1. Also shown in this table are sex- and age-adjusted mortality rates and hazard ratios for death. In these univariate analyses, the Mediterranean-diet score was not associated with the body-mass index, but it was positively associated with the waist-to-hip ratio and with physical activity. As expected, the mortality rate was higher among men than among women, increased exponentially with age, and was inversely associated with the level of physical activity and the educational level (Table 1).

DIET SCORES, DIETARY INTAKE, AND MORTALITY

Table 2 shows the distribution of study subjects according to sex, major categories of Mediterranean-diet score, and intake of the studied dietary variables, using as cutoffs the sex-specific medians. As expected, high Mediterranean-diet scores are characterized by high intakes of vegetables, legumes, fruits and nuts, cereals, fish, and olive oil and relatively low intakes of dairy products and meat. Positive associations with the Mediterranean-diet score are evident for total energy intake and potato consumption, whereas no such association is evident for egg consumption. The latter three variables are not part of the Mediterranean-diet score but were controlled for in analyses focusing on the association of the score with mortality.

Table 3 shows the mean values among men and women for the dietary intake of 18 major food groups or nutritional variables, including energy intake. Consumption of vegetables, fruits and nuts, legumes, and olive oil is high in the Greek population, and as expected, consumption of all food groups is higher among men than among women. Round numbers close to the standard deviations for each measure were used as increments in the regression models in order to provide comparable esti-

Table 3. Daily Intake of Selected Food Groups and Associated Risk of Death from Any Cause.*

Dietary Variable	Men	Women	Increment	Hazard Ratio for Death (95% CI)
Vegetables (g/day)	583.6±233.9	536.1±232.8	230	0.88 (0.74–1.04)
Legumes (g/day)	10.4±7.4	7.9±5.8	5	0.92 (0.83–1.03)
Fruits and nuts (g/day)	393.0±214.6	385.7±205.1	200	0.82 (0.70–0.96)
Dairy products (g/day)	222.6±147.6	216.2±146.6	140	1.11 (0.98–1.26)
Cereals (g/day)†	191.0±80.2	145.7±55.2	60	0.95 (0.83–1.08)
Meat (g/day)	129.3±60.4	94.9±45.2	50	1.06 (0.93–1.22)
Fish (g/day)	26.4±20.3	21.7±15.4	15	1.02 (0.92–1.12)
Olive oil (g/day)	46.2±21.2	38.9±19.2	20	0.96 (0.83–1.10)
Potatoes (g/day)	98.9±63.3	73.5±47.9	50	1.07 (0.95–1.21)
Eggs (g/day)	19.0±13.3	15.7±10.2	10	1.07 (0.98–1.17)
Sweets (g/day)	26.8±19.7	23.5±17.5	15	1.01 (0.90–1.13)
Nonalcoholic beverages and juices (g/day)	387.1±244.0	293.0±201.5	220	1.00 (0.85–1.17)
Monounsaturated lipids (g/day)	58.4±20.0	48.7±17.8	15	0.98 (0.84–1.15)
Saturated lipids (g/day)	34.6±13.2	28.6±11.6	10	1.05 (0.89–1.23)
Polyunsaturated lipids (g/day)	17.5±9.2	15.0±8.2	5	1.00 (0.92–1.08)
Percentage of energy from saturated lipids	12.6±2.5	13.1±2.6	2.5	1.12 (0.99–1.27)
Ratio of monounsaturated lipids to saturated lipids	1.8±0.5	1.8±0.5	0.5	0.86 (0.76–0.98)
Energy intake (kJ/day)‡	10,202.6±2949.3	8077.9±2393.4	2700	1.04 (0.92–1.19)

* Plus–minus values are means ±SD. The chosen increment for the calculation of the hazard ratio for death for each variable is a round number slightly lower than the standard deviation for the daily intake for that variable. Hazard ratios were adjusted for sex, age (<35 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, or ≥65 years), waist-to-hip ratio (in ordered quintiles), energy-expenditure score (in ordered quintiles), years of education (≤5, 6 to 11, 12, or ≥13), smoking status (never smoked, former smoker, and five categories of current smoker: 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, 21 to 30 cigarettes per day, 31 to 40 cigarettes per day, and ≥41 cigarettes per day, considered as an ordered variable), body-mass index (in ordered quintiles), and total energy intake (in ordered quintiles); the hazard ratio associated with energy intake was adjusted for all these variables except for energy intake itself. CI denotes confidence interval.
† Cereals included flour, cereal flakes, starches, pasta, rice, other grain, bread, crisp bread, rusks, breakfast cereals, biscuits, dough, pastry, and other cereal products.
‡ To convert values for energy intake to kilocalories, divide by 4.184.

mates. In analyses adjusted for age, sex, years of education, smoking status, body-mass index, waist-to-hip ratio, energy-expenditure score, and total energy intake (except when energy intake was the focus of the analysis), the only individual measures that were predictive of total mortality were the intake of fruits and nuts and the ratio of monounsaturated lipids to saturated lipids; associations between other individual dietary components and mortality were nonsignificant.

A two-point increment in the Mediterranean-diet score was associated with a 25 percent reduction in total mortality (P<0.001) (Table 4). (An example of dietary changes resulting in such an increment would be a substantial increase in the intake of monounsaturated lipids relative to saturated lipids and a substantial reduction in the intake of meat.) The association with the Mediterranean-diet score appeared to be slightly stronger for mortality from coronary heart disease than for mortality from cancer, although mortality from cancer was also reduced significantly. The inverse association between the Mediterranean-diet score and total mortality was evident irrespective of sex, smoking status, level of

Table 4. Hazard Ratios for Death Associated with a Two-Point Increment in the Mediterranean-Diet Score.*

Variable	No. of Deaths/ No. of Participants	Hazard Ratio for Death (95% CI)		
		Crude	Age- and Sex-Adjusted	Fully Adjusted
Death from any cause	275/22,043	0.74 (0.65–0.86)	0.79 (0.69–0.91)	0.75 (0.64–0.87)
Death from coronary heart disease	54/22,043	0.68 (0.50–0.94)	0.74 (0.54–1.02)	0.67 (0.47–0.94)
Death from cancer	97/22,043	0.81 (0.64–1.03)	0.85 (0.67–1.08)	0.76 (0.59–0.98)
Sex				
Male	179/8895	0.72 (0.61–0.86)	0.77 (0.65–0.92)	0.78 (0.65–0.94)
Female	96/13,148	0.67 (0.52–0.86)	0.71 (0.55–0.91)	0.69 (0.53–0.90)
Age				
<55 Yr	46/12,645	0.98 (0.69–1.38)	0.86 (0.61–1.21)	0.89 (0.62–1.27)
≥55 Yr	229/9398	0.72 (0.62–0.84)	0.75 (0.64–0.88)	0.73 (0.61–0.86)
Smoking status				
Never smoked	121/11,908	0.67 (0.54–0.83)	0.72 (0.58–0.89)	0.67 (0.53–0.84)
Ever smoked	154/10,135	0.79 (0.65–0.95)	0.77 (0.64–0.93)	0.82 (0.67–1.00)
Body-mass index				
<28.06	122/10,969	0.72 (0.59–0.90)	0.74 (0.59–0.92)	0.77 (0.61–0.97)
≥28.06	153/11,074	0.76 (0.63–0.92)	0.76 (0.63–0.92)	0.73 (0.60–0.89)
Waist-to-hip ratio				
≥0.87	204/10,967	0.75 (0.63–0.88)	0.79 (0.67–0.93)	0.79 (0.66–0.94)
<0.87	71/11,076	0.61 (0.45–0.81)	0.65 (0.49–0.87)	0.64 (0.48–0.88)
Education				
≥6 Yr	164/17,887	0.79 (0.66–0.95)	0.77 (0.64–0.92)	0.77 (0.63–0.93)
<6 Yr	111/4156	0.73 (0.58–0.91)	0.74 (0.59–0.93)	0.72 (0.56–0.91)
Level of physical activity				
≥35.01 MET-hr/day	79/11,009	0.93 (0.71–1.22)	0.88 (0.67–1.14)	0.83 (0.63–1.09)
<35.01 MET-hr/day	196/11,034	0.72 (0.61–0.85)	0.72 (0.61–0.85)	0.74 (0.61–0.88)

* The cutoff points for body-mass index, waist-to-hip ratio, and level of physical activity were the median values for those variables. Fully adjusted hazard ratios were adjusted for sex, age (<35 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, or ≥65 years), waist-to-hip ratio (in ordered quintiles), energy-expenditure score (in ordered quintiles), years of education (≤5, 6 to 11, 12, or ≥13), smoking status (never smoked, former smoker, and five categories of current smoker: 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, 21 to 30 cigarettes per day, 31 to 40 cigarettes per day, and ≥41 cigarettes per day, considered as an ordered variable), body-mass index (in ordered quintiles), consumption of potatoes (as a continuous variable), consumption of eggs (as a continuous variable), and total energy intake (in ordered quintiles). CI denotes confidence interval, and MET metabolic equivalents.

education, body-mass index, waist-to-hip ratio, and level of physical activity; none of the terms for the interaction with these variables was statistically significant. In analyses stratified according to age, the relation between the Mediterranean-diet score and mortality was significant among participants 55 years of age or older but not among participants younger than 55 years of age; however, the difference between the point estimate for younger participants and that for older participants was not statistically significant (P=0.34).

DISCUSSION

In this large, population-based cohort study, we found that a higher degree of adherence to the traditional Mediterranean diet was associated with a reduction in total mortality, with a two-point increment in the score corresponding to a 25 percent reduction in total mortality. The reduction in mortality was evident with respect to both deaths due to coronary heart disease and deaths due to cancer, although it was slightly more pronounced with re-

spect to the former. The reduction in mortality in relation to the Mediterranean-diet score was apparent even though no strong associations with mortality were evident for each of the components of the Mediterranean-diet score. Several explanations for this finding are possible. Individual components may have small effects that emerge only when the components are integrated into a simple, unidimensional score. There may be biologic interactions between different components of the Mediterranean diet that may be difficult to detect unless very large samples are used. In analyses focusing on individual components, effects are examined against the background of average risk associated with other nutritional components, whereas an inclusive dietary score can account for extremes of cumulative exposure (from 0 to 9) in the absence of other major nutritional effects.[21]

The Mediterranean-diet scale relies on generally strong epidemiologic evidence concerning the individual dietary components. The addition to the score of a ninth component incorporating fish intake was deemed necessary not only because fish is an important part of the Mediterranean diet, but also because of recent strong evidence of an inverse correlation between fish consumption and the risk of death from coronary heart disease.[35] From a population perspective, the dietary habits of a large fraction of the contemporary Greek population closely resemble the Mediterranean diet.[28] We have avoided using a risk score derived from the combination of partial regression coefficients in a fully adjusted proportional-hazards model, because this score generates biased estimates of risk reduction, and the fitting of the model is hampered by the high correlation among food groups.[39]

Advantages of this study include its prospective nature, its large size, its reliance on a sample of the general population, and its use of a score that has been used previously in various forms[6,8,10,12] and whose components have been validated.[29] However, we cannot rule out the possibility of residual confounding by factors that have not been evaluated or are suboptimally measured. A longer follow-up period would have resulted in a greater number of deaths, but it would have reduced the relevance of diet as assessed at enrollment, unless additional measurements of diet had been undertaken; this approach would have been complicated by uncertainty about the latency of dietary influences on the risk of death. The observation that the association between greater adherence to the Mediterranean diet and reduced mortality becomes stronger with increasing age might reflect increasing cumulative exposure to a more or less healthy diet; another potential explanation is that the study had limited statistical power to detect an association among participants younger than 55 years of age, given the relatively small number of deaths in this subgroup (46 deaths, of which only 5 were due to coronary heart disease).

In previous small studies involving elderly persons,[6,8,10,12] in which a Mediterranean-diet score similar to ours was used, the reduction in overall mortality associated with increased adherence to the Mediterranean diet was similar to that found in our investigation. Our results are also compatible with those of two randomized trials of the secondary prevention of coronary heart disease through the use of variants of the Mediterranean diet.[40,41]

In conclusion, in a prospective study in the general population that relied on an extensive and validated dietary questionnaire, we found that a higher score on a scale that reflects the level of adherence to the traditional Mediterranean diet and integrates current views about the attributes of a healthy diet is associated with a significant and substantial reduction in overall mortality. The magnitude of the reduction in mortality associated with greater adherence to a Mediterranean diet is compatible with the reported survival advantage of adult Mediterranean populations over North American and northern European populations.[42]

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