

TCF7L2, dietary carbohydrate, and risk of type 2 diabetes in US women^{1–3}

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ABSTRACT

Background: *TCF7L2* is the strongest type 2 diabetes (T2D) locus identified to date, and evidence suggests it plays an important role in insulin synthesis, processing, and secretion. Dietary factors that increase the insulin demand might enhance the risk of T2D associated with *TCF7L2* variants.

Objective: The objective was to determine whether the risk of T2D associated with *TCF7L2* is modified by the glycemic load (GL), glycemic index (GI), cereal fiber content, and total carbohydrate content of the diet.

Design: T2D cases ($n = 1140$) and controls ($n = 1915$) from the Nurses' Health Study were genotyped for *TCF7L2* (rs12255372). Dietary intake was assessed with a semiquantitative food-frequency questionnaire.

Results: Significant differences in odds ratios (ORs) of T2D associated with the *TCF7L2* genotype between high and low strata of GL ($P = 0.03$) and GI ($P = 0.05$) were suggested. Compared with the *GG* genotype, multivariate-adjusted ORs (95% CI) of T2D associated with the *TT* genotype were 2.71 (1.64, 4.46) and 2.69 (1.64, 4.43) among individuals in the highest tertile of GL and GI, respectively. Corresponding ORs (95% CIs) among individuals in the lowest tertiles of GL and GI were 1.66 (0.95, 2.88) and 1.82 (1.11, 3.01). The risk of T2D associated with the *TCF7L2* single nucleotide polymorphism did not significantly differ by cereal fiber or carbohydrate intake.

Conclusion: Carbohydrate quality and quantity modified risk of T2D associated with *TCF7L2*, which suggests that changes in risk attributable to the *TCF7L2* variant are magnified under conditions of increased insulin demand. *Am J Clin Nutr* 2009;89:1256–62.

INTRODUCTION

Type 2 diabetes (T2D) is a rapidly growing public health issue with a major effect on morbidity and premature mortality worldwide (1). Both environmental and genetic factors have been implicated in the development of this disease (1–3). To date, *TCF7L2* (transcription factor 7–like 2 protein) is the strongest and most widely replicated locus associated with T2D (4, 5). Indeed, we previously reported a 1.53- and 1.32-fold increased risk of T2D for each copy of a *TCF7L2* risk allele among men and women, respectively (6). *TCF7L2* is a *Wnt* signaling-associated transcription factor expressed in several tissues, including the gut (7) and pancreas (8). Although the precise mechanism by which *TCF7L2* affects susceptibility to T2D remains to be elucidated, recent data implicate the protein's

role in glucose homeostasis (9, 10). *TCF7L2* polymorphisms are associated with several diabetic phenotypes characterized by impaired insulin secretion, β cell function, and GLP-1 potentiation of insulin secretion, but not with insulin sensitivity (11–21). Moreover, variation in *TCF7L2* influences the efficacy of sulfonylureas (agents that promote insulin secretion) but not the efficacy of metformin (insulin sensitizer) (22). Taken together, these studies suggest that progressive loss of insulin secretion might be the essential component of the phenotype, which predisposes *TCF7L2* variant carriers to T2D development.

Because insulin is secreted in response to elevated blood glucose concentrations, dietary carbohydrate—which markedly influences glucose concentrations or insulin demands—might modify the risk associated with *TCF7L2*. Dietary glycemic index (GI) is an indicator of carbohydrate quality that reflects the effect on blood glucose, and the dietary glycemic load (GL) is an indicator of both carbohydrate quality and quantity (23–25). Epidemiologic evidence suggests that low glycemic diets or diets rich in whole-grain cereals may protect against T2D (26, 27), probably through reductions in postprandial glucose concentrations, insulin demand, and insulin resistance (24, 28, 29). The purpose of the current study was to determine whether the change in risk of T2D associated with *TCF7L2* locus genotypes is modified by the GL, GI, cereal fiber content, and total carbohydrate content of the diet.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study (NHS) was established in 1976 when 121,700 female registered nurses aged 30–55 y and residing

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in 11 large US states completed a mailed questionnaire on their medical history and lifestyle characteristics (30). Beginning in 1980, dietary information has been updated by using validated semiquantitative food-frequency questionnaires (FFQs). Every 2 y, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of T2D and other diseases (31). Blood was collected from 32,826 NHS participants between 1989 and 1990. Women in the present study were selected from those who provided blood samples (32). Demographic characteristics and the health status of participants who provided blood samples were generally similar to those who did not. Diabetes cases were defined as initially self-reported diabetes subsequently confirmed by a validated supplementary questionnaire (33, 34). For cases before 1998 ($n = 977$), the diagnosis was made by using criteria consistent with those proposed by the National Diabetes Data Group (35), which included one of the following: one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus, or coma) plus fasting plasma glucose ≥ 140 mg/dL (7.8 mmol/L), and/or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), and/or plasma glucose 2 h after an oral-glucose-tolerance test result ≥ 200 mg/dL; or ≥ 2 elevated plasma glucose concentrations (as described above) on different occasions in the absence of symptoms; or treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). We used the American Diabetes Association's diagnostic criteria for the diagnosis of diabetes cases during the 1998 and 2002 cycles ($n = 163$) (36). These criteria were the same as those proposed by the National Diabetes Data Group, except for the elevated fasting plasma glucose criterion for which the cutoff was changed from 140 to 126 mg/dL. Cases were matched to nondiabetic controls on age, month, and year of blood draw and fasting status. To minimize potential bias due to population stratification, we restricted our analyses to non-Hispanic whites. We further excluded prevalent or incident cases of T2D occurring before 1980 and women missing 1980 FFQs and *TCF7L2* genotypes. This study included 1140 incident cases of T2D occurring between 1980 and 2002 and 1915 nondiabetic control women. All participants provided written informed consent, and the study was approved by the Human Research Committee at the Brigham and Women's Hospital (Boston, MA).

Genotyping

DNA was extracted from the buffy coat fraction of centrifuged blood by using a QIAmp blood kit (Qiagen, Chatsworth, CA). DNA samples were genotyped for the *TCF7L2* rs12255372 G to T single nucleotide polymorphism (SNP) by using the Open-Array SNP Genotyping System (BioTrove, Woburn, MA) according to the manufacturer's instructions. Primers and probes are available on request. Genotyping success rates exceeded 95% for both cases and controls. Replicate quality-control samples (10%) were included and genotyped with $>99\%$ concordance. *TCF7L2* genotypes among controls did not significantly depart from Hardy-Weinberg equilibrium ($P = 0.09$).

Dietary assessment

Dietary intakes were obtained from the 1980 FFQ. Detailed information regarding the development of the FFQ, procedures

used to calculate energy-adjusted nutrient values, and reproducibility and validity of the questionnaire were documented elsewhere (31). For each food, a commonly used unit or portion size was specified on the FFQ, and participants were asked how frequently they had consumed the food over the previous year. Nine responses were possible ranging from "never or less than once per month" to "6 or more times per day." We estimated nutrient intakes by multiplying the frequency of consumption of each food by the nutrient content estimated using food-composition tables from the Harvard University food-composition database, which was derived from US Department of Agriculture sources (37). The GI of foods is a measure of the relative postprandial blood glucose response per gram of carbohydrate. The GI values for single food items on the questionnaire were derived with the assistance of D Jenkins (University of Toronto), which were based on available databases and publications (23, 38, 39). GL was calculated by multiplying the carbohydrate content of each food by its GI and then multiplying this value by the frequency of consumption and summing these values for all foods. Dietary GL, therefore, represents both the quality and quantity of carbohydrate consumed. Each unit of GL represents the equivalent of 1 g carbohydrate from white bread or pure glucose. Additionally, the overall dietary GI, a variable representing the overall quality of carbohydrate intake for each participant, was created by dividing the dietary GL by the total amount of carbohydrate consumed. In a validation study with 176 nurses, the corrected correlation coefficients between the FFQ and multiple dietary records for carbohydrates and fiber were 0.64 and 0.56 (31, 40). High correlations for individual carbohydrate-rich food items have also been reported (white bread: 0.71; dark bread: 0.77; cold breakfast cereal: 0.79; potatoes: 0.66) (41). The ability of the FFQ to assess dietary GI and GL was documented in a study that evaluated the relations of these 2 variables to plasma concentrations of HDL and triacylglycerol in postmenopausal women (42).

Nondietary covariate assessment

Information about medical history, anthropometric data, lifestyle factors, and family history of diabetes in first-degree relatives was derived from the 1980 questionnaires (43, 44). Body mass index (BMI) was calculated as weight (in kg) divided by the height squared (in m). Physical activity was expressed as hours per week. Self-administered questionnaires about body weight and physical activity were validated as described previously (45, 46).

Statistical analysis

Statistical analyses were performed by using the SAS statistical package (version 9.1 for UNIX; SAS Institute, Cary, NC). Student's *t* tests and chi-square tests were used for comparisons of means and proportions between cases and controls and across *TCF7L2* genotypes and tertiles (low, intermediate, and high) of dietary intake among controls. To determine the main effects of *TCF7L2* genotype, GI, GL, cereal fiber, and carbohydrate on the risk of T2D, odds ratios (ORs), and 95% CIs were estimated by unconditional logistic regression and adjusted for age (continuous) and BMI (<23 , 23–24.9, 25–29.9, 30–34.9, or ≥ 35). In multivariate analysis, we further adjusted for smoking (never, past, or current), alcohol intake (g/d), coffee intake (≤ 1 cup/wk, 5–6 cups/

wk, 1 cup/d, 2–3 cups/d, or ≥ 4 cups/d; 1 cup = 237 mL), menopausal status [pre- or postmenopausal (never, past, or current hormone use)], and quintiles of physical activity, ratio of polyunsaturated to saturated fatty acids, cereal fiber (g/d), and *trans* fat (g/d) intake. In a secondary analysis we also adjusted for family history of diabetes (yes or no). Codominant and additive genetic models were evaluated with reference to the “nonrisk” *G* allele. Tertiles of dietary intake were modeled by using indicator variables in logistic models with the lowest tertile of intake as the reference. Tests of linear trend across increasing tertiles of intakes were conducted by assigning the median value for each tertile as a continuous variable. Departures from a multiplicative OR interaction model were tested by using the likelihood ratio test comparing a model with and without the product (*TCF7L2* \times dietary factor) interaction term. Power calculations were performed by using Quanto 1.2.3 (<http://hydra.usc.edu/gxe>). Given an α of 0.05, an allele frequency of 0.30, and a main effect OR of 1.30, the current study provided 80% power to detect gene-diet interactions with risk ratios >1.40 . Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Cases of T2D had a significantly higher BMI, consumed less alcohol, engaged in less physical activity, were more likely to smoke, and were more likely to have a family history of diabetes than were control subjects ($P < 0.05$). Baseline (1980) characteristics of control subjects based on *TCF7L2* genotype and tertiles of GL and diet GI are presented in **Table 1** and **Table 2**, respectively. No significant and consistent difference in characteristics was observed across *TCF7L2* genotypes. The fre-

quency of the *TCF7L2* risk allele (*T*) was 33% for cases and 27% for controls. Compared with individuals with the *GG* genotype, the age- and BMI-adjusted ORs (95% CIs) of T2D were 1.29 (1.08, 1.53) and 2.14 (1.61, 2.84) for those with the *GT* and *TT* genotypes, respectively. Corresponding multivariate-adjusted ORs (95% CI) were 1.24 (1.04, 1.47) and 2.11 (1.58, 2.82). Compared with a low-GL diet, the multivariate-adjusted OR (95% CI) of T2D associated with an intermediate and a high-GL diet was 1.10 (0.88, 1.36) and 1.20 (0.95, 1.52), respectively ($P = 0.12$ for trend). Compared with a low-GI diet, the multivariate-adjusted ORs (95% CIs) of T2D associated with an intermediate- and a high-GI diet were 1.01 (0.82, 1.26) and 1.16 (0.93, 1.44), respectively ($P = 0.18$ for trend). Cereal fiber and carbohydrate (percentage of calories) intakes were not significantly associated with risk of T2D (multivariate-adjusted P for trend = 0.44 and 0.56, respectively).

A significant *TCF7L2*-GL interaction in relation to diabetes risk was observed both before and after multivariate adjustment ($P = 0.03$; **Table 3**). We observed a marginally significant *TCF7L2*-GI interaction in models adjusting for age and BMI ($P = 0.05$) and for other covariates ($P = 0.06$). The risk of T2D associated with the *TCF7L2* *TT* genotype was greatest among individuals consuming a high-GL or high-GI diet. Compared with the *GG* genotype, multivariate-adjusted ORs (95% CI) of T2D associated with the *TT* genotype were 2.71 (1.64, 4.47) and 2.69 (1.64, 4.43) among individuals in the highest tertile of GL and GI, respectively. When family history of T2D was further adjusted in the model, interactions were no longer evident (*TCF7L2*-GL: $P = 0.13$; *TCF7L2*-GI: $P = 0.14$). A greater risk associated with the *TT* genotype was also observed among individuals in the lowest tertile of cereal fiber intake [multivariate-

TABLE 1
Baseline characteristics according to *TCF7L2* genotype among controls¹

Characteristic	<i>TCF7L2</i> genotype			<i>P</i>
	<i>GG</i>	<i>GT</i>	<i>TT</i>	
<i>n</i>	1021	755	139	0.73
Age (y)	47.5 \pm 6.9 ²	47.5 \pm 6.8	48.0 \pm 6.8	0.69
BMI (kg/m ²)	24.6 \pm 4.8	24.3 \pm 4.3	24.2 \pm 4.4	0.41
Family history of diabetes (%)	21	24	24	0.85
Current smoking (%)	19	20	22	0.95
Alcohol intake (g/d)	6.9 \pm 10.4	5.7 \pm 8.8	6.4 \pm 9.0	0.03
Coffee intake (cups/d) ³	1.9 \pm 1.6	1.7 \pm 1.6	1.8 \pm 1.5	0.12
Physical activity (h/wk)	4.24 \pm 2.92	3.87 \pm 2.88	4.40 \pm 2.77	0.02
Postmenopausal (%)	52	49	51	0.55
Current PMH users (%)	19	21	23	0.76
Energy (kcal/d)	1595 \pm 474	1584 \pm 500	1558 \pm 498	0.67
Carbohydrate (% of energy)	39 \pm 9	38 \pm 9	39 \pm 9	0.98
Total fat (% of energy)	39 \pm 8	40 \pm 8	39 \pm 8	0.41
Protein (% of energy)	19 \pm 4	19 \pm 4	19 \pm 3	0.80
Energy-adjusted intakes				
P:S ratio	0.35 \pm 0.14	0.35 \pm 0.13	0.37 \pm 0.13	0.24
<i>trans</i> Fat (g/d)	3.96 \pm 1.34	4.07 \pm 1.30	4.16 \pm 1.38	0.11
Cereal fiber (g/d)	2.5 \pm 1.5	2.7 \pm 1.7	2.6 \pm 1.5	0.02
Glycemic index	51.2 \pm 4.6	51.2 \pm 4.5	50.9 \pm 4.1	0.75
Glycemic load (g)	84.1 \pm 24.5	83.4 \pm 22.9	82.4 \pm 23.1	0.65

¹ PMH, postmenopausal hormone; P:S, ratio of polyunsaturated to saturated fatty acids. Differences between genotypes were tested with a chi-square test for categorical variables and by ANOVA for continuous variables.

² Mean \pm SD (all such values).

³ 1 cup = 237 mL.

TABLE 2

Baseline characteristics according to median (range) tertiles of dietary glycemic load and glycemic index among controls¹

Characteristic	Tertiles of glycemic load			P	Tertiles of glycemic index			P
	Low 63.0 (1.0–72.0)	Intermediate 82.0 (73.0–91.0)	High 104.0 (92.0–196.0)		Low 47.5 (5.7–49.7)	Intermediate 51.3 (49.7–53.0)	High 55.0 (53.1–64.0)	
Age (y)	47.9 ± 6.6 ²	47.4 ± 6.8	47.3 ± 7.1	0.25	48.0 ± 6.8	47.9 ± 6.6	46.8 ± 7.0	0.003
BMI (kg/m ²)	24.5 ± 4.4	24.6 ± 4.8	24.3 ± 4.6	0.59	24.6 ± 4.6	24.2 ± 4.4	24.5 ± 4.8	0.10
Family history of diabetes (%)	25	20	22	0.07	23	24	21	0.53
Current smoking (%)	21	20	18	<0.0001	19	17	23	<0.0001
Alcohol intake (g/d)	9.7 ± 12.2	5.7 ± 8.7	3.7 ± 6.4	<0.0001	8.4 ± 12.0	6.2 ± 8.9	4.6 ± 7.4	<0.0001
Coffee intake (cups/d) ³	2.0 ± 1.6	1.8 ± 1.6	1.7 ± 1.6	0.0008	1.9 ± 1.6	1.9 ± 1.6	1.7 ± 1.6	0.006
Physical (h/wk)	4.02 ± 2.93	4.39 ± 2.96	3.9 ± 2.79	0.02	4.62 ± 2.92	4.06 ± 2.91	3.68 ± 2.80	<0.0001
Postmenopausal (%)	53	49	50	0.23	52	51	49	0.70
Current PMH users (%)	22	20	18	0.61	21	21	18	0.63
Energy (kcal/d)	1606 ± 508	1599 ± 476	1560 ± 472	0.19	1597 ± 520	1598 ± 468	1570 ± 469	0.52
Carbohydrate (% of energy)	30 ± 6	39 ± 4	47 ± 6	<0.0001	36 ± 9	38 ± 8	41 ± 9	<0.0001
Total fat (% of energy)	45 ± 7	39 ± 6	34 ± 6	<0.0001	40 ± 8	39 ± 7	39 ± 8	0.26
Protein (% of energy)	21 ± 3	19 ± 3	17 ± 3	<0.0001	21 ± 4	19 ± 3	18 ± 3	<0.0001
Energy-adjusted intakes								
P:S ratio	0.31 ± 0.1	0.34 ± 0.11	0.40 ± 0.16	<0.0001	0.32 ± 0.13	0.35 ± 0.12	0.38 ± 0.16	<0.0001
trans Fat (g/d)	4.14 ± 1.3	4.06 ± 1.3	3.86 ± 1.37	0.0004	3.48 ± 1.14	4.14 ± 1.32	4.43 ± 1.34	<0.0001
Cereal fiber (g/d)	2.0 ± 1.3	2.7 ± 1.6	3.1 ± 1.6	<0.0001	2.1 ± 1.3	2.67 ± 1.49	3.09 ± 1.68	<0.0001
Glycemic index	48.5 ± 5.0	51.2 ± 3.4	53.7 ± 3.4	<0.0001	46.5 ± 3.8	51.4 ± 0.97	55.5 ± 1.97	<0.0001
Glycemic load (g)	59.4 ± 11.6	82.2 ± 5.2	109.3 ± 17.0	<0.0001	69.8 ± 19.7	83.3 ± 18.3	97.7 ± 24.1	<0.0001

¹ PMH, postmenopausal hormone; P:S, ratio of polyunsaturated to saturated fatty acids. Differences between genotypes were tested with a chi-square test for categorical variables and by ANOVA for continuous variables.

² Mean ± SD (all such values).

³ 1 cup = 237 mL.

adjusted OR (95% CI): 2.62 (1.61, 4.27)], even though the *TCF7L2*–cereal fiber interaction was not significant ($P = 0.14$). The risk of T2D associated with *TCF7L2* did not significantly differ by carbohydrate intake ($P = 0.18$ for interaction). We also tested the same interaction using the Pro12Ala substitution in peroxisome proliferator–activated receptor- γ , which has no presumed influence on insulin secretion. No interaction was observed (data not shown).

DISCUSSION

TCF7L2 is the strongest locus associated with T2D identified thus far (4, 5). *TCF7L2* variants have been shown to predict the incidence of T2D in persons who were already at high risk (ie, those with impaired glucose tolerance) of the disease (15, 47), which suggests potential synergistic effects between different risk factors. In the current study we found that the risk associated with a *TCF7L2* variant was modified by the carbohydrate quality and quantity of the diet; the increased risk was more pronounced among women consuming a high-GL or high-GI diet. To our knowledge, this was the first study to examine the interaction between *TCF7L2* genetic variation and specific components of the diet.

TCF7L2 variants have been associated with impaired insulin synthesis, processing, and secretion (13–18). Adverse consequences of this impairment may be exacerbated under conditions of increased insulin demand. Consistent with this notion, a high-GL or high-GI diet, previously shown to increase postprandial glucose concentrations and thus, insulin demand (24,

25, 28, 29), augmented the change in log odds of T2D associated with the *TCF7L2* risk variant in the current study. In contrast, total carbohydrate (expressed as a proportion of total energy intake) did not modify risk of T2D associated with *TCF7L2* genotype, which suggests that carbohydrate quality may mediate the modification effect. Our findings further corroborate those reported by Lyssenko et al (9). In their study, *TCF7L2* risk variant carriers showed a weaker insulin response to oral than to intravenous glucose than did nonrisk variant carriers—an effect restricted to the hyperglycemic state (9). Taken together, these findings suggest that the association between *TCF7L2* and T2D might also be mediated by defects in the enteroinsular axis (9). Although no significant interaction was observed between *TCF7L2* and cereal fiber, a high cereal fiber intake also attenuated the variant-associated risk, possibly by influencing carbohydrate quality or reducing the amount or rate of carbohydrates absorbed (25, 48). Alternatively, these dietary factors might modify risk by improving insulin sensitivity (25), which would indirectly affect insulin demand.

The increased risk of T2D associated with the *TCF7L2* TT variant was not completely abolished by consumption of a low-GL or low-GI diet. Besides the carbohydrate quality of the diet, other factors influencing insulin demand may also modify the risk associated with *TCF7L2*. Recent intervention studies report no risk associated with *TCF7L2* among subjects assigned to a lifestyle modification arm (15, 47). Because diet was only one of the lifestyle components modified, other components of the intervention may also be contributing to the effect and warrant further investigation. Interestingly, the interactions we observed were no longer significant when models were adjusted for

TABLE 3

TCF7L2 genotype and risk of type 2 diabetes by tertile of dietary glycemic load, glycemic index, and cereal fiber and carbohydrate intakes

<i>TCF7L2</i> genotype	Dietary factors			<i>P</i> for interaction
	Low	Intermediate	High	
Glycemic load				
Model 1 ¹				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.03 (0.76, 1.41)	1.18 (0.88, 1.59)	1.70 (1.27, 2.28)	
<i>TT</i>	1.54 (0.91, 2.61)	2.36 (1.45, 3.84)	2.49 (1.54, 4.04)	
Additive	1.15 (0.92, 1.45)	1.39 (1.13, 1.72)	1.62 (1.32, 2.00)	0.03
Model 2 ²				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.06 (0.77, 1.47)	1.16 (0.86, 1.58)	1.75 (1.29, 2.36)	
<i>TT</i>	1.66 (0.95, 2.88)	2.27 (1.37, 3.75)	2.71 (1.64, 4.46)	
Additive	1.19 (0.94, 1.51)	1.37 (1.10, 1.71)	1.68 (1.35, 2.09)	0.03
Glycemic index				
Model 1 ¹				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	0.96 (0.70, 1.30)	1.45 (1.07, 1.95)	1.43 (1.07, 1.91)	
<i>TT</i>	1.71 (1.06, 2.77)	1.86 (1.09, 3.16)	2.80 (1.72, 4.54)	
Additive	1.17 (0.95, 1.45)	1.40 (1.12, 1.75)	1.58 (1.28, 1.95)	0.05
Model 2 ²				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	0.88 (0.64, 1.21)	1.45 (1.06, 1.97)	1.39 (1.03, 1.87)	
<i>TT</i>	1.82 (1.11, 3.01)	1.88 (1.09, 3.23)	2.69 (1.64, 4.43)	
Additive	1.16 (0.93, 1.46)	1.40 (1.12, 1.76)	1.54 (1.24, 1.92)	0.06
Cereal fiber				
Model 1 ¹				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.57 (1.16, 2.13)	1.20 (0.90, 1.59)	1.12 (0.82, 1.52)	
<i>TT</i>	2.43 (1.52, 3.88)	2.13 (1.30, 3.50)	1.85 (1.09, 3.13)	
Additive	1.56 (1.27, 1.93)	1.35 (1.09, 1.66)	1.26 (1.00, 1.57)	0.18
Model 2 ²				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.55 (1.14, 2.12)	1.16 (0.86, 1.56)	1.01 (0.73, 1.38)	
<i>TT</i>	2.62 (1.61, 4.27)	1.86 (1.11, 3.12)	1.69 (0.99, 2.91)	
Additive	1.60 (1.28, 1.98)	1.28 (1.03, 1.59)	1.18 (0.93, 1.49)	0.14
%Carbohydrate				
Model 1 ¹				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.12 (0.82, 1.52)	1.32 (0.98, 1.78)	1.40 (1.05, 1.87)	
<i>TT</i>	1.80 (1.08, 3.02)	2.55 (1.50, 4.35)	2.25 (1.43, 3.55)	
Additive	1.25 (1.00, 1.57)	1.47 (1.18, 1.84)	1.47 (1.20, 1.80)	0.19
Model 2 ²				
<i>GG</i>	1.00 (reference)	1.00 (reference)	1.00 (reference)	
<i>GT</i>	1.13 (0.82, 1.56)	1.24 (0.91, 1.69)	1.38 (1.03, 1.86)	
<i>TT</i>	1.92 (1.12, 3.30)	2.42 (1.40, 4.18)	2.33 (1.46, 3.72)	
Additive	1.28 (1.02, 1.62)	1.42 (1.12, 1.78)	1.48 (1.20, 1.82)	0.18

¹ Results from unconditional logistic regression that included age and BMI (5 categories).

² Model 1 plus adjustments for smoking (never, past, or current), alcohol (g/d), coffee (5 categories), menopausal status [pre- or postmenopausal (never, past, or current hormone use)], quintiles of physical activity (h/wk), and quintiles of energy-adjusted ratio of polyunsaturated to saturated fatty acids and *trans* fat (g/d) and cereal fiber (g/d) intakes.

family history of diabetes. Because family history encompasses both genetic and shared environmental components, the effect of family history may, in part, be explained by its correlation with *TCF7L2* (genetic) and GL (environment).

Several limitations need to be considered when interpreting the results. Some of the control subjects may have undiagnosed T2D that would bias the results toward the null. However, in a previous validation study (49), the prevalence of undiagnosed

T2D in these health professionals ($\approx 2\%$) was substantially lower than that in the general population ($\approx 30\%$) (50). Population stratification may also affect the observed associations. However, because subjects were selected from a well-characterized cohort with a defined study base and the analysis restricted to non-Hispanic whites, biases due to population stratification are likely minimized. Because we examined only women of European ancestry and of a specific age range, the

generalizability of our findings to men, other age groups, or other ethnic groups is unknown. Errors in the measurement of dietary intake (eg, errors resulting from the limited quality of available food-composition data and by random error) may have limited our ability to obtain accurate risk estimates. Although our FFQ was not initially designed to identify differences in the GI of foods, it was designed to explain variance in the quantity and quality of carbohydrate intake (40). Moreover, any dietary measurement error may have only attenuated associations and are not likely to have explained the gene-diet interactions observed, assuming that errors occur independent of *TCF7L2* genotype. Interactions were also robust to adjustment for various lifestyle and dietary factors. Nevertheless, we cannot exclude the possibility that some other variable, highly correlated with GL, is interacting with *TCF7L2*. Finally, because this is the first study to explore the interaction between carbohydrate quality and *TCF7L2*, replication is required to confirm our findings.

In conclusion, carbohydrate quality and quantity of the diet-modified risk of T2D associated with *TCF7L2*, which suggests that, in situations of high glucose concentrations or insulin demand, the changes in risk of T2D attributable to *TCF7L2*-associated risk alleles is magnified. The current findings contribute to our understanding of the etiologic role of *TCF7L2* in T2D development and may also have implications for prevention of T2D in individuals harboring *TCF7L2* risk alleles through dietary intervention.

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