ORIGINAL ARTICLE

Low-Carbohydrate-Diet Score and the Risk of Coronary Heart Disease in Women

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ABSTRACT

BACKGROUND

Low-carbohydrate diets have been advocated for weight loss and to prevent obesity, but the long-term safety of these diets has not been determined.

METHODS

We evaluated data on 82,802 women in the Nurses' Health Study who had completed a validated food-frequency questionnaire. Data from the questionnaire were used to calculate a low-carbohydrate-diet score, which was based on the percentage of energy as carbohydrate, fat, and protein (a higher score reflects a higher intake of fat and protein and a lower intake of carbohydrate). The association between the low-carbohydrate-diet score and the risk of coronary heart disease was examined.

RESULTS

During 20 years of follow-up, we documented 1994 new cases of coronary heart disease. After multivariate adjustment, the relative risk of coronary heart disease comparing highest and lowest deciles of the low-carbohydrate-diet score was 0.94 (95% confidence interval [CI], 0.76 to 1.18; P for trend=0.19). The relative risk comparing highest and lowest deciles of a low-carbohydrate-diet score on the basis of the percentage of energy from carbohydrate, animal protein, and animal fat was 0.94 (95% CI, 0.74 to 1.19; P for trend=0.52), whereas the relative risk on the basis of the percentage of energy from intake of carbohydrates, vegetable protein, and vegetable fat was 0.70 (95% CI, 0.56 to 0.88; P for trend=0.002). A higher glycemic load was strongly associated with an increased risk of coronary heart disease (relative risk comparing highest and lowest deciles, 1.90; 95% CI, 1.15 to 3.15; P for trend=0.003).

CONCLUSIONS

Our findings suggest that diets lower in carbohydrate and higher in protein and fat are not associated with increased risk of coronary heart disease in women. When vegetable sources of fat and protein are chosen, these diets may moderately reduce the risk of coronary heart disease.

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Obesity in the United States has reached epidemic proportions. Leading research and medical societies advocate a low-fat, high-carbohydrate, energy-deficient diet to manage weight.[1-4] Despite these recommendations, diets high in fat and protein and low in carbohydrate remain popular, and several best-selling books endorse this strategy for weight loss.[5-9]

The long-term safety of carbohydrate-restricted diets remains controversial. Most such diets tend to encourage increased consumption of animal products and therefore often contain high amounts of saturated fat and cholesterol. This may cause unfavorable changes in serum lipid levels and increase the risk of coronary heart disease. Several professional organizations have cautioned against the use of low-carbohydrate diets.[10-13]

We devised a system to classify women who participated in the Nurses' Health Study according to their relative levels of fat, protein, and carbohydrate intake and created a simple summary score designated the "low-carbohydrate-diet score." We then examined prospectively the association between the low-carbohydrate-diet score and the risk of coronary heart disease in this cohort.

METHODS

STUDY POPULATION

The Nurses' Health Study was initiated in 1976, when 121,700 female registered nurses 30 to 55 years of age completed a mailed questionnaire. Since 1976, information on disease status and lifestyle factors has been collected from this same cohort every 2 years. Diet was assessed by means of a semiquantitative food-frequency questionnaire in 1980, 1984, 1986, 1990, 1994, and 1998; 98,462 women completed the 1980 questionnaire.

For this investigation we excluded all women at baseline who left 10 or more food items blank or had implausibly high (>3500 kcal) or low (<500 kcal) daily energy intakes on the food-frequency questionnaire. We further excluded women with a history of diabetes, cancer, or cardiovascular disease before 1980, because these diagnoses may cause alterations in diet. After these exclusions, 82,802 women remained in this investigation. The study was approved by the Human Research Committee of Brigham and Women's Hospital in Boston; the completion of the self-administered questionnaire was considered to imply informed consent.

ASSESSMENT OF DIET AND GLYCEMIC LOAD

The 1980 food-frequency questionnaire included 61 food items and was revised in 1984 to include about twice that number.[14,15] Study participants reported average frequency of consumption of specific foods throughout the previous year. The validity and reproducibility of the questionnaire have been documented elsewhere.[14,15]

To calculate the intake of specific foods, a commonly used portion size for each food was specified (e.g., one egg or one slice of bread) and participants were asked how often, on average, during the previous year they had consumed that amount. The possible responses ranged from never or less than once per month to six or more times per day.

Nutrient values were computed by multiplying the frequency of consumption of each food by the nutrient content of the portion and then adding these products across all food items. All food-composition values were obtained from the Harvard University food-composition database, which was derived from U.S. Department of Agriculture sources[16] and supplemented with information from the manufacturer. The validity of estimated nutrient intake as assessed by the questionnaire has previously been evaluated with the use of multiple diet records. The correlation between the 1986 questionnaire and the average of six 1-week diet records collected in 1980 and 1986 was 0.73 for carbohydrate, 0.67 for total fat, and 0.56 for protein.[15]

The method used to assess glycemic load in the Nurses' Health Study has been described elsewhere.[17] Briefly, we calculated the total dietary glycemic load by multiplying the carbohydrate content of each food by its glycemic index (the glycemic index of glucose is 100) and then multiplied this value by the frequency of consumption and summed these values for all foods. Dietary glycemic load, therefore, represents both the quality and quantity of carbohydrate consumed. Each unit of glycemic load represents the equivalent blood glucose–raising effect of 1 g of pure glucose.

CALCULATION OF THE LOW-CARBOHYDRATE-DIET SCORE

We divided the study participants into 11 strata each of fat, protein, and carbohydrate intake, expressed as a percentage of energy (Table 1). For fat and protein, women in the highest stratum received 10 points for that macronutrient, women in the next stratum received 9 points, and so on down to women in the lowest stratum, who received 0 points. For carbohydrate, the order of the strata was reversed; those with the lowest carbohydrate intake received 10 points and those with the highest carbohydrate intake received 0 points. We used the percentage of energy consumed instead of absolute intake to reduce bias due to underreporting of food consumption and to represent dietary composition.

The points for each of the three macronutrients were then summed to create the overall diet score, which ranged from 0 (the lowest fat and protein intake and the highest carbohydrate intake) to 30 (the highest protein and fat intake and the lowest carbohydrate intake). Therefore, the higher the score, the more closely the participant's diet followed the pattern of a low-carbohydrate diet. Thus, the score was termed the "low-carbohydrate-diet score."

We also created two additional low-carbohydrate-diet scores. One was calculated according to the percentage of energy as carbohydrate, the percentage of energy as animal protein, and the percentage of energy as animal fat, and the other was calculated according to the percentage of energy as carbohydrate, the percentage of energy as vegetable protein, and the percentage of energy as vegetable fat (Table 1).

MEASUREMENT OF NONDIETARY FACTORS

In 1976, women provided information regarding parental history of myocardial infarction. Beginning in 1976, participants also provided information every 2 years on the use of postmenopausal hormones, smoking status, body weight, and other covariates. They provided information on aspirin use repeatedly throughout the follow-up. The correlation coefficient between self-reported body weight and measured weight was 0.96.[18] Physical activity was assessed in 1980, 1982, 1986, 1988, 1992, 1996, and 1998, and we calculated the cumulative average number of hours per week spent in moderate or vigorous physical activity.[19]

OUTCOME

The outcome of this study was incident coronary heart disease, including nonfatal myocardial infarctions or fatal coronary events. Each participant contributed follow-up time from the date of returning the 1980 questionnaire to the date of the first end point (death or nonfatal myocardial infarction) or until the censoring date of June 1, 2000.

We requested permission to examine the medical records of all participants who reported a diagnosis of coronary heart disease on one of the follow-up questionnaires that were completed every two years. A myocardial infarction was considered to be confirmed if it met the World Health Organization criteria of symptoms and either typical electrocardiographic changes or elevated cardiac-enzyme levels.[20] Infarctions that necessitated a hospital admission and for which confirmatory information was obtained by interview or letter but for which no medical records were available were designated as probable and were included in the analysis.

Table 1. Criteria for Determining the Low-Carbohydrate-Diet Score.

Points	Carbohydrate Intake	Total Protein Intake	Total Fat Intake	Animal-Protein Intake	Animal-Fat Intake	Vegetable-Protein Intake	Vegetable-Fat Intake
				percentage of energy			
0	>56.0	<14.1	<26.0	<9.6	<14.3	<2.6	<5.0
1	51.6–56.0	14.1–15.6	26.0–29.5	9.6–11.1	14.3–17.1	2.6–3.2	5.0–7.7
2	49.1–51.5	15.7–16.6	29.6–31.6	11.2–12.1	17.2–18.8	3.3–3.6	7.8–9.3
3	47.1–49.0	16.7–17.3	31.7–33.2	12.2–12.9	18.9–20.3	3.7–3.8	9.4–10.5
4	45.2–47.0	17.4–18.0	33.3–34.7	13.0–13.6	20.4–21.8	3.9–4.1	10.6–11.5
5	43.3–45.1	18.1–18.7	34.8–36.1	13.7–14.3	21.9–23.3	4.2–4.3	11.6–12.5
6	41.2–43.2	18.8–19.4	36.2–37.7	14.4–15.1	23.4–25.0	4.4–4.6	12.6–13.5
7	38.8–41.1	19.5–20.3	37.8–39.5	15.2–16.1	25.1–27.3	4.7–4.8	13.6–14.7
8	35.4–38.7	20.4–21.5	39.6–42.0	16.2–17.4	27.4–30.6	4.9–5.2	14.8–16.2
9	29.3–35.3	21.6–24.0	42.1–46.9	17.5–20.2	30.7–37.3	5.3–5.9	16.3–19.2
10	<29.3	>24.0	>46.9	>20.2	>37.3	>5.9	>19.2

Table 2. Characteristics of the Participants in 1990 According to the Low-Carbohydrate-Diet Scores.*

Variable	Intake of Carbohydrate, Total Protein, and Total Fat			Intake of Carbohydrate, Animal Protein, and Animal Fat			Intake of Carbohydrate, Vegetable Protein, and Vegetable Fat		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Low-carbohydrate-diet score									
Median	5.0	14.0	26.0	4.5	13.3	27.0	8.0	14.3	21.8
Interquartile range	3.7–6.3	13.5–14.2	24.5–27.0	3.0–5.5	13.0–13.8	26.0–28.0	6.0–9.0	14.0–14.5	21.0–23.0
No. of participants	7787	8381	3693	8305	9761	2902	5200	8080	7749
Age — yr	56.0±7.1	56.0±7.3	55.9±7.3	56.0±7.3	56.0±6.9	56.0±7.0	56.0±7.2	55.9±7.2	56.0±7.0
Body-mass index†	24.6±4.4	25.6±4.6	26.7±5.5	24.5±4.6	25.7±4.9	26.3±5.4	25.4±5.0	25.7±4.5	25.5±5.3
Parental history of myocardial infarction — % (no.)	19 (1480)	20 (1676)	21 (776)	19 (1578)	20 (1952)	22 (638)	20 (1040)	21 (1697)	20 (1550)
Use of postmenopausal hormones — % (no.)	26 (2025)	27 (2263)	22 (813)	27 (2242)	27 (2636)	18 (522)	20 (1040)	27 (2182)	28 (2170)
Physical activity — MET-hr/wk‡	21±25	19±23	17±21	21±25	19±24	16±22	19±25	20±24	19±21
Current smoker — % (no.)	17 (1324)	16 (1341)	26 (960)	15 (1246)	17 (1659)	27 (784)	24 (1248)	16 (1293)	20 (1550)
Alcohol consumption — g/day	4.0±8.5	5.5±10.1	4.3±7.2	3.1±6.6	5.6±9.9	4.9±8.4	3.9±9.0	5.0±8.9	6.3±9.5
History of hypertension — % (no.)	14 (1090)	13 (1090)	15 (554)	13 (1080)	13 (1269)	16 (464)	15 (780)	15 (1212)	13 (1007)
History of hypercholesterolemia — % (no.)	5 (389)	5 (419)	4 (148)	5 (415)	5 (488)	4 (116)	4 (208)	5 (404)	5 (388)
Calories — kcal/day	1814±528	1768±501	1539±490	1825±527	1764±504	1472±491	1740±523	1735±506	1775±513
Glycemic index§	54.3±3.9	52.8±3.4	50.8±4.6	54.2±3.3	52.8±3.6	50.4±5.6	53.4±4.8	52.8±4.0	52.6±3.2
Glycemic load§	145±48	117±37	73±28	143±47	116±38	65±27	131±49	118±42	107±37
Cereal fiber — g/day	6.3±3.9	5.7±3.4	3.4±2.3	6.7±4.1	5.6±3.6	2.9±2.3	4.5±3.2	5.6±4.0	5.6±3.2
Fruits and vegetables — servings/day	5.8±2.6	5.1±1.8	4.2±1.8	5.8±2.7	5.1±2.0	4.3±2.2	5.2±2.9	5.2±1.8	4.7±1.8
Coffee — cups/day	1.6±1.8	1.9±1.8	2.3±1.8	1.6±1.8	1.9±2.0	2.3±2.1	1.7±1.4	1.8±1.8	2.1±1.8

Red meat — servings/day¶	0.8±0.9	1.2±0.9	2.4±1.2	0.8±0.9	1.2±1.0	2.7±1.6	1.4±0.7	1.2±0.9	1.2±0.9
Whole grains — servings/day	1.6±1.6	1.5±0.9	1.0±1.2	1.8±1.7	1.5±0.9	0.8±1.1	1.0±1.1	1.4±0.8	1.7±1.6
Refined grains — servings/day	2.3±1.6	2.1±1.7	1.5±1.2	2.4±1.7	2.1±1.8	1.3±2.1	1.7±1.1	2.0±1.6	2.2±1.6
Nuts — servings/day	0.1±0.2	0.1±0.2	0.2±0.3	0.2±0.3	0.1±0.2	0.1±0.2	0.1±0.1	0.1±0.1	0.4±0.5
Poultry — servings/day	0.2±0.2	0.3±0.2	0.4±0.2	0.2±0.2	0.3±0.2	0.4±0.2	0.3±0.2	0.3±0.2	0.3±0.2
Fish — servings/day	0.2±0.2	0.3±0.2	0.3±0.3	0.2±0.2	0.3±0.2	0.3±0.3	0.3±0.3	0.3±0.2	0.3±0.2
Magnesium — mg/day	294±78	304±78	284±71	300±79	302±75	281±68	284±82	303±83	302±70
Multivitamin use — % (no.)	32 (2492)	33 (2766)	14 (517)	32 (2658)	32 (3124)	8 (232)	23 (1196)	32 (2586)	29 (2247)
Macronutrient intake — % of energy									
Protein	15.9±2.3	19.0±3.4	22.8±3.4	16.0±2.5	19.0±2.7	24.2±3.8	18.2±3.7	19.1±3.2	18.7±3.2
Animal protein	10.5±3.1	13.9±3.4	18.3±3.8	10.4±2.5	13.9±2.7	20.3±3.8	14.0±3.7	14.1±4.0	13.0±3.2
Vegetable protein	5.3±1.6	5.1±0.8	4.5±1.1	5.6±1.6	5.1±0.9	4.0±0.8	4.2±1.1	5.0±0.8	5.6±0.8
Carbohydrate	58.8±7.0	49.9±5.9	36.8±6.1	57.9±6.6	49.7±6.3	34.7±6.3	55.6±8.0	50.9±7.3	45.4±7.1
Total fat	26.9±5.4	31.4±5.1	39.8±5.3	28.1±5.7	31.5±5.4	39.6±5.8	27.1±5.8	30.4±5.7	35.8±5.5
Animal fat	13.3±3.9	17.0±4.2	24.4±5.7	13.0±4.1	17.1±4.5	27.4±5.3	17.5±5.3	17.2±4.9	16.9±4.8
Vegetable fat	13.6±3.9	14.3±4.2	15.3±5.3	15.2±4.9	14.3±4.5	12.2±4.3	9.6±2.7	13.1±3.2	18.9±4.8
Polyunsaturated fat	5.3±1.6	5.9±1.7	7.0±1.9	5.7±1.6	5.9±1.8	6.3±1.8	4.4±1.1	5.6±1.6	7.4±1.6
Trans fat	1.4±0.8	1.5±0.8	1.7±0.8	1.5±0.8	1.5±0.9	1.6±0.5	1.2±0.5	1.4±0.8	1.7±0.8
Saturated fat	9.0±2.3	10.6±2.5	13.7±2.7	9.1±2.5	10.7±2.7	14.3±3.0	10.1±2.7	10.5±2.4	11.4±2.4

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Data for metabolic equivalents (MET) per week are from 1992.
§ Glucose was used as the reference for calculations of glycemic index and glycemic load.
¶ Red meat is the composite score of beef, pork, and lamb as a main dish or mixed dish; hamburgers; hot dogs; bacon; and processed meats.

Table 3. Relative Risk of Coronary Heart Disease in Women According to Low-Carbohydrate-Diet Score.*

Variable	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5
Intake of carbohydrate, total protein, and total fat					
No. of cases	209	231	237	220	193
No. of person-yr	159,884	154,779	159,889	172,548	139,412
Low-carbohydrate-diet score					
Median	5.0	8.5	10.5	12.3	14.0
Range	0–7.0	7.2–9.6	9.7–11.4	11.5–13.0	13.2–14.6
Age- and smoking-adjusted relative risk (95% CI)	1.0	1.01 (0.84–1.22)	1.03 (0.86–1.25)	0.94 (0.78–1.14)	0.96 (0.79–1.17)
Multivariate relative risk (95% CI)	1.0	1.07 (0.88–1.29)	1.07 (0.89–1.29)	0.96 (0.80–1.17)	0.98 (0.81–1.20)
Intake of carbohydrate, animal protein, and animal fat					
No. of cases	203	236	225	193	207
No. of person-yr	159,405	154,190	160,608	151,959	163,035
Low-carbohydrate-diet score					
Median	4.5	7.8	10.0	11.6	13.3
Range	0–6.3	6.4–8.8	9.0–10.7	10.8–12.4	12.5–14.0
Age- and smoking-adjusted relative risk (95% CI)	1.0	1.10 (0.91–1.32)	1.06 (0.88–1.28)	0.98 (0.80–1.19)	1.03 (0.85–1.25)
Multivariate relative risk (95% CI)	1.0	1.12 (0.93–1.35)	1.07 (0.88–1.29)	0.97 (0.79–1.18)	1.02 (0.84–1.24)
Intake of carbohydrate, vegetable protein, and vegetable fat					
No. of cases	188	207	201	208	214
No. of person-yr	159,133	168,416	150,037	155,131	147,974
Low-carbohydrate-diet score					
Median	8.0	10.5	12.0	13.0	14.3
Range	0–9.5	9.6–11.0	11.2–12.6	12.7–13.8	14.0–14.8
Age- and smoking-adjusted relative risk (95% CI)	1.0	0.98 (0.80–1.19)	0.86 (0.70–1.05)	0.82 (0.67–1.0)	0.89 (0.73–1.09)
Multivariate relative risk (95% CI)	1.0	0.99 (0.81–1.21)	0.93 (0.76–1.14)	0.89 (0.73–1.09)	0.98 (0.80–1.20)

* Multivariate relative risks were adjusted for age (in 5-year categories), body-mass index (<22.0, 22.0 to 22.9, 23.0 to 23.9, 24.0 to 24.9, 25.0 to 27.9, 28.0 to 29.9, 30.0 to 31.9, 32.0 to 33.9, 34.0 to 39.9, or ≥40.0), smoking status (never, past, or current [1 to 14, 15 to 24, or ≥25 cigarettes a day]), postmenopausal hormone use (never, current use, or past use), hours of physical activity per week (<1, 1 to 2, 2 to 4, 4 to 7, or >7), alcohol intake (0, <5 g per day, 5 to 14 g per day, or ≥15 g per day), number of times aspirin was used per week (<1, 1 to 2, 3 to 6, 7 to 14, or ≥15), use of multivitamins (yes or no), use of vitamin E supplement (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), and parental history of myocardial infarction (yes or no).

Deaths were identified from state vital records and the National Death Index or reported by the participants' next of kin or the U.S. Postal Service.[21] Fatal coronary heart disease was confirmed by an examination of autopsy or hospital records, by a listing of coronary heart disease as the cause of death on the death certificate, and by the availability of evidence of previous coronary heart disease. Those deaths in which coronary heart disease was the underlying cause on the death certificate but for which no medical records were available were designated as deaths from presumed coronary disease.

STATISTICAL ANALYSIS

We divided women into 10 categories (deciles) according to their low-carbohydrate-diet score. To represent long-term intake and reduce measurement error, we calculated the cumulative average low-carbohydrate-diet score based on the infor-

Table 3. (Continued.)

Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	P Value for Trend
189	219	186	163	147	—
159,210	172,499	146,394	159,179	160,248	—
15.4	17.0	19.0	22.0	26.0	—
14.7–16.2	16.3–18.0	18.2–20.2	20.3–23.3	23.4–30.0	—
0.92 (0.75–1.12)	1.02 (0.85–1.24)	1.08 (0.89–1.32)	0.97 (0.79–1.20)	1.11 (0.89–1.38)	0.54
0.90 (0.74–1.10)	1.00 (0.82–1.21)	1.02 (0.83–1.24)	0.90 (0.73–1.11)	0.94 (0.76–1.18)	0.19
250	193	180	172	135	—
171,442	149,805	145,890	168,039	159,668	—
15.0	17.0	19.3	22.5	27.0	—
14.2–16.0	16.2–18.0	18.2–20.8	21.0–24.5	24.6–30.0	—
1.18 (0.98–1.43)	1.11 (0.91–1.35)	1.12 (0.91–1.37)	1.15 (0.94–1.42)	1.16 (0.92–1.46)	0.09
1.13 (0.94–1.36)	1.04 (0.85–1.27)	1.02 (0.83–1.26)	1.01 (0.81–1.24)	0.94 (0.74–1.19)	0.52
175	258	188	217	138	—
151,136	201,153	136,944	168,976	145,143	—
15.3	16.5	17.8	19.0	21.8	—
15.0–15.8	16.0–17.0	17.2–18.2	18.3–20.0	20.2–30.0	—
0.70 (0.57–0.87)	0.81 (0.67–0.98)	0.79 (0.64–0.97)	0.77 (0.63–0.94)	0.60 (0.48–0.75)	<0.001
0.78 (0.63–0.97)	0.92 (0.76–1.11)	0.90 (0.73–1.11)	0.88 (0.72–1.08)	0.70 (0.56–0.88)	0.002

mation from the 1980, 1984, 1986, 1990, 1994, and 1998 questionnaires.[22] For example, the low-carbohydrate-diet score from the 1980 questionnaire was related to the incidence of coronary heart disease between 1980 and 1984, and the low-carbohydrate-diet score from the average of the 1980 and 1984 questionnaires was related to the incidence of coronary heart disease between 1984 and 1986. Incidence rates for coronary heart disease were calculated by dividing cases by the person-years of follow-up for each decile of the low-carbohydrate-diet score. Relative risks of coronary heart disease were calculated by dividing the rate of occurrence of coronary heart disease in each decile by the rate in the first (lowest) decile. We used Cox proportional-hazards models[23] to adjust for potentially confounding variables. Because low-carbohydrate diets may decrease subsequent energy intake,[24] we did not control for total energy intake in multivariate models. However, further adjustment for caloric intake was performed in a secondary analysis. We also examined the association between each macronutrient and the risk of coronary heart disease in multivariate nutrient-density models.[22] All P values are two-sided.

RESULTS

The cumulative average low-carbohydrate-diet score ranged from a median of 5.0 in the 1st decile

Table 4. Relative Risk of Coronary Heart Disease in Women According to Consumption of Macronutrients.*

Variable	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5
			relative risk (95% CI)		
Carbohydrate					
Age- and smoking-adjusted	1.0	1.07 (0.86–1.33)	1.19 (0.96–1.48)	1.06 (0.85–1.33)	1.06 (0.85–1.33)
Multivariate†	1.0	1.07 (0.86–1.34)	1.21 (0.97–1.51)	1.09 (0.87–1.37)	1.09 (0.86–1.38)
Glycemic load					
Age- and smoking-adjusted	1.0	0.96 (0.76–1.21)	0.88 (0.69–1.11)	0.93 (0.73–1.17)	0.80 (0.62–1.02)
Multivariate‡	1.0	1.02 (0.80–1.30)	0.99 (0.75–1.30)	1.07 (0.79–1.45)	0.93 (0.66–1.30)
Total protein					
Age- and smoking-adjusted	1.0	0.90 (0.74–1.09)	0.92 (0.76–1.12)	0.85 (0.69–1.03)	1.03 (0.85–1.24)
Multivariate§	1.0	0.94 (0.77–1.14)	0.97 (0.80–1.19)	0.89 (0.73–1.09)	1.09 (0.90–1.32)
Animal protein					
Age- and smoking-adjusted	1.0	1.05 (0.86–1.28)	1.11 (0.91–1.35)	1.04 (0.85–1.26)	1.04 (0.85–1.27)
Multivariate¶	1.0	1.08 (0.89–1.32)	1.15 (0.95–1.40)	1.07 (0.87–1.31)	1.08 (0.88–1.32)
Vegetable protein					
Age- and smoking-adjusted	1.0	0.88 (0.70–1.10)	0.89 (0.71–1.11)	0.99 (0.80–1.23)	0.87 (0.69–1.08)
Multivariate‖	1.0	0.93 (0.74–1.16)	0.98 (0.77–1.23)	1.11 (0.88–1.41)	1.02 (0.80–1.30)
Total fat					
Age- and smoking-adjusted	1.0	1.19 (0.99–1.42)	1.02 (0.85–1.24)	1.06 (0.87–1.28)	1.03 (0.85–1.25)
Multivariate**	1.0	1.18 (0.99–1.42)	1.02 (0.84–1.23)	1.04 (0.86–1.26)	0.99 (0.81–1.20)
Animal fat					
Age- and smoking-adjusted	1.0	1.11 (0.93–1.34)	1.20 (1.00–1.45)	1.03 (0.85–1.25)	0.93 (0.76–1.13)
Multivariate††	1.0	1.07 (0.89–1.29)	1.13 (0.94–1.37)	0.95 (0.78–1.16)	0.82 (0.67–1.01)
Vegetable fat					
Age- and smoking-adjusted	1.0	0.86 (0.69–1.07)	1.09 (0.88–1.34)	1.01 (0.81–1.25)	0.96 (0.77–1.19)
Multivariate‡‡	1.0	0.87 (0.70–1.09)	1.10 (0.89–1.37)	1.01 (0.81–1.27)	0.94 (0.74–1.18)

* Multivariate relative risks were adjusted for age (in 5-year categories), body-mass index (<22.0, 22.0 to 22.9, 23.0 to 23.9, 24.0 to 24.9, 25.0 to 27.9, 28.0 to 29.9, 30.0 to 31.9, 32.0 to 33.9, 34.0 to 39.9, or ≥40.0), smoking status (never, past, or current [1 to 14, 15 to 24, or ≥25 cigarettes a day]), postmenopausal hormone use (never, current use, or past use), hours of physical activity per week (<1, 1 to 2, 2 to 4, 4 to 7, or >7), alcohol intake (0, <5 g per day, 5 to 14 g per day, or ≥15 g per day), number of times aspirin was used per week (<1, 1 to 2, 3 to 6, 7 to 14, or ≥15), use of multivitamins (yes or no), use of vitamin E supplement (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), and parental history of myocardial infarction (yes or no).

† The multivariate model included total protein, cereal fiber, and total calories.

‡ The multivariate model included total protein, cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, and total calories (glycemic load was assessed from 1984 to 2000).

§ The multivariate model included cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, and total calories.

¶ The multivariate model included cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, vegetable protein, and total calories.

‖ The multivariate model included cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, animal protein, and total calories.

** The multivariate model included protein and total calories.

†† The multivariate model included protein, vegetable fat, trans fat, and total calories.

‡‡ The multivariate model included protein, animal fat, trans fat, and total calories.

to a median of 26.0 in the 10th decile (Table 2). The mean daily carbohydrate intake ranged from 234.4 g in the 1st decile to 116.7 g in the 10th decile. At the midpoint of follow-up (1990), women who had a higher score were more likely to smoke and had a higher body-mass index, a lower dietary glycemic load, a lower caloric intake, and a higher intake of saturated fat. On average, body-mass

Table 4. (Continued.)

Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	P Value for Trend
		relative risk (95% CI)			
1.21 (0.97–1.50)	1.10 (0.89–1.37)	1.18 (0.95–1.47)	1.21 (0.98–1.50)	1.17 (0.94–1.45)	0.09
1.26 (1.00–1.58)	1.15 (0.91–1.46)	1.24 (0.98–1.57)	1.28 (1.01–1.62)	1.22 (0.95–1.56)	0.06
0.76 (0.60–0.98)	0.98 (0.78–1.24)	0.87 (0.68–1.10)	1.08 (0.86–1.37)	1.13 (0.90–1.43)	0.10
0.95 (0.66–1.37)	1.27 (0.87–1.86)	1.20 (0.79–1.82)	1.64 (1.04–2.57)	1.90 (1.15–3.15)	0.003
0.85 (0.70–1.04)	0.99 (0.82–1.20)	0.95 (0.78–1.15)	0.85 (0.69–1.03)	1.14 (0.94–1.38)	0.23
0.89 (0.72–1.09)	1.02 (0.83–1.24)	0.96 (0.78–1.17)	0.82 (0.67–1.02)	1.06 (0.86–1.30)	0.97
1.17 (0.96–1.42)	1.05 (0.86–1.28)	1.07 (0.87–1.31)	1.10 (0.90–1.35)	1.22 (0.99–1.50)	0.10
1.16 (0.95–1.42)	1.04 (0.85–1.28)	1.06 (0.86–1.30)	1.05 (0.85–1.30)	1.13 (0.91–1.41)	0.65
0.78 (0.63–0.98)	0.87 (0.70–1.08)	0.84 (0.67–1.04)	0.76 (0.61–0.95)	0.80 (0.63–1.00)	0.009
0.94 (0.73–1.21)	1.06 (0.82–1.36)	1.05 (0.81–1.35)	0.97 (0.74–1.26)	1.08 (0.82–1.43)	0.59
1.13 (0.93–1.37)	1.18 (0.97–1.43)	1.15 (0.94–1.40)	1.26 (1.04–1.54)	1.18 (0.95–1.46)	0.05
1.07 (0.88–1.30)	1.10 (0.88–1.30)	1.03 (0.84–1.26)	1.11 (0.91–1.36)	0.99 (0.79–1.23)	0.86
1.21 (1.00–1.47)	1.22 (1.01–1.49)	1.24 (1.01–1.52)	1.30 (1.06–1.61)	1.36 (1.08–1.72)	0.003
1.06 (0.86–1.29)	1.03 (0.84–1.27)	1.01 (0.82–1.26)	1.02 (0.81–1.28)	0.98 (0.75–1.28)	0.66
1.02 (0.82–1.27)	0.91 (0.73–1.14)	0.89 (0.71–1.11)	0.91 (0.72–1.14)	0.86 (0.69–1.09)	0.09
0.99 (0.78–1.25)	0.87 (0.68–1.11)	0.82 (0.64–1.06)	0.82 (0.63–1.06)	0.75 (0.57–0.98)	0.006

index increased by approximately 2.5 units from baseline to the end of follow-up, regardless of the low-carbohydrate-diet score.

Because the Nurses' Health Study did not routinely collect data on blood lipid levels, the effect of a low-carbohydrate diet on lipids could not be assessed for the entire study cohort. However, a subgroup of women from the study (466 women) had blood drawn in 1990 for determinations of lipid levels. In this subgroup, the low-carbohydrate-diet score was not associated with the total cholesterol level or with the levels of high-density lipoprotein (HDL) cholesterol or low-density lipoprotein (LDL) cholesterol after adjustment for age, smoking status, and other covariates. The low-carbohydrate-diet score was inversely associated with the triglyceride level (126.5 mg per deciliter in the lowest quintile and 99.3 mg per deciliter in the highest quintile of the low-carbohydrate-diet score, P for trend=0.05).

During 20 years of follow-up (1,584,042 person-years), we documented 1994 cases of coronary heart disease. In age-adjusted analyses, the relative risk comparing women in the 10th decile with those in the 1st decile of the low-carbohydrate-diet score was 1.29 (95% confidence interval [CI], 1.04 to 1.60). After further adjustment for smoking status, the relative risk of coronary heart disease was 1.11 (95% CI, 0.89 to 1.38) comparing women in the same deciles of the low-carbohydrate-diet score (P for trend=0.54) (Table 3). After controlling for potential confounders, the relative risk was 0.94 (95% CI, 0.76 to 1.18; P for trend=0.19). Further adjustment for total calories did not appreciably alter the results (relative risk, 0.96; 95% CI, 0.77 to 1.20; P for trend=0.27).

When body-mass index was removed from the multivariate model, the results did not change significantly.

In stratified analyses, there was no evidence that the relationship between the low-carbohydrate-diet score and coronary heart disease was modified as a result of body-mass index, level of physical activity, smoking status, or the presence or absence of diabetes, hypertension, or hypercholesterolemia. Specific data on blood lipid levels were not available for most of the cohort. As a result, it was not feasible to adjust or stratify our analysis for this factor.

We also created a second low-carbohydrate-diet score according to the percentages of energy from carbohydrate, animal protein, and animal fat (Table 1). The multivariate relative risk of coronary heart disease was 0.94 (95% CI, 0.74 to 1.19) for the comparison of the 10th with the 1st decile (P for trend=0.52) (Table 3). We also created a third low-carbohydrate-diet score according to the percentages of energy from carbohydrate, vegetable protein, and vegetable fat (Table 1). For the comparison of the 10th with the 1st decile, the multivariate relative risk of coronary heart disease was 0.70 (95% CI, 0.56 to 0.88; P for trend=0.002) (Table 3).

We examined the association between coronary heart disease and each macronutrient separately (Table 4). Total carbohydrate intake was associated with a moderately increased risk of coronary heart disease (P for trend for the comparison of the 10th decile with the 1st decile=0.06). For the comparison of the 10th with the 1st decile, there was a significant direct association between dietary glycemic load and coronary heart disease (relative risk, 1.90; 95% CI, 1.15 to 3.15; P for trend=0.003). The overall dietary glycemic index had a direct association with the risk of coronary heart disease (relative risk comparing extreme deciles, 1.19; 95% CI, 0.91 to 1.55; P for trend=0.04). There was a significant inverse association between vegetable-fat consumption and the risk of coronary heart disease (relative risk comparing extreme deciles, 0.75; 95% CI, 0.57 to 0.98; P for trend=0.006). Total fat, animal fat, total protein, animal protein, and vegetable protein were not significantly associated with the risk of coronary heart disease according to multivariate analyses.

DISCUSSION

We found that after taking into account confounding variables (especially smoking status), a low-carbohydrate diet was not associated with a risk of coronary heart disease in this large prospective cohort of women. In fact, when vegetable sources of fat and protein were chosen, the low-carbohydrate-diet score was associated with a moderately lower risk of coronary heart disease than when animal sources were chosen.

The 20-year follow-up incorporating updated dietary data and the large number of women in the study provided adequate power for this study. We reduced the measurement error in assessing long-term diet in this analysis with the use of repeated measures of diet during the follow-up. Although we adjusted for many known risk factors, we cannot completely exclude the possibility of residual or unmeasured confounding, because of the observational nature of the study.

Few people in our cohort followed the strict version of the Atkins low-carbohydrate-diet program long-term.[7] However, the amount of carbohydrate in the highest category of carbohydrate intake in our cohort (<29.3% of calories) was similar to that consumed by participants in the clinical trials of low-carbohydrate diets.[25] When preset cutoff points were used with more extreme variation in macronutrients (<20% of diet as carbohydrate, >50% of diet as fat, and >27% of diet as protein), our results did not change significantly.

The low-carbohydrate-diet score did not have a significant long-term effect on weight. On average, body-mass index increased by approximately 2.5 units from baseline to the end of follow-up, regardless of the score. Since the participants in the Nurses' Health Study did not necessarily subscribe to a low-carbohydrate diet for the specific purpose of weight loss, this result is not unexpected. However, it does indicate that the effects of the low-carbohydrate-diet score on outcomes in this analysis were not mediated by weight loss.

Any assessment of the association between the low-carbohydrate-diet score and a risk of coronary heart disease must take each macronutrient into consideration. Different types of fat appear to have different effects on the risk of coronary heart disease. In epidemiologic studies, saturated[22,26,27] and trans[22,28-30] fats have been associated with an increased risk of coronary heart disease, and polyunsaturated and monounsaturated fats with decreased risk.[22] Total dietary fat, however, has not been associated with a risk of coronary heart disease. In the Women's Health Initiative, a low-fat dietary pattern was not associated with a reduced risk of coronary heart disease during an 8-year follow-up.[31] Therefore, the increase in total fat that is common among women who follow low-carbohydrate diets would not be expected to increase the risk of coronary heart disease.[32]

In low-carbohydrate diets, dietary protein usually increases at the expense of carbohydrate. In our previous analyses, we found that a moderately high protein intake was significantly associated with a slightly reduced risk of coronary heart disease.[33] In this study, however, only vegetable protein was associated with a significantly reduced risk in age-adjusted analyses, and this association became nonsignificant in multivariate analyses.

Another possible explanation for the null association between a low-carbohydrate-diet score and the risk of coronary heart disease relates to the amount and quality of carbohydrate present in the diet.[34] A low-carbohydrate diet tends to have a lower dietary glycemic index and glycemic load than a high-carbohydrate diet. In a 10-year prospective analysis of the Nurses' Health Study, Liu et al. found a relative risk of coronary heart disease of 1.98 (95% CI, 1.41 to 2.77) for the comparison between the fifth and the first quintile of dietary glycemic load.[17] In our investigation, we found that the direct association between glycemic load and coronary heart disease was much stronger than the association between carbohydrate and coronary heart disease, probably because glycemic load reflects both the quantity and quality of carbohydrates.

In a meta-analysis of five randomized trials comparing a low-carbohydrate diet with a low-fat diet for at least 6 months, the low-carbohydrate diet was found to have a beneficial effect on HDL cholesterol and triglyceride levels but an adverse effect on total cholesterol and LDL cholesterol levels.[25] However, none of the trials have a sufficiently large sample size or a sufficiently long duration of follow-up to be used to study the outcomes of coronary heart disease. In our study, data on lipid levels were available for only a small subgroup of participants. In this group, the low-carbohydrate-diet score was not associated with total cholesterol, HDL cholesterol, or LDL cholesterol levels but was inversely associated with the triglyceride level. Therefore, it is not clear whether these findings are applicable to any low-carbohydrate diet that has an adverse effect on serum lipid levels.

Proponents of low-carbohydrate diets assert that ketogenesis (the production of ketone bodies) is an important component of the overall effects of such diets.[7] We were not able to measure ketogenesis in this investigation. Our investigation also did not address other possible adverse consequences of a low-carbohydrate diet in terms of a decline in renal function, osteoporosis, a decrease in micronutrient and fiber intake, and the risk of malignant conditions. We have observed previously in a subgroup of the Nurses' Health Study that dietary protein was not associated with a decline in renal function in women with normal renal function but may accelerate such a decline in women who have mild renal insufficiency.[35] Therefore, the long-term effects of high protein intake on renal function should be investigated further, especially among people with compromised renal function, such as those with diabetes or renal disease.

In conclusion, diets lower in carbohydrate and higher in protein and fat were not associated with an increased risk of coronary heart disease in this cohort of women. When vegetable sources of fat and protein were chosen, these diets were related to a lower risk of coronary heart disease.

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REFERENCES

1. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults — the Evidence Report. Obes Res 1998;6:Suppl 2:51S-209S. [Erratum, Obes Res 1998;6:464.]

2. Thomas PR, ed. Weighing the options: criteria for evaluating weight-management programs. Washington, DC: National Academy Press, 1995.

3. Position of the American Dietetic Association: weight management. J Am Diet Assoc 1997;97:71-4.
4. Krauss RM, Deckelbaum RJ, Ernst N, et al. Dietary guidelines for healthy American adults: a statement for health professionals from the National Committee, American Heart Association. Circulation 1996;94:1795-800.
5. Steward HL, Bethea MC, Andrews SS, Balart LA. Sugar busters! New York: Ballantine Books, 1995.
6. Eades MR, Eades MD. Protein power. New York: Bantam Books, 1999.
7. Atkins RC. Dr. Atkins' new diet revolution. Rev. ed. New York: Avon Books, 1998.
8. Sears B, Lawren B. The Zone: a dietary road map to lose weight permanently, reset your genetic code, prevent disease, achieve maximum physical performance. New York: HarperCollins, 1995.
9. Heller RF, Heller RF. The carbohydrate addict's diet: the lifelong solution to yo-yo dieting. New York: New American Library, 1993.
10. Stein K. High-protein, low-carbohydrate diets: do they work? J Am Diet Assoc 2000;100:760-1.
11. St Jeor ST, Howard BV, Prewitt TE, Bovee V, Bazzarre T, Eckel RH. Dietary protein and weight reduction: a statement for healthcare professionals from the nutrition committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Circulation 2001;104:1869-74.
12. American Heart Association statement on high-protein, low-carbohydrate diet study presented at scientific sessions, November 19, 2002. Chicago: American Heart Association, 2002. (Accessed October 16, 2006, at http://www.americanheart.org/presenter.jhtml?identifier=3006728.)
13. High-protein diets: AHA recommendation. Chicago: American Heart Association, 2006. (Accessed October 16, 2006, at http://www.americanheart.org/presenter.jhtml?identifier=11234.)
14. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
15. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press, 1998.
16. Composition of foods: raw, processed, prepared. Washington, DC: Department of Agriculture, 1993.
17. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455-61.
18. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self reported waist and hip circumferences in men and women. Epidemiology 1990;1:466-73.
19. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790-7.
20. Rose GA, Blackburn H. Cardiovascular survey methods. WHO monograph series no. 58. Geneva: World Health Organization, 1982.
21. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837-9.
22. Hu FB, Stampfer MJ, Manson JA, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491-9.
23. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
24. Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. J Am Coll Nutr 2004;23:373-85.
25. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:285-93. [Erratum, Arch Intern Med 2006;166:932.]
26. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. Am J Epidemiol 1984;119:667-76.
27. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: the Ireland–Boston Diet–Heart Study. N Engl J Med 1985;312:811-8.
28. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer MJ, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ 1996;313:84-90.
29. Pietinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Epidemiol 1997;145:876-87.
30. Oomen CM, Ocke MC, Feskens JM, van Erp-Baarrt MJ, Kok FJ, Kromhout D. Association between *trans* fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. Lancet 2001;357:746-51.
31. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655-66.
32. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569-78.
33. Hu FB, Stampfer MJ, Manson JE, et al. Dietary protein and risk of ischemic heart disease in women. Am J Clin Nutr 1999;70:221-7.
34. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414-23.
35. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 2003;138:460-7.