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Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women[1–3]

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ABSTRACT

Background: Increasing evidence suggests an important role of carbohydrate quality in the development of type 2 diabetes.

Objective: Our objective was to prospectively examine the association between glycemic index, glycemic load, and dietary fiber and the risk of type 2 diabetes in a large cohort of young women.

Design: In 1991, 91 249 women completed a semiquantitative food-frequency questionnaire that assessed dietary intake. The women were followed for 8 y for the development of incident type 2 diabetes, and dietary information was updated in 1995.

Results: We identified 741 incident cases of confirmed type 2 diabetes during 8 y (716 300 person-years) of follow-up. After adjustment for age, body mass index, family history of diabetes, and other potential confounders, glycemic index was significantly associated with an increased risk of diabetes (multivariate relative risks for quintiles 1–5, respectively: 1, 1.15, 1.07, 1.27, and 1.59; 95% CI: 1.21, 2.10; *P* for trend = 0.001). Conversely, cereal fiber intake was associated with a decreased risk of diabetes (multivariate relative risks for quintiles 1–5, respectively: 1, 0.85, 0.87, 0.82, and 0.64; 95% CI: 0.48, 0.86; *P* for trend = 0.004). Glycemic load was not significantly associated with risk in the overall cohort (multivariate relative risks for quintiles 1–5, respectively: 1, 1.31, 1.20, 1.14, and 1.33; 95% CI: 0.92, 1.91; *P* for trend = 0.21).

Conclusions: A diet high in rapidly absorbed carbohydrates and low in cereal fiber is associated with an increased risk of type 2 diabetes. *Am J Clin Nutr* 2004;80:348–56.

KEY WORDS Glycemic index, glycemic load, dietary fiber, type 2 diabetes, prospective studies, women

INTRODUCTION

The prevalence of type 2 diabetes has increased rapidly during the past decades in the United States (1–3). Although an increase in the prevalence of type 2 diabetes has been observed in all age groups, it has been found to be most dramatic in younger age groups. From 1990 to 2001, the prevalence of self-reported diabetes nearly doubled within the group aged 30–39 y and increased by 83% within the group aged 40–49 y (1, 3). Although lifestyle characteristics such as obesity (4), physical activity (5, 6), and smoking (7) are established risk factors for this disease (8), less is known about dietary factors (9). The quality of carbohydrates has received particular interest (10) because it can influence the digestion rate and thus the blood glucose response. Because the glycemic response varies substantially between different foods and because this variability is not explainable by glucose chain length (11, 12), the concept of glycemic index was developed to quantify the glycemic responses induced by carbohydrates in different foods (13–15). Although animal studies (16, 17) and short-term studies in humans (18, 19) suggest a potential role of high-glycemic-index diets in the development of diabetes, no long-term intervention studies have examined the association between the glycemic index and the risk of type 2 diabetes. In prospective cohort studies, higher glycemic index and load predicted an increased risk of diabetes in the Nurses' Health Study I (8, 20) and the Health Professionals Follow-Up Study (21), no associations were observed in the Iowa Women's Health Study (22), and only moderate associations with glycemic load and no associations with glycemic index were reported in the Atherosclerosis Risk in Communities (ARIC) Study (23). Nevertheless, a higher intake of dietary fiber, especially cereal fiber, has been consistently associated with a lower risk of diabetes (20–23).

Although the overall data suggest a potential preventive role of diets with a low glycemic index and a high cereal fiber content, the evidence from prospective studies is limited. Furthermore, previous studies on this topic have focused on older participants and women who were largely postmenopausal (20–23). We therefore examined the associations of glycemic index and load and different sources of dietary fiber with incidence of type 2 diabetes in a group of younger women.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study II, established in 1989, is a prospective cohort study of 116 671 female nurses in the United States who were 24–44 y of age at study initiation. This cohort is followed up with the use of biennial mailed questionnaires

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focusing on various lifestyle factors and health outcomes; the follow-up rate exceeds 90% for every 2-y period, and we estimate that there is almost complete (98%) ascertainment of mortality (24). For the analyses presented here, women were excluded from the baseline population if they did not complete a dietary questionnaire in 1991 or if >9 items on it were left blank; if the reported total energy intake was implausible (ie, <500 or >3500 kcal/d); if they had a history of diabetes, cancer (except nonmelanoma skin cancer), or cardiovascular disease reported on either the 1989 or 1991 questionnaire; or if they had no data on physical activity in 1991. These exclusions left a total of 91 249 women for the analyses. The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Dietary assessment

In 1991 the mailed questionnaire included a 133-food item semiquantitative food-frequency questionnaire (FFQ) to obtain dietary information. A similar questionnaire was used to update dietary information in 1995. For each food, a commonly used unit or portion size was specified, and women were asked how often they had consumed that amount of each food on average over the previous year. There were 9 possible responses ranging from "never" to "6 or more times per day." Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes. Values for nutrients were derived from the US Department of Agriculture sources (25) and supplemented with information from manufacturers. Dietary fiber was determined by enzymatic-gravimetric methods 985.29 and 991.43 of the Association of Official Analytical Chemists (26). The glycemic index values for single food items on the questionnaire were derived with the assistance of Jenkins (University of Toronto), which were based on available databases and publications (13, 27, 28). We calculated the average dietary glycemic index for each participant by summing the products of the carbohydrate content per serving for each food item times the average number of servings of that food per day, times its glycemic index, and divided by the total daily carbohydrate intake (20, 21). Because the amount of carbohydrate in an overall diet can vary, we also applied the concept of glycemic load, which represents the amount of carbohydrates multiplied by the average glycemic index. Glycemic load, glycemic index, and intakes of dietary fiber, magnesium, and caffeine were energy-adjusted by using the residuals method (29). Intakes of carbohydrates and fatty acids were expressed as nutrient density (% of total energy intake) (30). The validity and reliability of FFQs similar to those used in the Nurses' Health Study II were described elsewhere (31–34). Briefly, the corrected correlation coefficients between the FFQ and multiple dietary records for carbohydrates and fiber were 0.64 and 0.56 in a validation study with 173 nurses aged 34–59 y in the Nurses' Health Study I (32, 35) and 0.73 and 0.68 in a cohort of men aged 40–74 y in the Health Professionals Follow-Up Study (33). Correlations for individual carbohydrate-rich food items were found to be high as well (white bread: 0.71; dark bread: 0.77; cold breakfast cereal: 0.79; potatoes: 0.66) (31). The ability of the FFQ to assess dietary glycemic index and glycemic load was documented further in a study that evaluated the relations of these 2 variables to plasma concentrations of HDL and triacylglycerol in postmenopausal women (36).

Ascertainment of type 2 diabetes

Women reporting a new diagnosis of diabetes (except gestational diabetes) on any of the biennial questionnaires were sent supplementary questionnaires asking about diagnosis, treatment, and history of ketoacidosis to confirm the self-report. The supplementary questionnaire also asked for the type of diabetes diagnosed, which was used to distinguish between type 2 and type 1 diabetes ($n = 27$) and gestational diabetes. In accordance with the criteria of the National Diabetes Data Group (37), confirmation of diabetes required at least one of the following: *1*) an elevated plasma glucose concentration (fasting plasma glucose ≥7.8 mmol/L, random plasma glucose ≥11.1 mmol/L, or plasma glucose ≥11.1 mmol/L ≥2 h after the beginning of an oral-glucose-tolerance test) plus at least one classic symptom of diabetes (excessive thirst, polyuria, weight loss, or hunger), *2*) no symptoms but ≥2 elevated plasma glucose concentrations (by the above criteria) on different occasions, or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). We used the National Diabetes Data Group criteria to define diabetes because most of our cases were diagnosed before the release of the American Diabetes Association criteria in 1997 (38). The validity of self-reported diabetes by medical professionals using the same supplementary questionnaire was documented in the Nurses' Health Study I and the Health Professionals Follow-Up Study, in which substudies showed that 98% and 97%, respectively, of the self-reported cases documented by supplementary questionnaires were confirmed by medical record review (39, 40).

Assessment of nondietary exposure

Participants provided information biennially on their age, weight, smoking status, contraceptive use, postmenopausal hormone replacement therapy, history of high blood pressure, and history of high blood cholesterol. We calculated body mass index (BMI) as the ratio of weight (in kg) to squared height (in m), the latter being assessed at baseline only. Self-reports of body weight have been shown to be highly correlated with technician-measured weights ($r = 0.96$) in the Nurses' Health Study I (41). Family history of diabetes was reported in 1989 only. Physical activity was assessed with the 1991 and 1997 questionnaires and was computed as metabolic equivalents per week using the duration per week of various forms of exercise, with each activity weighted by its intensity level. Correlations between physical activity reported on recalls and diaries and that reported on the questionnaire were high in our cohort (0.79 and 0.62) (42).

Statistical analysis

We used Cox proportional hazards analysis stratified on 5-y age categories to estimate relative risks for each category of intake compared with the lowest category. Participants who were diagnosed with diabetes (type 1 or type 2) or who died during follow-up were censored at the date of diagnosis or death. The 1991 intake was used for the follow-up between 1991 and 1995, and we used the average of the 1991 and 1995 intakes for the follow-up between 1995 and 1999 to reduce within-subject variation and best represent long-term diet (43). We used only the 1991 intake data, and not the 1995 data, for those persons who reported on the 1993 or 1995 questionnaire a diagnosis of cancer (except nonmelanoma skin cancer) or cardiovascular disease, because changes in diet after the development of these conditions

TABLE 1
Age-standardized baseline characteristics according to quintiles of energy-adjusted glycemic index, glycemic load, and cereal fiber intake in 91 249 women[1]

	Quintiles of glycemic index			Quintiles of glycemic load			Quintiles of cereal fiber intake		
Characteristic	1	3	5	1	3	5	1	3	5
Age (y)	36.7 ± 4.6[2]	36.1 ± 4.6	35.5 ± 4.8	36.6 ± 4.6	36.0 ± 4.7	35.8 ± 4.7	36.0 ± 4.8	36.1 ± 4.7	36.3 ± 4.6
BMI (kg/m^2)[3]	24.7 ± 5.0	24.6 ± 5.3	24.5 ± 5.5	25.7 ± 5.8	24.5 ± 5.1	23.6 ± 4.8	25.2 ± 5.9	24.7 ± 5.3	23.7 ± 4.5
Physical activity (METs/wk)	25.9 ± 31.2	20.5 ± 25.6	16.5 ± 23.5	19.5 ± 25.5	20.6 ± 25.8	22.9 ± 30.9	19.0 ± 26.9	20.1 ± 25.7	24.7 ± 31.3
Current smoking (%)	14.2	11.1	12.3	18.5	10.8	10.4	21.3	10.7	6.3
Family history of diabetes (%)	17.0	16.0	16.5	17.7	16.2	15.5	17.4	16.0	14.8
History of hypertension (%)	3.1	3.0	3.7	4.0	2.9	3.2	4.5	3.2	2.3
History of high blood cholesterol (%)	9.0	9.0	10.1	9.7	8.9	9.9	10.1	9.2	8.8
Current use of oral contraceptives (%)	11.2	10.7	11.0	11.3	10.4	10.7	11.1	10.6	10.6
Current hormone replacement therapy (%)	2.7	2.3	2.6	2.4	2.5	2.4	2.5	2.6	2.3
Alcohol intake (g/d)	4.8 ± 8.6	3.0 ± 4.7	1.7 ± 3.8	5.7 ± 9.9	2.7 ± 4.5	1.5 ± 2.9	4.0 ± 8.5	3.0 ± 5.3	2.5 ± 4.4
Carbohydrates (% of daily energy)	47.4 ± 7.6	49.5 ± 7.1	52.7 ± 7.9	40.3 ± 4.4	49.6 ± 2.8	59.7 ± 5.1	47.1 ± 8.9	49.2 ± 6.3	54.2 ± 6.8
Protein (% of daily energy)	20.9 ± 3.7	19.3 ± 3.2	17.8 ± 3.5	21.8 ± 3.6	19.4 ± 2.8	16.5 ± 2.9	19.4 ± 4.1	19.4 ± 3.2	19.1 ± 3.3
Saturated fat (% of daily energy)	11.6 ± 2.6	11.3 ± 2.3	10.6 ± 2.3	13.3 ± 2.4	11.3 ± 1.7	8.9 ± 1.9	12.3 ± 2.7	11.3 ± 2.1	9.8 ± 2.1
Monounsaturated fat (% of daily energy)	11.8 ± 2.6	12.1 ± 2.4	11.8 ± 2.5	14.0 ± 2.3	12.1 ± 1.8	9.7 ± 1.9	12.7 ± 2.6	12.2 ± 2.2	10.7 ± 2.3
Polyunsaturated fat (% of daily energy)	5.7 ± 1.6	5.7 ± 1.3	5.4 ± 1.3	6.3 ± 1.6	5.7 ± 1.2	4.8 ± 1.1	5.5 ± 1.5	5.7 ± 1.3	5.5 ± 1.3
trans Fat (% of daily energy)	1.6 ± 0.6	1.7 ± 0.6	1.8 ± 0.7	1.8 ± 0.6	1.7 ± 0.6	1.4 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	1.4 ± 0.6
Energy-adjusted nutrient intakes									
Magnesium (mg/d)	356 ± 76	316 ± 64	271 ± 69	310 ± 67	318 ± 69	313 ± 92	282 ± 70	308 ± 65	367 ± 79
Caffeine (mg/d)	304 ± 254	239 ± 204	191 ± 186	304 ± 249	240 ± 219	197 ± 196	266 ± 240	243 ± 217	219 ± 214
Total fiber (g/d)	19.4 ± 6.5	18.5 ± 4.9	16.5 ± 4.9	15.9 ± 4.2	18.5 ± 4.6	20.1 ± 7.5	15.1 ± 4.7	17.7 ± 4.1	23.1 ± 6.3
Cereal fiber (g/d)	5.2 ± 3.7	5.8 ± 2.8	5.6 ± 2.8	4.2 ± 1.8	5.7 ± 2.5	6.8 ± 4.4	2.8 ± 0.6	5.1 ± 0.3	9.9 ± 4.0
Glycemic index	69.9 ± 3.0	76.9 ± 0.8	83.1 ± 2.2	73.0 ± 4.9	76.7 ± 3.7	80.6 ± 4.0	76.0 ± 5.9	76.8 ± 4.4	77.3 ± 4.4
Glycemic load	150 ± 25	172 ± 25	199 ± 31	133 ± 14	171 ± 41	217 ± 19	163 ± 37	171 ± 26	190 ± 27

[1] METs, metabolic equivalents. Tests for trend (based on ordinal variables containing median values for each quintile) were all significant ($P < 0.01$), except for current hormone replacement therapy, current use of oral contraceptives, family history of diabetes (for glycemic index), monounsaturated fat intake (for glycemic index), history of high blood cholesterol (for glycemic load), and *trans* fat intake (for cereal fiber).

[2] $\bar{x}$ ± SD (all such values).

[3] Analysis was limited to 88 710 women because of missing values.

may confound the relation between dietary intake and diabetes (43). Covariates obtained from the baseline or subsequent questionnaires were used in multivariate analyses, including BMI (<21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–32.9, 33.0–34.9, and ≥35.0), total caloric intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, ≥10 g/d), physical activity (quintiles), family history of diabetes (yes or no), smoking (never, past, or current), history of high blood pressure (yes or no), history of high blood cholesterol (yes or no), postmenopausal hormone use (never or ever), oral contraceptive use (never, past, or current), magnesium intake (quintiles), caffeine intake (quintiles), and types of fatty acids (quintiles). Nondietary covariates were updated during follow-up by using the most recent data for each 2-y follow-up interval.

The significance of linear trends across categories of dietary intake was tested by assigning each participant the median value for the category and modeling this value as a continuous variable. We also tested for effect modification by BMI, physical activity, and family history of diabetes by performing analyses stratified by these variables and by evaluating interaction terms. All statistical analyses were performed by using SAS statistical software (version, 6.12; SAS institute Inc, Cary, NC).

RESULTS

During 716 300 person-years of follow-up, we documented 741 new cases of type 2 diabetes. Among the study population of 91 249 women, a higher glycemic index was related to higher carbohydrate intake, higher glycemic load, higher *trans* fatty acid intake, lower alcohol intake, lower total fiber intake, lower magnesium and caffeine intakes, and lower physical activity (**Table 1**). Differences among quintiles of glycemic index for other characteristics, such as specific fatty acid intakes, cereal fiber intake, BMI, smoking, history of hypertension or high blood cholesterol, or oral contraception or hormone replacement therapy use were generally small. Participants with diets relatively high in glycemic load and cereal fiber were less likely to smoke, reported less frequently a family history of diabetes and

TABLE 2
Adjusted relative risks (RRs) and 95% CIs of type 2 diabetes according to quintiles of energy-adjusted glycemic index, glycemic load, and carbohydrate intake in 91 249 women

	Quintile					
Variable	1	2	3	4	5	*P* for trend[1]
Glycemic index						
Range	<73.1	73.1–75.6	75.7–77.8	77.9–80.2	>80.2	
Median	71.1	74.6	76.8	79.0	82.1	
Cases	125	141	131	152	192	
Person-years	143 397	142 881	143 326	142 992	143 704	
RR[2]						
Age-adjusted	1.00	1.13 (0.89, 1.44)	1.08 (0.85, 1.38)	1.31 (1.03, 1.66)	1.79 (1.43, 2.25)	<0.001
Age- and BMI-adjusted	1.00	1.17 (0.92, 1.49)	1.11 (0.87, 1.42)	1.35 (1.07, 1.71)	1.84 (1.47, 2.30)	<0.001
Multivariate adjusted[3]	1.00	1.13 (0.89, 1.44)	1.04 (0.81, 1.33)	1.25 (0.98, 1.59)	1.62 (1.28, 2.03)	<0.001
Further adjustment for diet[4]	1.00	1.16 (0.90, 1.48)	1.07 (0.82, 1.38)	1.25 (0.97, 1.62)	1.51 (1.16, 1.97)	0.002
Further adjustment for fat[5]	1.00	1.15 (0.90, 1.48)	1.07 (0.83, 1.39)	1.27 (0.98, 1.66)	1.59 (1.21, 2.10)	0.001
Glycemic load						
Range	<150	150–165	166–179	180–196	>196	
Median	139	159	172	187	211	
Cases	184	192	141	115	109	
Person-years	143 635	143 236	143 031	143 152	143 246	
RR[2]						
Age-adjusted	1.00	1.05 (0.86, 1.29)	0.78 (0.63, 0.97)	0.64 (0.51, 0.81)	0.62 (0.49, 0.79)	<0.001
Age- and BMI-adjusted	1.00	1.24 (1.01, 1.51)	1.07 (0.86, 1.33)	1.01 (0.80, 1.28)	1.18 (0.93, 1.49)	0.50
Multivariate adjusted[3]	1.00	1.23 (1.00, 1.51)	1.06 (0.85, 1.33)	0.97 (0.77, 1.23)	1.09 (0.86, 1.39)	0.98
Further adjustment for diet[4]	1.00	1.28 (1.04, 1.57)	1.11 (0.89, 1.40)	1.01 (0.79, 1.29)	1.07 (0.83, 1.37)	0.93
Further adjustment for fat[5]	1.00	1.31 (1.05, 1.64)	1.20 (0.92, 1.56)	1.14 (0.84, 1.55)	1.33 (0.92, 1.91)	0.21
Total carbohydrates (% of total energy)						
Range	<44.4	44.4–48.3	48.4–51.7	51.8–55.9	>55.9	
Median	41.3	46.5	50.1	53.7	59.4	
Cases	205	179	145	124	88	
Person-years	143 683	143 289	143 171	142 988	143 169	
RR[2]						
Age-adjusted	1.00	0.87 (0.71, 1.06)	0.71 (0.57, 0.87)	0.60 (0.48, 0.75)	0.43 (0.34, 0.56)	<0.001
Age- and BMI-adjusted	1.00	1.03 (0.85, 1.26)	0.97 (0.78, 1.20)	0.95 (0.76, 1.18)	0.87 (0.67, 1.11)	0.22
Multivariate adjusted[3]	1.00	1.03 (0.84, 1.26)	0.96 (0.77, 1.19)	0.91 (0.72, 1.14)	0.82 (0.63, 1.05)	0.082
Further adjustment for diet[4]	1.00	1.09 (0.89, 1.34)	1.02 (0.82, 1.27)	0.96 (0.76, 1.21)	0.84 (0.64, 1.09)	0.174
Further adjustment for fat[5]	1.00	1.09 (0.87, 1.37)	1.05 (0.80, 1.38)	1.01 (0.74, 1.39)	0.89 (0.60, 1.33)	0.69

[1] Based on ordinal variable containing median value for each quintile.
[2] 95% CI in parentheses.
[3] Adjusted for age, BMI (9 categories), energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, or ≥10 g/d), physical activity (quintiles), family history of diabetes, smoking (never, past, or current), history of high blood pressure, history of high blood cholesterol, postmenopausal hormone use (never or ever), oral contraceptive use (never, past, or current)
[4] Multivariate model with additional adjustment for intakes (quintiles) of cereal fiber, magnesium, and caffeine.
[5] Multivariate and diet-adjusted model with additional adjustment for intakes (quintiles) of saturated, monounsaturated, polyunsaturated, and *trans* fatty acids.

a history of hypertension, and were on average leaner and more physically active. In addition, glycemic load and cereal fiber intake were positively related to carbohydrate and total fiber intakes and inversely related to saturated fat, monounsaturated fat, *trans* fat, alcohol, and caffeine intakes. Glycemic load was furthermore inversely related to polyunsaturated fat intake, whereas cereal fiber intake was positively related to magnesium intake.

Increasing glycemic index was strongly associated with a progressively higher risk of type 2 diabetes (**Table 2**). The age-adjusted relative risks across quintiles 1–5 were 1.00, 1.13, 1.08, 1.31, and 1.79 (P for trend < 0.001). This association remained strong after further adjustment for BMI, alcohol consumption, smoking, family history of diabetes, and other covariates. Further adjustment for intakes of cereal fiber, magnesium, caffeine, and different fatty acids did not materially change this observation. In addition, glycemic index remained positively associated with diabetes risk after adjustment for total fiber instead of cereal fiber (relative risk for extreme quintiles: 1.46; 95% CI: 1.12, 1.92; P for trend $= 0.007$). In an age-adjusted analysis, both glycemic load and total carbohydrate intake were inversely associated with the risk of type 2 diabetes. This significant association disappeared after adjustment for BMI.

We observed a significant inverse association between total dietary fiber intake and risk of diabetes, but this effect was largely attenuated after multivariate adjustment (**Table 3**). Of the different sources of fiber, cereal fiber was most strongly associated with decreased risk. The multivariate-adjusted relative risks across quintiles were 1.00, 0.84, 0.86, 0.81, and 0.63 (P for trend $= 0.004$). Adjustment for other sources of dietary fiber did

TABLE 3
Adjusted relative risks (RRs) and 95% CIs of type 2 diabetes according to quintiles of energy-adjusted fiber intake in 91 249 women

	Quintiles					*P* for trend[1]
Variable	1	2	3	4	5	
Total fiber (g/d)						
Range	<14.2	14.2–16.5	16.6–18.8	18.9–22.0	>22.0	
Median	12.5	15.4	17.7	20.2	24.9	
Cases	198	162	136	123	122	
Person-years	142 664	144 071	141 846	145 110	142 609	
RR[2]						
Age-adjusted	1.00	0.77 (0.63, 0.95)	0.64 (0.51, 0.79)	0.55 (0.44, 0.68)	0.53 (0.42, 0.67)	<0.001
Age- and BMI-adjusted	1.00	0.84 (0.68, 1.03)	0.73 (0.59, 0.91)	0.68 (0.54, 0.85)	0.78 (0.62, 0.98)	0.008
Multivariate adjusted[3]	1.00	0.94 (0.76, 1.17)	0.87 (0.68, 1.11)	0.84 (0.65, 1.10)	1.00 (0.75, 1.34)	0.80
Cereal fiber (g/d)						
Range	<3.8	3.8–4.7	4.8–5.7	5.8–7.3	>7.3	
Median	3.1	4.2	5.2	6.4	8.8	
Cases	219	162	151	132	77	
Person-years	145 258	141 933	139 945	146 011	143 153	
RR[2]						
Age-adjusted	1.00	0.71 (0.58, 0.87)	0.65 (0.53, 0.80)	0.54 (0.44, 0.68)	0.32 (0.25, 0.41)	<0.001
Age- and BMI-adjusted	1.00	0.79 (0.65, 0.97)	0.78 (0.63, 0.96)	0.72 (0.58, 0.90)	0.54 (0.42, 0.70)	<0.001
Multivariate adjusted[3]	1.00	0.84 (0.69, 1.04)	0.86 (0.69, 1.07)	0.81 (0.64, 1.03)	0.63 (0.47, 0.85)	0.004
Further adjustment for fiber[4]	1.00	0.85 (0.69, 1.05)	0.87 (0.69, 1.08)	0.82 (0.65, 1.04)	0.64 (0.48, 0.86)	0.004
Fruit fiber (g/d)						
Range	<1.6	1.6–2.4	2.5–3.4	3.5–4.8	>4.8	
Median	1.1	2.0	2.9	4.1	6.2	
Cases	198	171	133	123	116	
Person-years	139 954	145 573	143 226	143 143	144 404	
RR[2]						
Age-adjusted	1.00	0.80 (0.65, 0.98)	0.61 (0.49, 0.76)	0.55 (0.44, 0.69)	0.50 (0.40, 0.63)	<0.001
Age- and BMI-adjusted	1.00	0.87 (0.71, 1.07)	0.72 (0.58, 0.89)	0.70 (0.56, 0.87)	0.70 (0.56, 0.88)	<0.001
Multivariate adjusted[3]	1.00	0.94 (0.76, 1.15)	0.81 (0.64, 1.01)	0.79 (0.62, 1.00)	0.82 (0.63, 1.06)	0.086
Further adjustment for fiber[4]	1.00	0.93 (0.75–1.15)	0.80 (0.63–1.00)	0.77 (0.60–0.98)	0.79 (0.60–1.02)	0.040
Vegetable fiber (g/d)						
Range	<4.2	4.2–5.4	5.5–6.7	6.8–8.6	>8.6	
Median	3.4	4.8	6.1	7.6	10.4	
Cases	168	140	136	156	141	
Person-years	141 420	145 073	143 149	143 214	143 443	
RR[2]						
Age-adjusted	1.00	0.77 (0.62, 0.97)	0.73 (0.58, 0.91)	0.82 (0.66, 1.02)	0.74 (0.59, 0.92)	0.042
Age- and BMI-adjusted	1.00	0.84 (0.67, 1.05)	0.82 (0.66, 1.03)	0.94 (0.76, 1.17)	0.87 (0.69, 1.09)	0.50
Multivariate adjusted[3]	1.00	0.95 (0.75, 1.19)	0.99 (0.78, 1.25)	1.16 (0.92, 1.46)	1.12 (0.87, 1.44)	0.175
Further adjustment for fiber[4]	1.00	0.97 (0.77, 1.22)	1.01 (0.80, 1.28)	1.19 (0.94, 1.51)	1.12 (0.87, 1.46)	0.192

[1] Based on ordinal variable containing median value for each quintile.
[2] 95% CIs in parentheses.
[3] Adjusted for age, BMI (9 categories), energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, ≥10 g/d), physical activity (quintiles), family history of diabetes, smoking (never, past, or current), history of high blood pressure, history of high blood cholesterol, postmenopausal hormone use (never or ever), oral contraceptive use (never, past, or current), glycemic load (quintiles), magnesium intake (quintiles), and caffeine intake (quintiles).
[4] Multivariate model with additional adjustment for intake (quintiles) of other fiber types (cereal, fruit, or vegetable).

not change this observation. Fruit fiber was also associated with a reduced risk after adjustment of multivariate models for other sources of dietary fiber (P for trend = 0.040). No significant associations were observed for vegetable fiber after adjustment for potential confounders.

We also used a stratified analysis to assess whether the associations with glycemic index, glycemic load, and total carbohydrate intake were modified by BMI, physical activity, and family history of diabetes (**Table 4**). No major modifications were observed for BMI. Among women within the lower 2 quintiles of activity scores, the multivariate-adjusted relative risks for extreme quintiles were 2.01 for glycemic index (95% CI: 1.38, 2.93) and 1.65 for glycemic load (95% CI: 1.01, 2.70). Tests for statistical interactions were not significant ($P = 0.38$ and 0.48). In addition, among women with no family history of diabetes, the relative risk across extreme quintiles of glycemic load was 1.02 (95% CI: 0.64, 1.63); among women with a family history of diabetes, the relative risk was 2.04 (95% CI: 1.13, 3.66). The test for statistical interaction was not significant ($P = 0.59$). No effect modification was observed for total carbohydrate intake.

We examined the joint effect of the glycemic index and the cereal fiber intake by cross-classifying participants by both

TABLE 4
Adjusted relative risks (RRs) and 95% CIs of type 2 diabetes according to quintiles of energy-adjusted glycemic index, glycemic load, and total carbohydrate intake by baseline BMI, physical activity, and family history of diabetes in 91 249 women[1]

	Quintiles				
Variable	1	2	3	4	5
Glycemic index					
BMI <27 (n = 114)	1.00	1.30 (0.71, 2.37)	1.19 (0.62, 2.25)	0.98 (0.49, 1.97)	1.69 (0.84, 3.40)
BMI ≥27 (n = 608)	1.00	1.17 (0.89, 1.54)	1.09 (0.81, 1.45)	1.31 (0.98, 1.75)	1.50 (1.10, 2.05)
Low physical activity (n = 421)	1.00	1.30 (0.91, 1.84)	1.09 (0.75, 1.59)	1.26 (0.87, 1.84)	2.01 (1.38, 2.93)
High physical activity (n = 320)	1.00	1.00 (0.70, 1.43)	1.04 (0.72, 1.50)	1.30 (0.90, 1.89)	1.08 (0.70, 1.66)
No family history of diabetes (n = 459)	1.00	1.33 (0.97, 1.83)	1.04 (0.73, 1.46)	1.46 (1.04, 2.05)	1.69 (1.18, 2.43)
Family history of diabetes (n = 282)	1.00	0.91 (0.61, 1.35)	1.15 (0.77, 1.70)	1.05 (0.69, 1.62)	1.50 (0.97, 2.32)
Glycemic load					
BMI <27 (n = 114)	1.00	1.38 (0.74, 2.56)	1.37 (0.68, 2.77)	1.24 (0.56, 2.76)	1.38 (0.55, 3.48)
BMI ≥27 (n = 608)	1.00	1.25 (0.99, 1.59)	1.16 (0.87, 1.55)	1.10 (0.79, 1.54)	1.29 (0.86, 1.93)
Low physical activity (n = 421)	1.00	1.38 (1.04, 1.84)	1.38 (0.98, 1.96)	1.27 (0.84, 1.91)	1.65 (1.01, 2.70)
High physical activity (n = 320)	1.00	1.19 (0.84, 1.68)	0.98 (0.65, 1.48)	0.98 (0.62, 1.54)	1.01 (0.58, 1.75)
No family history of diabetes (n = 459)	1.00	1.11 (0.84, 1.48)	1.16 (0.83, 1.61)	1.01 (0.69, 1.48)	1.02 (0.64, 1.63)
Family history of diabetes (n = 282)	1.00	1.66 (1.16, 2.36)	1.23 (0.79, 1.92)	1.40 (0.85, 2.31)	2.04 (1.13, 3.66)
Total carbohydrates					
BMI <27 (n = 114)	1.00	1.04 (0.55, 1.97)	1.44 (0.71, 2.91)	1.31 (0.57, 2.99)	0.78 (0.29, 2.11)
BMI ≥27 (n = 608)	1.00	1.12 (0.88, 1.44)	1.02 (0.75, 1.37)	0.98 (0.69, 1.39)	0.94 (0.60, 1.46)
Low physical activity (n = 421)	1.00	1.14 (0.85, 1.52)	1.11 (0.78, 1.58)	1.13 (0.74, 1.73)	0.96 (0.55, 1.66)
High physical activity (n = 320)	1.00	1.00 (0.70, 1.43)	0.96 (0.63, 1.46)	0.87 (0.54, 1.40)	0.81 (0.45, 1.45)
No family history of diabetes (n = 459)	1.00	1.00 (0.75, 1.34)	0.95 (0.67, 1.34)	1.00 (0.67, 1.49)	0.81 (0.49, 1.34)
Family history of diabetes (n = 282)	1.00	1.26 (0.88, 1.80)	1.22 (0.79, 1.88)	0.99 (0.59, 1.68)	1.02 (0.53, 1.95)

[1] Values were adjusted for age, energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, or ≥10 g/d), smoking (never, past, or current), history of high blood pressure, history of high blood cholesterol, postmenopausal hormone use (never or ever), oral contraceptive use (never, past, or current), and intake (quintiles) of cereal fiber, magnesium, caffeine, and saturated, monounsaturated, polyunsaturated, and *trans* fatty acids. RRs and 95% CIs for BMI strata were additionally adjusted for family history of diabetes, BMI (continuous), and physical activity (quintiles); those for physical activity strata were additionally adjusted for family history of diabetes, BMI (9 categories), and physical activity (continuous); and those for family history of diabetes were additionally adjusted for BMI (9 categories) and physical activity (quintiles). Analysis of BMI strata was limited to 88 710 women because of missing values. Low physical activity = lower 2 quintiles of activity level; high physical activity = upper 3 quintiles of activity level. Tests for interaction (based on ordinal variables containing median values for each quintile and dichotomized variables for strata) were all nonsignificant ($P > 0.05$).

variables (**Figure 1**). The relative risk for the combination of a high glycemic index and a low cereal fiber intake compared with the opposite extreme was 1.75 (95% CI: 1.22, 2.52). The positive association between glycemic index and diabetes was more evident among those with a lower intake of cereal fiber, and the benefit of cereal fiber was more evident among those with high-glycemic-index diets. The test of interaction was significant ($P = 0.004$).

DISCUSSION

In this 8-y follow-up study of 91 249 female nurses, we found a positive association between glycemic index and risk of type 2 diabetes, independent of known risk factors such as other measured dietary variables. The 59% increase in risk observed in the highest quintile compared with the lowest quintile was somewhat higher than the associations for other dietary risk factors previously observed, particularly *trans* fatty acids and the ratio of polyunsaturated to saturated fat intake (8). In addition, high intakes of cereal and fruit fiber were associated with a lower risk of diabetes.

Although the exact mechanisms by which high-glycemic-index diets may alter the risk of type 2 diabetes are unclear, 2 major pathways have been proposed (14, 15). First, the same amount of carbohydrates from high-glycemic-index foods, by definition, produce higher blood glucose concentrations and a greater insulin demand than do low-glycemic index foods. It is possible that chronically increased insulin demand results in pancreatic exhaustion that can result in glucose intolerance (15). Second, high-glycemic-index diets may directly increase insulin resistance. In animal studies, diets high in amylopectin or glucose produced more rapid and severe insulin resistance than did amylose-based diets (16, 17). In a 4-wk study of 32 patients with advanced coronary heart disease, insulin-stimulated glucose uptake in isolated adipocytes harvested from a presternal fat biopsy sample was significantly greater after a low-glycemic-index diet (18). Similarly, a 3-wk trial in 28 premenopausal women observed improved insulin sensitivity (on the basis of a short glucose tolerance test) with a low-glycemic-index diet (19). A 4-mo trial in 34 subjects with impaired glucose tolerance observed lower plasma glucose and free fatty acid concentrations with a high-carbohydrate, low-glycemic-index diet than with a high-carbohydrate, high-glycemic-index diet (44).

Our data were broadly consistent with those observed among older participants in the Nurses' Health Study I (20) and the Health Professionals Follow-Up Study (21). The relative risks comparing extreme quintiles of glycemic index were 1.37 (95% CI: 1.09, 1.71; P for trend = 0.005) in the Nurses' Health Study I and 1.37 (95% CI: 1.02, 1.83; P for trend = 0.03) in the Health Professionals Follow-Up Study. In contrast, no associations between glycemic index and risk of diabetes were observed in the Iowa Women's Health Study (22) and the ARIC Study (23). However, neither study collected repeated measurements of diet

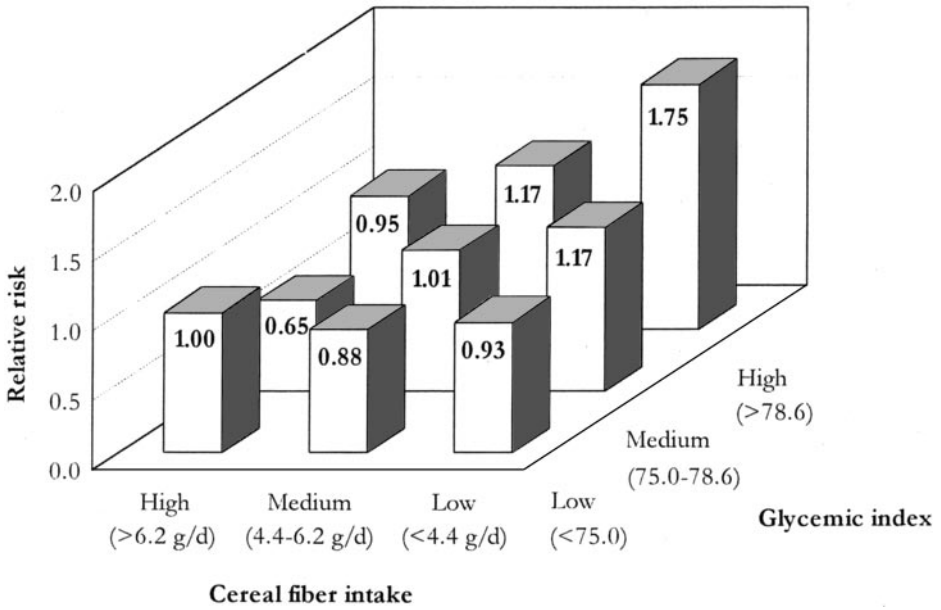

FIGURE 1. Relative risk of type 2 diabetes by different levels of cereal fiber intake and glycemic index. *P* for interaction = 0.004. Tests for interaction were based on ordinal variables containing median values for each tertile.

that might have led to an underestimation of the effect size (43). In addition, the questionnaire used in the ARIC Study was a shorter version of the Nurses' Health Study I questionnaire that did not address carbohydrate quality in detail (35). Also, the diagnosis of diabetes in the Iowa Women's Health Study was based entirely on self-report (22), and the ARIC Study did not distinguish type 1 and type 2 diabetes (23). Misclassification of either exposure or disease status might, therefore, have led to an underestimation of the association between glycemic index and diabetes in these studies (45). A high glycemic load was related to a more health conscious lifestyle in our cohort, whereas the opposite was observed for the glycemic index. In contrast with our study, glycemic index and load were associated with lower physical activity and higher BMI in the Nurses' Health Study I (20) and the Health Professionals Follow-Up Study (21). A health-conscious diet and lifestyle would tend to negatively confound the association for glycemic load, which might explain the lack of association observed in the overall cohort in our study in contrast with the positive association observed in the Nurses' Health Study I (20).

Previous studies have not presented an analysis stratified by BMI, physical activity, or family history of diabetes. The individual response to a given carbohydrate load is influenced by the degree of underlying insulin resistance. Physical activity strongly influences glucose tolerance and insulin sensitivity (46) and is a strong predictor of reduced diabetes risk in epidemiologic studies (39, 40, 47, 48). Similarly, a family history of diabetes has been identified to be a strong risk factor for diabetes (49) and insulin resistance, independent of BMI (50–52). Thus, it is expected that the effects of high-glycemic-index foods are stronger in obese, sedentary, and genetically susceptible persons (15). Although the effects of glycemic index and load seemed to be more pronounced among sedentary persons and persons with a family history of diabetes in our study, tests for interaction were not significant. Also, obesity did not significantly modify the effect of glycemic index and load in our study, but our analyses of these effect modifications were limited by a relatively small number of cases.

It is not clear why cereal fiber exerts stronger inverse associations than do other sources of fiber. Viscous fibers seem to affect gastric emptying rate and absorption in the small intestine (53–56). Similarly, viscous fibers were found to have effects on postprandial glycemic response to high-carbohydrate test meals (53). In contrast, insoluble fiber but not soluble fiber, was found to be inversely associated with diabetes risk in previous cohort studies (22, 57). Although cereal products from oat, barley, and psyllium are high in soluble fiber, major sources of soluble fiber are fruit, vegetables, nuts, legumes, and seeds. Whole-grain and bran products from wheat and corn, the major source of cereal fiber in our cohort (58), typically contain insoluble fiber. Despite the lack of an obvious mechanism for the benefits of cereal fiber in preventing diabetes, in all 5 prospective cohort studies that examined associations between different types of dietary fiber and risk of type 2 diabetes, cereal fiber appeared to be most strongly inversely associated with risk (20–23, 57). The intake of cereal fiber in our cohort (energy-adjusted median intake in third quintile: 5.2 g/d) was higher than the intake in older nurses in the Nurse's Health Study I (3.7 g/d) but was similar to that in the older women in the Iowa Women's Health Study (4.9 g/d). Because trials of the effects of high-fiber cereal foods and markers of blood glucose control have provided conflicting results (59, 60), it is possible that the consistent effects of cereal fiber observed in observational studies are due to residual confounding. We adjusted for glycemic load, magnesium intake, and lifestyle characteristics in our analysis, which had a minimal effect on the observed associations. Thus, it is unlikely that the effects of cereal fiber can be explained by residual confounding.

Several limitations apply to our study. Although the validity and reliability of FFQs similar to those used in the Nurses' Health Study II have been evaluated in similar cohort studies of US health professionals (31–34), we did not validate the questionnaire in our study population but rather assumed that the validation data from

these other studies applied to our sample. Because these validation studies were carried out in men and older women, the validation data may not have actually applied to our sample. A direct comparison of risk estimates across studies needs to be done cautiously.

Furthermore, errors in the measurement of dietary intake (eg, errors resulting from the limited quality of available food-composition data, particularly with regard to carbohydrates and dietary fiber, and by random error) may have limited our ability to obtain accurate risk estimates.

Concerns have also been raised about the application of the glycemic index to mixed meals, because other aspects of diet might lead to varying glucose and insulin responses. However, studies showed that the glycemic index of a mixed meal can be predicted consistently as the weighted average of the glycemic index values of each of the component foods, weighted by their relative contribution to total carbohydrates (61–63). In addition, although fat and protein affect the absolute glycemic response, they do not affect the relative differences between foods (64, 65). Furthermore, studies using standardized techniques have found excellent correlations between observed glycemic index values of mixed meals and the calculated values based on individual component foods (61–63). Moreover, metabolic studies in hyperlipidemic (66, 67), diabetic (68–71), and healthy persons (72) have shown adverse metabolic effects of high-glycemic index diets, particularly elevated triacylglycerol concentrations. These effects were replicated in apparently healthy postmenopausal women in the Nurses' Health Study I (36) by using a dietary questionnaire similar to the one used in our study. This suggests a physiologic relevance of the estimated average glycemic index and load in our study, although this has not been shown in healthy young women. Although our FFQ was not initially designed to pick up differences in the glycemic index of foods, it was designed to explain variance in the quantity and quality of carbohydrate intake (35). Correlations between similar questionnaires and diet records were found to be high for both total carbohydrates and fiber (31). Because the calculated glycemic index represents an average over all food items, weighed by their contribution to total carbohydrate intake, the design of the questionnaire should have ensured a relative accurate estimation of glycemic index.

Misclassification of disease status should not have biased our observations. We previously reported that our case definition, which was based on self-reports on an extended questionnaire, is highly accurate compared with medical records (39, 40). Given the resulting high specificity of the classification, the remaining misclassification (nonidentified cases) should not have biased our results (73). We did not directly validate the case definition in our cohort, but assumed that women participating in the Nurses' Health Study II are similar with respect to the validity of self-reports compared with the Nurses' Health Study I. However, our results were very similar to those reported from the Nurses' Health Study I (20), and consistent associations were observed for alcohol intake and the risk of diabetes in both cohorts (74, 75), which supports this assumption.

In conclusion, our findings support the hypothesis that diets with a high glycemic index and low in cereal fiber increase the risk of type 2 diabetes, particularly in women with a sedentary lifestyle and a family history of diabetes. This study reinforces the importance of the quality of carbohydrates consumed in preventing type 2 diabetes.

MBS contributed to the development of the analysis plan, conducted the statistical analyses, collaborated on the interpretation of the results, and wrote the manuscript. FBH provided significant consultation on the statistical analysis plan, interpretation of results, and writing of the manuscript. SL, EBR, JEM, and WCW provided significant consultation on the interpretation of results and writing of the manuscript. None of the authors had any financial or personal interest in any company or organization sponsoring this research, including advisory board affiliations.

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