

Low-carbohydrate-diet score and risk of type 2 diabetes in women^{1–3}

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ABSTRACT

Background: Low-carbohydrate weight-loss diets remain popular; however, the long-term effects of these diets are not known.

Objective: The objective was to examine the association between low-carbohydrate-diet score and risk of type 2 diabetes

Design: We prospectively examined the association between low-carbohydrate-diet score (based on percentage of energy as carbohydrate, fat, and protein) and risk of diabetes among 85 059 women in the Nurses' Health Study.

Results: During 20 y of follow-up, we documented 4670 cases of type 2 diabetes. The multivariate relative risk (RR) of diabetes, after adjustment for body mass index and other covariates, in a comparison of the highest decile of low-carbohydrate-diet score with the lowest was 0.90 (95% CI: 0.78, 1.04; *P* for trend = 0.26). The multivariate RR for the comparison of extreme deciles of low-carbohydrate-diet score based on total carbohydrate, animal protein, and animal fat was 0.99 (95% CI: 0.85, 1.16; *P* for trend = 1.0), whereas the RR for a low-carbohydrate-diet score based on total carbohydrate, vegetable protein, and vegetable fat was 0.82 (95% CI: 0.71, 0.94; *P* for trend = 0.001). A higher dietary glycemic load was strongly associated with an increased risk of diabetes in a comparison of extreme deciles (RR: 2.47; 95% CI: 1.75, 3.47; *P* for trend < 0.0001). A higher carbohydrate consumption was also associated with an increased risk of diabetes in a comparison of extreme deciles (RR: 1.26; 95% CI: 1.07, 1.49; *P* for trend = 0.003).

Conclusion: These data suggest that diets lower in carbohydrate and higher in fat and protein do not increase the risk of type 2 diabetes in women. In fact, diets rich in vegetable sources of fat and protein may modestly reduce the risk of diabetes. *Am J Clin Nutr* 2008;87:339–46.

KEY WORDS Low-carbohydrate diet, Nurses' Health Study, type 2 diabetes, women, glycemic load, glycemic index

INTRODUCTION

Obesity in the United States has become a major public health concern. At any given time, ≈45% of women and ≈30% of men are attempting to lose weight (1). A low-fat, high-carbohydrate, hypocaloric diet has been advocated by a variety of research and medical societies for weight management (2–5). Despite these guidelines, low-carbohydrate diets remain a popular option for those attempting to lose weight. A number of best-selling books promote this strategy for weight loss (6–10).

The long-term effects of low-carbohydrate diets are yet to be determined. Low-carbohydrate diets result in an increase in total

and saturated fat intakes and a decrease in consumption of whole grains, cereal fiber, fruit, and vegetables. These changes in diet have the potential to increase the risk of type 2 diabetes. The American Diabetes Association advocates a low-fat diet to prevent type 2 diabetes (11).

We created the low-carbohydrate-diet score by dividing women from the Nurses' Health Study into deciles of fat, protein, and carbohydrate consumption as a percentage of energy consumed. The highest score, 30, represents the highest intake of fat and protein and the lowest intake of carbohydrate, whereas the lowest score, 0, represents the lowest intake of fat and protein and the highest intake of carbohydrate. The low-carbohydrate-diet score, therefore, represents how closely a participant followed a low-carbohydrate diet. In a previous investigation, we found that this score was not associated with an increased risk of coronary heart disease in women from the Nurses' Health Study (12). In the present study, we examined prospectively the association between a low-carbohydrate-diet score and the risk of type 2 diabetes in participants from the Nurses' Health Study.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study was initiated in 1976 when 121 700 female registered nurses aged 30–55 y completed a mailed questionnaire. Ninety-eight percent of these women were white, which reflected the ethnic composition of US registered nurses at the time. Since 1976, information on disease status as well as lifestyle factors has been collected every 2 y. Diet was assessed by means of a semiquantitative food-frequency questionnaire (SFFQ) in 1980, 1984, 1986, 1990, 1994, and 1998.

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For this investigation, we excluded all women at baseline who left ≥ 10 food items blank or had implausibly high (>3500 kcal) or low (<500 kcal) energy intakes on the SFFQ. We further excluded women with a history of diabetes, cancer (not including nonmelanoma skin cancer), or cardiovascular disease at baseline because these diseases can cause alterations in diet. After these exclusions, 85 059 women remained in this investigation. Participants were followed for 20 y (1980–2000). The study was conducted according to the ethical guidelines of Brigham and Women's Hospital, Boston. The completion of the self-administered questionnaire was considered to imply informed consent.

Dietary assessment

At baseline, the SFFQ contained 61 food items and was revised in subsequent cycles to include about twice that number (13, 14). Study participants reported average frequency of consumption of foods with a commonly used portion size throughout the previous year. The validity and reproducibility of the questionnaire were documented elsewhere (14).

To calculate intakes of specific foods, a commonly used portion size for each food was specified, and the 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 ≥ 6 times/d.

Nutrient values for carbohydrate, total fat, protein, *trans* fat, saturated fat, polyunsaturated fat, and cereal fiber were computed by multiplying the frequency of consumption of each food by the nutrient content of the portion and then adding these products across each food item. When corrected for week-to-week variations in diet records that were used to assess validity, the correlation between the expanded food-frequency questionnaire and two 1-wk diet records was 0.64 for carbohydrate, 0.57 for fat, and 0.50 for protein (15). All food composition values were obtained from the Harvard University food-composition database, which was derived from US Department of Agriculture sources (16). This database was further supplemented with manufacturer's information.

The method used to assess dietary glycemic load in the Nurses' Health Study was documented elsewhere. Briefly, we calculated the glycemic load by multiplying the carbohydrate content of each food by its glycemic index 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 of 1 g carbohydrate from white bread or pure glucose.

Measurement of nondietary factors

In 1982 and 1988 women provided information regarding family history of diabetes in first-degree relatives. Participants also provided information on the use of postmenopausal hormones, smoking status, and body weight every 2 y throughout the follow-up. The correlation coefficient between self-reported body weight and measured weight was 0.96 (17).

Participants reported specific physical activities in hours per week in 1980, 1982, 1986, 1988, 1992, 1996, and 1998. From each questionnaire we calculated the average number of hours per week spent in moderate or vigorous activity, including brisk walking, vigorous sports, jogging, cycling, heavy gardening, and housework (18).

Outcome ascertainment

The outcome of this study is incident type 2 diabetes mellitus. If a participant reported a diagnosis of diabetes on any of the 2-y follow-up questionnaires, a supplementary questionnaire was mailed regarding symptoms, diagnostic testing, and treatment. A diagnosis of type 2 diabetes was defined by at least one of the following criteria reported on the supplemental questionnaire: 1) ≥ 1 classic symptom (excessive thirst, polyuria, hunger, or weight loss) plus a fasting plasma glucose concentration of ≥ 140 mg/dL (7.8 mmol/L) or a random plasma glucose concentration of ≥ 200 mg/dL (11.1 mmol/L); 2) ≥ 2 elevated plasma glucose concentrations on different occasions [fasting ≥ 140 mg/dL (7.8 mmol/L), random ≥ 200 mg/dL (11.1 mmol/L)] or random ≥ 200 mg/dL (11.1 mmol/L) after ≥ 2 h of oral-glucose-tolerance testing in the absence of symptoms; or 3) treatment with hypoglycemic medications (insulin or oral hypoglycemic agents). These criteria correspond to those of the National Diabetes Data Group (19). In 1997, the diagnostic criteria for type 2 diabetes was changed so that lower fasting glucose concentrations (≥ 126 mg/dL, or 7 mmol/L) would now be considered diagnostic. Therefore, we used the American Diabetes Association criteria for diagnosis of type 2 diabetes after 1998 (20). We excluded women classified as having only gestational diabetes as well as those with type 1 diabetes. In the Nurses' Health Study, the supplemental questionnaire was highly reliable regarding confirmation of diabetes diagnosis. In a random sample of 84 women classified as having type 2 diabetes according to the supplemental questionnaire, medical records were available for 62 of these women. An endocrinologist who was blinded to the supplemental questionnaire data reviewed the records and confirmed the diagnosis of type 2 diabetes in 61 of the 62 women (98%) (21).

Statistical analysis

Each participant contributed follow-up time from the date of returning the 1980 baseline questionnaire to the date of the first endpoint, death, or 1 June 2000. Women were excluded from follow-up once they were diagnosed with diabetes. We divided the participants into deciles of fat, protein, and carbohydrate intakes (12). For fat and protein, women in the highest decile received a score of 10 for that macronutrient and women in the ninth decile received a 9 and so on down to the lowest decile, which received a score of 0. For carbohydrate, the scoring was the same but the order was reversed. Those with the lowest carbohydrate intake received a score of 10, and those with the highest carbohydrate intake received a score of 0.

The macronutrient scores were summed to create the low-carbohydrate-diet score, which ranged from 0 (lowest fat and protein intakes and highest carbohydrate intake) to 30 (highest protein and fat intakes and lowest carbohydrate intake). Therefore, the higher the score, the more closely the participant followed a low-carbohydrate diet. We divided women into 10 categories (deciles) according to low-carbohydrate-diet score. To represent long-term intake and reduce measurement error, the cumulative average low-carbohydrate-diet score was calculated (22). For example, the low-carbohydrate-diet score from the 1980 questionnaire was related to diabetes incidence between 1980 and 1984 and the low-carbohydrate-diet score from the average of the 1980 and 1984 questionnaires was related to diabetes incidence between 1984 and 1986. Incidence rates for type 2 diabetes were calculated by dividing cases by the person-years



of follow-up for each decile of low-carbohydrate-diet score. The relative risk (RR) of type 2 diabetes was calculated by dividing the rate of occurrence of type 2 diabetes in each decile by the rate in the first (lowest) decile. We used Cox proportional hazards models (23) to adjust for potentially confounding variables, including body mass index, family history of diabetes, smoking, alcohol use, postmenopausal hormone use, and physical activity.

We also examined the association between each macronutrient and risk of type 2 diabetes in multivariate nutrient density models. When modeling carbohydrate, the percentage of energy from carbohydrate, the percentage of energy from protein, and total energy were simultaneously included in the model to examine the effect of substituting carbohydrate for fat. When modeling protein, the percentage of energy from protein, the percent of energy from fat and total energy were simultaneously included in the model to examine the effect of substituting protein for carbohydrate. When modeling fat, the percentage of energy from fat, the percentage of energy from protein, and total energy were simultaneously included in the model to examine the effect of substituting fat for carbohydrate. We also examined the association between dietary glycemic load and the risk of type 2 diabetes.

All *P* values were 2 sided. Tests for trend were examined by using the median value for each category of low-carbohydrate-diet score, which was analyzed as a continuous variable in the regression models. All statistical analyses were performed with SAS version 8.2 software (SAS Institute, Cary, NC).

RESULTS

At baseline in 1980, the mean (\pm SE) low-carbohydrate-diet score was 18.2 ± 7.2 and ranged from 0 to 30 (10th to 90th percentile: 8–27). The cumulative average low-carbohydrate-diet score ranged from 5 in the first decile to 26 in the 10th decile. Women who had a higher low-carbohydrate dietary score tended to have a lower dietary glycemic load; lower cereal fiber, refined grain, and fruit and vegetable intakes; and higher red meat, animal fat, and saturated fat intakes. Family history of type 2 diabetes, body mass index, postmenopausal hormone use, physical activity, *trans* fat, and total calories were not significantly different across deciles (Table 1).

During 20 y of follow-up (1 606 716 person years), we documented 4670 cases of type 2 diabetes. The age-adjusted RR of type 2 diabetes was 1.40 (95% CI: 1.21, 1.61) in a comparison of women in the 10th decile of low-carbohydrate-diet score with women in the first decile (*P* for trend < 0.0001) (Table 2). Control for smoking, postmenopausal hormone use, physical activity, alcohol use, and family history of type 2 diabetes in a first-degree relative did not change the RR. Further control for BMI attenuated the RR to 0.90 (95% CI: 0.78, 1.04; *P* for trend = 0.26).

In a stratified analysis, there was no association between low-carbohydrate-diet score and risk of type 2 diabetes in either obese or nonobese women (data not shown). There was no evidence of effect modification of the relation between low-carbohydrate-diet score and type 2 diabetes when the data were stratified by smoking status, family history of type 2 diabetes, or physical activity (data not shown).

We created a low-carbohydrate-diet score using percentage of energy as carbohydrate, percentage of energy as animal protein, and percentage of energy as animal fat (12). The multivariate RR

of type 2 diabetes was 0.99 (95% CI: 0.85, 1.16) in a comparison of the 10th with the 1st decile for this score (*P* for trend = 1.0) (Table 2). We also created a low-carbohydrate-diet score using percentage of energy as carbohydrate, percentage of energy as vegetable protein, and percentage of energy as vegetable fat (12). The multivariate RR of type 2 diabetes was 0.82 (95% CI: 0.71, 0.94) in a comparison of the 10th with the 1st decile for this score (*P* for trend = 0.001) (Table 2).

We examined the association between each macronutrient and type 2 diabetes separately (Table 3). Comparison of the 10th with the 1st decile showed a significant positive association between carbohydrate consumption and risk of type 2 diabetes (multivariate RR: 1.26; 95% CI: 1.07, 1.49; *P* for trend = 0.003). A significant positive association was also observed between dietary glycemic load and risk of type 2 diabetes in a comparison of the 10th with the 1st decile (multivariate RR: 2.47; 95% CI: 1.75, 3.47; *P* for trend < 0.0001). In contrast, a significant inverse association was observed between vegetable fat consumption and type 2 diabetes in a comparison of the 10th with the 1st decile (multivariate RR: 0.74; 95% CI: 0.62, 0.89; *P* for trend < 0.0001). Total fat, animal fat, total protein, vegetable protein, and animal protein intakes were not associated with risk of type 2 diabetes.

DISCUSSION

In this large prospective cohort of women, we found that after adjustment for confounding variables, especially BMI, a higher low-carbohydrate-diet score was not associated with risk of type 2 diabetes. This dietary score was associated with a modest decreased risk of type 2 diabetes when vegetable sources rather than animal sources of fat and protein were chosen.

Although little research has been conducted on the association between low-carbohydrate-diet score and risk of type 2 diabetes, several investigations have examined the effects of a low-carbohydrate diet on risk factors for type 2 diabetes for 6 mo or longer (24–27). After 6 mo, Samaha et al (24) found that insulin sensitivity improved more in subjects who consumed a low-carbohydrate diet than in those who consumed a low-fat diet. Among diabetic subjects, the mean fasting glucose concentration decreased more in the low-carbohydrate-diet group. In a 1-y follow-up study, Stern et al (25) found that, in diabetic subjects, hemoglobin A_{1c} concentrations improved more in persons who consumed a low-carbohydrate diet than in those who consumed a low-fat diet. Foster et al (26), in a 1-y trial, compared a low-carbohydrate diet with a conventional low-fat diet and found no differences in insulin sensitivity between the 2 groups. Finally, Brehm et al (27) compared a low-carbohydrate diet with a low-fat diet for 6 mo and reported no differences in fasting glucose and fasting insulin between the 2 groups. These studies are difficult to interpret because of the various degrees of weight loss between the diet groups.

In shorter investigations, Boden et al (28) found a significantly lower hemoglobin A_{1c} concentration, fasting plasma glucose concentration, mean 24-h insulin concentration, and improved insulin sensitivity in obese persons with type 2 diabetes after 2 wk of a low-carbohydrate diet. McAuley et al (29) observed no difference in fasting insulin or fasting glucose concentrations after 16 wk of either a low-fat or a low-carbohydrate diet. In a 5-wk randomized crossover trial, Gannon and Nuttall (30) found



TABLE 1

Baseline characteristics according to low-carbohydrate-diet score in participants of the Nurses' Health Study¹

Variable	Total low-carbohydrate score ²			Animal low-carbohydrate score ³			Vegetable low-carbohydrate score ⁴		
	Dec 1	Dec 5	Dec 10	Dec 1	Dec 5	Dec 10	Dec 1	Dec 5	Dec 10
Median score	5	14.0	26.0	4.3	13.3	27	8	14.3	21.8
Age	45.9 ± 0.1 ⁵	45.8 ± 0.1	46.2 ± 0.1	46.0 ± 0.1	45.9 ± 0.1	46.2 ± 0.04	45.9 ± 0.1	46.1 ± 0.1	46.2 ± 0.1
BMI (kg/m ²)	24.0 ± 0.1	24.0 ± 0.1	24.7 ± 0.03	23.9 ± 0.1	24.0 ± 0.1	24.6 ± 0.03	24.5 ± 0.03	24.3 ± 0.1	23.9 ± 0.1
Family history of type 2 diabetes (%)	18	17	19	17	18	19	19	18	18
Postmenopausal hormone use (%)	8	7	9	7	8	9	9	8	8
Physical activity (h/wk)	3.9 ± 0.03	4.0 ± 0.1	3.9 ± 0.02	3.8 ± 0.04	3.9 ± 0.04	3.9 ± 0.02	3.9 ± 0.02	3.9 ± 0.04	4.0 ± 0.04
Current smokers (%)	29	27	30	27	28	31	28	30	29
Alcohol consumption (g/d)	4.9 ± 0.1	7.3 ± 0.2	5.1 ± 0.1	4.0 ± 0.1	6.8 ± 0.2	6.2 ± 0.1	4.6 ± 0.1	6.6 ± 0.1	5.9 ± 0.1
Energy (kcal)	1533 ± 5.7	1559 ± 9.1	1559 ± 3.3	1550 ± 6.8	1555 ± 7.5	1551 ± 3.0	1565 ± 3.7	1552 ± 6.6	1591 ± 6.3
Glycemic index ⁶	54.0 ± 0.1	52.1 ± 0.1	49.8 ± 0.03	54.1 ± 0.1	52.4 ± 0.1	49.8 ± 0.03	51.8 ± 0.04	51.6 ± 0.1	50.8 ± 0.1
Glycemic load ⁶	124 ± 0.6	94 ± 0.7	61 ± 0.2	126 ± 0.7	97 ± 0.5	62.4 ± 0.2	102.9 ± 0.3	80.1 ± 0.5	77.2 ± 0.4
Cereal fiber (g/d)	3.0 ± 0.03	2.7 ± 0.03	1.8 ± 0.01	3.3 ± 0.03	2.8 ± 0.03	1.8 ± 0.01	2.3 ± 0.01	2.5 ± 0.02	2.9 ± 0.02
Fruit and vegetable (servings/d)	4.9 ± 0.03	4.2 ± 0.04	3.5 ± 0.01	4.9 ± 0.04	4.2 ± 0.03	3.6 ± 0.01	4.5 ± 0.02	3.9 ± 0.03	3.8 ± 0.02
Coffee (cups/d)	2.0 ± 0.02	2.1 ± 0.03	2.3 ± 0.01	2.0 ± 0.02	2.2 ± 0.03	2.3 ± 0.01	2.0 ± 0.01	2.3 ± 0.03	2.4 ± 0.02
Magnesium intake (mg/d)	286 ± 0.8	296 ± 1.3	287 ± 0.4	294 ± 1.0	298 ± 1.1	284 ± 0.4	281 ± 0.5	297 ± 1.0	329 ± 0.9
Multivitamin use (%)	34	34	34	33	34	34	35	34	36
Red meat (servings/d) ⁷	0.8 ± 0.01	1.2 ± 0.01	1.8 ± 0.01	0.7 ± 0.01	1.1 ± 0.01	1.8 ± 0.01	1.2 ± 0.01	1.4 ± 0.01	1.2 ± 0.01
Whole grains (servings/d)	1.2 ± 0.01	1.1 ± 0.02	1.0 ± 0.01	1.3 ± 0.02	1.2 ± 0.02	1.0 ± 0.01	1.0 ± 0.01	1.2 ± 0.02	1.4 ± 0.02
Refined grains (servings/d)	2.3 ± 0.02	2.3 ± 0.03	1.9 ± 0.01	2.4 ± 0.03	2.3 ± 0.03	1.9 ± 0.01	2.0 ± 0.01	2.2 ± 0.02	2.2 ± 0.02
Nuts (servings/d)	0.1 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.1 ± 0.001	0.1 ± 0.001	0.1 ± 0.0004	0.1 ± 0.001	0.4 ± 0.002
Poultry (servings/d)	0.2 ± 0.001	0.3 ± 0.001	0.3 ± 0.001	0.2 ± 0.001	0.3 ± 0.001	0.3 ± 0.001	0.3 ± 0.001	0.3 ± 0.001	0.2 ± 0.001
Fish (servings/d)	0.1 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.1 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.2 ± 0.001	0.2 ± 0.001
Protein (% of energy)	14.7 ± 0.03	17.8 ± 0.1	21.9 ± 0.02	14.2 ± 0.03	17.3 ± 0.04	21.9 ± 0.02	18.4 ± 0.03	19.2 ± 0.1	18.4 ± 0.04
Carbohydrate (% of energy)	54.7 ± 0.1	43.4 ± 0.1	29.6 ± 0.04	55.3 ± 0.1	44.8 ± 0.1	30.2 ± 0.04	46.5 ± 0.1	37.7 ± 0.1	36.5 ± 0.1
Total fat (% of energy)	28.3 ± 0.1	35.2 ± 0.1	46.1 ± 0.03	28.9 ± 0.1	34.6 ± 0.1	44.9 ± 0.04	32.9 ± 0.1	39.9 ± 0.1	42.4 ± 0.1
Animal fat (% of energy)	18.4 ± 0.1	24.8 ± 0.1	37.5 ± 0.04	15.9 ± 0.1	23.3 ± 0.1	37.5 ± 0.04	26.7 ± 0.1	29.6 ± 0.1	23.8 ± 0.1
Vegetable fat (% energy)	9.9 ± 0.1	10.4 ± 0.1	8.6 ± 0.03	12.7 ± 0.1	11.3 ± 0.1	7.5 ± 0.02	6.3 ± 0.02	10.3 ± 0.04	18.6 ± 0.1
Polyunsaturated fat (% of energy)	4.7 ± 0.02	5.2 ± 0.03	5.4 ± 0.01	5.2 ± 0.02	5.4 ± 0.03	5.1 ± 0.01	4.1 ± 0.01	5.5 ± 0.02	7.4 ± 0.02
trans fat (% of energy)	2.0 ± 0.003	2.3 ± 0.003	2.4 ± 0.002	2.1 ± 0.003	2.2 ± 0.003	2.3 ± 0.002	1.8 ± 0.002	2.2 ± 0.002	2.5 ± 0.003
Saturated fat (% of energy)	11.1 ± 0.03	14.1 ± 0.04	18.7 ± 0.02	10.6 ± 0.03	13.6 ± 0.04	18.5 ± 0.02	14.0 ± 0.02	15.8 ± 0.04	15.0 ± 0.03

¹ Tests for trend (based on ordinal variables containing median values for each quintile) were all significant ($P < 0.05$), except for multivitamin use (for total low-score and animal low-carbohydrate score), physical activity (for total low-carbohydrate score, animal low-carbohydrate score, and vegetable low-carbohydrate score), age (for vegetable low-carbohydrate score), family history of type 2 diabetes (for vegetable low-carbohydrate score), and saturated fat (for vegetable low-carbohydrate score).

² Sum of carbohydrate, total fat, and total protein scores.

³ Sum of carbohydrate, animal fat, and animal protein scores.

⁴ Sum of carbohydrate, vegetable fat, and vegetable protein scores.

⁵ $\bar{x} \pm \text{SEM}$ (all such values).

⁶ Glucose was used as the reference for glycemic index and glycemic load calculations.

⁷ Composite score of beef, pork, and lamb as a main dish or mixed dish; hamburgers; hot dogs; bacon; and processed meats.

that, compared with a low-fat diet, a low-carbohydrate diet significantly reduced fasting glucose and glycated hemoglobin concentrations. In contrast, Swinburn et al (31) reported a significant improvement in oral glucose tolerance and a significant reduction in fasting plasma glucose in subjects who consumed a high-carbohydrate diet relative to those who consumed a low-carbohydrate diet. Once again, these studies are difficult to interpret because of various degrees of weight loss between the diet groups and because oral-glucose-tolerance tests are greatly affected by carbohydrate consumption over the few days before the test is conducted (32).

When compared with low-fat, high-carbohydrate diets, low-carbohydrate diets tend to have a relatively higher percentage of fat and protein and a lower percentage of carbohydrate. When evaluating the association between low-carbohydrate-diet score and risk of type 2 diabetes, each of the macronutrients must be taken into consideration.

Distinct types of fats have various effects on risk factors for type 2 diabetes. Substituting unsaturated fats for saturated fats increases insulin sensitivity in diabetic (33), overweight (34), and healthy (35) subjects. In epidemiologic studies, polyunsaturated fat has been shown to be associated with a reduced risk of

TABLE 2
Relative risk (RR) of type 2 diabetes in women according to low-carbohydrate-diet score

Low-carbohydrate-diet score	Decile 1	Decile 3	Decile 5	Decile 7	Decile 10	P for trend
By total carbohydrate, total protein, and total fat						
No. of cases	413	453	446	514	381	—
Person-years	163, 768	158, 745	141, 252	173, 757	163, 403	—
Median score	5	10.5	14	17	26	—
Range	0–7	9.7–11.3	13.2–14.6	16.3–18	23.5–30	—
Age-adjusted RR (95% CI)	1.0	1.06 (0.93, 1.22)	1.17 (1.02, 1.33)	1.23 (1.08, 1.40)	1.40 (1.21, 1.61)	< .0001
Multivariate ¹	1.0	1.12 (0.98, 1.28)	1.24 (1.09, 1.42)	1.31 (1.15, 1.49)	1.40 (1.21, 1.61)	< .0001
Multivariate plus BMI ²	1.0	0.98 (0.85, 1.12)	0.96 (0.84, 1.10)	0.92 (0.81, 1.05)	0.90 (0.78, 1.04)	0.26
By total carbohydrate, animal protein, and animal fat						
No. of cases	376	481	494	477	349	—
Person-years	157, 985	162, 955	165, 364	151, 145	162, 697	—
Median score	4.3	10	13.3	17	27	—
Range	0–6.3	9–10.8	12.5–14.2	16.2–18	24.8–30	—
Age-adjusted RR (95% CI)	1.0	1.21 (1.06, 1.38)	1.30 (1.13, 1.48)	1.47 (1.29, 1.69)	1.53 (1.31, 1.78)	< .0001
Multivariate ¹	1.0	1.27 (1.11, 1.45)	1.39 (1.21, 1.59)	1.58 (1.38, 1.81)	1.61 (1.37, 1.88)	< .0001
Multivariate plus BMI ²	1.0	1.05 (0.92, 1.21)	1.02 (0.89, 1.17)	1.03 (0.90, 1.18)	0.99 (0.85, 1.16)	1.0
By total carbohydrate, vegetable protein, and vegetable fat						
No. of cases	478	442	470	605	395	—
Person-years	161, 658	152, 041	150, 484	204, 564	147, 649	—
Median score	8	12	14.3	16.5	21.8	—
Range	0–9.6	11.2–12.6	14–14.8	16–17	20.2–30	—
Age-adjusted RR (95% CI)	1.0	0.79 (0.70, 0.90)	0.81 (0.71, 0.92)	0.78 (0.69, 0.88)	0.74 (0.64, 0.84)	< .0001
Multivariate ¹	1.0	0.84 (0.74, 0.96)	0.88 (0.77, 1.0)	0.86 (0.76, 0.97)	0.83 (0.73, 0.95)	0.002
Multivariate plus BMI ²	1.0	0.82 (0.72, 0.94)	0.85 (0.74, 0.97)	0.83 (0.73, 0.94)	0.82 (0.71, 0.94)	0.001

¹ RR was adjusted for age in 5-y categories, smoking (never, past, or current smoking of 1–14, 15–24, or ≥ 25 cigarettes/d), postmenopausal hormone use (never, current use, past use), physical activity (<1, 1–2, 2–4, 4–7, or > 7 h/wk), alcohol intake (0, 1–4.9, 5–14.9, or ≥ 15 g/d), and family history of type 2 diabetes in a first-degree relative.

² Adjusted for the variables in footnote 1 plus BMI (<22, 22–22.9, 23–23.9, 24–24.9, 25–27.9, 28–29.9, 30–31.9, 32–33.9, 34–39.9, or ≥ 40 kg/m²).

type 2 diabetes (36, 37). Generally, no association has been found between saturated fat (37–39) or monounsaturated fat (38–40) and risk of type 2 diabetes. Results from cohort studies on the association between *trans* fat and risk of type 2 diabetes have not been consistent (36, 37, 41). Dietary interventions in humans have shown no consistent adverse effects of high-fat diets on insulin sensitivity (31, 42–45) and in epidemiologic studies, total fat has not been shown to increase risk of type 2 diabetes (36, 37, 41). Therefore, the increase in total fat common in low-carbohydrate diets would not be expected to increase the risk of type 2 diabetes.

In low-carbohydrate diets, dietary protein is substituted for some of the carbohydrate. Dietary protein has not been shown to raise peripheral glucose concentrations after ingestion in healthy subjects or in persons with type 2 diabetes (46–51). However, protein does tend to stimulate insulin secretion in healthy persons (52, 53) and even more so in persons with type 2 diabetes (54). In metabolic studies, Gannon et al (55) found that 24-h integrated glucose area response and glycated hemoglobin decreased significantly more after 5 wk of a high-protein diet than after 5 wk of a low-fat control diet. In a similar investigation, Sargrad et al (56) found no beneficial effects of a high-protein diet relative to a low-fat diet. Epidemiologic studies of protein intake and risk of type 2 diabetes are limited. In a 6-y follow-up of subjects in the Nurses' Health Study, Colditz et al (38) found no association between protein consumption and risk of type 2 diabetes. In these

updated analyses, we found no association between total protein, animal protein, or vegetable protein and risk of type 2 diabetes.

The lack of an association between a low-carbohydrate-diet score and risk of type 2 diabetes when adjusted for confounders may also be explained by the amount and quality of carbohydrate present in the diet. High-carbohydrate diets generally result in high postprandial glucose and insulin responses. The total percentage of energy from carbohydrate has generally not been found to increase the risk of type 2 diabetes (39, 57–59). However, in the present analysis, we found a modest but positive association between carbohydrate consumption and risk of type 2 diabetes.

A carbohydrate-restricted diet tends to have a lower glycemic index and lower glycemic load than does a high-carbohydrate diet. The glycemic index of a carbohydrate is a measure of how much that food raises blood glucose compared with a standard carbohydrate (usually glucose or white bread) (60). The glycemic load takes into account the amount of carbohydrate in addition to its glycemic index (61). Compared with higher glycemic diets, low glycemic diets have been shown in epidemiologic studies to decrease glucose and insulin responses (62–64) and glycated hemoglobin (65) and to increase insulin sensitivity (64, 66). In addition, several prospective studies have shown an association between dietary glycemic index or glycemic load and risk of type 2 diabetes (39, 58, 59), whereas 2 prospective studies

TABLE 3
Relative risk of type 2 diabetes in women according to macronutrient consumption¹

	Decile 1	Decile 3	Decile 5	Decile 7	Decile 10	P for trend
Carbohydrate						
Age adjusted	1.0	1.13 (0.98, 1.31)	1.22 (1.05, 1.40)	1.16 (1.0, 1.34)	1.04 (0.90, 1.20)	0.80
Multivariate ²	1.0	1.06 (0.91, 1.23)	1.14 (0.98, 1.33)	1.12 (0.96, 1.32)	1.26 (1.07, 1.49)	0.003
Glycemic load						
Age adjusted	1.0	1.04 (.88, 1.22)	1.16 (.99, 1.35)	1.26 (1.08, 1.47)	1.37 (1.18, 1.60)	<.0001
Multivariate ³	1.0	1.23 (1.0, 1.49)	1.56 (1.24, 1.97)	1.88 (1.45, 2.45)	2.47 (1.75, 3.47)	<.0001
Total fat						
Age adjusted	1.0	1.20 (1.06, 1.37)	1.30 (1.15, 1.49)	1.36 (1.19, 1.55)	1.45 (1.26, 1.67)	<.0001
Multivariate ⁴	1.0	1.04 (0.91, 1.18)	1.01 (0.89, 1.15)	0.98 (0.86, 1.12)	0.91 (0.79, 1.06)	0.44
Animal fat						
Age adjusted	1.0	1.44 (1.26, 1.65)	1.68 (1.47, 1.92)	1.65 (1.44, 1.90)	1.79 (1.52, 2.10)	<.0001
Multivariate ⁵	1.0	1.09 (0.95, 1.25)	1.11 (0.96, 1.27)	1.0 (0.86, 1.16)	0.96 (0.80, 1.16)	0.98
Vegetable fat						
Age adjusted	1.0	1.02 (0.88, 1.17)	1.03 (0.89, 1.19)	0.90 (0.78, 1.05)	1.01 (0.87, 1.18)	0.74
Multivariate ⁶	1.0	0.89 (0.77, 1.03)	0.86 (0.74, 1.0)	0.73 (0.62, 0.86)	0.74 (0.62, 0.89)	<.0001
Total protein						
Age adjusted	1.0	1.13 (0.98, 1.31)	1.24 (1.08, 1.43)	1.43 (1.25, 1.64)	1.69 (1.48, 1.94)	<.0001
Multivariate ⁷	1.0	1.16 (1.0, 1.34)	1.16 (1.0, 1.34)	1.20 (1.04, 1.38)	1.03 (0.89, 1.19)	0.72
Animal protein						
Age adjusted	1.0	1.15 (1.0, 1.33)	1.30 (1.13, 1.50)	1.51 (1.32, 1.74)	1.74 (1.51, 2.01)	<.0001
Multivariate ⁸	1.0	1.10 (0.95, 1.27)	1.12 (0.97, 1.30)	1.16 (1.0, 1.33)	1.01 (0.87, 1.17)	0.55
Vegetable protein						
Age adjusted	1.0	1.03 (0.90, 1.19)	1.04 (0.91, 1.21)	1.04 (0.90, 1.20)	0.90 (0.77, 1.04)	0.001
Multivariate ⁹	1.0	0.96 (0.83, 1.12)	0.98 (0.84, 1.15)	1.0 (0.85, 1.18)	0.97 (0.81, 1.17)	0.36

¹ Nondietary factors: relative risk was adjusted for age in 5-y categories, BMI (<22, 22–22.9, 23–23.9, 24–24.9, 25–27.9, 28–29.9, 30–31.9, 32–33.9, 34–39.9, or ≥40 kg/m²), smoking (never, past, or current smoking of 1–14, 15–24, or ≥25 cigarettes/d), postmenopausal hormone use (never, current use, or past use), physical activity (<1, 1–2, 2–4, 4–7, or >7 h/wk), alcohol intake (0, 1–4.9, 5–14.9, or ≥15 g/d), and family history of type 2 diabetes in a first-degree relative.

² Adjusted for nondietary factors plus protein, cereal fiber, and total calories.

³ Adjusted for nondietary factors plus protein, cereal fiber, saturated fat, polyunsaturated fat, *trans* fat, and total calories (glycemic load was assessed from 1984 to 2000).

⁴ Adjusted for nondietary factors plus protein and total calories.

⁵ Adjusted for nondietary factors plus protein, vegetable fat, *trans* fat, and total calories.

⁶ Adjusted for nondietary factors plus protein, animal fat, *trans* fat, and total calories.

⁷ Adjusted for nondietary factors plus cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, *trans* fat, and total calories.

⁸ Adjusted for nondietary factors plus cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, *trans* fat, vegetable protein, and total calories.

⁹ Adjusted for nondietary factors plus cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, *trans* fat, animal protein, and total calories.

have not reported this association (57, 67). In the present investigation we found a statistically significant positive association for both dietary glycemic load and total carbohydrate and risk of type 2 diabetes. The positive association between dietary glycemic load and type 2 diabetes was much stronger than that for total carbohydrate because glycemic load captures both the quality and quantity of carbohydrate.

Adequate power for this investigation was provided by the large sample size and 20-y follow-up with updated dietary data. The prospective design and high follow-up rate served to minimize bias. Because diet was assessed with a self-reported questionnaire, some degree of misclassification of intakes of fat, protein, and carbohydrate will have occurred. Measurement error in assessing long-term diet was reduced in this analysis by using the average of all available measurements of diet up to the start of each 2-y follow-up interval.

In this investigation we measured and adjusted for a variety of potential confounding variables. However, we cannot rule out the possibility of residual confounding. A concern in this analysis was whether to consider body mass index as a mediator of the relation between low-carbohydrate-diet score and risk of type 2

diabetes or as a potential confounder of the relation. In our cohort, total calories were similar across deciles of low-carbohydrate-diet score (Table 1). Furthermore, in most weight-loss trials, a low-carbohydrate-diet has not been associated with a significant increase in body weight (24–27). Therefore, we considered body mass index as a potential confounder and included it in the multivariate analyses.

The Nurses' Health Study consists of mostly white women with some college education. Although this homogeneity increases the internal validity of the study by reducing confounding by factors that are difficult to measure, the association between low-carbohydrate-diet score and risk of type 2 diabetes among women of other educational and racial backgrounds should also be investigated.

In conclusion, a diet lower in carbohydrate and higher in protein and fat did not increase the risk of type 2 diabetes in this cohort of women. In fact, when vegetable sources of fat and protein were chosen, these diets were associated with a modest reduction in the risk of type 2 diabetes. These data support a potential benefit in reducing the glycemic load of the diet and for substituting low-glycemic fruit, vegetables, whole grains, and

healthful sources of fat and protein for high-glycemic refined carbohydrates.

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