

Dietary Glycemic Index and Glycemic Load, Carbohydrate and Fiber Intake, and Measures of Insulin Sensitivity, Secretion, and Adiposity in the Insulin Resistance Atherosclerosis Study

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OBJECTIVE — We studied the association of digestible carbohydrates, fiber intake, glycemic index, and glycemic load with insulin sensitivity (S_1), fasting insulin, acute insulin response (AIR), disposition index, BMI, and waist circumference.

RESEARCH DESIGN AND METHODS — Data on 979 adults with normal (67%) and impaired (33%) glucose tolerance from the Insulin Resistance Atherosclerosis Study (1992–1994) were analyzed. Usual dietary intake was assessed via a 114-item interviewer-administered food frequency questionnaire from which nutrient intakes were estimated. Published glycemic index values were assigned to food items and average dietary glycemic index and glycemic load calculated per subject. S_1 and AIR were determined by frequently sampled intravenous glucose tolerance test. Disposition index was calculated by multiplying S_1 with AIR. Multiple linear regression modeling was employed.

RESULTS — No association was observed between glycemic index and S_1 , fasting insulin, AIR, disposition index, BMI, or waist circumference after adjustment for demographic characteristics or family history of diabetes, energy expenditure, and smoking. Associations observed for digestible carbohydrates and glycemic load, respectively, with S_1 , insulin secretion, and adiposity (adjusted for demographics and main confounders) were entirely explained by energy intake. In contrast, fiber was associated positively with S_1 and disposition index and inversely with fasting insulin, BMI, and waist circumference but not with AIR.

CONCLUSION — Carbohydrates as reflected in glycemic index and glycemic load may not be related to measures of insulin sensitivity, insulin secretion, and adiposity. Fiber intake may not only have beneficial effects on insulin sensitivity and adiposity, but also on pancreatic functionality.

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Abbreviations: AIR, acute insulin response; FFQ, food frequency questionnaire; FSIPT, frequently sampled intravenous glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; IRAS, Insulin Resistance Atherosclerosis Study.

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

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See accompanying editorial, p. 2978.

In the U.S., 52% of energy intake is consumed via carbohydrates (1). Carbohydrate-containing foods vary systematically with respect to their effects on postprandial glucose and insulin response, these differences being quantified in the glycemic index (2). Foods with higher glycemic index values elicit by definition an increased acute glucose and insulin response (3). Extending this concept to whole meals or the total diet, it is conceivable that the glycemic index characteristics of a diet may have an impact on glucose metabolism, including effects on insulin secretion and eventual insulin resistance.

The glycemic load is a concept mathematically derived from both glycemic index and the amount of carbohydrate intake and intended to represent the overall glycemic effect of a diet (4). The glycemic load has recently been shown to have physiologic meaning, as increases in dietary glycemic load resulted in predictable increases in glycemia and insulinemia (5). It is therefore informative to evaluate the concepts of glycemic index and glycemic load in parallel. In addition, digestible carbohydrates and fiber support understanding some of the functional attributes of glycemic index and glycemic load.

High-glycemic index diets have been linked, albeit inconsistently, with higher insulin levels (6,7) and an elevated risk of developing diabetes (4,8,9). No epidemiologic data, to our knowledge, exist on the relation of glycemic index to direct measures of insulin sensitivity (S_1) and insulin secretion, both of which are involved in the pathogenesis of diabetes. The disposition index is based on the hyperbolic relation of insulin secretion to S_1 and expresses the ability of the pancreatic β -cell to compensate for changes in S_1 by increasing insulin secretion (10–12). The purpose of our study was to evaluate the relation of dietary glycemic index, glycemic load, and carbohydrate and fiber intake to measures of insulin sensitivity, insulin secretion, and adiposity in the In-

ulin Resistance Atherosclerosis Study (IRAS).

RESEARCH DESIGN AND METHODS

Subject selection

The design of IRAS has been described in detail elsewhere (11). More than 1,600 participants were recruited at four clinical centers between 1992 and 1994 for the IRAS baseline exam. The goal was to obtain nearly equal representation of participants across glucose tolerance status (normal glucose tolerance, impaired glucose tolerance, and non-insulin-taking type 2 diabetes), ethnicity (African American, Hispanic, and non-Hispanic white), sex, and age (40–49 years, 50–59 years, and 60–69 years). All participants provided written informed consent as approved by their respective field center's institutional review board.

Data collection

IRAS required a two-visit protocol, the first to determine glucose tolerance status and the second to measure S_1 . Participants were asked to fast for 12 h before each of the two visits, abstain from heavy exercise and alcohol for 24 h, and refrain from smoking the morning of the visit. A 2-h, 75-g oral glucose tolerance test (Orangedex; Custom Laboratories, Baltimore, MD) was performed during the first visit, and World Health Organization criteria (13) were used to assign glucose tolerance status. Individuals currently taking oral hypoglycemic medications were classified as having type 2 diabetes regardless of the results of the oral glucose tolerance test.

S_1 and acute insulin response (AIR) were assessed using a 12-sample, insulin-enhanced, frequently sampled intravenous glucose tolerance test (FSIGT) (14,15) with minimal model analysis (16). Two modifications of the protocol were used: injection of insulin rather than tolbutamide (17) and a reduced number of plasma samples (12 rather than 30) (18). S_1 was calculated by mathematical modeling methods; the time course of plasma glucose was fit using nonlinear least squares methods with the plasma insulin values as a known input to the system (according to the method known as MINMOD, which was developed by Richard N. Bergman, Ph.D., in 1986) (19). AIR was calculated based on insulin levels through the 8-min blood samples before insulin infusion. Fasting plasma insulin

was determined by radioimmunoassay (20).

Anthropometric measures were taken with the participant in lightweight clothing with shoes removed. Height and weight were measured in duplicate and recorded to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight (in kilograms) divided by the square of height (in meters) (2). Minimum waist circumference was measured using a flexible steel tape measure at the natural indentation or at a level midway between the iliac crest and the lower edge of the rib cage if no natural indentation was visible. Waist was recorded to the nearest 0.5 cm, and the mean of two measures within 1 cm of each other was used. Total energy expenditure was estimated based on an interviewer-administered, 1-year activity recall that incorporated activities current among IRAS participants, the details of which have been described (21).

Usual intake of diet was assessed by interview using a 1-year, semiquantitative, 114-item food frequency interview modified from the National Cancer Institute-Health History and Habits Questionnaire to include regional and ethnic food choices across the four clinical centers (22). Participants were asked to recall intake of foods and beverages over the past year. Validity and reproducibility of the IRAS food frequency questionnaire (FFQ) has been demonstrated (22). Interviewers were centrally trained and certified, and audiotapes of interviews were reviewed quarterly. Alcohol intake was evaluated separately using a frequency approach with additional questions about recent use and average lifetime use. Subjects were asked about their usual consumption of wine, beer, mixed drinks/mixers, and liquors. Frequency of consumption was expressed as servings per day standardized to a medium serving size.

Estimation of nutrients, glycemic index, and glycemic load

Daily nutrient and energy intake was estimated from the FFQ and the alcohol questionnaire using an expanded nutrient database (HHHQ-DIETSYS analysis software, version 3.0; National Cancer Institute, Bethesda, MD, 1993). All analyses of carbohydrates are based on digestible carbohydrates, which were calculated by subtracting fiber intake from total carbohydrate intake. We chose this approach to be in line with the approach to testing of glycemic index values of foods, where

measurements are based only on the carbohydrates that are absorbable, i.e., the digestible fraction (2,23).

We assigned mean glycemic index values based on the white bread standard from published data (23) and other available resources (T.M.S.W., personal communication) to all 114 FFQ line items plus three items assessed in the exam I interview on alcohol consumption (beer, wine, liquors) plus several additional foods (that were identified in open-ended questions as being consumed more than once per week). Details of the glycemic index and glycemic load estimation procedures in our study have been published (24).

Average dietary glycemic index was computed by summing the products of the digestible carbohydrate content per serving for each item, multiplied by the average number of servings of that food per day, multiplied by its glycemic index, all divided by the total amount of digestible carbohydrate daily intake (25). The average dietary glycemic load was computed like the glycemic index but by dividing by 100 instead of the total digestible carbohydrate intake. Finally, the average dietary glycemic index and glycemic load values were converted to the glucose = 100 scale by multiplication with the factor 0.7.

Statistical analysis

Analyses were limited to 1,087 individuals with normal (66%) or impaired (34%) glucose tolerance, excluding individuals with diabetes at baseline because this might have altered their dietary behavior. We subsequently excluded 16 participants due to missing data on glycemic index or glycemic load, 79 with missing values for S_1 , 2 with missing fasting insulin, 4 with missing anthropometric data, and another 6 subjects with missing covariates. After model diagnostics, one outlier was excluded. This left 979 participants with complete data for analysis. Because the distribution of S_1 is skewed right and 58 individuals had an S_1 value of 0, we calculated the natural logarithm (log) after adding a constant 1 since the log of 0 cannot be taken. AIR and fasting insulin were also log transformed. For AIR, so that all values were positive before transformation, a constant of 20 was added. Given these logarithmic transformations, the disposition index, typically calculated as the product of AIR and S_1 , was created as the sum of log (AIR + 20) and log ($S_1 + 1$). With these transformations, the

Table 1—Characteristics of participants with normal or impaired glucose tolerance in IRAS Exam I, 1992–1994 (n = 979)

Characteristics	Value
Population characteristics	
Age (years)	54.8 ± 8.5
Sex (female)	54.9
Ethnicity	
Non-Hispanic white	39.8
Hispanic	34.2
African American	26.0
Impaired glucose tolerance	32.8
Current smoking	16.2
Family history of diabetes (first degree relative)	39.6
Total energy expenditure (kcal · kg ⁻¹ · year ⁻¹)	14,841.7 ± 2,758.5
Dietary characteristics	
Glycemic index	58.0 ± 4.0
Glycemic load (g/day)	128.3 ± 55.9
Carbohydrates (g/day)	220.5 ± 92.4
Fiber (g/day)	16.9 ± 7.9
Total energy intake (kJ/day)	8,224.1 ± 3,481.1
Physiological and anthropometric characteristics	
Insulin sensitivity (min ⁻¹ · μU ⁻¹ · mL ⁻¹ · 10 ⁻⁴)	1.72 ± 0.04*
Fasting insulin (pmol/l)	76.7 ± 1.9*
AIR (μU · ml ⁻¹ · min ⁻¹)	62.3 ± 1.7*
Disposition index	223.6 ± 8.9*
BMI (kg/m ²)	28.4 ± 5.6
Waist circumference (cm)	90.6 ± 12.8

Data are means ± SD or %. *Values shown are geometric means and SEs derived by the Delta method.

distributions of the resulting residual values for the models we fit approached normality, based on visual inspection of residual plots and normal probability plots. No transformations were necessary for BMI and waist. To evaluate the relation of the dietary exposures with measures of S_1 and adiposity, we conducted linear regression analyses because all variables under study were continuous in nature and no threshold effects were observed in descriptive analyses. Results were presented as β coefficients and P values of the carbohydrate-related exposure variables. To evaluate our results in a manner directly comparable to previous work, we categorized the IRAS population into quintiles of carbohydrate intake, fiber intake, glycemic index, and glycemic load and estimated mean levels of S_1 and adiposity within those categories. Results of the categorical approach were entirely consistent with the linear approach and hence not shown.

We evaluated the impact of potential effect modifiers, including age-groups, ethnicity, sex, family history of diabetes, BMI (in categories), and glucose tolerance status by conducting stratified analyses and comparing the size and direction of

the effect estimates. In addition, two-way interactions between exposures and effect-modifiers were examined. There was no evidence for significant interaction with the factors listed above, including level of overweight. The associations of carbohydrate-related exposures were first described at the unadjusted level and subsequently adjusted for confounders that were associated at the $P < 0.05$ level. The confounders in the most parsimonious models were age, sex, ethnicity/clinic, family history of diabetes, current smoking, and total energy expenditure (21). Education effects were not significant, and thus this variable was omitted from final models. Because we explicitly wanted to evaluate the contribution of demographic and lifestyle variables to the associations under study, we present this model second. In a third and final step, we additionally adjusted for total energy intake using the energy partition method, which controls for the noncarbohydrate contribution of correlated foods (26). We chose this approach over other methods because in the categorical analyses, the ensuing categories retained information on amount of total dietary intake, allowing us to parse out the contribution of

carbohydrates from noncarbohydrate sources such as protein and fat. Subsequently, we repeated this analysis using the residual method for energy adjustment (27) to be able to compare our results directly with other studies. Our conclusions were unchanged. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS— Descriptive characteristics of the IRAS population are shown in Table 1. The IRAS population consumed an average of 220 g/day of digestible carbohydrates and 17 g/day of fiber. The average glycemic index and glycemic load were 58 and 128 g/day, respectively. A higher S_1 value expresses increased insulin sensitivity, while a higher fasting insulin implies increased insulin resistance. A higher AIR indicates greater insulin secretion in response to glucose, and a higher disposition index implies increasing pancreatic functionality.

Table 2 shows the relation of the total intake of digestible carbohydrates, fiber, glycemic index, and glycemic load to measures of S_1 , insulin secretion, and adiposity. A significant positive linear relationship was observed between carbohydrate intake and levels of fasting insulin, BMI, and waist circumference both in unadjusted models and after adjustment for age, sex, ethnicity/clinic, family history of diabetes, current smoking, and total energy expenditure. Consistent with this finding, an inverse association was observed between carbohydrate intake and S_1 . However, adjustment for total energy intake (from noncarbohydrate sources) completely explained the associations, a finding replicated using the residual method. The crude association of digestible carbohydrates and AIR was explained entirely by demographic and lifestyle correlates. After adjustment, no association was observed with either AIR or disposition index. When the final models were additionally adjusted for fiber intake, a small but significant positive association of digestible carbohydrates with fasting insulin and waist circumference emerged, as did an inverse association with S_1 (data not shown). For BMI, AIR, and disposition index, results remained unchanged.

The association of dietary fiber intake and measures of S_1 , insulin secretion, and adiposity are shown in the second column of Table 2. Fiber was significantly associated with S_1 , fasting insulin, BMI, and waist circumference after full multivariate

Table 2—Association of digestible carbohydrate intake, fiber, glycemic index, and glycemic load with measures of S_I , insulin secretion, and adiposity, IRAS Exam I, 1992–1994 (n = 979)

Model	Digestible carbohydrate		Fiber		Glycemic index		Glycemic load	
	β (SE)*	P	β (SE)*	P	β (SE)*	P	β (SE)*	P
S_I ($\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{mL}^{-1} \cdot 10^{-4}$)								
1	-0.0048 (0.0019)	0.010	-0.0068 (0.0217)	0.754	-0.0048 (0.0030)	0.111	-0.0058 (0.0021)	0.007
2	-0.0039 (0.0020)	0.055	0.0288 (0.0229)	0.210	-0.0048 (0.0033)	0.138	-0.0051 (0.0024)	0.032
3	0.0002 (0.0028)	0.942	0.1250 (0.0306)†	<0.001	-0.0034 (0.0033)	0.296	-0.0005 (0.0035)	0.881
Fasting insulin (pmol/ml)								
1	0.0097 (0.0021)	<0.001	0.0641 (0.0253)	0.012	0.0047 (0.0035)	0.181	0.0113 (0.0025)	<0.001
2	0.0086 (0.0024)	<0.001	0.0327 (0.0271)	0.227	0.0034 (0.0039)	0.378	0.0105 (0.0028)	<0.001
3	0.0030 (0.0033)	0.360	-0.0815 (0.0361)†	0.024	0.0008 (0.0039)	0.842	0.0038 (0.0041)	0.348
AIR ($\mu\text{U} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$)								
1	0.0049 (0.0024)	0.041	0.0056 (0.0279)	0.842	0.0119 (0.0038)	0.002	0.0067 (0.0027)	0.015
2	0.0009 (0.0026)	0.736	-0.0078 (0.0291)	0.789	0.0013 (0.0041)	0.760	0.0011 (0.0030)	0.709
3	-0.0003 (0.0036)	0.944	-0.0317 (0.0393)†	0.420	0.0009 (0.0042)	0.827	-0.0002 (0.0045)	0.968
Disposition index								
1	0.0001 (0.0027)	0.971	-0.0013 (0.0319)	0.969	0.0071 (0.0044)	0.107	0.0008 (0.0032)	0.790
2	-0.0030 (0.0029)	0.310	0.0210 (0.0336)	0.533	-0.0036 (0.0048)	0.456	-0.0040 (0.0035)	0.256
3	-0.00005 (0.0042)	0.990	0.0933 (0.0452)†	0.039	-0.0025 (0.0048)	0.602	-0.0007 (0.0051)	0.891
BMI (kg/m^2)								
1	0.0618 (0.0194)	0.001	0.3851 (0.2273)	0.091	-0.0063 (0.0315)	0.841	0.0676 (0.0224)	0.003
2	0.0773 (0.0211)	<0.001	0.3415 (0.2416)	0.158	0.0279 (0.0344)	0.418	0.0947 (0.0250)	<0.001
3	0.0004 (0.0295)	0.990	-0.7954 (0.3212)†	0.013	-0.0009 (0.0344)	0.978	-0.0006 (0.0364)	0.988
Waist (cm)								
1	0.2880 (0.0433)	<0.001	1.8627 (0.5148)	<0.001	0.2650 (0.0713)	<0.001	0.3540 (0.0500)	<0.001
2	0.1889 (0.0463)	<0.001	0.7238 (0.5320)	0.174	0.1148 (0.0757)	0.130	0.2378 (0.0550)	<0.001
3	0.0449 (0.0650)	0.490	-1.8755 (0.7067)†	0.008	0.0542 (0.0758)	0.475	0.0708 (0.0803)	0.378

* β values are shown for $\ln S_I$, \ln fasting insulin, \ln AIR, \ln disposition index, BMI, and waist circumference for a 10-unit increase in digestible carbohydrate intake, fiber intake, and glycemic load and for a 1-unit increase in glycemic index. Model 1: Unadjusted. Model 2: Adjusted for age, sex, ethnicity/clinic, family history of diabetes, current smoking status, and total energy expenditure. Model 3: Model 2 further adjusted for energy intake from noncarbohydrates by energy partition method. †Model 3 for fiber: Model 2 further adjusted for total energy intake.

adjustment including total energy intake. For example, a 10-g-higher fiber intake was associated with a 1.88-cm-smaller waist circumference, a 0.80- kg/m^2 -lower BMI, a 0.08-pmol/ml-lower level of fasting insulin, and a 0.123-higher level of S_I . While in the unadjusted analyses, increased fiber intake was associated with more insulin resistance and higher levels of adiposity; this was explained entirely by confounding due to energy intake. While there was no association of fiber with AIR, disposition index was related to fiber intake after full adjustment. To address the question to what extent the association of fiber with measures of S_I could be explained by concurrent BMI, we additionally adjusted the final models for S_I and fasting insulin for BMI (data not shown). Fiber continued to be significantly associated with increased S_I after adjustment for BMI. However, the association with fasting insulin was markedly attenuated.

No association of glycemic index was observed with levels of S_I , fasting insulin,

AIR, disposition index, BMI, or waist circumference by linear regression analysis. Adjustment for relevant confounders including energy intake did not impact the findings. Additional adjustment for fiber intake, which in other studies had increased the strength of the associations, had no impact in our data.

In contrast, a significant, consistent, and linear relationship between glycemic load and outcome levels was observed that was positive for fasting insulin, BMI, and waist circumference and inverse for S_I . This association was present both in the crude models and after multivariate adjustment. In parallel to the findings for total carbohydrate intake, additionally adjusting for total energy intake from noncarbohydrate sources (or alternatively with the residual method) entirely explained the association. There was no association of glycemic load with AIR or disposition index after taking into account demographic and lifestyle correlates. After additional adjustment for fiber intake, a small but significant negative as-

sociation between glycemic load and S_I and a positive association between glycemic load and waist emerged. No effect was seen on the relation with AIR, disposition index, and BMI.

CONCLUSIONS— To our knowledge, the present study is the first to address the relation of glycemic index and glycemic load with a direct measure of insulin sensitivity determined by a FSIGT. No association of glycemic index, glycemic load, or carbohydrate intake was observed with S_I or with fasting insulin levels taking into account total energy intake. Previously published reports have been based on indirect estimates of S_I . The Zutphen Elderly study (6), focusing on glycemic index, observed no association with levels of fasting insulin. Two studies to date have used the homeostasis model assessment of insulin resistance (HOMA-IR) with contrasting results (7,28). Similar to our findings, Lau et al. (28) found no evidence of an association of glycemic index with HOMA-IR. The association

with glycemic load was marginal and explained after adjusting for fiber. In contrast, McKeown et al. (7) reported positive associations of both glycemic index and glycemic load with HOMA-IR, independent of energy intake.

The suggestion that dietary glycemic index and load may be associated with insulin resistance-related diseases was initially supported by two epidemiologic studies reporting that high-glycemic index diets predicted the development of diabetes (4,8). The body of evidence that has since emerged is truly equivocal. Two negative prospective studies (29,30) demonstrated a lack of an association for both glycemic index and glycemic load. A total of three studies have shown positive associations (4,8,9), one showing consistent associations for both glycemic index and glycemic load (4), while in the other two only glycemic index was predictive of diabetes (8,9).

We also explored the relation of glycemic index, glycemic load, and carbohydrate intake to measures of insulin secretion and pancreatic functionality. No association of glycemic index, glycemic load, or carbohydrates was observed with AIR or disposition index. Previous work in our population on alcohol intake, fat intake, and physical activity similarly reported no impact of these behavioral factors on AIR or disposition index (31). A recent intervention study, however, observed a significant improvement in disposition index among individuals with impaired glucose tolerance randomized to a high-carbohydrate, low-glycemic index diet (32). Smaller improvements in S_1 did not reach statistical significance. In an animal model, high-glycemic index diets led to hypersecretion of insulin but did not impact S_1 (33).

Because insulin resistance is influenced by level of adiposity, we also focused on BMI and waist circumference. Glycemic index was not associated with BMI or waist circumference. While total carbohydrate intake and glycemic load were positively associated with higher levels of BMI and waist circumference, these associations were explained entirely by confounding due to correlated energy intake. To our knowledge, there are no published epidemiologic data with which to compare our data on glycemic index and adiposity. In contrast to our findings, experimental and intervention studies seem to imply health-promoting effects of low-glycemic index and glycemic load diets. In overweight populations, weight

and fat loss was achieved after several months in the low-glycemic index group compared with the control groups (34,35). As recently reviewed, data from animal models and acute and short-term studies in humans support the concept that high-glycemic index diets affect appetite control, nutrient portioning, and therefore fat storage and promote weight gain (36).

The discrepancy between the experimental evidence on low-glycemic index intervention diets and our epidemiologic findings may be partially explained by the fact that the glycemic index distribution of observational populations is generally centered around the high-glycemic index diets of experiments. The median glycemic index in IRAS of 58 (glucose standard) is similar to averages in the high-glycemic index groups (37,38). Moreover, the level of low-glycemic index diets in experiments (e.g., 39–41) (37,38) may be only seen in the most extreme tails of general populations. In IRAS, the absolute lowest glycemic index value was 45, i.e., well above typical low-glycemic index intervention diets. In other populations, the averages for the lowest glycemic index quintiles have ranged from 48 to 50 (29,30,39). Thus, diets consumed by free-living individuals may not approach the glycemic index values needed to achieve preventive potential.

Our data indicate that an increased fiber intake was associated with decreased levels of fasting insulin, waist circumference, and BMI. Additionally, we observed a significant positive relation with S_1 and disposition index, while no effect on AIR was observed. Of note is the importance of adjusting for caloric intake in this analysis. Ludwig et al. (40) have previously documented the relation of total dietary fiber with weight gain, central and overall adiposity, and fasting insulin levels. More recently, fiber intake, especially cereal fiber, was inversely related to the metabolic syndrome and HOMA-IR (7,41). Previous work has also shown that low cereal fiber intake increased the risk of type 2 diabetes (8,29). Unfortunately, our data do not allow us to differentiate between various sources of fiber. A recent study indicates that fiber may not be associated with insulin secretion as assessed by the insulinogenic index (41), a finding confirmed by the negative association with our AIR measure based on FSIGT. However, our study did observe an association with disposition index, which indicates

that fiber may play a role in stimulating insulin secretion relative to levels of S_1 .

The role of fiber in the context of analyses relating glycemic index or glycemic load to health outcomes merits special consideration. While most naturally occurring foods high in viscous fiber (e.g., barley, legumes) are low in glycemic index due to reduced rate of carbohydrate absorption (42), foods containing processed fibers such as cereal fiber do not reduce glycemic response (e.g., white bread and wholemeal bread have very similar, rather high-glycemic index values). This raises the question of how to conceptualize fiber intake relative to glycemic index and glycemic load in statistical analyses. Most studies have treated fiber intake essentially as a confounder of glycemic index or glycemic load (7,29,30). Even though conceptually this may be an overadjustment (leading to a bias toward the null), several investigations reported an increase in the strength of their respective glycemic index outcome associations after adjustment for fiber (4,8). In addition, the joint effect of fiber intake and dietary glycemic index on health outcomes was explored (4,8,9) by testing for statistical interactions. These findings are similarly difficult to interpret because of the interrelation of glycemic index and fiber (24).

Consistent with previous studies, the associations of total carbohydrate intake were not independent of energy intake (4,7,8,43). Because glycemic load is a function of both glycemic index and carbohydrate intake, the relative contribution of glycemic index depends on the amount of carbohydrates. In IRAS, with a narrow distribution of dietary glycemic index contrasting with a large amount of variation in total carbohydrates, in effect, carbohydrate intake plays a more important role in determining glycemic load, as we have shown (24). One would therefore expect to find similar results for glycemic load and carbohydrates, which, in fact, was the case in our study.

A methodological limitation of our study is that the IRAS FFQ, like most others, was not developed with glycemic index estimation in mind, thus no validation data for dietary glycemic index estimation exist. The IRAS FFQ was validated in a multiethnic subsample of the IRAS population with respect to nutrients including total carbohydrate intake and fractions of carbohydrates (fructose and starch) (22). Pearson correlation coefficients for FFQ carbohydrate estimates

compared with eight 24-h recalls were moderate at $r = 0.39$ unadjusted ($r = 0.37$ adjusted for energy). However, they differed substantially across ethnic group and center, ranging from 0.25 in rural Hispanics and 0.39 in urban African Americans to 0.64 in urban non-Hispanic whites. These findings are highly comparable to other work indicating lower levels of validity in minority populations (44,45). It is therefore important to note that our conclusions were unchanged when we stratified our analyses on ethnic group.

In conclusion, our results demonstrate a remarkable degree of consistency in finding a lack of association of glycemic index, glycemic load, and carbohydrate intake with measures of insulin sensitivity, insulin secretion, and adiposity. Consistent with previous findings, fiber intake was positively associated with S_I and inversely with adiposity and may additionally have a positive impact on pancreatic functionality.

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