ORIGINAL INVESTIGATION

ONLINE FIRST

Vegetarian Dietary Patterns and Mortality in Adventist Health Study 2

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Importance: Some evidence suggests vegetarian dietary patterns may be associated with reduced mortality, but the relationship is not well established.

Objective: To evaluate the association between vegetarian dietary patterns and mortality.

Design: Prospective cohort study; mortality analysis by Cox proportional hazards regression, controlling for important demographic and lifestyle confounders.

Setting: Adventist Health Study 2 (AHS-2), a large North American cohort.

Participants: A total of 96 469 Seventh-day Adventist men and women recruited between 2002 and 2007, from which an analytic sample of 73 308 participants remained after exclusions.

Exposures: Diet was assessed at baseline by a quantitative food frequency questionnaire and categorized into 5 dietary patterns: nonvegetarian, semi-vegetarian, pesco-vegetarian, lacto-ovo–vegetarian, and vegan.

Main Outcome and Measure: The relationship between vegetarian dietary patterns and all-cause and cause-specific mortality; deaths through 2009 were identified from the National Death Index.

Results: There were 2570 deaths among 73 308 participants during a mean follow-up time of 5.79 years. The mortality rate was 6.05 (95% CI, 5.82-6.29) deaths per 1000 person-years. The adjusted hazard ratio (HR) for all-cause mortality in all vegetarians combined vs nonvegetarians was 0.88 (95% CI, 0.80-0.97). The adjusted HR for all-cause mortality in vegans was 0.85 (95% CI, 0.73-1.01); in lacto-ovo–vegetarians, 0.91 (95% CI, 0.82-1.00); in pesco-vegetarians, 0.81 (95% CI, 0.69-0.94); and in semi-vegetarians, 0.92 (95% CI, 0.75-1.13) compared with nonvegetarians. Significant associations with vegetarian diets were detected for cardiovascular mortality, noncardiovascular noncancer mortality, renal mortality, and endocrine mortality. Associations in men were larger and more often significant than were those in women.

Conclusions and Relevance: Vegetarian diets are associated with lower all-cause mortality and with some reductions in cause-specific mortality. Results appeared to be more robust in males. These favorable associations should be considered carefully by those offering dietary guidance.

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THE POSSIBLE RELATIONSHIP between diet and mortality remains an important area of investigation. Previous studies have identified dietary factors associated with mortality. Those found to correlate with reduced mortality include nuts,[1-4] fruit,[5,6] cereal fiber,[2] polyunsaturated fatty acids (PUFAs),[2] ω-3PUFAs,[3] green salad,[7] Mediterranean dietary patterns,[8-11] "healthy" or "prudent" dietary patterns,[10,12,13] plant-based diet scores,[14] plant-based low-carbohydrate diets,[15] and vegetarian diets.[4,16,17] Associations with increased mortality have been found for a high glycemic load,[2] meat,[6,7] red meat,[18,19] processed meat,[18,19] eggs,[7] potatoes,[5] increased energy intake,[20] and animal-based low-carbohydrate diets.[15]

See Invited Commentary

Vegetarian dietary patterns may contain many of the above-listed foods and nutrients associated with reduced mortality while having reduced intakes of some foods associated with increased mortality. Vegetarian dietary patterns have been associated with reductions in risk for sev-

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eral chronic diseases, such as hypertension,[21,22] metabolic syndrome,[23] diabetes mellitus,[24,25] and ischemic heart disease (IHD),[17,26] which might be expected to result in lower mortality. Vegetarian diets represent common, real-world dietary patterns and are thus attractive targets for study.

Previous studies of the relationship between vegetarian dietary patterns and mortality have yielded mixed results. In the first Adventist Health Study, a study of 34 198 California Seventh-day Adventists,[27] vegetarian dietary patterns were associated with reduced all-cause mortality and increased longevity.[4,17] In contrast, the European Prospective Investigation into Cancer and Nutrition–Oxford (EPIC-Oxford) cohort study did not show an all-cause mortality advantage for British vegetarians (among 47 254 vegetarian and nonvegetarian participants),[28] and pooled results have shown reductions only for IHD mortality.[16]

Our objective, in light of the potential benefits of vegetarian diets and the existing uncertainty in the literature, was to evaluate the possible association of vegetarian dietary patterns with reduced mortality in a large American cohort including many vegetarians.

METHODS

STUDY POPULATION

Adventist Health Study 2 (AHS-2) is a cohort of 96 469 Seventh-day Adventist men and women recruited at churches in the United States and Canada between 2002 and 2007.[29] Butler et al[29] provided a detailed explanation of the cohort formation and characteristics. Written informed consent was obtained from all participants upon enrollment. The study was approved by the institutional review board of Loma Linda University.

Exclusions were applied in the following order: missing data for questionnaire return date, birth date, sex, or race (n = 1702); age younger than 25 years (n = 434); estimated energy intake (not including write-in items) less than 500 kcal/d or more than 4500 kcal/d; improbable response patterns (eg, identical responses to all questions on a page) or more than 69 missing values in dietary data (n = 4961); non-US residents (n = 4108); or history of a specific prior cancer diagnosis (except nonmelanoma skin cancers) or of cardiovascular disease (CVD) (coronary bypass, angioplasty/stent, carotid artery surgery, myocardial infarction, or stroke; or angina pectoris or congestive heart failure treated in the past 12 months) (n = 11 956). After exclusions, there remained an analytic sample of 73 308.

MORTALITY DATA

Mortality data through December 31, 2009, were obtained from the National Death Index. *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) codes for the underlying cause of death were used for causal classification. Unnatural causes of death (*ICD-10* letters U, V, W, X, and Y) were considered as censoring events. Deaths associated with IHD were identified as *ICD-10* I20-25; CVD deaths, as those starting with the letter I; and cancer deaths, as those starting with the letter C. Noncardiovascular, noncancer deaths were identified as all natural deaths not classified as CVD or cancer deaths. Infectious disease deaths were identified as those starting with the letters A or B; neurologic deaths, the letter G; respiratory deaths, the letter J; renal deaths, the letter N; and endocrine deaths, the letter E. Stroke deaths were identified using the code I60-69; diabetes mellitus deaths, E10-14; and renal failure deaths, N17-19.

DIETARY DATA

Usual dietary intake during the previous year was assessed at baseline by a self-administered quantitative food frequency questionnaire of more than 200 food items. Dietary patterns were determined according to the reported intake of foods of animal origin. Thus, vegans consumed eggs/dairy, fish, and all other meats less than 1 time/mo; lacto-ovo–vegetarians consumed eggs/dairy 1 time/mo or more but fish and all other meats less than 1 time/mo; pesco-vegetarians consumed fish 1 time/mo or more but all other meats less than 1 time/mo; semi-vegetarians consumed nonfish meats 1 time/mo or more and all meats combined (fish included) 1 time/mo or more but no more than 1 time/wk; and last, nonvegetarians consumed nonfish meats 1 time/mo or more and all meats combined (fish included) more than 1 time/wk. For some analyses, the 4 vegetarian categories (vegan, lacto-ovo–vegetarian, pesco-vegetarian, and semi-vegetarian) were combined as "vegetarian." The food frequency questionnaire was previously validated against six 24-hour dietary recalls for intake of nutrients[30] and selected foods/food groups.[31] Validity correlations for red meat, poultry, fish, dairy, and eggs were 0.76, 0.76, 0.53, 0.86, and 0.64, respectively, in whites and 0.72, 0.77, 0.57, 0.82, and 0.52, respectively, in blacks.[31] Mean duration of adherence to dietary patterns was calculated for respondents to a follow-up questionnaire in which participants were asked to characterize their consumption of meat and dairy products at that time and in previous decades.

COVARIATES

Other variables, all measured at baseline, were as follows (**Table 1** footnotes for category specification): sex (dichotomous), race (dichotomous), geographic region (6 levels), personal income (4 levels), educational level (4 levels), marital status (dichotomous), smoking (8 levels), alcohol use (5 levels), exercise (ie, "vigorous activities, such as brisk walking, jogging, bicycling, etc, long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath") (5 levels), sleep (3 levels), menopausal status of women (dichotomous), hormone therapy in postmenopausal women (dichotomous), dietary energy (7 levels: <1000 kcal, 1000-1499 kcal,1500-1999 kcal, 2000-2499 kcal, 2500-2999 kcal, 3000-3999 kcal, and ≥4000 kcal), body mass index (calculated as weight in kilograms divided by height in meters squared) (9 levels: <18, 18 to <20, 20 to <23, 23 to <25, 25 to <27, 27 to <30, 30 to <35, 35 to <40, and ≥40). Race was included as a potentially important covariate. Participants self-identified their race/ethnicity in 1 or more of 21 categories. Those self-identifying as black/African American, West Indian/Caribbean, African, or other black were categorized as black for this analysis and all others were categorized as nonblack.

STATISTICAL ANALYSIS

Baseline descriptive statistics were calculated according to the 5 dietary-pattern categories. Means and percentages were adjusted for age, sex, and race by direct standardization using the entire analytic sample as the standard distribution. Age-sex-race standardized mortality rates were computed by dietary pattern. Analyses of mortality were performed using Cox proportional hazards regression with attained age as the time variable and left truncation by age at study entry. Covariates were selected on an a priori basis as likely confounders based on prior studies and suspected relationships. Menopausal status and hormone therapy were represented in models as nested covariates (ie, sex + [sex × menopause] + [sex × menopause × hor-

Table 1. Comparison of Vegetarian With Nonvegetarian Dietary Patterns With Respect to All-Cause and Cause-Specific Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009

	Deaths, Hazard Ratio (95% CI)				
Characteristic	All-Cause	Ischemic Heart Disease	Cardiovascular Disease	Cancer	Other
All (N = 73 308), No. of deaths[a,b]	2560	372	987	706	867
Vegetarian	0.88 (0.80-0.97)	0.81 (0.64-1.02)	0.87 (0.75-1.01)	0.92 (0.78-1.08)	0.85 (0.73-0.99)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Men (n = 25 105), No. of deaths[a]	1031	169	390	273	368
Vegetarian	0.82 (0.72-0.94)	0.71 (0.51-1.00)	0.71 (0.57-0.90)	1.02 (0.78-1.32)	0.83 (0.66-1.04)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Women (n = 48 203), No. of deaths[a,c]	1529	203	597	433	499
Vegetarian	0.93 (0.82-1.05)	0.88 (0.65-1.20)	0.99 (0.83-1.18)	0.87 (0.71-1.07)	0.88 (0.72-1.08)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

[a] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/wk, 21-60 min/wk, 61-150 min/wk, and ≥151 min/wk), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night);

[b] Also adjusted by sex (male and female), menopause (in women) (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[c] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

mone therapy]). Covariates were tested for possible interaction with the diet variable and for suspected interactions between selected covariates. The Cox proportional hazards assumption was evaluated using Schönfeld residuals, log (−log) plots, and attained-age interaction terms. Significant nonproportionality of hazards was present for race and marital status, so attained-age interaction terms for these variables were retained in the models. Residual methods were used to evaluate possible outliers and influential data points; no data points required removal. Multiple imputation of missing values was done for the small amount of missing data in the dietary variables used to calculate vegetarian status and for all covariates; a guided multiple-imputation approach was used when possible,[32] as we have evidence that many of the missing dietary data are true zeroes.[33] Analyses were performed using commercial software (SAS, version 9.3; SAS Institute, Inc). Guided multiple imputation was performed using R, version 2.13.1 software[34] and the Hmisc package.[35]

RESULTS

BASELINE CHARACTERISTICS

Among the 73 308 individuals in our analytic sample, 5548 (7.6%) were vegans, 21 177 (28.9%) were lacto-ovo–vegetarians, 7194 (9.8%) were pesco-vegetarians, 4031 (5.5%) were semi-vegetarians, and 35 359 (48.2%) were nonvegetarians. **Table 2** presents characteristics of the participants at baseline according to the 5 dietary patterns. Percentages and means were age-sex-race standardized as appropriate. Vegetarian groups tended to be older, more highly educated, and more likely to be married, to drink less alcohol, to smoke less, to exercise more, and to be thinner. The proportion of blacks was highest among pesco-vegetarians and lowest in lacto-ovo–vegetarians. Of postmenopausal women, far fewer vegans were receiving hormone therapy. Mean reported duration of adherence to current dietary pattern (not included in Table 2) was 21 years for vegans, 39 years for lacto-ovo–vegetarians, 19 years for pesco-vegetarians, 24 years for semi-vegetarians, and 48 years for nonvegetarians.

MORTALITY

The mean (SD) follow-up time was 5.79 (1.31) years. During this time, there were 2570 deaths among 73 308 participants, and the overall mortality rate was 6.05 (95% CI, 5.82-6.29) deaths per 1000 person-years. **Table 3** gives the age-sex-race standardized mortality rates by dietary pattern. Vegans, lacto-ovo–vegetarians, and pesco-vegetarians had significantly lower mortality rates compared with nonvegetarians.

Table 1 reports the comparison of multivariate-adjusted risk of death for all vegetarians combined with that for nonvegetarians. Vegetarians had 0.88 (95% CI, 0.80-0.97) times the risk of all-cause mortality of nonvegetarians. In men, the hazard ratio (HR) was 0.82 (95% CI, 0.72-0.94) and in women, 0.93 (0.82-1.05). Significantly reduced risk in both sexes combined was also seen for other mortality (ie, non-CVD, noncancer) (HR, 0.85; 95% CI, 0.73-0.99) but not clearly for IHD mortality (0.81; 0.64-1.02), CVD mortality (0.87; 0.75-1.01), or cancer mortality (0.92; 0.78-1.08). For men, CVD mortality (0.71; 0.57-0.90) and IHD mortality (0.71; 0.51-1.00) achieved significance, and other mortality had a notable but nonsignificant reduction (0.83; 0.66-1.04). In women, there were no significant reductions in these causal categories of mortality, although the effect estimates for IHD mortality, cancer mortality, and other mortality were moderately less than 1.0. Results (not included in table) for stroke were, for both sexes combined, HR, 1.10 (95% CI, 0.82-1.47); for men, 0.83 (0.52-1.31); and for women, 1.27 (0.89-1.80).

Table 4 reports the comparison of the multivariate-adjusted risk of death for 4 categories of vegetarians com-

Table 2. Standardized Distribution of Baseline Characteristics Among 73 308 Adventist Health Study 2 Participants According to Dietary Pattern[a]

	No. (%)				
	Vegetarian				Nonvegetarian
Characteristic	Vegan	Lacto-Ovo	Pesco	Semi	
Participants	5548 (7.6)	21 177 (28.9)	7194 (9.8)	4031 (5.5)	35 359 (48.2)
Age, mean (SD), y	57.9 (13.6)	57.5 (13.9)	58.8 (13.7)	57.8 (14.1)	55.9 (13.1)
Sex, women	3533 (63.8)	13 644 (64.9)	4925 (68.0)	2785 (69.7)	23 315 (65.3)
Race, black	1139 (21.0)	2823 (13.6)	2745 (39.1)	711 (17.8)	12 362 (34.0)
Marital status, married	4227 (75.6)	16 634 (76.3)	5081 (73.1)	2868 (71.5)	24 575 (70.3)
Personal income, $1000/y					
≤20.0	2736 (48.8)	8414 (38.4)	2762 (37.7)	1696 (41.0)	13 911 (40.3)
20.1-50.0	1983 (36.3)	8520 (41.2)	2818 (38.7)	1570 (39.2)	14 253 (39.6)
50.1-100.0	646 (11.8)	3238 (15.9)	1282 (18.3)	616 (16.2)	5777 (16.0)
≥100.0	182 (3.1)	1005 (4.6)	332 (5.3)	148 (3.6)	1417 (4.1)
Educational level					
High school or less	968 (16.7)	3005 (13.9)	1426 (18.4)	859 (21.3)	8455 (24.4)
Trade school, associate degree, or some college	2175 (39.4)	7534 (35.7)	2755 (38.1)	1605 (39.2)	15 014 (42.2)
Bachelor degree	1341 (24.4)	5386 (25.3)	1575 (23.0)	858 (21.3)	6857 (19.2)
Graduate degree	1063 (19.5)	5251 (25.1)	1439 (20.5)	708 (18.3)	5032 (14.1)
Geographic region					
West	1117 (19.6)	4696 (20.8)	1446 (21.9)	950 (22.5)	7262 (21.9)
Northwest	854 (14.2)	3765 (15.2)	882 (14.2)	663 (14.6)	4056 (12.7)
Mountain	188 (3.2)	866 (3.6)	199 (3.2)	178 (4.1)	1453 (4.5)
Midwest	1103 (19.6)	3860 (18.3)	970 (14.1)	802 (19.8)	6704 (19.2)
East	556 (10.7)	2212 (12.0)	1493 (18.0)	415 (11.4)	5347 (13.7)
South	1731 (32.8)	5778 (30.1)	2204 (28.6)	1022 (27.7)	10 536 (28.0)
Postmenopausal[b]	2056 (54.7)	7667 (53.7)	2669 (53.1)	1572 (53.7)	11 647 (52.9)
Hormone therapy[c]	166 (8.2)	1312 (19.6)	381 (16.7)	312 (25.0)	2131 (22.8)
Alcohol consumption					
None	5487 (98.8)	20 484 (96.8)	6720 (92.5)	3722 (92.4)	29 502 (83.4)
Rare	33 (0.6)	386 (1.8)	257 (4.0)	176 (4.2)	2652 (7.5)
Monthly	11 (0.2)	112 (0.5)	68 (1.1)	42 (1.1)	1083 (3.1)
Weekly	13 (0.3)	154 (0.7)	119 (1.9)	76 (2.0)	1652 (4.7)
Daily	3 (0.1)	41 (0.2)	31 (0.5)	14 (0.3)	470 (1.3)
Smoking					
Never	4697 (85.0)	18 748 (88.2)	6092 (84.1)	3312 (81.4)	26 866 (75.7)
Quit, y					
≥30	335 (5.6)	1019 (4.6)	393 (5.3)	264 (6.5)	2076 (6.4)
20-29	262 (4.7)	606 (3.2)	310 (4.4)	157 (4.3)	1939 (5.5)
10-19	156 (2.8)	471 (2.4)	224 (3.4)	148 (4.0)	1866 (5.2)
5-9	53 (1.0)	178 (0.8)	82 (1.3)	72 (1.8)	844 (2.3)
1-4	38 (0.6)	110 (0.5)	57 (0.9)	53 (1.4)	794 (2.2)
<1	3 (0.0)	20 (0.1)	11 (0.2)	11 (0.4)	233 (0.6)
Current	4 (0.1)	25 (0.1)	26 (0.4)	13 (0.3)	741 (2.0)
Exercise, min/wk[d]					
None	882 (15.1)	3753 (17.3)	1354 (18.0)	873 (20.6)	8061 (23.4)
≤20	889 (16.2)	3971 (18.6)	1217 (16.8)	809 (20.5)	7196 (20.0)
21-60	885 (16.1)	3486 (16.5)	1151 (16.2)	627 (16.1)	5684 (15.8)
61-150	1525 (27.8)	5619 (26.8)	1941 (27.5)	980 (24.5)	8366 (23.6)
≥151	1367 (24.8)	4349 (20.8)	1531 (21.6)	742 (18.3)	6051 (17.2)
Sleep, h/night					
≤4	107 (2.1)	252 (1.6)	203 (2.5)	73 (2.2)	1250 (3.2)
5-8	5154 (93.0)	19 668 (93.0)	6634 (92.2)	3728 (92.5)	32 283 (91.3)
≥9	287 (4.9)	1256 (5.4)	358 (5.3)	230 (5.3)	1826 (5.5)
BMI, mean (SD)	24.1 (4.7)	26.1 (5.3)	26.0 (5.0)	27.3 (5.6)	28.3 (6.1)
Energy intake, mean (SD), kcal/d	1897 (729)	1912 (735)	1939 (772)	1720 (713)	1884 (773)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Multiple imputation of missing values was used to calculate all values. All counts are actual and unadjusted. Means and percentages were standardized by age, sex, and race, as appropriate, by the direct standardization technique using the entire analytic sample as the standard distribution.

[b] Among women only.

[c] Among postmenopausal women.

[d] Exercise defined as "vigorous activities, such as brisk walking, jogging, bicycling, etc, long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath."

pared with nonvegetarians. Pesco-vegetarians had significantly reduced risk in both sexes combined for all-cause mortality (HR, 0.81; 95% CI, 0.69-0.94), IHD mortality (0.65; 0.43-0.97), and other mortality (0.71;

Table 3. Age-Sex-Race Standardized Mortality Rates Among 73 308 Adventist Health Study 2 Participants According to Dietary Pattern

Characteristic	No. of People	Time, Person-years	Mean Time, y	Deaths	Death Rate, Deaths/1000 Person-years (95% CI)[a]	*P* Value[b]
Vegetarian[c]						
Vegan	5548	32 810.3	5.92	197	5.40 (4.62-6.17)	.009
Lacto-ovo	21 177	124 660.5	5.88	815	5.61 (5.21-6.01)	.001
Pesco	7194	41 225.7	5.73	251	5.33 (4.61-6.05)	.004
Semi	4031	23 714.6	5.86	160	6.16 (5.03-7.30)	.30
Nonvegetarian	35 359	202 098.4	5.72	1147	6.61 (6.21-7.03)	
All participants	73 308	424 509.4	5.79	2570	6.05 (5.82-6.29)	

[a] Adjusted for age, race, and sex by direct standardization.
[b] From *Z* tests that test null hypotheses of no difference from the nonvegetarian death rate.
[c] Dietary pattern classified after multiple imputation of missing values. Values for number of people, person time, mean time, deaths, and death rate represent the mean of values from 5 imputed data sets; thus, summed values for number of people, person-time, and deaths may not equal the value for all participants.

Table 4. Associations of Dietary Patterns With All-Cause and Cause-Specific Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009

	Deaths, Hazard Ratio (95% CI)				
Characteristic	All-Cause	Ischemic Heart Disease	Cardiovascular Disease	Cancer	Other
All (N = 73 308), No. of deaths[a,b]	2560	372	987	706	867
Vegetarian					
Vegan	0.85 (0.73-1.01)	0.90 (0.60-1.33)	0.91 (0.71-1.16)	0.92 (0.68-1.24)	0.74 (0.56-0.99)
Lacto-ovo	0.91 (0.82-1.00)	0.82 (0.62-1.06)	0.90 (0.76-1.06)	0.90 (0.75-1.09)	0.91 (0.77-1.07)
Pesco	0.81 (0.69-0.94)	0.65 (0.43-0.97)	0.80 (0.62-1.03)	0.94 (0.72-1.22)	0.71 (0.54-0.94)
Semi	0.92 (0.75-1.13)	0.92 (0.57-1.51)	0.85 (0.63-1.16)	0.94 (0.66-1.35)	0.99 (0.72-1.36)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Men (n = 25 105), No. of deaths[a]	1031	169	390	273	368
Vegetarian					
Vegan	0.72 (0.56-0.92)	0.45 (0.21-0.94)	0.58 (0.38-0.89)	0.81 (0.48-1.36)	0.81 (0.53-1.22)
Lacto-ovo	0.86 (0.74-1.01)	0.76 (0.52-1.12)	0.77 (0.59-0.99)	1.01 (0.75-1.37)	0.89 (0.69-1.15)
Pesco	0.73 (0.57-0.93)	0.77 (0.45-1.30)	0.66 (0.44-0.98)	1.10 (0.73-1.67)	0.60 (0.39-0.93)
Semi	0.93 (0.68-1.26)	0.73 (0.33-1.60)	0.75 (0.43-1.32)	1.15 (0.65-2.03)	1.03 (0.62-1.71)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Women (n = 48 203), No. of deaths[a,c]	1529	203	597	433	499
Vegetarian					
Vegan	0.97 (0.78-1.20)	1.39 (0.87-2.24)	1.18 (0.88-1.60)	0.99 (0.69-1.44)	0.70 (0.47-1.05)
Lacto-ovo	0.94 (0.83-1.07)	0.85 (0.59-1.22)	0.99 (0.81-1.22)	0.85 (0.67-1.09)	0.93 (0.75-1.17)
Pesco	0.88 (0.72-1.07)	0.51 (0.26-0.99)	0.90 (0.66-1.23)	0.86 (0.61-1.21)	0.81 (0.58-1.15)
Semi	0.92 (0.70-1.22)	1.09 (0.60-1.98)	0.93 (0.64-1.34)	0.85 (0.56-1.30)	0.97 (0.64-1.47)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

[a] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/week, 21-60 min/week, 61-150 min/week, and ≥151 min/week), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night).
[b] Also adjusted by sex (male and female), menopause (in women) (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy);
[c] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (postmenopausal women) (not taking hormone therapy, taking hormone therapy).

0.54-0.94); in men for all-cause mortality (0.73; 0.57-0.93), CVD mortality (0.66; 0.44-0.98), and other mortality (0.60; 0.39-0.93); and in women for IHD mortality (0.51; 0.26-0.99). Lacto-ovo–vegetarians had significantly reduced risk in both sexes combined for all-cause mortality (HR, 0.91; 95% CI, 0.82-1.00) and in men for CVD mortality (0.77; 0.59-0.99). Vegans had significantly reduced risk in both sexes combined for other mortality (HR, 0.74; 95% CI, 0.56-0.99) and in men for all-cause mortality (0.72; 0.56-0.92), IHD mortality (0.45; 0.21-0.94), and CVD mortality (0.58;0.38-0.89).

Table 5 presents the results of multivariate-adjusted Cox analyses for several more-specific categories of mortality within the broad "other" mortality of Table 1 (ie, non-CVD, noncancer mortality), comparing all vegetarians with nonvegetarians. In men and women combined, vegetarians had a significantly reduced risk of renal mortality (HR, 0.48; 95% CI, 0.28-0.82) and endocrine mortality (0.61;

Table 5. Comparison of Vegetarian With Nonvegetarian Dietary Patterns With Respect to Categories of Noncancer, Noncardiovascular Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009

	Hazard Ratio (95% CI)				
Characteristic	Infectious[a]	Neurologic[a]	Respiratory[a]	Renal[a]	Endocrine[a]
All (N = 73 308), No. of deaths[b,c]	64	182	172	67	104
Vegetarian	0.93 (0.53-1.62)	0.93 (0.67-1.29)	0.95 (0.68-1.32)	0.48 (0.28-0.82)	0.61 (0.40-0.92)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Men (n = 25 105), No. of deaths[b]	31	80	72	34	41
Vegetarian	0.85 (0.39-1.86)	0.86 (0.53-1.40)	1.13 (0.67-1.92)	0.42 (0.19-0.91)	0.48 (0.25-0.92)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Women (n = 48 203), No. of deaths[b,d]	33	102	100	33	63
Vegetarian	0.97 (0.44-2.11)	0.97 (0.63-1.49)	0.88 (0.57-1.36)	0.57 (0.28-1.19)	0.76 (0.44-1.30)
Nonvegetarian	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

[a] The most common specific causes of mortality for each category: infectious (septicemia, *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*] code A41, 32 deaths); neurologic (Alzheimer disease, *ICD-10* G30, 93 deaths; Parkinson disease, *ICD-10* G20, 34 deaths); respiratory (influenza and pneumonia, *ICD-10* J10-18, 59 deaths; emphysema and chronic obstructive pulmonary disease, *ICD-10* J43-44, 49 deaths; interstitial lung disease, *ICD-10* J84, 29 deaths); renal (renal failure, *ICD-10* N17-19, 40 deaths); and endocrine (diabetes mellitus, *ICD-10* E10-14, 67 deaths).

[b] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/wk, 21-60 min/wk, 61-150 min/wk, and ≥151 min/wk), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), geographic region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night).

[c] Also adjusted by sex (male and female), menopause (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[d] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

0.40-0.92); in men, vegetarians had reduced risk of renal mortality (0.42; 0.19-0.91) and endocrine mortality (0.48; 0.25-0.92); and in women, nonsignificant reductions for both renal mortality (0.57; 0.28-1.19) and endocrine mortality (0.76; 0.44-1.30). Forty of 67 renal deaths were associated with renal failure (for both sexes combined, HR, 0.26; 95% CI, 0.12-0.57; for women, 0.39; 0.13-1.17; and for men, 0.21; 0.07-0.63). Sixty-seven of 104 endocrine deaths were associated with diabetes mellitus (for both sexes combined, HR, 0.53; 95% CI, 0.32-0.89; for women, 0.78; 0.41-1.48; and for men, 0.27; 0.11-0.66).

A sensitivity analysis in which body mass index was added to the model generally had only a modest effect on the results. Overall HRs for vegetarians were then 0.90 (95% CI, 0.82-0.98) for both sexes combined, 0.83 (0.72-0.96) for men, and 0.95 (0.84-1.06) for women. The adjustment for body mass index did not consistently move results toward the null. Mortality results adjusted for body mass index affected statistical significance in the following instances. For all vegetarians combined compared with nonvegetarians: IHD mortality in men (HR, 0.77; 95% CI, 0.54-1.10), endocrine mortality in both sexes combined (HR, 0.71; 95% CI, 0.46-1.09), and diabetes mortality in both sexes combined (HR, 0.65; 95% CI, 0.38-1.11). For specific vegetarian dietary patterns compared with nonvegetarians: vegans, all-cause mortality in both sexes combined (HR, 0.84; 95% CI, 0.72-1.00) and IHD mortality in men (0.50; 0.24-1.06); lacto-ovo–vegetarians, all-cause mortality in both sexes combined (0.92; 0.84-1.02) and CVD mortality in men (0.81; 0.63-1.05); pesco-vegetarians, IHD mortality in both sexes combined (0.69; 0.45-1.05), other mortality in both sexes combined (0.77; 0.60-1.00), CVD mortality in men (0.68; 0.45-1.04), and other mortality in men (0.65; 0.43-1.00). Additional adjustment by dietary energy intake resulted in negligible changes. Formal tests for interaction of the diet variable (vegetarian vs nonvegetarian) with sex revealed significant interaction for CVD mortality ($P = .01$), but no significant interaction for all-cause mortality or other categories of mortality.

DISCUSSION

These results demonstrate an overall association of vegetarian dietary patterns with lower mortality compared with the nonvegetarian dietary pattern. They also demonstrate some associations with lower mortality of the pesco-vegetarian, vegan, and lacto-ovo–vegetarian diets specifically compared with the nonvegetarian diet.

Some associations of vegetarian diets with lower cardiovascular mortality and lower noncardiovascular, noncancer mortality were observed. Vegetarian diets have been associated with more favorable levels of cardiovascular risk factors,[17,22-25,36,37] and nutrient profiles of the vegetarian dietary patterns suggest possible reasons for reduced cardiovascular risk, such as lower saturated fat and higher fiber consumption.[38] Analysis within the non-CVD, noncancer category revealed notable reductions in mortality with underlying cause classified as endocrine or renal (diabetes mellitus and renal failure, in particular). These apparent protective associations seem consistent with previously published findings showing an association of vegetarian diets with reduced risk of incident diabetes[25] and of prevalent diabetes, hypertension, and metabolic syndrome.[21,23,24]

No significant associations with reduced cancer mortality were detected. The heterogeneous nature of cancer may obscure specific diet-cancer associations in analyses of combined cancer mortality, and lack of significance may reflect insufficient power to detect weaker associations at early follow-up. Early analyses of vegetarian dietary patterns and cancer incidence in AHS-2 demonstrated significantly reduced risks of female-specific and gastrointestinal cancers.[39]

Effects were generally stronger and more significant in men than women. Previous studies[40-42] among Adventists have demonstrated effect modification by sex of the association of vegetarian diets with reduced ischemic heart disease mortality. It is possible that within dietary groups the diets of men and women differ in important ways; however, a recent evaluation[38] of the nutrient profile of the dietary patterns in this cohort did not reveal striking differences. Alternatively, the biological effect of dietary factors on mortality may be different in men and women. Future analysis will evaluate possible effect modification by sex for particular foods or nutrients, which may suggest sex-specific mechanisms.

Strengths of this study include the large number of participants consuming various vegetarian diets; the diverse nature of this cohort in terms of sex, race, geography, and socioeconomic status, enhancing generalizability; the low use of tobacco and alcohol, making residual confounding from these unlikely; the shared religious affiliation of the cohort, which may lead to greater homogeneity across several possible unmeasured confounders, enhancing internal validity; and precise dietary pattern definitions based on measured food intake rather than self-identification of dietary patterns.

This analysis is limited by relatively early follow-up. If dietary patterns affect mortality, they may do so with moderate effect sizes, via complex pathways, and with long latency periods. Early follow-up analysis may thus have bias toward the null, and true associations may remain undetected. Observed mortality benefits may be affected by factors related to the conscious lifestyle choice of a vegetarian diet other than dietary components. Potential for uncontrolled confounding remains. Dietary patterns may change over time, whereas the analysis relies on a single measurement of diet at baseline. Caution must be used in generalizing results to other populations in which attitudes, motivations, and applications of vegetarian dietary patterns may differ; dietary pattern definitions used may not reflect some common uses of these terms.

Further study of the possible association with mortality of specific foods and nutrients that characterize the different diet-pattern groups is a major future goal of the AHS-2 study. Later follow-up may yield more statistically robust results; allow direct comparisons between vegetarian groups and enable subgroup analysis, particularly by race/ethnicity; and allow for analysis by more specific causes of mortality.

The lack of similar findings in British vegetarians[28] remains interesting, and this difference deserves careful study. In both cohorts, the nonvegetarians are a relatively healthy reference group. In both studies, the nutrient profiles of vegetarians differ in important ways from those of nonvegetarians, with vegetarians (especially vegans) consuming less saturated fat and more fiber.[38,43] It appears that British vegetarians and US Adventist vegetarians eat somewhat differently.[44] For instance, the vegetarians in our study consume more fiber and vitamin C than those of the EPIC-Oxford cohort: mean dietary fiber in EPIC-Oxford vegans was 27.7 g/d in men and 26.4 g/d in women compared with 45.6 g/d in men and 47.3 g/d in women in AHS-2 vegans; mean vitamin C in EPIC-Oxford vegans was 125 mg/d in men and 143 mg/d in women compared with 224 mg/d in men and 250 mg/d in women in AHS-2 vegans.[38,43] Individuals electing vegetarian diets for ethical or environmental reasons may eat differently from those who choose vegetarian diets primarily for reasons of perceived superiority for health promotion. We believe that perceived healthfulness of vegetarian diets may be a major motivator of Adventist vegetarians. More important, other large cohort studies have linked increased red and processed meat consumption to higher mortality,[18,19,45] and our findings build on this work by demonstrating reduced mortality in those consuming low-meat dietary patterns. Notably, the findings of the present study are similar to those of prior North American Adventist cohorts, demonstrating a consistent association over several decades and replicating prior results in a population with greater geographic and ethnic diversity.[46]

In conclusion, in a large American cohort, we found that vegetarian dietary patterns were associated with lower mortality. The evidence that vegetarian diets, or similar diets with reduced meat consumption, may be associated with a lower risk of death should be considered carefully by individuals as they make dietary choices and by those offering dietary guidance.

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