Carbohydrate Nutrition, Insulin Resistance, and the Prevalence of the Metabolic Syndrome in the Framingham Offspring Cohort

NICOLA M. MCKEOWN, PHD[1]
JAMES B. MEIGS, MD, MPH[2]
SIMIN LIU, MD, SCD[3]
EDWARD SALTZMAN, MD[1]
PETER W.F. WILSON, MD[4]
PAUL F. JACQUES, SCD[1]

OBJECTIVE — The aim of this study was to examine the relation between carbohydrate-related dietary factors, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort.

RESEARCH DESIGN AND METHODS — We examined cross-sectional associations between carbohydrate-related dietary factors, insulin resistance, and the prevalence of the metabolic syndrome in 2,834 subjects at the fifth examination (1991–1995) of the Framingham Offspring Study. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula (fasting plasma insulin × plasma glucose)/22.5. The metabolic syndrome was defined using the National Cholesterol Education Program criteria.

RESULTS — After adjustment for potential confounding variables, intakes of total dietary fiber, cereal fiber, fruit fiber, and whole grains were inversely associated, whereas glycemic index and glycemic load were positively associated with HOMA-IR. The prevalence of the metabolic syndrome was significantly lower among those in the highest quintile of cereal fiber (odds ratio [OR] 0.62; 95% CI 0.45–0.86) and whole-grain (0.67; 0.48–0.91) intakes relative to those in the lowest quintile category after adjustment for confounding lifestyle and dietary factors. Conversely, the prevalence of the metabolic syndrome was significantly higher among individuals in the highest relative to the lowest quintile category of glycemic index (1.41; 1.04–1.91). Total carbohydrate, dietary fiber, fruit fiber, vegetable fiber, legume fiber, glycemic load, and refined grain intakes were not associated with prevalence of the metabolic syndrome.

CONCLUSIONS — Whole-grain intake, largely attributed to the cereal fiber, is inversely associated with HOMA-IR and a lower prevalence of the metabolic syndrome. Dietary glycemic index is positively associated with HOMA-IR and prevalence of the metabolic syndrome. Given that both a high cereal fiber content and lower glycemic index are attributes of whole-grain foods, recommendation to increase whole-grain intake may reduce the risk of developing the metabolic syndrome.

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From the [1]Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts; the [2]General Medicine Division and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; the [3]Department of Epidemiology, Harvard School of Public Health and Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the [4]Department of Endocrinology, Diabetes, and Medical Genetics, Medical University of South Carolina, Charleston, South Carolina.

Address correspondence and reprint requests to Paul Jacques, Epidemiology Program, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111-1524. E-mail: paul.jacques@tufts.edu.

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Abbreviations: FFQ, food frequency questionnaire; HOMA-IR, homeostasis model assessment of insulin resistance.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 613.

Type 2 diabetes is a major cause of morbidity and mortality in the U.S. (1), and the prevalence of this disease continues to rise (2). One subgroup of the population at increased risk of developing type 2 diabetes are individuals with the "metabolic syndrome," a condition characterized by disturbed glucose and insulin metabolism, central obesity, mild dyslipidemia, and hypertension (3). Recent estimates indicate that the metabolic syndrome is highly prevalent in the U.S., with an estimated 24% of the adult population affected (4). The etiology of this syndrome is largely unknown, but presumably represents a complex interaction between genetic, metabolic, and environmental factors, including diet (5–7). Whereas aspects of diet have been linked to individual metabolic features of the syndrome (8,9), the role of diet in the etiology of the metabolic syndrome is poorly understood and limited to only a few observational studies (10,11).

There is conflicting evidence on the influence of total carbohydrate intake on insulin sensitivity (12) and in fact, a recent dietary intervention found that after 6 months on a low-carbohydrate, high-fat diet, insulin sensitivity improved among obese individuals (13). However, the source and quality of dietary carbohydrates may differentially optimize insulin action and thereby affect the degree of insulin resistance, which is a key underlying metabolic feature of this syndrome. Observational studies have found that fasting insulin concentrations are lower among individuals reporting higher dietary fiber (14–16) or whole-grain intakes (17,18) after adjustment for other lifestyle and dietary factors. The role of high-fiber carbohydrate sources, however, in influencing insulin sensitivity in randomized feeding studies is inconsistent. For instance, some studies report a beneficial effect on insulin sensitivity with a high consumption of dietary fiber (19) or whole-grain foods (20), whereas others showed no effect on insu-

lin sensitivity (21,22). The glycemic index, a measure of the glycemic response to carbohydrate-containing foods, has been used to physiologically classify dietary carbohydrates (23). Evidence from observational data suggests that a high dietary glycemic index is associated with components of the metabolic syndrome, such as elevated triglyceride concentrations (9) and low HDL cholesterol (24,25). Some clinical studies have demonstrated that low glycemic index carbohydrates improve glycemic control and lipid profiles in individuals with (26,27) and without type 2 diabetes (28,29). The glycemic load, a measure of both carbohydrate quality and quantity, has been linked to increased risk of type 2 diabetes in some (30,31) but not all observational studies (32,33). To date, no observational study has examined the glycemic index and glycemic load of the diet in relation to insulin resistance or the metabolic syndrome.

Dietary recommendations emphasize the benefits of high-carbohydrate, low-fat diets in reducing chronic diseases (34,35). However, increasing carbohydrate intake may adversely affect blood lipid and lipoprotein concentrations and glucose metabolism (36,37), predisposing some individuals to develop the metabolic syndrome. Thereby, understanding the association of carbohydrate nutrition with metabolic syndrome may provide a strategy for early intervention in the natural progression of type 2 diabetes. The purpose of the present study was to examine the relation between carbohydrate-related dietary factors, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort.

RESEARCH DESIGN AND METHODS

Study population

The Framingham Offspring Study is a longitudinal community-based study of cardiovascular disease among the offspring of the original participants of the Framingham Heart Study Cohort and their spouses (38). In 1971, 5,135 participants were enrolled into the study (39), and since then, the cohort has been examined every 3 to 4 years. Between 1991 and 1995, during the fifth examination cycle of the Framingham Offspring Study, 3,799 participants underwent a standardized medical history and physical examination. Valid food frequency questionnaire (FFQ) data were available for 3,418 participants. Dietary information was judged as valid if reported energy intakes were ≥2.51 MJ/day (600 kcal) for men and women or <16.74 MJ/day (4,000 kcal/day) for women and <17.57 MJ/day (4,200 kcal/day) for men, respectively, or if fewer than 13 food items were left blank. Participants were excluded from these analyses if they were taking cholesterol-lowering medication (n = 229) or if they had previously diagnosed diabetes (n = 122) based on use of insulin or oral hypoglycemic medication. Furthermore, we excluded participants with missing covariate information (n = 112) and those with missing values for fasting plasma glucose or insulin concentrations (n = 122), reducing the final sample to 2,834 (1,290 men and 1,544 women). Excluding participants with previously undiagnosed diabetes (n = 118) based on either a fasting blood glucose level (≥7.0 mmol/l) or an oral glucose tolerance test (2-h postchallenge plasma glucose level ≥11.1 mmol/l) did not alter the findings of the present study, and therefore these participants were included in the analyses. The Institutional Review Board for Human Research at Boston University and the Human Investigation Research Committee of New England Medical Center approved the protocol.

Dietary data

Usual dietary intake for the previous year was assessed at the fifth cycle using a semiquantitative 126-item FFQ (40). The questionnaires were mailed to the participants before the examination, and the participants were asked to bring the completed questionnaire with them to their appointment. The FFQ consisted of a list of foods with a standard serving size and a selection of nine frequency categories ranging from never or <1 serving/month to >6 servings/day. Participants were asked to report their frequency of consumption of each food item during the last year. Separate questions about use of vitamin and mineral supplements and type of breakfast cereal most commonly consumed were also included in the FFQ. Nutrient intakes were calculated by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient content of the specified portion. The relative validity of this FFQ has been examined in several populations for both nutrients and foods (40–42). Energy-adjusted intake between the FFQ and multiple diet records are moderately correlated for total carbohydrate and fiber intake. In men and women, respectively, the correlation coefficients were 0.69 and 0.45 for total carbohydrate and 0.64 and 0.58 for fiber (40,41). Dietary exposures included intakes of total dietary carbohydrate, dietary fiber, whole- and refined-grain foods, glycemic index, and glycemic load. In addition, the contribution of total dietary fiber was calculated for each of the food categories: cereals, fruits, vegetables, and legumes.

The average dietary glycemic index value based on a white bread standard was calculated for each participant. A food's glycemic index is defined as the incremental area under the blood glucose curve induced by a specific carbohydrate-containing food and is expressed as a percentage of the area produced by the same amount of carbohydrates from a standard source, either glucose or white bread (23). Glycemic index values for foods in the FFQ were obtained either from published estimates (27), from direct testing of food items, or imputed when necessary by matching similar foods based on calories, carbohydrate, sucrose, fat, and dietary fiber content. In addition for cereals, whenever possible, the method of processing was taken into account.

The dietary glycemic load was calculated by multiplying the carbohydrate content of each food by its glycemic index; this value was then multiplied by the frequency of consumption and summed for all food items. Each unit of dietary glycemic load is the equivalent to 1 g of carbohydrate from white bread (9,43). As an indirect measure of validity, dietary intakes of glycemic index and glycemic load estimated from the FFQ have been related to triglyceride concentrations (9), a metabolic marker known to respond to carbohydrate intake.

Laboratory methods

As part of the fifth offspring cohort examinations, blood samples were obtained from subjects who had fasted for at least 10 h, and the blood samples were stored at −70°C. Fasting plasma glucose was measured in fresh specimens with a hexokinase reagent kit. Glucose assays were run in duplicate, and the intra-assay coefficient of variation (CV) was <3%. Fast-

ing plasma insulin levels were determined using the Coat-A-Count ^{125}I-radioimmunoassay (Diagnostic Products, Los Angeles, CA). This is a polyclonal assay with cross-reactivity with proinsulin at the midcurve of 40%. The intra- and interassay CV ranged from 5 to 10% for concentrations reported here, and the lower limit of sensitivity was 1.1 μU/ml (7.9 pmol/l). Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA) from fasting glucose and insulin concentrations (44) using the following formula: HOMA-IR = (fasting plasma insulin [μU/ml] × fasting plasma glucose [mmol/l])/22.5.

The HOMA-IR method has been validated by comparison with results of glucose clamp studies (44) and frequently sampled intravenous glucose tolerance tests (45,46). The correlation between HOMA-IR and fasting insulin was high in the present study ($r = 0.94$).

Lifestyle variables

Height, weight, and waist-to-hip circumferences were measured with the subject standing. BMI was calculated (kg/m^2). Smoking was categorized based on the number of cigarettes smoked per day (none, 1–15, 16–25, >25). Additional covariate information included age, alcohol intake (grams/day), current multivitamin use (yes/no), treatment for blood pressure (yes/no), and physical activity score (47).

Ascertainment of the metabolic syndrome

Metabolic syndrome was defined as the presence of three or more of the following components, as recommended by the Adult Treatment Panel (48): *1*) abdominal adiposity as defined by a waist circumference of >40 inches in men and >35 inches in women; *2*) low serum HDL cholesterol (<40 mg/dl [1.04 mmol/l] or <50 mg/dl [1.29 mmol/l] in men and women, respectively); *3*) hypertriglyceridemia as defined by an elevated triglyceride of ≥150 mg/dl (≥1.69 mmol/l); *4*) elevated blood pressure as defined by a blood pressure of at least 130/85 mmHg; and *5*) abnormal glucose homeostasis as defined by a fasting plasma glucose concentration of ≥6.1 mmol/l (110 mg/dl). In addition, if individuals reported taking hypertensive medication, they were categorized as having elevated blood pressure.

Statistical methods

Statistical analyses were conducted using SAS statistical software (version 8; SAS Institute, Cary, NC). Because HOMA-IR levels were positively skewed, analyses were performed on the natural logarithm transformations. Inverse transformations were performed to provide geometric mean HOMA-IR concentrations and their 95% CI. Baseline characteristics of the participants were computed across quintile categories of HOMA-IR. Associations among continuous variables were assessed by tests for linear trend using linear regression, and for categorical variables, the Mantel-Haenszel χ^2 test for trend was applied. Statistical significance was defined as a two-tailed P value ≤0.05.

To examine the relation between carbohydrate nutrition and HOMA-IR, we compared geometric mean HOMA-IR across quintile categories of energy-adjusted carbohydrate, dietary fiber, and source of fiber intakes, glycemic index, and glycemic load. We tested each association for age and sex interactions, but no interactions were statistically significant. Nutrient intakes were adjusted for total energy intake by the residual method, as described by Willett and Stampfer (49). We used multiple logistic regression to calculate the odds ratios (ORs) and their 95% CIs for metabolic syndrome with individuals in the lowest quintile category of carbohydrate, fiber type, glycemic index, glycemic load, and grain intakes as the referent category. OR and mean HOMA-IR were adjusted for sex, age, cigarette dose, total energy intake, alcohol intake, percentage saturated and polyunsaturated fat, multivitamin use, and physical activity. In addition, mean HOMA-IR was also adjusted for BMI, waist-to-hip ratio, and treatment for blood pressure. To assess trends across quintile categories, we assigned the median intake of each quintile category to individuals with intakes in the category and then included this quintile median variable as a continuous factor in the linear or logistic regression models. The P for trend was the resulting P value for the associated linear or logistic regression coefficient.

Given that obesity is strongly correlated with an individual's underlying degree of insulin resistance, we tested for interactions between dietary factor quintile categories and BMI on HOMA-IR by introducing a multiplicative term for overweight and the median nutrient intake in each model.

RESULTS — The 2,834 participants (1,290 men and 1,544 women) in this study ranged in age from 26 to 82 years; their mean age was 54 ± 9.8 years. The characteristics of the study population across quintile categories of HOMA-IR are presented in Table 1. Higher quintile categories of HOMA-IR included a greater proportion of men, older participants, those with hypertension, glucose intolerances, and undiagnosed diabetes. In addition, BMI, waist-to-hip ratio, and concentrations of fasting insulin were all higher with increasing HOMA-IR. The prevalence of alcohol use, current smoking, and estrogen replacement therapy among postmenopausal women decreased across quintiles of HOMA-IR, whereas physical activity remained constant. HOMA-IR clearly captures characteristics of the metabolic syndrome, with 59% of individuals in the highest quintile category of HOMA-IR with the metabolic syndrome. Only 3% of those participants with a BMI <25 kg/m^2 had the metabolic syndrome compared with 32% of the participants with a BMI ≥25 kg/m^2.

The multivariate-adjusted analyses for intakes of carbohydrates, dietary fiber, fiber source, glycemic index and load, and whole and refined grains are shown in Table 2. After adjustment for potential confounding variables, intakes of total dietary fiber, cereal fiber, fruit fiber, and whole grains were associated with lower HOMA-IR. The association between fruit and cereal fiber and HOMA-IR remained significant after mutual adjustment for each other. The association between whole-grain intake and HOMA-IR was attenuated and no longer remained significant after adjustment for cereal (lowest versus highest quintile, 6.8 vs. 6.7, $P = 0.34$ for trend) and fruit (6.8 vs.6.6, $P = 0.09$) fiber. However, cereal fiber remained significantly associated with HOMA-IR after adjustment for whole grains (6.9 vs. 6.5, $P = 0.003$). As the glycemic index increased, the multivariate-adjusted HOMA-IR increased from 6.4 in the lowest to 7.0 in the highest quintile category of glycemic index. A similar increase in HOMA-IR was observed with increasing dietary glycemic load, and these associations remained significant after further adjustment of the model for cereal fiber and whole-grain in-

Table 1—*Characteristics of subjects in the Framingham Offspring Cohort across quintile categories of HOMA-IR insulin resistance*

	Quintile categories					
HOMA-IR	<4.83	4.84–5.71	5.72–6.79	6.79–8.64	>8.64	*P* value*
Participants (*n*)	568	565	567	568	565	
Characteristics						
Women (%)	71	64	51	46	41	<0.0001
Age (years)	52	53	54	55	56	<0.0001
BMI (kg/m^2)	24.2	25.4	26.6	28.4	31.3	<0.0001
Physical activity score	34.6	34.7	34.8	35.2	34.5	0.74
Alcohol use (%)	78	75	76	73	67	<0.0001
Current cigarette smoking (%)	21	20	19	20	16	0.07
Estrogen replacement therapy (women only) (%)	18	21	18	14	9	<0.001
Normal glucose tolerance (%)†	94	91	90	77	50	<0.0001
Impaired fasting glucose/impaired glucose tolerance (%)†	6	8	9	20	33	<0.0001
Undiagnosed diabetes (%)†	0	1	1	3	17	<0.0001
Fasting serum insulin (μU/ml)	1.9	4.3	6.8	10.0	19.3	<0.0001
Insulin resistance phenotype						
Abnormal waist circumference (%)‡	13	25	31	50	72	<0.0001
Low HDL cholesterol (%)§	19	24	35	45	64	<0.0001
Elevated triglycerides (%)‖	12	19	29	41	61	<0.0001
Elevated fasting glucose (%)¶	0	2	2	11	38	<0.0001
Abnormal blood pressure (%)#	10	14	18	29	42	<0.0001
Metabolic syndrome ≥3 components (%)	2	7	11	28	59	<0.0001

Data are means unless otherwise indicated. Geometric means are given for levels of fasting insulin. **P* values for trend for continuous variables or Mantel-Haenzel χ^2 for categorical variables across quintiles of HOMA-IR. †Previously undiagnosed diabetes was defined as a fasting plasma glucose concentration ≥126 mg/dl (7.0 mmol/l) or a 2-h postchallenge glucose concentration ≥200 mg/dl (11.1 mmol/l). Impaired fasting glucose was defined as a fasting plasma glucose concentration of 110–126 mg/dl (6.1–7.0 mmol/l). Impaired glucose tolerance was defined as a 2-h postchallenge glucose concentration of 140–200 mg/dl (11.1 mmol/l). Normal glucose tolerance was defined as a fasting glucose concentration of <110 mg/dl (6.1 mmol/l) and a 2-h postchallange glucose concentration of <140 mg/dl (7.8 mmol/l). ‡Waist circumference >40 inches in men and >35 inches in women. §Serum HDL cholesterol <40 mg/dl or <50 mg/dl in men and women, respectively. ‖Triglyceride level ≥150 mg/dl. #Blood pressure of at least 130/85 mmHg or taking hypertensive medication. ¶Fasting plasma glucose concentration ≥6.1 mmol/l.

takes. Furthermore, the associations between whole-grain and cereal fiber and HOMA-IR were independent of glycemic index.

Dietary intakes of total carbohydrate, refined grains, and fiber from vegetables and legumes were not associated with improved HOMA-IR. The lack of an association between vegetable fiber and HOMA-IR did not change after excluding potatoes, a high glycemic index food source. The findings in Table 2 were essentially identical when analyses were repeated using fasting insulin, rather than the HOMA-IR, as a measure of insulin resistance.

Given that obesity has a strong effect on insulin concentrations, obesity may alter the relation between the carbohydrate source and insulin concentration. When a continuous interaction term between BMI and dietary factors was included in the model, the inverse relation between HOMA-IR and dietary fiber, cereal fiber, and whole-grain intake became stronger as BMI increased (*P* for interactions <0.05). However, when specific BMI cut points of 25 and 30 were applied to the models, a significant interaction was only found between HOMA-IR and whole-grain intake ($P = 0.04$). The inverse association between whole grain and HOMA-IR was much stronger for those with a BMI ≥30 kg/m^2 (9.8 vs. 8.6, $P = 0.02$ for trend) compared with those with a BMI <30 kg/m^2 (6.1 vs. 6.1, $P = 0.57$ for trend).

The relation between the prevalence of metabolic syndrome and intakes of carbohydrates, dietary fiber, fiber source, glycemic index and load, and whole and refined grains are shown in Table 2. Cereal fiber and whole-grain intakes were significantly inversely associated with the metabolic syndrome after adjustment for sex, age, cigarette dose, total energy intake, saturated and polyunsaturated fat, alcohol intake, multivitamin use, and physical activity. A substantial reduction in the prevalence odds of metabolic syndrome was observed with increasing cereal fiber intake and whole-grain intake. The reduction in odds was 38% (OR 0.62; 95% CI 0.45–0.86) and 33% (0.67; 0.48–0.91) for the lowest relative to the highest category of cereal fiber and whole-grain intake, respectively. These associations remained significant after adjustment for glycemic index. The inverse association between whole-grain intake and metabolic syndrome was largely explained by cereal fiber, and a significant association was no longer observed between whole-grain intake and the risk of metabolic syndrome after adjusting for cereal fiber (0.77; 0.55–1.09; $P = 0.20$). The glycemic index demonstrated a significant positive association with prevalence of metabolic syndrome with 41% increased risk in highest compared with lowest category (1.41; 1.04–1.91; $P =$

Table 2—*Multivariate adjusted geometric mean HOMA-IR and prevalence OR of metabolic syndrome across quintiles of carbohydrate-related dietary factors*

	Quintiles of carbohydrate source§					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
n	566	567	567	567	567	
Total carbohydrate						
Median intake (g/day)	179	207	226	244	272	
Range of intake (g/day)	<194	195–217	218–234	235–257	>258	
Mean HOMA-IR*	6.8 (6.5–7.1)	6.7 (6.5–7.0)	6.6 (6.3–6.8)	6.7 (6.5–7.0)	6.9 (6.6–7.2)	0.52
OR IRS†	1.00	0.90 (0.65–1.23)	0.76 (0.53–1.09)	1.03 (0.69–1.52)	0.92 (0.57–1.49)	0.97
Dietary fiber						
Median intake (g/day)	11.6	14.9	17.4	20.1	25.5	
Range of intake (g/day)	<13.5	13.6–16.0	16.1–18.6	18.6–22.1	>22.2	
Mean HOMA-IR	7.0 (6.8–7.3)	6.7 (6.5–7.0)	6.7 (6.5–7.0)	6.7 (6.5–7.0)	6.4 (6.1–6.6)	<0.001
OR IRS	1.0	0.81 (0.61–1.09)	0.88 (0.65–1.19)	0.81 (0.59–1.07)	0.73 (0.51–1.03)	0.11
Cereal fiber						
Median intake (g/day)	2.6	3.7	4.6	5.8	8.0	
Range of intake (g/day)	<3.1	3.2–4.2	4.3–5.1	5.2–6.7	>6.8	
Mean HOMA-IR	6.8 (6.5–7.0)	6.9 (6.7–7.2)	6.8 (6.6–7.0)	6.6 (6.4–6.9)	6.5 (6.3–6.8)	0.02
OR IRS	1.0	0.87 (0.65–1.16)	0.88 (0.66–1.18)	0.74 (0.54–1.00)	0.62 (0.45–0.86)	0.002
Fruit fiber						
Median intake (g/day)	0.7	1.7	2.8	4.2	5.8	
Range of intake (g/day)	<1.2	1.2–2.2	2.2–3.4	3.4–5.1	>5.2	
Mean HOMA-IR	7.0 (6.7–7.2)	6.8 (6.5–7.0)	6.8 (6.5–7.0)	6.6 (6.4–6.8)	6.5 (6.2–6.7)	<0.001
OR IRS	1.0	1.07 (0.80–1.43)	0.74 (0.55–1.01)	0.89 (0.65–1.21)	0.88 (0.64–1.22)	0.36
Vegetable fiber						
Median intake (g/day)	2.4	3.7	4.8	6.1	8.4	
Range of intake (g/day)	<3.1	3.1–4.2	4.2–5.3	5.3–6.9	>6.9	
Mean HOMA-IR	6.7 (6.4–6.9)	6.9 (6.6–7.2)	6.7 (6.4–6.9)	6.8 (6.5–7.0)	6.8 (6.5–7.0)	0.64
OR IRS	1.0	1.08 (0.81–1.45)	1.04 (0.77–1.40)	1.00 (0.74–1.36)	1.15 (0.84–1.57)	0.51
Legume fiber						
Median intake (g/day)	0.23	0.69	1.0	1.4	2.5	
Range of intake (g/day)	<0.5	0.6–0.8	0.8–1.2	1.2–1.8	>1.8	
Mean HOMA-IR	6.8 (6.5–7.0)	6.8 (6.6–7.1)	6.8 (6.5–7.0)	6.7 (6.5–6.9)	6.7 (6.5–7.0)	0.58
OR IRS	1.00	0.91 (0.68–1.23)	0.90 (0.67–1.20)	1.00 (0.75–1.34)	0.96 (0.72–1.29)	0.98
Glycemic index‡						
Median intake (per day)	72	76	78	81	84	
Range of intake (per day)	<74	74–77	77–79	79–82	82–98	
Mean HOMA-IR	6.4 (6.2–6.7)	6.7 (6.5–7.0)	6.8 (6.5–7.0)	6.8 (6.5–7.0)	7.0 (6.7–7.2)	<0.001
OR IRS	1.00	1.17 (0.86–1.59)	1.21 (0.89–1.64)	1.19 (0.88–1.62)	1.41 (1.04–1.91)	0.04
Glycemic load						
Median intake (g/day)	131	158.6	174.5	190.8	220.3	
Range of intake (g/day)	<147.0	147.1–166.3	166.4–182.3	182.3–202.1	>202.2	
Mean HOMA-IR	6.7 (6.4–7.0)	6.5 (6.2–6.7)	6.7 (6.5–7.0)	6.8 (6.6–7.1)	7.0 (6.7–7.3)	0.03
OR IRS	1.00	0.74 (0.53–1.02)	0.71 (0.50–1.00)	1.00 (0.69–1.46)	0.82 (0.52–1.27)	0.74
Whole grains						
Median intake (serving/week)	0.90	3.5	6.4	9.5	20.4	
Range of intake (serving/week)	<1.5	1.9–4.4	4.5–7.5	7.9–12.9	>13	
Mean HOMA-IR	6.8 (6.6–7.1)	6.9 (6.6–7.1)	6.7 (6.5–7.0)	6.6 (6.4–6.8)	6.6 (6.4–6.9)	0.05
OR IRS	1.0	0.81 (0.60–1.08)	1.09 (0.82–1.44)	0.82 (0.61–1.10)	0.67 (0.48–0.91)	0.01
Refined grains						
Median intake (serving/week)	6.9	11.9	16.7	23.7	38.8	
Range of intake (serving/week)	<9.7	9.7–13.9	14.0–19.8	19.9–29.3	>29.3	
Mean HOMA-IR	6.8 (6.6–7.1)	6.6 (6.4–6.9)	6.8 (6.6–7.1)	6.8 (6.5–7.0)	6.7 (6.5–7.0)	0.81
OR IRS	1.0	1.13 (0.84–1.52)	1.01 (0.74–1.38)	1.03 (0.75–1.42)	0.76 (0.53–1.09)	0.05

*Geometric mean HOMA-IR adjusted for sex, age, BMI, waist-to-hip ratio, cigarette dose, total energy intake, alcohol intake, percentage saturated fat, percentage polyunsaturated fat, multivitamin use, physical activity, and treatment for blood pressure. Results were essentially the same when the analysis was repeated using fasting insulin rather than the HOMA-IR. †Adjusted for sex, age, cigarette dose, total energy intake, alcohol intake, percentage saturated fat, percentage polyunsaturated fat, multivitamin use, and physical activity. ‡Values are based on a white bread standard. §Quintile categories are based on energy-adjusted values using the residual method, with the exception of whole and refined grains. IRS, insulin resistance syndrome.

0.04), whereas the glycemic load was not significantly associated with prevalence of the metabolic syndrome. The association between glycemic load and prevalence of the syndrome did not change after adjustment for cereal fiber.

CONCLUSIONS— Our findings suggest that higher intakes of whole-grain foods, dietary fiber, cereal, and fruit fiber

and diets with a lower glycemic index and glycemic load are associated with lower insulin resistance as determined using the HOMA method. Insulin resistance is a common feature of and a possible contributing factor to the metabolic syndrome. However, after considering several aspects of carbohydrate nutrition, only whole-grain, cereal fiber, and glycemic index intakes were associated with the prevalence of the metabolic syndrome. The prevalence of the metabolic syndrome was 38 and 33% less in the highest relative to the lowest categories of cereal fiber and whole-grain intake, respectively. A high dietary glycemic index was positively associated with the metabolic syndrome; participants with the highest glycemic index intakes were ~40% more likely to have the metabolic syndrome than were participants with the lowest dietary glycemic index. To our knowledge, this is the first observational study to examine associations between different aspects of carbohydrate nutrition and prevalence of the metabolic syndrome.

Our data confirm other observational studies that diets rich in whole-grain foods are associated with lower insulin concentrations (17,50). One intervention study further supports the hypothesis that diets rich in whole-grain foods improve insulin sensitivity. Pereira et al. (20) found that insulin sensitivity, as measured by the euglycemic-hyperinsulinemic clamp, improved after 6 weeks on a whole-grain diet compared with a refined grain diet, independent of change in body weight in 11 overweight subjects. Improved insulin sensitivity associated with high whole-grain diets appear in part to be attributed to the high dietary or cereal fiber content of whole-grain foods. Chandalia et al. (51) found that increasing dietary fiber intake for 6 weeks reduced glucose and insulin concentrations in type 2 diabetic patients. A recent controlled metabolic trial found that supplementing a high-carbohydrate diet with soluble fiber improved blood lipid and lipoprotein concentrations and improved glycemic control in pre-diabetic patients with several metabolic abnormalities that define the metabolic syndrome (52). In contrast, other intervention studies have found no effect on insulin sensitivity with consumption of high-fiber or whole-grain foods, particularly among older individuals (19,21,22). The interpretation of these intervention studies is complicated by the varied patient populations (e.g., obese nondiabetic subjects, type 2 diabetic subjects), the different age ranges studied, and the short-term nature of most of these interventions. Whereas some intervention studies may have missed potential effects because of the short duration on diets, it is also not known whether observed effects in these short-term interventions would remain over time.

In the present study, fiber from cereals was inversely related with the prevalence of the metabolic syndrome, whereas fiber from fruit, vegetable, and legumes was not. Observational data consistently indicate a greater protective role of fiber from cereal than from other sources in the development of type 2 diabetes (30–33,53). Adjustment for cereal fiber considerably weakened the associations between whole-grain intake and both HOMA-IR and metabolic syndrome, suggesting that the relation of whole grain may be due in part to cereal fiber or to factors related to cereal fiber intake. Collectively, these data suggest a greater role for cereal fiber rather than other fiber sources in the development of insulin resistance and the metabolic syndrome. However, further experimental and longitudinal studies are needed to examine if fiber source is differentially related to change in metabolic risk factors and the incidence of the metabolic syndrome.

Magnesium is another component of whole grains that may improve insulin sensitivity. Low magnesium status has been associated with decreased insulin sensitivity (54), metabolic syndrome (55), and increased risk of type 2 diabetes (30–32). Clinical studies further support a role for magnesium by demonstrating that supplementation with magnesium improved insulin sensitivity in type 2 diabetic patients (56,57). We previously found that the relationship between whole-grain intake and fasting insulin was mediated, in part, by magnesium (18).

Although the lack of a formal definition for the metabolic syndrome previously hampered investigation into the role of diet in the etiology of this condition, observational studies have examined the role of carbohydrate-related dietary factors and individual metabolic risk factors associated with this syndrome. Wirfalt et al. (8) found that a refined bread food pattern was associated with hyperinsulinemia in women, whereas a high-fiber bread food pattern was associated with lower central obesity and dyslipidemia in men. In the Framingham Offspring Cohort, we found that whole-grain intake was favorably associated with several metabolic risk factors of this syndrome, including central obesity, insulin sensitivity, and dyslipidemia (18).

We found no evidence for an effect of total carbohydrate intake on insulin resistance or prevalence of the metabolic syndrome. Other observational studies have found that total carbohydrate intake is unrelated to fasting insulin (14) and the risk of developing type 2 diabetes (30–32). Because total carbohydrate intake fails to take into account the glycemic effect of different carbohydrate foods, the glycemic index has been proposed to classify carbohydrate-containing foods. A high dietary glycemic index was positively associated with both HOMA-IR and the prevalence of the metabolic syndrome. This is not unexpected given that high glycemic index foods produce higher postprandial blood glucose concentrations than those with a low glycemic index, which over the long term will generate a higher insulin demand (23,27). Two intervention studies have found that after 4 weeks on a low glycemic index diet, insulin sensitivity was improved in both normal (58) patients and those with coronary heart disease (59). More recently, a high glycemic index diet was associated with increased postprandial insulin resistance among overweight middle-aged men (60). Although our data provide evidence that a high glycemic index diet is associated with a greater risk of metabolic syndrome, they are insufficient to examine the potential mechanisms by which a high glycemic index diet might affect risk of metabolic syndrome.

In our study, glycemic load was highly correlated with total carbohydrate intake ($r = 0.92$). Thereby, it is likely that the inverse association between glycemic load and HOMA-IR was largely explained by the glycemic index part of the equation. Based on regression analyses, Brand-Miller and Holt (61) reported that carbohydrate intake alone explained 68% of variation in glycemic load compared with 49% explained by the glycemic index. In the present study, a higher prevalence of the metabolic syndrome was found with a high dietary glycemic index, but no association was found with the gly-

cemic load. Furthermore, no difference was found in the association between glycemic load and prevalence to the metabolic syndrome after adjustment for cereal fiber intake. Stevens et al. (33) reported a marginal significant association between dietary glycemic load and diabetes risk after adjustment for cereal fiber, supporting other observational data that found that diets with a high glycemic load and a low cereal fiber content increase risk of type 2 diabetes (30,31).

The FFQ has many limitations with respect to determining carbohydrate-related dietary intakes that may have caused some misclassification of subjects, in particular with respect to fiber and whole-grain intake. For example, the assumption that dark breads are largely made from whole-grain flour would lead to measurement error, thereby attenuating associations with cereal fiber and whole-grain intake. Despite this potential misclassification, significant associations among these carbohydrate-related dietary factors, HOMA-IR, and the metabolic syndrome were observed. Furthermore, the FFQ reportedly underestimates refined grain intake compared with diet records, and this may explain in part the lack of association between refined grain intake, insulin resistance, and the metabolic syndrome (62). Interpretation of the findings from the present study is subject to some additional caveats. Although the apparent protective association with whole-grain and cereal fiber intakes persisted after adjustment for lifestyle and dietary factors associated with a healthier lifestyle, we cannot rule out residual confounding. Another potential limitation is the use of a single measure of plasma insulin and glucose to calculated HOMA-IR. At the population level, HOMA-IR can be used as a surrogate measure of insulin resistance to identify those individuals who are most insulin resistant. It is perhaps less useful on an individual basis, given the modest intraindividual variability in insulin and glucose levels. Furthermore, if β-cell function is failing (i.e., among individuals with late impaired glucose tolerance, early diabetes, or established diabetes), true insulin resistance may be underestimated due to fasting insulin levels that are pathologically low given ambient glucose levels. However, the findings of the present study were not altered after removing those with newly diagnosed diabetes, and from the outset, we excluded individuals with established diabetes. Finally, the cross-sectional nature of this study precludes any causal inferences, therefore, more observational and experimental studies are needed before any firm conclusions can be drawn with regard to the influence of different aspects of carbohydrate nutrition, insulin resistance, and the metabolic syndrome.

No specific dietary recommendations have been advocated by health agencies for treatment of insulin resistance or the metabolic syndrome. A high cereal fiber content and low glycemic index are inherent attributes of most whole-grain foods. Therefore, in terms of implementing dietary change, emphases should be place on increasing dietary intakes of whole-grain foods. Given that the metabolic syndrome is an identifiable and potentially modifiable risk state for both type 2 diabetes and cardiovascular disease, increasing whole-grain cereal fiber may reduce the potential untoward effects of carbohydrate on risk of these diseases. However, more longitudinal studies are required to ascertain which aspects of carbohydrate nutrition are linked to development of the metabolic syndrome milieu.

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