

Mediterranean Dietary Pattern and Prediction of All-Cause Mortality in a US Population

Results From the NIH-AARP Diet and Health Study

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Background: The Mediterranean diet has been suggested to play a beneficial role for health and longevity. However, to our knowledge, no prospective US study has investigated the Mediterranean dietary pattern in relation to mortality.

Methods: Study participants included 214 284 men and 166 012 women in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. During follow-up for all-cause mortality (1995-2005), 27 799 deaths were documented. In the first 5 years of follow-up, 5985 cancer deaths and 3451 cardiovascular disease (CVD) deaths were reported. We used a 9-point score to assess conformity with the Mediterranean dietary pattern (components included vegetables, legumes, fruits, nuts, whole grains, fish, monounsaturated fat-saturated fat ratio, alcohol, and meat). We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using age- and multivariate-adjusted Cox models.

Results: The Mediterranean diet was associated with reduced all-cause and cause-specific mortality. In men, the multivariate HRs comparing high to low conformity for all-cause, CVD, and cancer mortality were 0.79 (95% CI, 0.76-0.83), 0.78 (95% CI, 0.69-0.87), and 0.83 (95% CI, 0.76-0.91), respectively. In women, an inverse association was seen with high conformity with this pattern: decreased risks that ranged from 12% for cancer mortality to 20% for all-cause mortality ($P = .04$ and $P < .001$, respectively, for the trend). When we restricted our analyses to never smokers, associations were virtually unchanged.

Conclusion: These results provide strong evidence for a beneficial effect of higher conformity with the Mediterranean dietary pattern on risk of death from all causes, including deaths due to CVD and cancer, in a US population.

Arch Intern Med. 2007;167(22):2461-2468

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THE MEDITERRANEAN DIET may play a beneficial role in health and longevity.¹ Its key components have been operationalized as a dietary pattern using a 9-point score.²⁻⁵ The Mediterranean dietary pattern has been associated with a decrease in overall mortality in a number of fairly small studies,^{3,4,6-11} and recently in the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort study of over half a million people from 10 countries across Europe.⁵

To date, no US study has investigated the effect of the Mediterranean dietary pattern on mortality. We examined the relation of the Mediterranean dietary pattern to all-cause and cause-specific mortality in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study.¹² We hypothesized that greater conformity with the Mediterranean dietary pattern is associated with a reduction in mortality. The large size of

the cohort allowed us to address potential smoking status confounding by restricting the analysis to participants who had never smoked and, in addition, to evaluate potential effect modification by lifestyle factors such as smoking status and body mass index (BMI).

METHODS

STUDY POPULATION

The NIH-AARP Diet and Health Study¹² was begun in 1995-1996, when questionnaires eliciting information on demographic and health-related behaviors were mailed to 3.5 million AARP members aged 50 to 71 years who resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). Of the 617 119 persons who returned the questionnaires, 566 407 respondents filled out the survey in satisfactory detail and consented to participate in the study. Additional study details have been described previously.¹²

We excluded proxy respondents (n=15 760) and subjects with a self-reported history of cancer (n=51 207), end-stage renal disease (n=997), heart disease (n=68 663), stroke (n=6435), emphysema (n=9481), or diabetes (n=30 181). We also excluded individuals who were outside 2 interquartile ranges of the 25th to 75th percentile interval of the normalized distribution for energy intake (n=3387). The resulting cohort included 380 296 participants (214 284 men and 166 012 women) with no history of chronic disease.

COHORT FOLLOW-UP AND MORTALITY ASCERTAINMENT

Addresses were updated annually by matching the cohort database to the National Change of Address maintained by the US Postal Service.¹³ Follow-up time for all-cause mortality was between 1995-1996 and December 31, 2005. Vital status was ascertained by the Social Security Administration Death Master File, which documented 27 799 deaths during 10 years of follow-up. Deaths occurring in the 1995-2001 period were linked to the National Death Index to ascertain underlying cause of death. We investigated cause-specific mortality, including cardiovascular disease (CVD) (n=3451), cancer (n=5985), and other-cause (n=2669) mortality using the Surveillance Epidemiology and End Results coding system.¹⁴ The NIH-AARP Diet and Health Study¹² was approved by the special studies institutional review board of the US National Cancer Institute.

EXPOSURE ASSESSMENT

Study participants completed an early version of the Diet History Questionnaire,¹⁵ a 124-item food frequency questionnaire (FFQ) that was validated against two 24-hour recalls.¹⁶ Pyramid servings for food groups were generated by linking the FFQ data with the Pyramid Servings Database, version 2.0.¹⁷ The FFQ provided estimates for intake of alcohol, monounsaturated fat, polyunsaturated fat, and saturated fat (grams). To adjust for energy intake, we divided daily intakes by an individual's reported total energy intake and multiplied by 2000 calories in women and 2500 calories in men.^{7-9,11} Information about demographics, smoking, physical activity, and menopausal hormone therapy were also reported at baseline.

MEDITERRANEAN DIET SCORE

Conformity with the Mediterranean dietary pattern was assessed by the traditional Mediterranean diet score (tMED), similar to that constructed by Trichopoulos et al,^{4,11} and the alternate Mediterranean diet score (aMED) created by Fung et al.² The tMED includes 9 components and takes values from 0 to 9 points (minimum to maximum conformity). One point each is given for intake at or above the sex-specific median intake for components considered to be healthy (vegetables [excluding potatoes], fruit and nuts, legumes, grains, fish, and monounsaturated fat-saturated fat ratio), and 1 point is given for intake less than the median for those components considered to be unhealthy (dairy and meat). In addition, 1 point is given for alcohol consumption within a specified range (5-25 g/d for women; 10-50 g/d for men). The aMED differs from the tMED in that the aMED separates fruit and nuts into 2 groups, eliminates dairy, includes only whole grains, only red and processed meat (beef, pork, luncheon meats, and organ meats), and uses the same alcohol range for both men and women (5-25 g/d).

The aMED and tMED scores were divided into 3 groups: 0 to 3, 4 and 5, and 6 to 9 points. In sensitivity analyses, we considered different sex-specific cut points by assigning points to intakes at or above the 75th percentile or below the 25th per-

centile for the components considered healthy and unhealthy, respectively, while maintaining the cut points for alcohol.

STATISTICAL ANALYSIS

Associations between nonnutritional covariates and the Mediterranean diet scores were examined by cross-tabulations. The median, 25th, and 75th percentiles of intake of food groups and macronutrients were determined for men and women separately at baseline. Spearman rank correlation coefficients relating the scores to food group and macronutrient intakes were calculated.

We used Cox proportional hazards regression,¹⁸ with person-years of follow-up as the time variable, to assess the association between aMED and tMED and all-cause mortality and mortality from CVD, cancer, and other causes with follow-up through 2001, separately for men and women. We verified that the proportional hazards assumption was not violated for our main exposure and other fixed covariates by including cross-product terms of the Mediterranean diet score and person-years and testing that all coefficients equaled 0.

All multivariate models were adjusted for potential risk factors for mortality, including age (continuous), total energy (continuous), smoking (never smokers, former smokers of ≤ 1 pack per day, former smokers of > 1 pack per day, current smokers of ≤ 1 pack per day, and current smokers of > 1 pack per day), education (less than high school, high school, some college, and completion of college and postgraduate college), BMI (calculated as weight in kilograms divided by height in meters squared) (< 18.5 , 18.5 to < 25.0 , 25.0 to < 30.0 , 30.0 to < 35.0 , 35.0 to < 40.0 , and ≥ 40.0), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, and ≥ 5 times per week), race (white, black, and other), marital status (married and not currently married), and in women, menopausal hormone therapy (never, past, and current). For finer control of smoking status, we used a multilevel variable that integrated combinations of smoking status (never, former, and current), time since quitting for former smokers (≥ 10 years, 5-9 years, 1-4 years, and within the last year), and smoking dose for both former and current smokers (1-10, 11-20, 21-30, 31-40, 41-60, and ≥ 61 cigarettes per day). Additional adjustment for other dietary variables (quintiles of polyunsaturated fatty acids, eggs, and potatoes) did not appreciably change the risk estimates, and these nutritional factors were not considered further. In a subanalysis we excluded smokers to evaluate the potential for residual confounding by smoking. Missing values for adjusting covariates were included as dummy variables in the models. Using the alternative Horvitz-Thompson method¹⁹ for missing data did not change the results appreciably.

Interactions between tMED and aMED and lifestyle factors such as smoking and BMI were tested using cross-product terms of the Mediterranean diet score and lifestyle factor and likelihood ratio test statistics comparing models with and without a cross-product term. We further conducted stratified analyses of all-cause mortality by examining the Mediterranean diet score in relation to mortality among 6 subgroups of smoking status (never/ever) and BMI (18.5 - 25.0 , > 25.0 to < 30.0 , ≥ 30.0). Age-adjusted incidence rates were calculated²⁰ with 5-year age bands standardized to the entire NIH-AARP population. All statistical analyses were carried out using SAS statistical software, version 9.1 (SAS Institute, Cary, North Carolina). A 2-sided *P* value of less than .05 was considered statistically significant.

RESULTS

During 5 years of follow-up, 12 105 deaths were documented (including 5985 cancer deaths and 3451 CVD

Table 1. Distribution of Participants by aMED Score in Conjunction With Nonnutritional Variables^a

Characteristic	aMED Score					
	Men			Women		
	0-3	4-5	6-9	0-3	4-5	6-9
Age >62 y ^b	46.94	50.31	52.89	47.35	49.35	51.07
BMI						
<18.5	0.65	0.64	0.68	1.61	1.41	1.54
18.5 to <25.0	26.44	28.62	35.04	39.28	43.73	51.62
25.0 to <30.0	49.05	49.98	48.26	31.94	32.31	30.03
30.0 to <35.0	17.13	15.13	11.93	14.90	13.04	10.15
35.0 to <40.0	3.71	2.96	1.98	5.69	4.38	2.76
≥40.0	1.08	0.88	0.53	3.22	2.23	1.22
Race						
White	93.14	92.10	92.74	90.70	89.38	90.05
Black	2.39	2.76	2.73	4.61	5.32	5.23
Other	3.21	3.99	3.55	3.12	3.78	3.40
Education						
<High school	6.77	4.80	3.23	7.24	5.08	3.17
High school	19.24	14.17	10.10	29.70	24.18	18.17
Some college	33.49	30.37	27.52	34.91	35.67	36.41
College/postgraduate college	37.70	48.12	57.06	24.72	31.94	40.50
Smoking status, pack/d						
Never	27.59	33.08	36.88	43.73	46.54	46.79
Past, ≤1	25.64	29.85	32.72	22.44	26.89	31.10
Past, >1	25.83	24.56	22.58	10.45	10.97	11.30
Current, ≤1	8.99	5.46	3.25	14.01	9.61	6.33
Current, >1	8.09	3.32	1.24	6.12	2.88	1.35
Marital status						
Married	83.99	85.50	86.01	44.68	45.33	46.34
Not currently married	15.25	13.84	13.54	54.21	53.72	52.86
Menopausal hormone therapy						
Never	NA	NA	NA	49.65	44.32	40.32
Past	NA	NA	NA	8.53	8.83	8.92
Current	NA	NA	NA	41.58	46.57	50.56
Physical activity						
Never	4.17	2.44	1.20	7.45	4.26	2.29
Rarely	14.39	9.82	6.17	20.95	14.53	9.40
1-3 Times/mo	16.29	13.31	9.97	16.83	14.54	10.85
1-2 Times/wk	23.69	23.25	21.35	21.26	21.86	20.79
3-4 Times/wk	23.58	28.88	33.65	19.77	26.46	33.10
Greater than or equal to 5 times/wk	16.83	21.37	27.05	12.31	17.11	22.74

Abbreviations: aMED, alternate Mediterranean diet; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

^aAll data are reported as percentages, which might not total 100 because of rounding or missing information.

^bMedian age was 62 years.

deaths). Five more years of follow-up resulted in a total of 27 799 deaths (18 126 men and 9673 women). The 2 Mediterranean scoring systems showed similar distributions among men and women (the scores were positively correlated; $r > 0.70$). Because the results from the 2 scores were similar, we present results for the aMED only because this score was modified for use in a US population.² In men, conformity with the Mediterranean diet tended to be higher among older people with the following characteristics: BMIs between 18.5 and less than 30.0, higher education, higher physical activity, married, and current nonsmokers or former smokers who had smoked 1 pack per day or less (**Table 1**). A similar pattern was seen in women, with the exception of marital status; in addition, higher conformity in women was associated with current use of menopausal hormone therapy (Table 1).

Table 2 reports the median, 25th, and 75th percentile values of intake of the score components and their

correlations with the total score (aMED). Energy intake was weakly negatively associated with the score. The median intakes for each of the components were similar in men and women, with the exception of alcohol and total energy, both of which were higher in men than in women.

Higher conformity with the Mediterranean dietary pattern was associated with a statistically significant reduction in all-cause mortality, including mortality due to cancer and CVD in both men and women (**Table 3** and **Table 4**). In men, the multivariate hazard ratios (HRs) of mortality from any cause, cancer, and CVD for the top vs the bottom level of conformity with the dietary pattern was 0.77 (95% confidence interval [CI], 0.74-0.80), 0.79 (95% CI, 0.73-0.87), and 0.76 (95% CI, 0.68-0.85), respectively. In women, higher conformity with aMED was associated with a 22%, 14%, and 21% decreased risk of all-cause ($P < .001$ for trend), cancer ($P = .01$ for trend), and CVD ($P = .01$ for trend) mortality,

Table 2. Daily Dietary Intakes of Food Groups and Nutrients and Spearman Correlation Coefficients (*r*) With aMED^a

Diet Score Components	Men				Women			
	25th Percentile	Median	75th Percentile	<i>r</i> ^b	25th Percentile	Median	75th Percentile	<i>r</i> ^b
Vegetables (no potatoes)	2.39	3.49	4.99	0.50	2.48	3.65	5.29	0.47
Legumes	0.09	0.17	0.33	0.41	0.05	0.12	0.23	0.39
Fruit and nuts	2.16	3.53	5.37	0.45	2.26	3.57	5.26	0.38
Total fruit	1.88	3.24	5.10	0.43	2.08	3.40	5.10	0.37
Nuts	0.06	0.14	0.31	0.21	0.04	0.09	0.19	0.18
Whole grain	0.80	1.42	2.19	0.41	0.72	1.18	1.79	0.36
Total grain	5.51	6.98	8.55	0.25	4.48	5.70	7.03	0.17
Total meat	2.85	4.02	5.40	-0.21	1.89	2.80	3.88	-0.20
Red and processed meat	1.86	2.84	3.97	-0.35	1.01	1.66	2.46	-0.36
Dairy products	0.84	1.42	2.30	-0.02	0.75	1.32	2.14	-0.04
Monounsaturated fat-saturated fat ratio	1.10	1.23	1.37	0.37	1.07	1.22	1.37	0.33
Fish	0.33	0.58	1.01	0.35	0.26	0.47	0.84	0.32
Alcohol, g	0.90	6.09	24.08	-0.02	0.04	1.44	7.35	0.09
Energy, cal	1455	1889	2440	-0.13	1119	1455	1881	-0.07

Abbreviations: aMED, alternate Mediterranean diet score; *r*, Spearman correlation coefficient.

^aUnless otherwise indicated data are reported as servings per day adjusted to 2000 calories in women and 2500 calories in men.

^bAll correlations are statistically significant from zero ($P < .001$).

Table 3. Results of Statistical Analysis for the Mediterranean Dietary Pattern (aMED) and All-Cause Mortality^a

Characteristic	aMED Score			<i>P</i> Value for Trend	aMED Score			<i>P</i> Value for Trend
	0-3	4-5	6-9		0-3	4-5	6-9	
All Subjects								
Men (n=214 284)								
Cases, No.	7616	6903	3607		4073	3891	1709	
Age-adjusted rates ^b	1167.6	870.5	658.5		782.1	583.2	462.1	
Age-adjusted HR	1 [Reference]	0.74 (0.72-0.77)	0.56 (0.54-0.59)	<.001	1 [Reference]	0.75 (0.71-0.78)	0.59 (0.56-0.63)	<.001
Multivariate HR ^c	1 [Reference]	0.89 (0.87-0.93)	0.77 (0.74-0.80)	<.001	1 [Reference]	0.88 (0.84-0.92)	0.78 (0.74-0.83)	<.001
Multivariate HR ^d	1 [Reference]	0.91 (0.88-0.94)	0.79 (0.76-0.83)	<.001	1 [Reference]	0.89 (0.85-0.93)	0.80 (0.75-0.85)	<.001
Never Smokers								
Men (n=68 971)								
Cases, No.	1236	1578	996		1106	1269	608	
Age-adjusted rates ^b	692.6	611.7	502.6		466.8	395.1	340.8	
Age-adjusted HR	1 [Reference]	0.88 (0.82-0.95)	0.72 (0.67-0.79)	<.001	1 [Reference]	0.85 (0.78-0.92)	0.73 (0.66-0.81)	<.001
Multivariate HR ^e	1 [Reference]	0.95 (0.88-1.02)	0.83 (0.76-0.90)	<.001	1 [Reference]	0.89 (0.82-0.97)	0.80 (0.73-0.89)	<.001
Women (n=75 740)								
Cases, No.	1236	1578	996		1106	1269	608	
Age-adjusted rates ^b	692.6	611.7	502.6		466.8	395.1	340.8	
Age-adjusted HR	1 [Reference]	0.88 (0.82-0.95)	0.72 (0.67-0.79)	<.001	1 [Reference]	0.85 (0.78-0.92)	0.73 (0.66-0.81)	<.001
Multivariate HR ^e	1 [Reference]	0.95 (0.88-1.02)	0.83 (0.76-0.90)	<.001	1 [Reference]	0.89 (0.82-0.97)	0.80 (0.73-0.89)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH-AARP, National Institutes of Health-AARP (formerly American Association of Retired Persons) Diet and Health Study.¹²

^aUnless otherwise indicated, data are reported as HR (95% CI).

^bIncidence rates per 100 000 person-years standardized to the age distribution of the entire baseline NIH-AARP population.

^cAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), MHT (never, past, current, unknown, and data missing) in women only, and for 6-level smoking variable (never smokers, former smokers ≤1 pack per day, former smokers >1 pack per day, current smokers ≤1 pack per day, current smokers >1 pack per day, and data missing).

^dAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), MHT (never, past, current, unknown, and data missing) in women only, and for 32-level smoking variable (integrating smoking status [never, former, and current]), years since quitting for former smokers [≥10, 5-9, 1-4, and within the last year], smoking dose for both former and current smokers [1-10, 11-20, 21-30, 31-40, 41-60, and ≥61 cigarettes per day], and data missing for smoking).

^eAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), and MHT (never, past, current, unknown, and data missing) in women only.

Table 4. Results of Statistical Analysis for the Mediterranean Dietary Pattern (aMED) and Cause-Specific Mortality^a

Characteristic	aMED Score			P Value for Trend	aMED Score			P Value for Trend
	Men (n=214 284)				Women (n=166 012)			
	0-3	4-5	6-9		0-3	4-5	6-9	
Cancer								
Cases, No.	1608	1346	763		919	921	428	
Age-adjusted rates ^b	409.2	284.0	234.9		295.5	233.6	196.3	
Age-adjusted HR	1 [Reference]	0.69 (0.65-0.75)	0.57 (0.53-0.63)	<.001	1 [Reference]	0.79 (0.72-0.87)	0.67 (0.60-0.75)	<.001
Multivariate HR ^c	1 [Reference]	0.84 (0.78-0.91)	0.79 (0.73-0.87)	<.001	1 [Reference]	0.92 (0.83-1.01)	0.86 (0.76-0.97)	.01
Multivariate HR ^d	1 [Reference]	0.86 (0.80-0.93)	0.83 (0.76-0.91)	<.001	1 [Reference]	0.93 (0.85-1.02)	0.88 (0.78-1.00)	.04
Cardiovascular Disease								
Cases, No.	1012	952	461		446	400	180	
Age-adjusted rates ^b	257.9	201.0	142.3		144.5	101.3	82.2	
Age-adjusted HR	1 [Reference]	0.78 (0.71-0.85)	0.55 (0.49-0.61)	<.001	1 [Reference]	0.70 (0.61-0.80)	0.57 (0.48-0.67)	<.001
Multivariate HR ^c	1 [Reference]	0.94 (0.86-1.03)	0.76 (0.68-0.85)	<.001	1 [Reference]	0.85 (0.74-0.97)	0.79 (0.66-0.95)	.01
Multivariate HR ^d	1 [Reference]	0.95 (0.86-1.04)	0.78 (0.69-0.87)	<.001	1 [Reference]	0.85 (0.74-0.98)	0.81 (0.68-0.97)	.01
Other Causes								
Cases, No.	761	657	329		421	354	147	
Age-adjusted rates ^b	193.8	138.8	101.1		135.9	89.8	67.6	
Age-adjusted HR	1 [Reference]	0.72 (0.65-0.80)	0.52 (0.46-0.60)	<.001	1 [Reference]	0.66 (0.57-0.76)	0.50 (0.41-0.60)	<.001
Multivariate HR ^c	1 [Reference]	0.88 (0.79-0.98)	0.74 (0.65-0.85)	<.001	1 [Reference]	0.81 (0.70-0.94)	0.70 (0.58-0.86)	<.001
Multivariate HR ^d	1 [Reference]	0.90 (0.81-1.00)	0.77 (0.70-0.88)	<.001	1 [Reference]	0.82 (0.71-0.95)	0.72 (0.59-0.87)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH-AARP, National Institutes of Health–AARP (formerly American Association of Retired Persons) Diet and Health Study.¹²

^aUnless otherwise indicated, data are reported as HR (95% CI).

^bIncidence rates per 100 000 person-years standardized to the age distribution of the entire baseline NIH-AARP population.

^cAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), MHT (never, past, current, unknown, and data missing) in women only, and for 6-level smoking variable (never smokers, former smokers ≤1 pack per day, former smokers >1 pack per day, current smokers ≤1 pack per day, current smokers >1 pack per day, and data missing).

^dAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), MHT (never, past, current, unknown, and data missing) in women only, and for 32-level smoking variable (integrating smoking status [never, former, and current]), years since quitting for former smokers [≥10, 5-9, 1-4, and within the last year], smoking dose for both former and current smokers [1-10, 11-20, 21-30, 31-40, 41-60, and ≥61 cigarettes per day], and data missing for smoking).

respectively. Analysis for 1-point increments in the scores showed a 5% decrease ($P < .001$) in all-cause mortality for both men and women. Finer adjustment for smoking showed similar results.

Similar results were seen with the tMED score: the multivariate HRs for high vs low conformity for all-cause mortality in men and women were 0.79 (95% CI, 0.76-0.82) and 0.84 (95% CI, 0.79-0.89), respectively. Higher conformity with the tMED score also conferred decreased risks for cause-specific mortality. In men, the multivariate HRs for high vs low conformity for cancer and CVD mortality were 0.79 (95% CI, 0.72-0.87) and 0.76 (95% CI, 0.68-0.85), respectively. In women, a 20% decreased risk of CVD mortality was seen with tMED ($P < .01$) and a weaker relation for cancer mortality (HR, 0.89; 95% CI, 0.79-1.01) (data not shown).

In separate analyses excluding 1, 2, 3, and 5 years of follow-up, the association between the Mediterranean dietary pattern and all-cause mortality remained in both men and women (data not shown). Also, when smokers were excluded from the analyses, the associations between aMED and all-cause mortality remained statistically significant (Table 3). In sensitivity analysis using alternate sex-specific cut points, the distribution shifted

toward lower conformity (0-2), with only 1% of the population having a score of 9 points for aMED. Higher conformity to this modified score was also associated with a significantly lower risk of all-cause mortality (for men, $n = 408$; 95% CI, 0.71-0.87; for women, $n = 144$; 95% CI, 0.66-0.92) (data not shown).

We conducted stratified analysis of all-cause mortality examining subgroups of smoking and BMI (**Table 5**). The results in all subgroups, with the exception of those among never smokers with a BMI of 30.0 or higher, showed a statistically significant inverse association between the Mediterranean dietary pattern and all-cause mortality. This inverse association appeared to be more pronounced among smokers and especially among smokers with normal BMI (18.5-25.0). The multivariate HR in the latter subgroup comparing high vs low level of adherence was 0.54 (95% CI, 0.50-0.59) in men and 0.59 (95% CI, 0.53-0.66) in women. In high vs low conformity, the pattern also conferred a decreased risk of death among smokers with high BMI. When we compared participants with contrasting diet and lifestyle behavior such as those who were obese and ever smokers with low conformity with the Mediterranean pattern vs those who were lean and never smokers with high conformity with the

Table 5. Results of Statistical Analysis Between the Mediterranean Dietary Pattern and All-Cause Mortality Within Smoking Status and BMI Strata^a

Smoking Status/BMI	Variable	aMED Score			P Value for Trend
		0-3	4-5	6-9	
Men					
Never/18.5-25.0	Cases, No.	307	462	396	
	Age-adjusted rate ^b	640.8	531.1	480.1	
	Age-adjusted HR	1 [Reference]	0.83 (0.72-0.96)	0.75 (0.64-0.87)	<.001
Never/>25.0 to <30.0	Cases, No.	576	721	409	
	Age-adjusted rate ^b	643.4	582.1	455.7	
	Age-adjusted HR	1 [Reference]	0.91 (0.81-1.01)	0.71 (0.62-0.81)	<.001
Never/≥30.0	Cases, No.	321	348	158	
	Age-adjusted rate ^b	875.7	862.9	748.1	
	Age-adjusted HR	1 [Reference]	0.97 (0.83-1.13)	0.84 (0.69-1.02)	.09
Ever/18.5-25.0	Cases, No.	1909	1402	728	
	Age-adjusted rate ^b	1561.1	998.8	673.4	
	Age-adjusted HR	1 [Reference]	0.64 (0.60-0.69)	0.43 (0.40-0.47)	<.001
Ever/>25.0 to <30.0	Cases, No.	2623	2358	1165	
	Age-adjusted rate ^b	1181.0	910.8	700.9	
	Age-adjusted HR	1 [Reference]	0.77 (0.73-0.81)	0.59 (0.55-0.64)	<.001
Ever/≥30.0	Cases, No.	1294	1113	493	
	Age-adjusted rate ^b	1415.5	1195.2	995.9	
	Age-adjusted HR	1 [Reference]	0.85 (0.78-0.92)	0.71 (0.64-0.79)	<.001
Women					
Never/18.5-25.0	Cases, No.	368	475	285	
	Age-adjusted rate ^b	428.3	342.5	308.0	
	Age-adjusted HR	1 [Reference]	0.80 (0.70-0.92)	0.72 (0.62-0.84)	<.001
Never/>25.0 to <30.0	Cases, No.	311	414	173	
	Age-adjusted rate ^b	389.0	393.0	325.8	
	Age-adjusted HR	1 [Reference]	1.01 (0.87-1.17)	0.82 (0.68-0.99)	.07
Never/≥30.0	Cases, No.	349	310	120	
	Age-adjusted rate ^b	588.1	491.3	498.6	
	Age-adjusted HR	1 [Reference]	0.84 (0.72-0.98)	0.85 (0.69-1.05)	.046
Ever/18.5-25.0	Cases, No.	1228	1050	498	
	Age-adjusted rate ^b	1088.2	720.3	537.3	
	Age-adjusted HR	1 [Reference]	0.66 (0.61-0.72)	0.49 (0.44-0.55)	<.001
Ever/>25.0 to <30.0	Cases, No.	760	719	305	
	Age-adjusted rate ^b	890.8	676.6	547.3	
	Age-adjusted HR	1 [Reference]	0.76 (0.685-0.84)	0.61 (0.54-0.70)	<.001
Ever/≥30.0	Cases, No.	557	538	163	
	Age-adjusted rate ^b	1026.5	904.5	663.4	
	Age-adjusted HR	1 [Reference]	0.88 (0.79-1.00)	0.65 (0.55-0.78)	<.001
	Cases, No.				
	Age-adjusted rate ^b				
	Age-adjusted HR	1 [Reference]	0.95 (0.84-1.07)	0.74 (0.62-0.88)	.002

Abbreviations: aMED, alternate Mediterranean diet; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH-AARP, National Institutes of Health–AARP (formerly American Association of Retired Persons) Diet and Health Study.¹²

^aUnless otherwise indicated, data are reported as HR (95% CI). Stratified analysis was restricted to participants with no missing information for smoking and BMI and with BMI of at least 18.5.

^bIncidence rates per 100 000 person-years standardized to the age distribution of the entire baseline NIH-AARP population.

^cAdjusted for age (continuous), race (white, black, other, and data missing), total energy (continuous), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40, and data missing), education (less than high school, high school, some college, college/postgraduate college, and data missing), marital status (married, not currently married, and data missing), physical activity (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥5 times per week, and data missing), MHT (never, past, current, unknown, and data missing) in women only, and for 6-level smoking variable (never smokers, former smokers ≤1 pack per day, former smokers >1 pack per day, current smokers ≤1 pack per day, current smokers >1 pack per day, and data missing).

diet, among the latter there was a 56% (95% CI, 0.39-0.49) decreased risk of death in men and a 61% (95% CI, 0.34-0.45) decreased risk in women, and the test for interaction was statistically significant ($P < .001$ for interaction) (data not shown).

COMMENT

In this large, prospective US study, conformity with the Mediterranean dietary pattern was associated with lower mortality. The inverse association in men and women remained statistically significant after restricting the analysis to nonsmokers. We also found similar results using different aMED cut points. The beneficial effect of the Mediterranean pattern was more pronounced in smokers, especially among smokers with a BMI of 18.5 to 25.0.

To our knowledge, 9 cohort studies (8 in Europe^{3-7,9-11} and 1 in Australia⁸) have used variations of the original score¹¹ to assess the Mediterranean diet and mortality relation. Despite these modifications, all studies reported inverse associations between the Mediterranean dietary pattern and mortality.²¹

Although our primary analysis was based on aMED, we also examined tMED, which includes dairy and total meat products and does not distinguish between total grains and whole grains.^{4,11} Recent evidence suggests that high glycemic load has adverse effects on blood lipid levels and is associated with an increased risk of CVD but that whole grains are beneficial, and therefore, the effects of grain products may depend on the degree of processing.^{22,23} In addition, the range of alcohol consumption in tMED is wider than that in most US studies. Although a higher intake of alcohol has been shown to be protective against heart disease,²⁴ it also increases the risk of several types of cancer.²⁵ In our study, higher conformity with tMED was also inversely associated with all-cause and cause-specific mortality in both men and women, indicating that both scores showed a beneficial effect on mortality.

In our study, the beneficial effect of the pattern was more pronounced among smokers with high conformity with the diet. Similarly, another study found that risk was lower among smokers with the highest conformity with the Mediterranean diet.⁶ Furthermore, the apparent benefit of high conformity with the Mediterranean dietary pattern was more pronounced among lean or overweight individuals, particularly among smokers. This held true for both men and women. Possibly, conformity with the Mediterranean diet plays a particularly important role among smokers, who are characterized by high levels of oxidative stress and an adverse blood lipid profile.²⁶ On the other hand, among obese individuals who do not smoke, conformity with the Mediterranean diet might not play so much of a role because the increased risk of death due to obesity may mask the inverse association of the Mediterranean diet with all-cause mortality. However, to our knowledge, this is the first study of mortality that examines the effect of the Mediterranean dietary pattern within both smoking and BMI strata, and therefore, additional studies should further investigate this finding.

The beneficial effect of the Mediterranean diet on mortality may be mediated by a number of mechanisms, including oxidative stress and chronic inflammation. Conformity with the Mediterranean dietary pattern is associated with high antioxidant capacity and low concentrations of oxidized low-density lipoprotein cholesterol,²⁷ suggesting that this dietary pattern could be capturing the combined effect of dietary antioxidants, which could, partially, explain a lower risk of mortality. The Mediterranean diet also includes other important dietary constituents such as fiber and a low omega-6-omega-3 fatty acid ratio, both of which potentially prevent cancer initiation and progression.^{28,29}

Additionally, chronic inflammation has been associated with a higher risk of CVD and possibly cancer.^{30,31} Conformity with the Mediterranean dietary pattern has also been associated with lower levels of C-reactive protein, interleukin-6, homocysteine, and fibrinogen and with lower white blood cell counts.³² In 1 US study,² it was associated with lower concentrations of biomarkers of inflammation and endothelial dysfunction.

To our knowledge, the present study is the first and largest US cohort to evaluate the Mediterranean dietary pattern and mortality. Although using such a score in an American population might not adequately represent conformity with the traditional Mediterranean diet, it does include the key features of this diet and, as we have shown, may have a substantial beneficial impact on mortality in the United States.

Because of concern that the median intake of some dietary components might be lower in the US population than in a Mediterranean population, we considered alternate cut points. Using this approach, we assigned points to only the highest intakes, and the diets consumed were more compatible with the traditional Mediterranean diet. This sensitivity analysis showed that higher conformity with the diet was also associated with a significantly lower risk of mortality, confirming that it was reasonable to use the median of intake as the cut point for constructing the score.

The Mediterranean dietary pattern has the potential to minimize confounding by including nutritional confounders in the score and capturing effect modification among the nutritional variables.³³ Smoking was associated with decreased conformity with the diet and may therefore confound the association between the Mediterranean dietary pattern and mortality. Although we carefully adjusted for smoking, this may not be sufficient to address potential confounding by smoking. We had adequate statistical power to restrict the analysis to participants who had never smoked (approximately 69 000 men and 76 000 women). When we did so, the relation of dietary pattern to mortality remained unchanged.

Food frequency questionnaires are known to contain a certain degree of measurement error, as suggested by studies using recovery biomarkers of energy and protein intakes.³⁴ Therefore, results that depend on FFQs to assess diet and risk of chronic disease might be affected by this measurement error.³⁵ In the present study, all individual components of the score were adjusted for total energy intake (density method) and standardized to 2000 calories in women and 2500 calories in men. Total energy intake was also included as a covariate in the model

to achieve the equivalent of an isocaloric diet and to reduce measurement error in the score.³⁴

In conclusion, this large prospective study demonstrates that higher conformity with the Mediterranean dietary pattern is associated with lower all-cause and cause-specific mortality. These findings confirm results from previous studies and suggest that the Mediterranean dietary score is a useful tool for evaluating diet and mortality in a non-Mediterranean US population.

Accepted for Publication: July 20, 2007.

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Financial Disclosure: None reported.

Funding/Support: This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Role of the Sponsors: The funding organization had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: The participants in the NIH-AARP Diet and Health Study provided outstanding cooperation; Neal Freedman, PhD, and Douglas Midthune, MA, provided statistical advice; and Tawanda Roy, BA, provided research assistance.

REFERENCES

1. Trichopoulos A. Traditional Mediterranean diet and longevity in the elderly: a review. *Public Health Nutr.* 2004;7(7):943-947.
2. Fung TT, McCullough ML, Newby PK, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr.* 2005;82(1):163-173.
3. Lagiou P, Trichopoulos D, Sandin S, et al. Mediterranean dietary pattern and mortality among young women. *Br J Nutr.* 2006;96(2):384-392.
4. Trichopoulos A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med.* 2003;348(26):2599-2608.
5. Trichopoulos A, Orfanos P, Norat T, et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ.* 2005;330(7498):991.
6. Haveman-Nies A, de Groot LP, Burema J, Cruz JA, Osler M, van Staveren WA. Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans: the SENECA study. *Am J Epidemiol.* 2002;156(10):962-968.
7. Knuops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA.* 2004;292(12):1433-1439.
8. Kouris-Blazos A, Gnardellis C, Wahlqvist ML, Trichopoulos D, Lukito W, Trichopoulou A. Are the advantages of the Mediterranean diet transferable to other populations? a cohort study in Melbourne, Australia. *Br J Nutr.* 1999;82(1):57-61.
9. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. *Am J Clin Nutr.* 2000;71(4):987-992.
10. Osler M, Schroll M. Diet and mortality in a cohort of elderly people in a north European community. *Int J Epidemiol.* 1997;26(1):155-159.
11. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. *BMJ.* 1995;311(7018):1457-1460.
12. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions. *Am J Epidemiol.* 2001;154(12):1119-1125.
13. Michaud D, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Registry Manage.* 2005;32:70-75.
14. National Cancer Institute. SEER Cause of Death Recode 1969+ (9/17/2004). http://seer.cancer.gov/codrecode/1969+_d09172004/index.html. Accessed May 28, 2007.
15. National Cancer Institute. Diet History Questionnaire. <http://riskfactor.cancer.gov/DHQ/>. Accessed May 28, 2007.
16. Thompson FE, Kipnis V, Midthune D, et al. Performance of a food frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study [published online ahead of print July 5, 2007]. *Public Health Nutr.*
17. Millen AE, Midthune D, Thompson FE, Kipnis V, Subar AF. The National Cancer Institute diet history questionnaire. *Am J Epidemiol.* 2006;163(3):279-288.
18. Cox DR. Regression models and life tables. *J Royal Stat Soc.* 1972;B34:187-220.
19. Horvitz DG, Thompson DJ. A generalization of sampling without replacement from a finite universe. *J Am Stat Assoc.* 1952;47:663-685.
20. Breslow N, Day N. *Statistical Methods in Cancer Research.* Lyon, France: International Agency for Research on Cancer; 1987.
21. Serra-Majem L, Trichopoulou A, Ngo de la Cruz J, et al. Does the definition of the Mediterranean diet need to be updated? *Public Health Nutr.* 2004;7(7):927-929.
22. Edge MS, Jones JM, Marquart L. A new life for whole grains. *J Am Diet Assoc.* 2005;105(12):1856-1860.
23. Slavin J, Jacobs D, Marquart L. Whole-grain consumption and chronic disease: protective mechanisms. *Nutr Cancer.* 1997;27(1):14-21.
24. Grønbaek M. Factors influencing the relation between alcohol and cardiovascular disease. *Curr Opin Lipidol.* 2006;17(1):17-21.
25. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol.* 2006;7(2):149-156.
26. Yanbaeva DG, Dentener MA, Creutzberg E, Wouters EF. Systemic effects of smoking. *Chest.* 2007;131(5):1557-1566.
27. Pitsavos C, Panagiotakos D, Trichopoulou A, et al. Interaction between Mediterranean diet and methylenetetrahydrofolate reductase C677T mutation on oxidized low density lipoprotein concentrations: the ATTICA study. *Nutr Metab Cardiovasc Dis.* 2006;16(2):91-99.
28. Klurfeld DM. Dietary fibre-mediated mechanisms in carcinogenesis. *Cancer Res.* 1992;52(7)(suppl):2055s-2059s.
29. Simopoulos AP. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation. *Biomed Pharmacother.* 2006;60(9):502-507.
30. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA.* 1998;279(18):1477-1482.
31. Lawrence T. Inflammation and cancer: a failure of resolution? *Trends Pharmacol Sci.* 2007;28(4):162-165.
32. Chrysohou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA study. *J Am Coll Cardiol.* 2004;44(1):152-158.
33. Trichopoulou A, Critselis E. Mediterranean diet and longevity. *Eur J Cancer Prev.* 2004;13(5):453-456.
34. Kipnis V, Subar AF, Midthune D, et al. Structure of dietary measurement error: results of the OPEN biomarker study. *Am J Epidemiol.* 2003;158(1):14-26.
35. Kristal AR, Peters U, Potter JD. Is it time to abandon the food frequency questionnaire? *Cancer Epidemiol Biomarkers Prev.* 2005;14(12):2826-2828.