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Low-Carbohydrate Diets and All-Cause and Cause-Specific Mortality

Two Cohort Studies

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Background: Data on the long-term association between low-carbohydrate diets and mortality are sparse.

Objective: To examine the association of low-carbohydrate diets with mortality during 26 years of follow-up in women and 20 years in men.

Design: Prospective cohort study of women and men who were followed from 1980 (women) or 1986 (men) until 2006. Low-carbohydrate diets, either animal-based (emphasizing animal sources of fat and protein) or vegetable-based (emphasizing vegetable sources of fat and protein), were computed from several validated food-frequency questionnaires assessed during follow-up.

Setting: Nurses' Health Study and Health Professionals' Follow-up Study.

Participants: 85 168 women (aged 34 to 59 years at baseline) and 44 548 men (aged 40 to 75 years at baseline) without heart disease, cancer, or diabetes.

Measurements: Investigators documented 12 555 deaths (2458 cardiovascular-related and 5780 cancer-related) in women and 8678 deaths (2746 cardiovascular-related and 2960 cancer-related) in men.

Results: The overall low-carbohydrate score was associated with a modest increase in overall mortality in a pooled analysis (hazard ratio [HR] comparing extreme deciles, 1.12 [95% CI, 1.01 to 1.24]; P for trend = 0.136). The animal low-carbohydrate score was associated with higher all-cause mortality (pooled HR comparing extreme deciles, 1.23 [CI, 1.11 to 1.37]; P for trend = 0.051), cardiovascular mortality (corresponding HR, 1.14 [CI, 1.01 to 1.29]; P for trend = 0.029), and cancer mortality (corresponding HR, 1.28 [CI, 1.02 to 1.60]; P for trend = 0.089). In contrast, a higher vegetable low-carbohydrate score was associated with lower all-cause mortality (HR, 0.80 [CI, 0.75 to 0.85]; P for trend $\leq$ 0.001) and cardiovascular mortality (HR, 0.77 [CI, 0.68 to 0.87]; P for trend $<$ 0.001).

Limitations: Diet and lifestyle characteristics were assessed with some degree of error. Sensitivity analyses indicated that results were probably not substantively affected by residual confounding or an unmeasured confounder. Participants were not a representative sample of the U.S. population.

Conclusion: A low-carbohydrate diet based on animal sources was associated with higher all-cause mortality in both men and women, whereas a vegetable-based low-carbohydrate diet was associated with lower all-cause and cardiovascular disease mortality rates.

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Low-carbohydrate diets have been claimed to promote weight loss and improve blood cholesterol levels and blood pressure (1, 2). Weight-loss trials lasting 6 months to 2 years have found low-carbohydrate diets to be as effective (3, 4) or more effective (5, 6) than diets with higher carbohydrate content. However, effects on blood lipid profiles for low-carbohydrate diets with substantial animal products were mixed, with low-carbohydrate diets resulting in greater improvements in high-density lipoprotein cholesterol levels but possibly less favorable changes in low-density lipoprotein cholesterol levels than higher-carbohydrate diets (6–9). In addition, these diets can be high in red meat and low in fruits, vegetables, and whole grains, which has been shown to increase risk for chronic diseases (10–12). In contrast, the "Eco-Atkins" diet, a low-calorie, low-carbohydrate diet with high amounts of plant protein and oils, has shown to improve low-density lipoprotein cholesterol levels compared with a high-carbohydrate, ovolactovegetarian diet (13). Because the leading causes of death in the United States—cardiovascular disease (CVD) and cancer (14)—develop over many years, long-term studies of low-carbohydrate diets are needed to evaluate effects on mortality. However, randomized trials of low-carbohydrate diets on mortality are not feasible because of the difficulty in maintaining adherence and follow-up over many years.

We previously developed 3 scores to characterize low-carbohydrate diets on the basis of the proportion of carbohydrate, fat, and protein in the diet and the contribution to these macronutrients from animal or vegetable sources (15). We found that women with higher low-carbohydrate diet scores did not have greater risk for type 2 diabetes and coronary heart disease, and a low-carbohydrate dietary pattern that emphasized vegetable sources of fat and protein was associated with a lower risk for both diseases (15, 16). However, long-term data on low-carbohydrate diets and mortality are scarce. Two European cohorts reported that a

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Context

The relative effects of animal-based and vegetable-based low-carbohydrate diets on mortality are uncertain.

Contribution

Two large, long-term cohort studies examined the relationships of animal-based and vegetable-based low-carbohydrate diets with mortality. Diets that emphasized animal sources of fat and protein were associated with higher all-cause, cardiovascular, and cancer mortality, whereas diets that emphasized vegetable sources of fat and protein were associated with lower all-cause and cardiovascular mortality.

Caution

Health care professionals, rather than a representative sample of the population, were studied. Some of the self-reported diet assessments could have been inaccurate.

Implication

A vegetable-based low-carbohydrate diet is probably healthier than an animal-based low-carbohydrate diet.

—The Editors

low-carbohydrate, high-protein diet was associated with a weak but statistically significantly higher mortality rate (17, 18). These studies included only a few hundred deaths and did not evaluate different sources of proteins and fat.

Therefore, we prospectively examined the relationship between different types of low-carbohydrate diets and all-cause and cause-specific mortality in 2 large cohorts in the United States.

METHODS

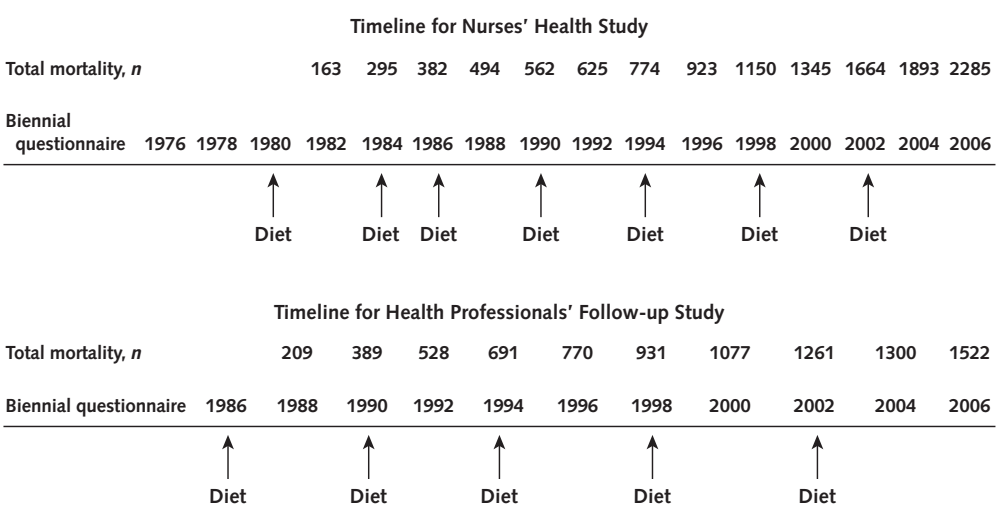
Study Population

The NHS (Nurses' Health Study) is a cohort study of 121 700 female nurses aged 30 to 55 years living in 11 U.S. states in 1976 (**Figure**, *top*). Questionnaires are sent biennially to collect medical, lifestyle, and other health-related information (19). In 1980, participants completed a 61-item food-frequency questionnaire. This was expanded to 116 items in 1984, and similar food-frequency questionnaires were sent in 1986, 1990, 1994, 1998, and 2002.

The HPFS (Health Professionals' Follow-up Study) was established in 1986 and included 51 529 male podiatrists, optometrists, pharmacists, dentists, and veterinarians aged 40 to 75 years (**Figure**, *bottom*). Questionnaires similar to the NHS are sent every 2 years, and a food-frequency questionnaire was sent every 4 years (20). Each food-frequency questionnaire contained approximately 130 questions about food intake. Follow-up was complete for more than 90% in each 2-year cycle for both cohorts.

For this analysis, we used 1980 as baseline for the NHS when the first dietary data were collected. We included women who completed the 1980 food-frequency questionnaire with less than 10 missing items and a plausible total energy intake (calculated from the food-frequency questionnaire) of 500 to 3500 kcal/d (21). For the HPFS, we included men with total energy intake (calculated from the food-frequency questionnaire) of 800 to 4200 kcal/d at baseline and less than 70 missing items. After excluding those with a history of cancer (except nonmelanoma skin cancer) (1579 women and 1998 men), heart disease (772 women and 2077 men), and diabetes mellitus at baseline (1858 women and 1284 men), we in-

Figure. **Timeline for the 2 cohorts.**



The arrows indicate time points at which food-frequency questionnaires were sent.

cluded 85 168 women with follow-up from 1980 to 2006 and 44 548 men with follow-up from 1986 to 2006. The institutional review board at Brigham and Women's Hospital, Boston, Massachusetts, approved this study.

Dietary Assessment

Self-administered semiquantitative food-frequency questionnaires were designed to assess average food intake during the preceding year. A standard portion size and 9 possible food-frequency categories, ranging from never or less than 1 month to 6 or more times per day, were given for each food. Total energy and nutrient intake was calculated by summing all foods. Previous validation studies revealed reasonably good correlations between energy-adjusted nutrients assessed by the food-frequency questionnaire and several food records completed during the preceding year in both NHS (21) and HPFS (20).

The computation of low-carbohydrate diet scores is described in detail elsewhere (15). In brief, percentages of energy from fat, protein, and carbohydrate were divided into deciles. For fat and protein, participants in the highest decile received 10 points for that macronutrient, participants in the ninth decile received 9 points, and so forth. For carbohydrate, the lowest decile received 10 points, and the highest received 0 points. The fat, protein, and carbohydrate scores were summed to create the overall low-carbohydrate diet score, which ranged from 0 to 30. In addition, we also created a vegetable low-carbohydrate score, on the basis of the percentage of energy of carbohydrate, vegetable protein, and vegetable fat. In addition, we created an animal low-carbohydrate score on the basis of the percentage of energy of carbohydrate, animal protein, and animal fat. Thus, each participant was given the overall animal and vegetable scores.

Ascertainment of Deaths

We identified deaths from state vital statistics records, the National Death Index, families, and the postal system. Cause of death was identified from death certificates or review of medical records. For this analysis, we evaluated all-cause mortality, death from CVD (International Classification of Diseases, Eighth Revision, codes 390 to 458), and various types of cancer (codes 140 to 207 [colorectal, codes 153 to 154; lung, code 162; breast, code 174; and prostate, code 185]). The follow-up for death in both cohorts is at least 95% complete (22).

Assessment of Covariates

Body mass index (BMI) was calculated from weight reported on each biennial questionnaire and height reported at the first questionnaire. Smoking status and number of cigarettes smoked, history of hypertension, aspirin use (number of tablets and frequency of use), regular intake of a multivitamin, menopausal status and use of postmenopausal hormone therapy, parity, and age at first birth were assessed every 2 years. In the NHS, hours per week of vigorous activities was collected in 1980, 1982, and 1984. Leisure-time physical activity was measured 7 times beginning in 1986 with validated questions on 10 common activities in NHS and biennially from baseline in HPFS. The information was then summed and calculated as metabolic equivalent hours (METs) (23). In NHS, we inquired about physical examinations (for screening purposes or to evaluate symptoms) at baseline and in both cohorts every 2 years beginning in 1988. Family history (first-degree relatives) of colorectal, breast (women only), and prostate (men only) cancer and information on having undergone colonoscopy and prostate-specific antigen (men only) screening were also collected several times during follow-up.

Statistical Analysis

We used a Cox proportional hazards model to assess the association between the 3 low-carbohydrate diet scores and risk for all-cause mortality during follow-up. In addition, we separately analyzed CVD mortality, overall cancer mortality, and the leading causes of cancer deaths: lung, colorectal, breast (women only), and prostate (men only). We conducted analyses separately for each cohort.

For analyses of all-cause, CVD, and cancer mortality, participants were divided into 10 categories (deciles) for each of the low-carbohydrate diet scores. For specific cancer deaths, we categorized participants into quintiles of low-carbohydrate diet scores because of fewer cases. To reduce random within-person variation and to best represent long-term dietary intake, we calculated cumulative averages of the 3 low-carbohydrate diet scores from our repeated food-frequency questionnaires (24). For example, in NHS, the low-carbohydrate diet score in 1980 was used to predict mortality from 1980 to 1984, the average score from 1980 to 1984 was used to predict mortality from 1984 to 1986, and so forth with cumulative dietary information for the entire follow-up. The same procedure was used in HPFS. However, dietary intake was not updated when the participants reported a diagnosis of cancer (except nonmelanoma skin cancer), diabetes, stroke, coronary heart disease, or angina because these conditions may lead to changes in diet.

In multivariate analyses, we adjusted for age (continuous), physical activity (quintiles), BMI (5 categories), energy intake (quintiles), alcohol intake (4 categories), history of hypertension (yes or no), smoking status (5 categories), and multivitamin use (yes or no), with updated information at each 2-year questionnaire cycle. In women, we also adjusted for menopausal status and postmenopausal hormone use (4 categories). In secondary analysis, we also adjusted for having had a physical examination (yes or no) at each 2-year questionnaire cycle because this may be related to early disease detection and hence better prognosis. Persons with missing BMI were excluded from baseline (2%). Smoking status was missing for 0.2% of the participants in NHS and 4% participants in HPFS at baseline. These persons were represented by a missing indicator variable for smoking.

For analyses of deaths due to specific types of cancer, we used multivariate models that also included disease-specific risk factors. For breast cancer, we additionally adjusted for family history of breast cancer (yes or no), weight change since age 18 years (7 categories), history of benign breast disease (yes or no), BMI at age 18 years (4 categories), and height (4 categories). For analysis of prostate cancer, we additionally adjusted for family history of prostate cancer (yes or no), history of diabetes (yes or no), ethnicity (4 categories), height (5 categories), vigorous (≥6 METs) physical activity (quintiles), history of vasectomy (3 categories), BMI at age 21 years (5 categories), and prostate-specific antigen screening (yes or no). For analysis of colorectal cancer, we additionally adjusted for history of colorectal polyps (yes or no), family history of colorectal cancer (yes or no), colonoscopy (yes or no), and aspirin use (yes or no). Cigarette smoking was modeled as pack-years (5 categories). For analysis of lung cancer, covariates used in each cohort were slightly different because of availability of data. Therefore, in women, we additionally adjusted for age at smoking initiation (continuous), and smoking status was modeled by using 6 categories. In men, we adjusted for

Table 1. **Age-Adjusted Baseline Lifestyle and 1986 Dietary Characteristics of Participants, by Low-Carbohydrate Score Decile***

Characteristic	Overall Low-Carbohydrate Score Decile			Animal Low-Carbohydrate Score Decile			Vegetable Low-Carbohydrate Score Decile		
Women	**1**	**5**	**10**	**1**	**5**	**10**	**1**	**5**	**10**
Median 1986 score	3	14	27	2	13	28	5	14	24
BMI, *kg/m²*	24.0	24.2	24.8	23.9	24.3	24.8	24.4	24.4	23.9
Current smoker, *%*	30	27	33	27	28	32	30	27	30
Physical activity, *h/wk*	3.0	3.2	3.0	3.0	3.2	3.0	3.1	3.1	3.1
Multivitamin use, *%*	33	34	35	33	35	35	36	34	35
Dietary intake									
Energy, *kcal/d*	1821	1795	1641	1817	1804	1630	1811	1759	1748
Alcohol, *g/d*	4	7	5	4	7	6	4	7	7
Carbohydrate, *% energy/d*	60.5	50.9	37.2	59.6	50.4	37.4	56.0	48.8	42.8
Animal protein, *% energy/d*	9.6	12.7	17.8	9.1	12.5	18.5	13.4	14.2	12.7
Vegetable protein, *% energy/d*	5.4	5.2	4.5	5.9	5.2	4.2	4.1	4.9	6.0
Animal fat, *% energy/d*	12.9	16.6	25.2	11.6	16.5	26.3	17.9	19.1	17.2
Vegetable fat, *% energy/d*	12.9	13.8	14.7	15.5	15.0	12.2	9.4	12.3	21.1
Saturated fat, *g/d*†	16	19	26	16	20	26	19	21	22
Trans fat, *g/d*†	2.1	2.3	2.7	2.2	2.4	2.6	1.9	2.3	2.7
Monounsaturated fat, *g/d*†	16	21	27	17	21	26	17	21	26
Polyunsaturated fat, *g/d*†	9	11	12	10	11	11	8	10	15
ω-3 Fatty acids, *g/d*†	1.0	1.2	1.3	1.1	1.2	1.3	1.0	1.2	1.4
Whole grains, *g/d*†	19	16	9	21	15	9	12	15	14
Fruits and vegetables, *servings/d*	7.4	6.8	5.2	7.6	6.7	5.1	6.5	6.5	6.0
Red or processed meat, *servings/d*	0.6	0.8	1.3	0.5	0.8	1.3	0.8	0.9	0.8
Sweetened soft drinks, *servings/d*	0.7	0.2	0.1	0.6	0.2	0.1	0.8	0.2	0.1
Men									
Median 1986 score	3	14	27	2	14	28	6	14	24
BMI, *kg/m²*	24.7	25.4	26.5	24.5	25.4	26.6	25.5	25.6	25.6
Current smoker, *%*	5	9	13	5	9	14	10	9	9
Physical activity, *METs/wk*	27	22	17	28	21	16	21	22	20
Multivitamin use, *%*	44	41	40	46	41	39	40	40	44
Dietary intake									
Energy, *kcal/d*	2012	2007	1881	2010	1995	1867	2012	1971	2034
Alcohol, *g/d*	9	13	8	7	12	10	8	12	12
Carbohydrates, *% energy/d*	60.6	47.6	35.2	60.2	47.3	35.2	53.7	46.9	40.1
Animal protein, *% energy/d*	9.2	13.1	18.2	8.9	13.2	18.8	13.7	13.9	12.6
Vegetable protein, *% energy/d*	5.7	5.0	4.3	6.2	5.0	3.9	4.0	4.8	6.1
Animal fat, *% energy/d*	11.8	17.6	26.2	10.6	17.8	27.4	18.4	19.0	17.1
Vegetable fat, *% energy/d*	12.3	13.5	13.8	14.4	13.9	11.5	8.9	12.5	21.1
Saturated fat, *g/d*†	18	24	32	24	40	57	23	25	26
Trans fat, *g/d*†	2.2	2.8	3.2	2.3	2.9	3.2	2.4	2.9	3.0
Monounsaturated fat, *g/d*†	20	26	35	21	27	33	23	27	34
Polyunsaturated fat, *g/d*†	11	13	15	12	13	14	10	13	18
ω-3 Fatty acids, *g/d*†	1.2	1.4	1.6	1.3	1.4	1.5	1.1	1.4	1.6
Whole grains, *g/d*†	32	22	14	36	21	13	18	22	21
Fruits and vegetables, *servings/d*	7.3	5.5	4.3	7.6	5.5	4.2	5.7	5.7	5.3
Red or processed meat, *servings/d*	0.4	0.6	1.2	0.3	0.8	1.3	0.8	0.8	0.8
Sweetened soft drinks, *servings/d*	0.8	0.3	0.1	0.6	0.4	0.2	0.9	0.3	0.1

BMI = body mass index; METs = metabolic equivalent hours.
* Data are means unless otherwise stated.
† Energy adjusted by using the residual method.

Table 2. **Hazard Ratios (95% CI) for All-Cause Mortality, by Low-Carbohydrate Score Decile**

All-Cause Mortality	Low-Carbohydrate Score Decile										*P* Value for Trend
	1	2	3	4	5	6	7	8	9	10	
Overall											
Men											
Cases, *n*	871	834	916	877	872	868	861	871	880	828	
Age- and energy-adjusted HR	1.0	0.91	1.05	0.98	0.96	1.07	1.07	1.14	1.17	1.33 (1.20–1.46)	<0.001
Multivariate-adjusted HR*	1.0	1.03	1.14	1.11	1.05	1.25	1.20	1.19	1.22	1.19 (1.07–1.31)	<0.001
Women											
Cases, *n*	1406	1350	1262	1297	1227	1146	1178	1258	1199	1232	
Age- and energy-adjusted HR	1.0	0.94	0.92	0.94	0.91	0.95	0.94	1.02	1.05	1.19 (1.10–1.28)	0.47
Multivariate-adjusted HR*	1.0	1.08	1.08	1.14	1.04	1.13	1.10	1.15	1.14	1.07 (0.99–1.15)	0.135
Pooled (multivariate-adjusted) HR	1.0	1.06	1.10	1.13	1.04	1.18	1.15	1.14	1.17	1.12 (1.01–1.24)	0.136†
Animal-based diet											
Men											
Cases, *n*	832	808	877	837	876	811	899	926	893	919	
Age- and energy-adjusted HR	1.0	1.00	1.03	1.03	1.07	1.10	1.19	1.27	1.33	1.52 (1.38–1.67)	<0.001
Multivariate-adjusted HR*	1.0	1.07	1.12	1.13	1.17	1.24	1.26	1.32	1.32	1.31 (1.19–1.44)	<0.001
Women											
Cases, *n*	1350	1269	1271	1185	1252	1106	1252	1218	1324	1328	
Age- and energy-adjusted HR	1.0	0.94	0.99	0.95	1.00	0.97	1.03	1.13	1.22	1.35 (1.25–1.46)	<0.001
Multivariate-adjusted HR*	1.0	1.07	1.16	1.09	1.14	1.13	1.16	1.22	1.26	1.17 (1.08–1.26)	<0.001
Pooled (multivariate-adjusted) HR	1.0	1.07	1.14	1.12	1.15	1.18	1.20	1.26	1.28	1.23 (1.11–1.37)	0.051†
Vegetable-based diet											
Men											
Cases, *n*	1095	971	903	936	767	903	788	830	764	721	
Age- and energy-adjusted HR	1.0	0.92	0.83	0.92	0.80	0.81	0.75	0.79	0.80	0.77 (0.70–0.85)	<0.001
Multivariate-adjusted HR*	1.0	0.97	0.94	0.98	0.92	0.93	0.84	0.96	0.87	0.81 (0.74–0.89)	<0.001
Women											
Cases, *n*	1565	1470	1342	1330	1101	1323	1180	1093	1029	1122	
Age- and energy-adjusted HR	1.0	0.91	0.86	0.79	0.81	0.75	0.75	0.73	0.69	0.76 (0.71–0.82)	<0.001
Multivariate-adjusted HR*	1.0	1.01	1.02	0.91	1.00	0.87	0.86	0.87	0.81	0.79 (0.73–0.85)	<0.001
Pooled (multivariate-adjusted) HR	1.0	0.99	0.98	0.94	0.97	0.90	0.85	0.91	0.85	0.80 (0.75–0.85)	<0.001

HR = hazard ratio.
* Adjusted for age, physical activity, body mass index, energy intake, alcohol intake, menopausal status and postmenopausal hormone use (women only), history of hypertension, smoking status, and multivitamin use.
† $P < 0.05$ for heterogeneity test.

pack-years (5 categories), parental smoking in childhood (3 categories), and adult environmental tobacco smoke exposure (4 categories).

Hazard ratios from each cohort were also pooled to obtain a summary risk estimate by using a random-effects model that allows for between-study heterogeneity (25). We calculated *P* values for heterogeneity of study results by using the Cochran *Q* test.

Proportional hazards assumption for total mortality was tested with a time-dependent variable by including an interaction term between the low-carbohydrate diet score and months to death. Statistical analysis was conducted by using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

For a sensitivity analysis, we repeated our analysis by using only baseline dietary information, and we corrected for measurement error (26) in the assessment of the overall low-carbohydrate diet score by using data from validation studies conducted in NHS (21) and HPFS (20). To explore residual confounding, we adjusted for major confounders with finer categories or as continuous variables in separate regression models, as well as computing and adjusting for a propensity score (27). We also conducted a sensitivity analysis to examine the robustness of our results from influence of unmeasured confounding (28). We did not observe any material difference in results from these precautionary measures, and therefore we presented results with covariates adjusted in their original categories. A multiple imputation procedure was used with 20 rounds of imputation and included all covariates to account for missing dietary and covariate data. The analysis was repeated by using noncumulative updating of dietary information, in which we used the most recent diet data to predict mortality rate (29).

Role of the Funding Source

The National Institutes of Health supported this study. The funding source had no role in the design and conduct of the study, analysis or interpretation of the data, preparation or final approval of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

In NHS, with up to 26 years of follow-up, we documented 12 555 deaths, of which 2458 were cardiovascular

Table 3. **Hazard Ratios (95% CI) for Cardiovascular Mortality, by Low-Carbohydrate Score Decile**

Cardiovascular Mortality	Low-Carbohydrate Score Decile										*P* Value for Trend
	1	2	3	4	5	6	7	8	9	10	
Overall											
Men											
Cases, *n*	284	264	295	296	281	275	267	276	263	245	
Age- and energy-adjusted HR	1.0	0.90	1.05	1.05	0.99	1.07	1.07	1.18	1.13	1.31 (1.10–1.56)	<0.001
Multivariate-adjusted HR*	1.0	0.98	1.10	1.14	1.04	1.17	1.14	1.20	1.14	1.15 (0.96–1.37)	0.008
Women											
Cases, *n*	280	284	251	274	248	207	214	239	224	237	
Age- and energy-adjusted HR	1.0	1.01	0.94	1.05	0.96	0.91	0.91	1.06	1.08	1.27 (1.07–1.51)	0.43
Multivariate-adjusted HR*	1.0	1.16	1.08	1.24	1.08	1.03	1.01	1.12	1.09	1.00 (0.84–1.20)	0.54
Pooled (multivariate-adjusted) HR	1.0	1.07	1.08	1.18	1.06	1.10	1.08	1.16	1.11	1.08 (0.95–1.22)	0.153
Animal-based diet											
Men											
Cases, *n*	270	269	270	271	306	254	267	284	291	264	
Age- and energy-adjusted HR	1.0	1.03	0.99	1.07	1.20	1.09	1.11	1.25	1.40	1.42 (1.20–1.69)	<0.001
Multivariate-adjusted HR*	1.0	1.09	1.04	1.13	1.25	1.19	1.13	1.25	1.36	1.21 (1.01–1.44)	<0.001
Women											
Cases, *n*	278	231	269	234	255	232	226	247	233	255	
Age- and energy-adjusted HR	1.0	0.85	1.04	0.96	1.04	1.04	0.97	1.19	1.15	1.39 (1.17–1.65)	0.29
Multivariate-adjusted HR*	1.0	0.95	1.19	1.07	1.14	1.15	1.03	1.21	1.09	1.07 (0.90–1.28)	0.102
Pooled (multivariate-adjusted) HR	1.0	1.01	1.11	1.10	1.20	1.17	1.08	1.23	1.22	1.14 (1.01–1.29)	0.029
Vegetable-based diet											
Men											
Cases, *n*	373	308	281	291	245	310	237	255	235	211	
Age- and energy-adjusted HR	1.0	0.86	0.79	0.78	0.78	0.85	0.69	0.76	0.76	0.72 (0.61–0.86)	<0.001
Multivariate-adjusted HR*	1.0	0.91	0.88	0.93	0.88	0.98	0.77	0.91	0.84	0.77 (0.65–0.92)	0.002
Women											
Cases, *n*	331	320	271	280	203	242	209	193	186	223	
Age- and energy-adjusted HR	1.0	0.94	0.82	0.79	0.72	0.67	0.63	0.63	0.61	0.74 (0.62–0.87)	<0.001
Multivariate-adjusted HR*	1.0	1.06	0.99	0.92	0.89	0.79	0.75	0.76	0.73	0.77 (0.66–0.91)	<0.001
Pooled (multivariate-adjusted) HR	1.0	0.98	0.93	0.93	0.89	0.88†	0.76	0.84	0.79	0.77 (0.68–0.87)	<0.001

HR = hazard ratio.
* Adjusted for age, physical activity, body mass index, energy intake, alcohol intake, menopausal status and postmenopausal hormone use (women only), history of hypertension, smoking status, and multivitamin use.

deaths and 5780 were cancer deaths. Among the cancer deaths, 1605 were from breast cancer, 547 were from colorectal cancer, and 1280 were from lung cancer. In HPFS, with up to 20 years of follow-up, there were 8678 deaths, of which 2746 were CVD deaths and 2960 were cancer deaths. Among cancer deaths, 335 were from colorectal cancer, 563 were from lung cancer, and 416 were from prostate cancer.

Both men and women who had higher overall and animal low-carbohydrate scores had higher BMI and were more likely to be current smokers but had lower intakes of fruits and vegetables (**Table 1**). Conversely, those with higher vegetable low-carbohydrate score tended to have higher alcohol and whole grain intake. We chose 1986 for consistency of data for men and women.

After adjustment for potential confounders, we observed a modest but statistically higher risk for all-cause mortality with the animal low-carbohydrate score (hazard ratio [HR] comparing extreme deciles of animal score for HPFS, 1.31 [95% CI, 1.19 to 1.44; *P* for trend < 0.001], and for NHS, 1.17 [CI, 1.08 to 1.26; *P* for trend < 0.001]) (**Table 2**); the pooled HR was 1.23 (CI, 1.11 to 1.37; *P* for trend = 0.051). In both cohorts, similar inverse associations were observed between the vegetable score and all-cause mortality. The pooled HR comparing extreme deciles was 0.80 (CI, 0.75 to 0.85; *P* for trend < 0.001).

For CVD mortality, a modest but statistically significant direct association was observed with the overall low-carbohydrate score in men only (**Table 3**). However, the animal-based score showed a direct association in the pooled analysis (HR, 1.14 [CI, 1.01 to 1.29]; *P* for trend = 0.029). Results for the vegetable-based score were similar for men and women for extreme deciles (pooled HR for CVD mortality, 0.77 [CI, 0.68 to 0.87]; *P* for trend < 0.001).

For total cancer deaths, a statistically significant direct association was observed with the overall low-carbohydrate score in men (HR comparing extreme deciles, 1.32 [CI, 1.11 to 1.57]; *P* for trend < 0.001) (**Table 4**). A slightly stronger association was observed with the animal low-carbohydrate score in men (HR, 1.45 [CI, 1.23 to 1.72]; *P* for trend < 0.001). However, the same association was weaker in women and did not reach statistical significance in the sensitivity analysis when smoking and physical ac-

tivity were modeled in finer categories. In addition, no association was observed with the vegetable low-carbohydrate score in either men or women.

A direct association was observed between the animal low-carbohydrate score and colorectal cancer death when data were combined (HR comparing extreme quintiles, 1.31 [CI, 1.06 to 1.62]; P for trend = 0.048) (**Appendix Table**, available at www.annals.org). In both cohorts, the overall and animal low-carbohydrate scores were positively associated with lung cancer mortality, with a pooled HR for overall low-carbohydrate score of 1.22 (CI, 1.05 to 1.42; P for trend = 0.003) comparing top with bottom quintiles (**Appendix Table**). The vegetable low-carbohydrate score was not associated with lung cancer deaths. After adjustment for risk factors relevant to specific types of cancer, none of the low-carbohydrate scores was associated with breast cancer or prostate cancer death.

Additional adjustment for physical examinations to reduce the possibility of confounding by late detection and hence more fatal diseases showed similar results. We also repeated our analysis by continuously updating dietary information, even after diagnosis of chronic diseases, but adjusted for the self-reported diagnosis in the regression models. In both cohorts, neither the relative risks nor the P values were changed. A Bonferroni correction for multiple comparisons for sex-specific analysis did not change the conclusion of the results for all-cause, CVD, or cancer mortality, and statistically significant associations remained significant.

Less than 25% of either NHS or HPFS participants missed more than 2 food-frequency questionnaires during follow-up. However, results for the animal and vegetable low-carbohydrate scores remained statistically significant when the multiple imputation procedure was used to account for missing data. In NHS, the HR for a 10-point increase in the animal score was 1.09 ($P < 0.001$) for total mortality, and the corresponding HR in HPFS was 1.06 ($P < 0.001$). By using baseline dietary data and after adjustment for measurement error in diet, conclusions for the overall low-carbohydrate diet score and total mortality were not materially changed. For example, the HR for a

Table 4. **Hazard Ratios (95% CI) for Cancer Mortality, by Low-Carbohydrate Score Decile**

Cancer Mortality	Low-Carbohydrate Score Decile										*P* Value for Trend
	1	2	3	4	5	6	7	8	9	10	
Overall											
Men											
Cases, *n*	260	270	303	311	296	302	293	307	327	291	
Age- and energy-adjusted HR	1.0	0.98	1.14	1.13	1.07	1.23	1.16	1.28	1.37	1.45 (1.22–1.71)	<0.001
Multivariate-adjusted HR*	1.0	1.08	1.22	1.25	1.15	1.40	1.29	1.33	1.41	1.32 (1.11–1.57)	<0.001
Women											
Cases, *n*	595	592	580	584	567	539	565	602	583	573	
Age- and energy-adjusted HR	1.0	0.95	0.96	0.96	0.94	0.99	1.00	1.06	1.11	1.16 (1.04–1.31)	0.28
Multivariate-adjusted HR*	1.0	1.06	1.10	1.12	1.05	1.15	1.14	1.17	1.20	1.10 (0.98–1.23)	0.056
Pooled (multivariate-adjusted) HR	1.0	1.07	1.16	1.16	1.08	1.26	1.20	1.23	1.29	1.19 (0.99–1.42)	0.128†
Animal-based diet											
Men											
Cases, *n*	255	253	316	272	287	293	338	312	307	327	
Age- and energy-adjusted HR	1.0	1.01	1.20	1.05	1.12	1.25	1.45	1.33	1.41	1.66 (1.40–1.96)	<0.001
Multivariate-adjusted HR*	1.0	1.07	1.28	1.15	1.21	1.38	1.53	1.38	1.40	1.45 (1.23–1.72)	<0.001
Women											
Cases, *n*	591	585	565	530	590	499	607	550	659	604	
Age- and energy-adjusted HR	1.0	0.98	0.97	0.93	1.02	0.95	1.07	1.08	1.27	1.26 (1.13–1.41)	0.005
Multivariate-adjusted HR*	1.0	1.08	1.10	1.04	1.14	1.08	1.19	1.15	1.32	1.15 (1.02–1.29)	0.001
Pooled (multivariate-adjusted) HR	1.0	1.08	1.17	1.07	1.16	1.21†	1.33†	1.25	1.34	1.28 (1.02–1.60)†	0.089†
Vegetable-based diet											
Men											
Cases, *n*	310	341	288	336	276	292	275	301	274	267	
Age- and energy-adjusted HR	1.0	1.16	0.93	1.01	1.02	0.88	0.93	0.85	0.99	0.97 (0.82–1.15)	0.120
Multivariate-adjusted HR*	1.0	1.21	1.03	1.16	1.15	0.98	1.02	1.11	1.09	1.00 (0.84–1.18)	0.35
Women											
Cases, *n*	612	637	632	538	535	634	567	557	522	546	
Age- and energy-adjusted HR	1.0	1.00	1.03	0.83	0.98	0.89	0.92	0.91	0.88	0.91 (0.81–1.02)	0.36
Multivariate-adjusted HR*	1.0	1.08	1.17	0.93	1.15	0.99	1.04	1.06	0.99	0.94 (0.84–1.06)	0.39
Pooled (multivariate-adjusted) HR	1.0	1.13	1.12	1.03†	1.15	0.99	1.04	1.07	1.03	0.96 (0.87–1.05)	0.23

HR = hazard ratio.
* Adjusted for age, physical activity, body mass index, energy intake, alcohol intake, menopausal status and postmenopausal hormone use (women only), history of hypertension, smoking status, and multivitamin use.
† $P < 0.05$ for heterogeneity test.

10-point increase in baseline overall score was 1.04 ($P = 0.38$) for corrected data and 1.01 ($P = 0.65$) for uncorrected data in NHS. In HPFS, the HR for a 10-point increase in the baseline overall score was 1.20 ($P < 0.001$) for corrected data and 1.10 ($P < 0.001$) for uncorrected data. The test for proportional hazards assumption for total mortality analysis was not significant ($P = 0.42$ for NHS; $P = 0.45$ for HPFS).

DISCUSSION

In our 2 cohorts of U.S. men and women who were followed for 20 to 26 years, we observed that the overall low-carbohydrate diet score was only weakly associated with all-cause mortality. However, a higher animal low-carbohydrate diet score was associated with higher all-cause and cancer mortality, whereas a higher vegetable low-carbohydrate score was associated with lower mortality, particularly CVD mortality.

After searching the English-language medical literature of the past 10 years, we found only 2 long-term observational studies of low-carbohydrate diet and mortality. A Swedish study in women used an overall score with a scoring algorithm similar to ours but only considered protein and carbohydrate intakes (17). After up to 12 years of follow-up, the high-protein, low-carbohydrate score was associated with CVD death only among women aged 40 to 49 years at baseline but not among younger women (HR, 1.21 for each 10% increase in score). No association with all-cause or cancer mortality was found. By using the same calculation as the Swedish study, the high-protein, low-carbohydrate score was associated with a weak but statistically significant increased risk in all-cause mortality (HR, 1.08 for each 10% increase) among Greek participants of the EPIC (European Prospective Investigation Cancer and Nutrition) study during 10 years of follow-up (18). Similar associations were observed for cardiovascular and cancer mortality. Dietary protein and fat can come from foods with widely different nutrient profiles. Our animal and vegetable low-carbohydrate scores allowed us to better discern whether any association between low-carbohydrate scores and mortality was due mainly to different sources of macronutrients, especially fat and protein. We observed stronger direct associations with mortality with the animal but not with the vegetable low-carbohydrate score, suggesting that animal- and plant-based foods have a differential effect on mortality.

Consistent with our results, higher intake of vegetable protein, but not animal protein, was associated with a lower risk for coronary heart disease mortality in the Iowa Women's Health Study (30). The lower CVD mortality observed with higher vegetable low-carbohydrate score in our study is probably due in part to the established benefit of unsaturated fats, dietary fiber, and micronutrients, such as magnesium and potassium, as well as other bioactive compounds, including vitamins, minerals, and phytochemicals (31). Because low-carbohydrate diets may have variable amounts of plant or animal fat, this may explain why low-carbohydrate diets showed mixed results on lipid profile (9).

We found a positive association between animal and low-carbohydrate score and cancer mortality. Diets high in red and processed meats have been associated with higher risk for lung cancer in case–control studies (32, 33) and prospective studies (34). Therefore, the direct association with the animal-based low-carbohydrate score in our study may be due in part to higher intake of red and processed meat. Dietary fat, however, does not seem to be associated with lung cancer risk (35). The association between red and processed meat intake and risk for colorectal cancer is well established (36) and may explain the higher risk for colorectal cancer deaths among participants with higher animal low-carbohydrate scores.

Low-carbohydrate diets from animal and vegetable sources may have similar major macronutrient content, but the source of the macronutrients can result in large differences in dietary components that may affect mortality, such as specific fatty acids, protein, fiber, vitamins and minerals, and phytochemicals. Therefore, the associations that we observed are more likely to be mediated by these bioactive components rather the carbohydrate content.

The large number of cases in our cohort allowed us to conduct meaningful statistical analysis for specific causes of death. The availability of detailed and updated data on covariates allowed us to better control for confounding, but as with other observational studies, some degree of measurement error in reporting dietary and other lifestyle characteristics is inevitable. Therefore, we used several strategies in an attempt to reduce some of those biases. We used a validated food-frequency questionnaire, and our participants' training in clinical sciences would allow them to report health data accurately. In sensitivity analyses, we modeled major confounders in finer categories, included a propensity score, and explored the influence of residual confounding. Our main results were compared with those corrected for measurement error in baseline diet with data from validation studies. Most of the risk estimates did not change substantially and the conclusions remained unchanged. We also considered the influence of unmeasured confounding by using a sensitivity analysis (28). We found that for HPFS, the unmeasured confounder would have to have a prevalence of 40% among those at the highest decile of animal score and an HR of 2.0 with total morality to attenuate the association to nonstatistical significance. In NHS, the unmeasured confounder would have a prevalence of 20% and an HR of 2.0 to attenuate the association to nonstatistical significance. Because important confounders for the analyses of total and disease-specific mortality were controlled for, it is unlikely that such strong confounding would remain to explain the observed associations.

Because of the long follow-up, participants could have changed their diet after they received a diagnosis of non-

fatal CVD or cancer. We reduced the effect of this by not updating dietary information after such a diagnosis in our main analysis. In a different approach, we updated dietary information, regardless of a diagnosis of chronic disease, but adjusted for the diagnosis in the regression model. Missing data were imputed by using a sophisticated procedure. None of these additional analyses materially changed the results.

Our study has limitations. The low-carbohydrate diet scores were not designed to mimic any particular versions of low-carbohydrate diets available in the popular literature. Therefore, the risk estimates do not directly translate to the assessment of benefit or risk associated with the popular versions of the diet. In addition, the participants of our cohorts have higher educational status and better availability of health care coverage. Therefore, results may not be directly generalizable to the general population.

In conclusion, consumption of a vegetable-based low-carbohydrate diet were associated with a lower risk for all-cause and CVD mortality, whereas high scores for the animal-based low-carbohydrate diet were associated with a higher risk for overall mortality. These results suggest that the health effects of a low-carbohydrate diet may depend on the type of protein and fat, and a diet that includes mostly vegetable sources of protein and fat is preferable to a diet with mostly animal sources of protein and fat.

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Appendix Table. **Hazard Ratios (95% CI) for Specific Cancer Mortality, by Low-Carbohydrate Diet Quintiles**

Cancer Mortality	Low-Carbohydrate Diet Quintile					*P* Value for Trend
	1	2	3	4	5	
Colorectal						
Overall low-carbohydrate score						
Men						
Cases, *n*	72	61	66	64	72	
Age- and energy-adjusted HR	1.0	0.85 (0.60–1.20)	0.96 (0.68–1.34)	0.97 (0.69–1.37)	1.25 (0.90–1.74)	0.166
Colorectal cancer–specific model HR*	1.0	0.86 (0.61–1.22)	0.98 (0.69–1.38)	1.02 (0.72–1.45)	1.13 (0.80–1.59)	0.39
Women						
Cases, *n*	112	91	125	101	118	
Age- and energy-adjusted HR	1.0	0.92 (0.70–1.21)	0.99 (0.77–1.28)	1.03 (0.79–1.35)	1.08 (0.84–1.40)	0.55
Colorectal cancer–specific model HR*	1.0	0.98 (0.74–1.29)	1.06 (0.82–1.37)	1.08 (0.82–1.42)	1.14 (0.88–1.48)	0.36
Pooled (multivariate-adjusted) HR	1.0	0.93 (0.75–1.16)	1.03 (0.84–1.26)	1.06 (0.86–1.32)	1.13 (0.92–1.40)	0.21
Animal low-carbohydrate score						
Men						
Cases, *n*	61	69	59	71	75	
Age- and energy-adjusted HR	1.0	1.08 (0.77–1.54)	0.99 (0.69–1.41)	1.23 (0.87–1.74)	1.47 (1.05–2.08)	0.016
Colorectal cancer–specific model HR*	1.0	1.11 (0.78–1.58)	1.05 (0.72–1.51)	1.22 (0.86–1.75)	1.31 (0.92–1.86)	0.122
Women						
Cases, *n*	103	115	99	103	127	
Age- and energy-adjusted HR	1.0	1.14 (0.89–1.49)	0.93 (0.71–1.23)	1.04 (0.79–1.37)	1.26 (0.97–1.64)	0.25
Colorectal cancer–specific model HR*	1.0	1.19 (0.91–1.56)	0.98 (0.74–1.30)	1.06 (0.81–1.40)	1.30 (1.00–1.70)	0.21
Pooled (multivariate-adjusted) HR	1.0	1.16 (0.94–1.44)	1.01 (0.81–1.26)	1.12 (0.90–1.40)	1.31 (1.06–1.62)	0.048
Vegetable low-carbohydrate score						
Men						
Cases, *n*	89	72	63	45	66	
Age- and energy-adjusted HR	1.0	0.75 (0.54–1.02)	0.72 (0.52–1.00)	0.50 (0.35–0.72)	0.83 (0.60–1.14)	0.026
Colorectal cancer–specific model HR*	1.0	0.86 (0.62–1.18)	0.80 (0.57–1.11)	0.58 (0.40–0.84)	0.91 (0.65–1.26)	0.096
Women						
Cases, *n*	121	131	90	91	114	
Age- and energy-adjusted HR	1.0	1.03 (0.81–1.32)	0.68 (0.52–0.90)	0.77 (0.59–1.01)	0.92 (0.71–1.19)	0.21
Colorectal cancer–specific model HR*	1.0	1.07 (0.84–1.38)	0.72 (0.55–0.95)	0.81 (0.62–1.07)	0.99 (0.77–1.28)	0.27
Pooled (multivariate-adjusted) HR	1.0	0.99 (0.81–1.21)	0.75 (0.61–0.93)	0.70 (0.51–0.97)	0.96 (0.78–1.17)	0.074
Lung						
Overall low-carbohydrate score						
Men						
Cases, *n*	71	117	109	137	129	
Age- and energy-adjusted HR	1.0	1.62 (1.20–2.18)	1.56 (1.15–2.11)	2.10 (1.57–2.81)	2.23 (1.66–3.00)	<0.001
Lung cancer–specific model HR†	1.0	1.41 (1.04–1.91)	1.23 (0.90–1.68)	1.60 (1.18–2.16)	1.40 (1.03–1.91)	0.021‡
Women						
Cases, *n*	266	234	259	244	277	
Age- and energy-adjusted HR	1.0	1.05 (0.87–1.26)	1.14 (0.96–1.35)	1.28 (1.07–1.53)	1.24 (1.04–1.47)	0.003
Lung cancer–specific model HR†	1.0	1.09 (0.90–1.31)	1.16 (0.98–1.38)	1.27 (1.06–1.52)	1.17 (0.98–1.39)	0.006
Pooled (multivariate-adjusted) HR	1.0	1.20 (0.93–1.55)	1.18 (1.01–1.37)	1.39 (1.11–1.74)	1.22 (1.05–1.42)	0.003
Animal low-carbohydrate score						
Men						
Cases, *n*	70	91	120	144	138	
Age- and energy-adjusted HR	1.0	1.29 (0.94–1.77)	1.75 (1.30–2.36)	2.20 (1.65–2.94)	2.42 (1.81–3.24)	<0.001
Lung cancer–specific model HR†	1.0	1.16 (0.84–1.61)	1.47 (1.08–2.01)	1.65 (1.22–1.23)	1.42 (1.04–1.92)	0.009‡
Women						
Cases, *n*	220	223	281	278	278	
Age- and energy-adjusted HR	1.0	1.04 (0.87–1.26)	1.25 (1.05–1.49)	1.32 (1.10–1.57)	1.28 (1.07–1.53)	0.0003
Lung cancer–specific model HR†	1.0	1.07 (0.88–1.29)	1.25 (1.04–1.49)	1.27 (1.06–1.52)	1.16 (0.97–1.39)	0.004
Pooled (multivariate-adjusted) HR	1.0	1.09 (0.92–1.28)	1.31 (1.12–1.53)	1.42 (1.09–1.85)	1.23 (1.03–1.46)	0.011
Vegetable low-carbohydrate score						
Men						
Cases, *n*	118	116	94	142	93	
Age- and energy-adjusted HR	1.0	0.91 (0.70–1.18)	0.80 (0.61–1.05)	1.15 (0.89–1.47)	0.86 (0.65–1.13)	0.96
Lung cancer–specific model HR†	1.0	0.92 (0.70–1.21)	0.91 (0.68–1.20)	1.25 (0.96–1.61)	0.81 (0.61–1.08)	0.95
Women						
Cases, *n*	227	210	228	209	238	
Age- and energy-adjusted HR	1.0	0.84 (0.70–1.00)	0.88 (0.74–1.05)	0.95 (0.80–1.13)	1.01 (0.85–1.19)	0.28
Lung cancer–specific model HR†	1.0	0.88 (0.74–1.06)	0.98 (0.82–1.16)	1.03 (0.87–1.23)	1.07 (0.90–1.27)	0.138
Pooled (multivariate-adjusted) HR	1.0	0.89 (0.77–1.04)	0.96 (0.83–1.11)	1.10 (0.93–1.30)	0.95 (0.73–1.25)	0.21

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Appendix Table—Continued

Cancer Mortality	Low-Carbohydrate Diet Quintile					*P* Value for Trend
	1	2	3	4	5	
Breast (women only)						
Overall low-carbohydrate score						
Cases, *n*	248	168	230	197	222	
Age- and energy-adjusted HR	1.0	0.80 (0.66–0.98)	0.83 (0.69–0.99)	0.92 (0.76–1.11)	0.91 (0.76–1.09)	0.43
Breast cancer–specific model HR§	1.0	0.82 (0.67–1.00)	0.87 (0.72–1.04)	0.96 (0.79–1.16)	0.98 (0.81–1.17)	0.99
Animal low-carbohydrate score						
Cases, *n*	231	192	214	199	229	
Age- and energy-adjusted HR	1.0	0.86 (0.71–1.04)	0.89 (0.74–1.08)	0.89 (0.74–1.08)	0.99 (0.83–1.19)	0.76
Breast cancer–specific model HR§	1.0	0.88 (0.72–1.07)	0.93 (0.77–1.12)	0.93 (0.77–1.13)	1.02 (0.85–1.23)	0.89
Vegetable low-carbohydrate score						
Cases, *n*	219	217	215	202	212	
Age- and energy-adjusted HR	1.0	0.95 (0.79–1.15)	0.89 (0.74–1.08)	0.93 (0.77–0.14)	0.94 (0.78–1.13)	0.64
Breast cancer–specific model HR§	1.0	0.99 (0.82–1.19)	0.94 (0.78–1.13)	0.99 (0.82–1.20)	1.02 (0.84–1.23)	0.75
Prostate (men only)						
Overall low-carbohydrate score						
Cases, *n*	82	80	84	91	79	
Age- and energy-adjusted HR	1.0	0.95 (0.70–1.30)	1.09 (0.80–1.48)	1.23 (0.91–1.67)	1.26 (0.92–1.73)	0.010
Prostate cancer–specific model HR‖	1.0	0.92 (0.67–1.26)	1.12 (0.81–1.53)	1.15 (0.84–1.57)	1.11 (0.80–1.53)	0.090
Animal low-carbohydrate score						
Cases, *n*	75	96	72	91	82	
Age- and energy-adjusted HR	1.0	1.29 (0.95–1.75)	1.03 (0.74–1.42)	1.42 (1.04–1.93)	1.48 (1.08–2.04)	0.011
Prostate cancer–specific model HR‖	1.0	1.29 (0.94–1.77)	1.06 (0.76–1.49)	1.35 (0.98–1.87)	1.28 (0.92–1.79)	0.121
Vegetable low-carbohydrate score						
Cases, *n*	95	80	76	83	82	
Age- and energy-adjusted HR	1.0	0.81 (0.60–1.09)	0.83 (0.61–1.12)	0.87 (0.64–1.17)	0.99 (0.73–1.33)	0.89
Prostate cancer–specific model HR‖	1.0	0.88 (0.65–1.19)	0.85 (0.62–1.16)	0.90 (0.67–1.23)	0.97 (0.71–1.31)	0.97

* Adjusted for age, body mass index, energy intake, multivitamin use, alcohol intake, menopausal status and postmenopausal hormone use (women only), physical activity, pack-years of smoking, history of polyps, family history, colonoscopy, and aspirin use.
† Adjusted for age, body mass index, energy intake, multivitamin use, alcohol intake, menopausal status and postmenopausal hormone use (women only), physical activity, age at smoking initiation, smoking status and years since quitting (women only), and the following variables for men only: adult environmental tobacco smoke exposure, parental smoking in childhood, and pack-years of smoking.
‡ *P* value no longer significant at the 0.05 level after Bonferroni correction. Pooled *P* values were not corrected.
§ Adjusted for age, body mass index, energy intake, multivitamin use, alcohol intake, menopausal status and postmenopausal hormone use, physical activity, smoking, family history, weight change since age 18 y, history of benign breast disease, body mass index at age 18 y, and height.
‖ Adjusted for age, body mass index, energy intake, multivitamin use, alcohol intake, physical activity, adult environmental tobacco smoke exposure, parental smoking in childhood, and pack-years of smoking.