

Whole and Refined Grain Intakes Are Related to Inflammatory Protein Concentrations in Human Plasma^{1,2}

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Abstract

Inflammation may play a role in the pathogenesis of cardiovascular disease and type 2 diabetes, and it has been suggested that the protective effects of whole-grain consumption could be mediated by an effect on inflammation, although few studies have examined the relationships between grain intakes and inflammatory protein concentrations. Our objectives in this study were to examine the associations of whole grain and refined grain intake with plasminogen activator inhibitor type 1 (PAI-1), C-reactive protein (CRP), and fibrinogen plasma concentrations. Cross-sectional data from the Insulin Resistance Atherosclerosis Study were used to perform multiple regression analyses using dietary information on whole and refined grain intakes from a FFQ and clinical measures of plasma inflammatory protein concentrations in participants free of type 2 diabetes. After adjustment for demographic, lifestyle, and dietary variables, whole-grain intake was inversely related to log PAI-1 ($\beta = -0.102$; SEM = 0.038; $P = 0.0077$) and log CRP ($\beta = -0.102$; SEM = 0.048; $P = 0.0340$). Adding insulin sensitivity, waist circumference, and 2-h postload glucose to the model attenuated both associations to nonsignificance. Refined grain was positively related to log PAI-1 in the multivariate model ($\beta = 0.076$; SEM = 0.034; $P = 0.0251$) and the relationship remained unchanged by additional adjustment for metabolic variables. Fibrinogen concentrations were not related to whole or refined grain intake. In summary, whole grain intake was inversely related to PAI-1 and CRP plasma concentrations, but these relationships were attenuated by the addition of metabolic variables to the model. Refined grain intake was positively independently related to plasma PAI-1 concentrations. J. Nutr. 140: 587–594, 2010.

Introduction

Type 2 diabetes and cardiovascular disease are widely recognized as conditions of chronic inflammation, characterized by subclinical elevations in circulating plasma concentrations of inflammatory proteins such as C-reactive protein (CRP),⁷ plasminogen activator inhibitor type 1 (PAI-1), and fibrinogen (1,2). Elevated CRP and fibrinogen concentrations are early risk markers of incident cardiovascular disease and are thought to

play a role in the etiology of cardiovascular disease, although the causal relationships between these proteins and cardiovascular disease are controversial (3–7). Additionally, both CRP and PAI-1 have been independently associated with incident type 2 diabetes (8–12), and there is evidence to suggest that both of these proteins may contribute to development of endothelial dysfunction and insulin resistance (6,13).

As inflammation has become increasingly recognized as having a role in cardiovascular disease and type 2 diabetes, there is reason to explore how diet relates to subclinical inflammation, because nutrition interventions could be used to modify inflammatory protein concentrations. Specifically, it is of interest to examine how whole grain intakes relate to inflammatory protein concentrations given the consistent evidence that consumption of whole grains is protective against incident type 2 diabetes and cardiovascular disease (14,15). However, it is unclear how these protective effects are mediated. Recently it was proposed that inflammatory protein concentrations could be modified by whole grain consumption, which in turn could impact cardiovascular disease and type 2 diabetes outcomes (16). However, data on the relationships between whole grain consumption and

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⁷ Abbreviations used: CRP, C-reactive protein; IQR, interquartile range; IRAS, Insulin Resistance Atherosclerosis Study; LS, least squares; PAI-1, plasminogen activator inhibitor type 1; S_i, insulin sensitivity.

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inflammatory protein concentrations are scarce and conflicting results have been reported (17–19). Furthermore, there have been no data on the relationship between whole grain intake and PAI-1 concentrations.

Additionally, it is less clear whether refined grain consumption is associated with risk of type 2 diabetes and cardiovascular disease, with some studies reporting a positive relationship whereas others reported no relationship (20–24). However, refined grain intakes are a part of dietary patterns that have been positively associated with risk of these diseases as well as with inflammatory protein concentrations (25–28). To date, no studies to our knowledge have specifically examined the relationships between refined grain intakes and plasma inflammatory protein concentrations.

Given the limited and conflicting data on relationships between whole and refined grain intakes and plasma inflammatory protein concentrations, the research objective for this study was to use data from the Insulin Resistance Atherosclerosis Study (IRAS) to examine the cross-sectional relationships between whole and refined grain intakes and CRP, fibrinogen, and PAI-1 plasma concentrations in participants free of type 2 diabetes.

Materials and Methods

Study design and population. All data used in the current analyses were collected at the baseline study visits of IRAS, which is a multi-center study of a tri-ethnic cohort of adults in the age range of 40–60 y. A detailed report of the study objectives, design, and recruitment results has been published (29). All baseline study visits occurred between October 1992 and April 1994. Written informed consent was obtained from all study participants and the study was approved by the institutional review boards at the study centers, which were the University of Texas Health Science Center at San Antonio, the University of Colorado, and Kaiser Permanente (Los Angeles and Oakland, CA).

A total of 1625 men and women were enrolled in IRAS. For the current analyses, 1088 participants without type 2 diabetes at baseline were included. Additionally, 44 participants were excluded because they did not have baseline measures of CRP, PAI-1, and/or fibrinogen, 12 because of missing information on dietary intakes and 17 because they had total energy intakes <2510 kJ/d or >20,920 kJ/d, resulting in a final sample size of 1015. Analyses focusing on CRP concentration as the outcome were restricted to individuals with CRP concentrations of ≤ 10 mg/L ($n = 941$).

Data collection. Dietary information was collected by interview using a 114-item FFQ modified from the National Cancer Institute Health Habits and History Questionnaire to include ethnic and regional food choices appropriate to the study population (30). The intakes of foods and beverages were quantified by asking participants to recall their frequency of consumption of each line item over the past year. There were 9 frequency options, ranging from “never or less than once a month” to “six or more times per day.” Additionally, participants were asked to identify their usual portion size as “small, medium, or large compared with other men or women about your age.” For analyses of food groups, the servings per day were standardized to the medium serving size by multiplying the intake frequency with the portion size after applying a weighting factor (small = 0.5, medium = 1.0, large = 1.5). Thus, 1 serving corresponds to 1 medium-sized portion of the respective food or food group. Nutrient and energy intake were 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) (30). Age- and sex-specific portion sizes (originally based on NHANES 24-h dietary recall data) were used that link a specific gram weight for each food item to a medium serving of each food. The FFQ used in this study was validated in a subsample of 186 women from the IRAS population (30).

Consistent with previous work in IRAS (31), whole grain intake was calculated by adding together reported intakes of 3 lines of the FFQ,

which were: 1) dark bread (including whole wheat, rye, pumpernickel, and other high-fiber bread); 2) high-fiber bran or granola cereals, shredded wheat; and 3) cooked cereal (including oatmeal, cream of wheat, and grits). These 3 lines of the FFQ were chosen to reflect whole grain intake, because at least 1 of the items in the line specified a whole grain food (31). The cooked cereals value was weighted by a factor of 0.5, because 2 of the 3 line items most often do not have any whole grain content.

The refined grain variable follows previous food grouping work in IRAS (32) and captures intakes of low-fiber breads and breakfast cereals that most often have no whole grain content. It included intakes of white bread products, biscuits, scones, croissants, flour and corn tortillas, muffins, fry bread, hush puppies, corn bread, corn muffins, highly fortified cereals, cold cereals that are low in fiber, pizza, burritos, Mexican dishes made with flour or corn tortillas or tacos, and cooked cereals weighted by a factor of 0.5.

Before each study visit, participants were asked to fast for 12 h, avoid alcohol and exercise for 24 h, and avoid smoking the morning of the study visit. Plasma samples for measurement of CRP, fibrinogen, and PAI-1 were frozen at -70°C within 90 min of collection and after centrifugation. Analyses of samples for the 3 analytes from all 4 research centers were conducted at the Laboratory for Clinical Biochemistry Research at the University of Vermont. Frozen samples were shipped on a monthly basis to the laboratory. An in-house ultrasensitive competitive immunoassay was used to measure CRP (33). The intra-assay CV for this assay was 3.0% for a sample with a mean concentration of 0.80 mg/L and the inter-assay variability ranged from 5.5 to 6.8% (33). A modified clot-rate assay with the use of the Diagnostica STAGO ST4 instrument was used to measure fibrinogen in citrated plasma (8). The assay used was based on the clot-rate fibrinogen assay (34). The inter-assay CV for this assay was reported to be 3.0% (8). A 2-site immunoassay was used to measure PAI-1 in the citrated plasma (35). The assay used was 12 times more sensitive to free PAI-1 than PAI-1 complexed with tissue-type plasminogen activator. The intra-assay CV for this assay was between 4 and 7% and the inter-assay CV was between 6 and 10% (35).

Study participants were administered a 75-g oral glucose tolerance test (Orange-dex, Custom Laboratories). Blood was collected prior to consumption of the drink and 2 h after consumption. Glucose tolerance status was defined according to the WHO criteria outlined in 1985 (36).

On a second day of baseline study visits, a frequently sampled i.v. glucose tolerance test was administered following a modified protocol (37), which included an injection of insulin at 20 min rather than tolbutamide and a reduced sampling protocol of 12 blood samples rather than 30, allowing for greater efficiency due to the large number of study participants (29).

Minimum waist circumference was measured as the point at the natural indentation between the 10th rib and iliac crest. Waist circumference and height were measured to the nearest 0.5 cm and body weight was measured to the nearest 0.1 kg. Duplicate measures were taken of each and an average was used in all analyses.

Data on ethnicity and age were obtained by self-report. Total estimated energy expenditure for 1 y was estimated from a physical activity recall that included questions on work, home, and leisure activity, and exercise habits. This recall was a modified version of a validated instrument (29). A value for total estimated energy expenditure was calculated by summing energy expenditures for activities plus energy expended for reported time of sleep and expressed as $\text{kJ}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$.

A detailed questionnaire was used to assess alcohol consumption in the past month and additional questions were asked to gain information on recent and lifetime use. Alcohol consumption was converted to g ethanol consumed/d. Smoking status was categorized into 3 groups: never, past, or current.

Statistical analyses. All analyses were carried out using SAS version 9.1 (SAS Institute). A P -value ≤ 0.05 was considered significant for all statistical comparisons. Univariate distributions of all exposure and outcome variables and potential covariates were examined and highly skewed variables were log-transformed, which included PAI-1, CRP, alcohol intake, and total estimated energy expenditure. Insulin sensitivity (S_1) was log-transformed after a constant (1 unit) was added to all

TABLE 1 Participant characteristics across quintiles of whole grain intake¹

Variable	Quintile of whole grain intake					P ²
	Q1	Q2	Q3	Q4	Q5	
<i>n</i>	203	241	163	208	200	—
Median whole grain intake, ^{3,4} <i>servings/d</i>	0.04 (0–0.15)	0.32 (0.16–0.50)	0.65 (0.51–0.81)	1.04 (0.82–1.29)	2.00 (1.30–4.07)	<0.0001
PAI-1, $\mu\text{g/L}$	20 (12–31)	19 (11–28)	15 (9–28)	16.00 (9–28)	14 (7–24)	0.0003
CRP, <i>mg/L</i>	1.75 (1.02–4.11)	1.88 (0.97–4.51)	1.75 (0.67–4.83)	1.68 (0.71–2.915)	1.55 (0.62–3.42)	0.0409
Fibrinogen, ⁵ <i>g/L</i>	2.77 ± 0.57	2.78 ± 0.53	2.80 ± 0.60	2.78 ± 0.56	2.73 ± 0.60	0.8367
Age, <i>y</i>	52.6 ± 8.4	55.2 ± 8.3	55.8 ± 8.3	55.3 ± 8.4	55.5 ± 8.8	0.0010
Sex, % <i>male</i>	47.29	43.98	38.65	37.98	50.00	0.0677
Ethnicity, %						<0.0001
Non-Hispanic White	27.59	41.08	35.58	52.88	43.50	
African American	20.69	28.22	28.22	20.19	30.50	
Hispanic	51.72	30.71	36.20	26.92	26.00	
Glucose tolerance status, %						0.5648
Normal	65.02	63.90	65.64	70.67	68.50	
IGT	34.98	36.10	34.36	29.33	31.50	
Smoking status, %						0.0006
Never	40.89	45.64	51.53	44.71	48.00	
Past	32.51	35.27	39.26	42.79	38.00	
Current	26.60	19.09	9.20	12.50	14.00	
Alcohol Intake, <i>g ethanol/d</i>	1.07 (0–10.39)	0.50 (0–5.20)	0.50 (0–5.73)	1.14 (0–8.65)	0.75 (0–8.29)	0.2653
Total energy intake, <i>kJ/d</i>	8241 ± 3498	7194 ± 3117	7004 ± 2689	8171 ± 2982	8775 ± 3347	<0.0001
Total estimated energy expenditure, <i>kJ·kg⁻¹·d⁻¹</i>	162.4 (149.5–191.0)	157.7 (146.7–180.9)	160.4 (149.0–178.5)	165.4 (148.6–183.1)	158.8 (149.7–176.9)	0.2260
BMI, <i>kg/m²</i>	28.75 ± 5.75	28.81 ± 6.26)	28.30 ± 4.91	28.05 ± 5.56	28.24 ± 5.83	0.5746
Waist circumference, <i>cm</i>	91.70 ± 12.91	91.09 ± 13.28	89.65 ± 11.98	89.80 ± 13.56	89.93 ± 12.70	0.4169
Fasting glucose, ⁶ <i>mg/L</i>	990 ± 110	990 ± 120	990 ± 120	980 ± 100	980 ± 110	0.6925
S ₁ 10 ⁻⁴ ·min ⁻¹ · μU^{-1} ·mL ⁻¹	1.61 (0.89–2.79)	1.62 (0.81–2.67)	1.50 (0.87–2.77)	1.55 (0.97–3.10)	1.91 (0.99–3.46)	0.1052
Dietary variables						
Vegetables, ⁴ <i>servings/d</i>	2.54 (2.33, 2.76)	2.67 (2.47, 2.86)	2.96 (2.72, 3.20)	3.22 (3.01, 3.43)	3.12 (2.90, 3.34)	<0.0001
Fruit, ⁴ <i>servings/d</i>	1.07 (0.89, 1.24)	1.45 (1.28, 1.61)	1.71 (1.51, 1.91)	1.76 (1.59, 1.94)	2.14 (1.95, 2.32)	<0.0001
Oleic acid, % of total energy	13.52 (13.14, 13.89)	13.40 (13.05, 13.74)	12.84 (12.42, 13.26)	12.73 (12.36, 13.10)	11.81 (11.43, 12.19)	<0.0001
PUFA, % of total energy	6.75 (6.49, 7.00)	6.70 (6.47, 6.94)	6.76 (6.47, 7.04)	6.70 (6.44, 6.95)	6.68 (6.42, 6.94)	0.9923
Saturated fat, % of total energy	13.06 (12.64, 13.48)	12.95 (12.57, 13.34)	12.06 (11.59, 12.53)	12.29 (11.87, 12.70)	10.78 (10.36, 11.21)	<0.0001
Refined grain intake, ⁴ <i>servings/d</i>	1.63 (1.52, 1.74)	1.45 (1.35, 1.55)	1.33 (1.21, 1.45)	1.13 (1.02, 1.23)	0.94 (0.83, 1.05)	<0.0001

¹ Continuous variables presented as mean ± SD or median (IQR). Categorical variables are presented as percent of participants in quintile. Dietary variables are presented as LS means (95% CI) adjusted for total energy intake.

² For continuous variables, *P*-value from ANOVA comparison across quintiles or from Kruskal-Wallis comparison across quintiles if variable was skewed. For categorical variables, *P*-value for chi square value for comparison across quintiles. For dietary variables, *P*-value for ANCOVA comparison across quintiles, adjusted for total energy intake.

³ Whole grain intake displayed as median and range for quintile.

⁴ One serving corresponds to a participant-identified, medium-sized serving of FFQ line items comparable to servings consumed by men or women of the same age.

⁵ To convert fibrinogen from *g/L* to $\mu\text{mol/L}$, multiply by 2.94.

⁶ To convert glucose from *mg/L* to *mmol/L*, multiply by 0.00555.

S₁ values. This was necessary because some participants had S₁ values of 0.

Means ± SD for all nonskewed continuous variables are presented across quintiles of intakes of whole and refined grains and were tested for differences in means by ANOVA. Skewed variables are presented as medians with interquartile ranges (IQR) and were tested by a nonparametric Kruskal-Wallis test for differences in rank scores across quintiles. Dietary variables are presented as energy-adjusted least square (LS) means and 95% CI across quintiles and were tested for differences in means by ANCOVA. Categorical variables are presented as percent of participants in the quintile. Chi square analyses were carried out to test for differences in frequencies across quintiles.

Unadjusted Spearman correlation coefficients between outcome variables and the exposure variables were examined. A partial Spearman correlation coefficient was examined for the correlation between whole and refined grain intakes adjusted for energy intake.

Multiple regression analyses were carried out to test the linear relationship between the continuous dietary variables of interest with

the outcome variables, fibrinogen, log-transformed PAI-1, and log-transformed CRP. Model 1 was adjusted for demographic and lifestyle variables including sex, ethnicity, smoking status, total daily energy intake, total estimated energy expenditure, and alcohol consumption. Model 2 was additionally adjusted for dietary variables that could potentially confound the relationships of interest and included adjustment for fruit intake, vegetable intake, and percent energy intake from saturated fat intake, polyunsaturated fat, oleic acid, and the opposing grain variable (i.e. whole grain intake or refined grain intake). Model 3, which was additionally adjusted for S₁, waist circumference, and 2-h postload glucose, was considered a mechanistic model, because these metabolic variables could possibly be on a physiologic pathway between the dietary intake variables and the plasma inflammatory protein concentrations.

Potential interactions between the dietary variables of interest and sex, ethnicity, central obesity, glucose tolerance, or smoking status were examined. Whole and refined grain intakes were categorized into tertiles of intake and the product term of the tertile variables with the interaction

TABLE 2 Participant characteristics across quintiles of refined grain intake¹

Variables	Quintile of refined grain intake					P-value ²
	Q1	Q2	Q3	Q4	Q5	
<i>n</i>	205	204	199	204	203	—
Median refined grain intake, ^{3,4} servings/d	0.27 (0.02–0.44)	0.59 (0.44–0.80)	1.04 (0.81–1.26)	1.58 (1.26–2.04)	2.73 (2.04–7.78)	<0.0001
PAI-1, $\mu\text{g/L}$	13 (7–21)	13 (7–24)	17 (11–28)	20 (11–29)	22 (15–35)	<0.0001
CRP, mg/L	1.86 (0.68–3.86)	1.63 (0.66–3.73)	1.53 (0.77–3.43)	1.72 (0.93–3.19)	2.06 (1.12–4.58)	0.0531
Fibrinogen, ⁵ g/L	2.78 \pm 0.61	2.71 \pm 0.56	2.81 \pm 0.59	2.73 \pm 0.52	2.82 \pm 0.55	0.1866
Age, y	56.2 \pm 8.5	54.9 \pm 8.6	55.3 \pm 8.3	53.9 \pm 8.5	53.9 \pm 8.4	0.0234
Sex, % male	37.07	44.12	43.22	47.55	46.80	0.2218
Ethnicity, %						<0.0001
Non-Hispanic White	44.39	50.00	43.72	37.75	26.11	
African American	47.32	34.80	25.13	14.22	5.91	
Hispanic	8.29	15.20	31.16	48.04	67.98	
Glucose tolerance status, %						0.3510
Normal	61.95	69.12	69.35	69.12	64.04	
IGT	38.05	30.88	30.65	30.88	35.96	
Smoking status, %						0.2138
Never	45.85	50.98	45.23	45.10	42.36	
Past	38.05	37.75	40.20	35.29	35.96	
Current	16.10	11.27	14.57	19.61	21.67	
Alcohol intake, g ethanol/d	1.51 (0–7.68)	0.69 (0–8.87)	0.85 (0–10.24)	0 (0–5.12)	0.43 (0–6.40)	0.0400
Total energy intake, kJ/d	5362 \pm 1744	6568 \pm 24889	7520 \pm 2367	8970 \pm 2821	11024 \pm 3113	<0.0001
Total estimated energy expenditure, kJ·kg ⁻¹ ·d ⁻¹	156.2 (145.7–174.9)	161.0 (148.5–181.1)	160.4 (147.8–177.8)	164.1 (149.7–191.4)	164.0 (149.7–185.8)	0.0080
BMI, kg/m ²	27.97 \pm 5.46	28.30 \pm 5.49	27.58 \pm 5.19	29.06 \pm 6.09	29.31 \pm 6.19	0.0112
Waist circumference, cm	88.55 \pm 13.25	89.50 \pm 11.99	89.18 \pm 12.23	91.98 \pm 12.99	93.22 \pm 13.70	0.0006
Fasting glucose, ⁶ mg/L	990 \pm 120	990 \pm 120	980 \pm 110	990 \pm 110	980 \pm 110	0.5127
S _i 10 ⁻⁴ ·min ⁻¹ · μU^{-1} ·mL ⁻¹	1.75 (0.99–3.14)	1.78 (0.96–3.14)	1.63 (1.05–2.51)	1.63 (0.83–2.98)	1.28 (0.65–2.80)	0.0253
Dietary variables						
Vegetables, ⁴ servings/d	2.95 (2.72, 3.19)	2.99 (2.77, 3.21)	2.88 (2.66, 3.10)	2.96 (2.74, 3.18)	2.66 (2.41, 2.91)	0.3540
Fruit, ⁴ servings/d	1.63 (1.43, 1.83)	1.82 (1.63, 2.01)	1.61 (1.42, 1.79)	1.69 (1.50, 1.88)	1.32 (1.11, 1.53)	0.0128
Oleic acid, % of total energy	12.07 (11.66, 12.48)	12.29 (11.91, 12.68)	12.99 (12.61, 13.37)	13.42 (13.04, 13.80)	13.65 (13.22, 14.08)	<0.0001
PUFA, % of total energy	6.52 (6.24, 6.79)	6.55 (6.29, 6.81)	6.62 (6.36, 6.87)	6.85 (6.59, 7.11)	7.04 (6.75, 7.33)	0.1060
Saturated fat, % of total energy	11.50 (11.04, 11.97)	11.90 (11.46, 12.34)	12.49 (12.05, 12.92)	12.73 (12.30, 13.17)	12.72 (12.23, 13.21)	0.0016
Whole grain intake, ⁴ servings/d	1.08 (0.98, 1.18)	1.04 (0.94, 1.13)	0.86 (0.76, 0.95)	0.72 (0.62, 0.82)	0.35 (0.24, 0.46)	<0.0001

¹ Continuous variables are means \pm SD or median (IQR). Categorical variables are percent of subjects in quintile. Dietary variables are LS means (95% CI) adjusted for total energy intake.

² For continuous variables, P-value from ANOVA comparison across quintiles or from Kruskal-Wallis comparison across quintiles if variable was skewed. For categorical variables, P-value for chi square value for comparison across quintiles. For dietary variables, P-value for ANCOVA comparison across quintiles, adjusted for total energy intake.

³ Refined grain intake displayed as median and range for quintile.

⁴ One serving corresponds to a participant-identified, medium-sized serving of FFO line items comparable to servings consumed by men or women of the same age.

⁵ To convert fibrinogen from g/L to $\mu\text{mol/L}$, multiply by 2.94.

⁶ To convert glucose from mg/L to mmol/L, multiply by 0.00555.

variables of interest were examined in a model adjusted for all variables in Model 2. When an interaction term was significant at a level of $P \leq 0.05$, stratified regression analyses were performed. Waist circumference was made into a categorical variable by classifying participants into above or below sex-specific waist circumference at-risk groups (>102 cm for males or >88 cm for females) for the purpose of the interaction analysis. Values in the text are mean \pm SD or median (IQR) unless otherwise noted.

Results

The intakes of whole grains and refined grains were 0.81 ± 0.73 and 1.30 ± 1.05 servings/d, respectively. The concentrations for PAI-1 and CRP were 17.00 (10.00–28.00) $\mu\text{g/L}$ and 1.75 (0.79–3.74) mg/L, respectively, and the concentration for fibrinogen was 2.77 ± 0.57 g/L (8.15 ± 1.67 $\mu\text{mol/L}$).

Age differed across whole grain intake quintiles with the lowest mean age observed in Q1 (Table 1). Ethnicity and smoking status also differed across quintiles, with Q1 having the highest proportion of Hispanic participants and current smokers. Total estimated energy expenditure did not differ across quintiles. The energy-adjusted means for intakes of fruit, vegetables, fiber, and magnesium were lowest in Q1 and the energy-adjusted means for percent of energy intake from saturated fat and oleic acid and refined grain intakes were highest in Q1.

None of the central tendency measures for the metabolic variables differed across quintiles of whole grain intake. The outcome measures, PAI-1 and CRP concentrations, differed across quintiles of whole grain intake, with the lowest median values found in Q5. Fibrinogen concentrations did not differ across whole grain intake quintiles.

Age and ethnicity differed across quintiles of refined grain intake (Table 2). The highest intake quintile of refined grains (Q5) had the youngest mean age and the highest percentage of Hispanic participants. Total estimated energy expenditure differed across quintiles but smoking status did not. Waist circumference, BMI, and S_1 differed across quintiles of refined grain intake. Higher means for waist circumference and BMI were observed in Q5 and the lowest median S_1 was found in Q5. The lowest energy-adjusted intake of whole grains was found in Q5 and the highest percentages of energy intake from saturated fat and oleic acid were in Q5. The PAI-1 concentrations were significantly different across quintiles, with the highest PAI-1 concentration in Q5. CRP and fibrinogen did not differ significantly across quintiles of refined grain intake.

The energy-adjusted Spearman correlation coefficient between whole and refined grain intake was -0.29 ($P < 0.0001$). In the unadjusted Spearman correlation analyses, both PAI-1 and CRP were inversely related to whole grain intake (PAI-1: $r = -0.14$, $P < 0.0001$; CRP: $r = -0.08$, $P = 0.011$). The Spearman correlation coefficient for refined grain intake and PAI-1 was 0.27 ($P < 0.0001$) and the Spearman correlation coefficient between refined grain intake and CRP concentration was 0.08 ($P = 0.0173$). Fibrinogen concentrations were not correlated with whole grain or refined grain intake (data not shown).

Whole grain intake was inversely related to both log PAI ($\beta = -0.167$; SEM = 0.035; $P < 0.0001$) and log CRP ($\beta = -0.103$; SEM = 0.044; $P = 0.0181$) in the first multiple regression model (Table 3). The addition of potential dietary confounders to the model slightly attenuated the relationship between whole grain intake and log PAI-1; however, the relationship remained strong and significant ($\beta = -0.102$; SEM = 0.038; $P = 0.0077$). This β corresponds to a 1.23- $\mu\text{g/L}$ decrease in PAI-1 associated with increasing whole grain consumption by 2 servings/d while holding all other variables in the model constant. The relationship between whole grain intake and CRP also remained

significant in model 2 ($\beta = -0.102$; SEM = 0.048; $P = 0.0340$). This β corresponds to a 1.23-mg/L decrease in CRP concentration associated with an increase of 2 servings whole grains/d, holding constant all other variables in the model.

When potential metabolic intermediates, namely S_1 , waist circumference, and 2-h postload glucose, were added (model 3), the relationship between whole grain and log PAI-1 was attenuated to nonsignificance ($\beta = -0.049$; SEM = 0.036; $P = 0.166$) as was the relationship between whole grain and CRP ($\beta = -0.036$; SEM = 0.044; $P = 0.4203$).

There was no evidence of a relationship between whole grain intake and fibrinogen in any of the regression models.

Refined grain intake was positively related to log PAI-1 in all of the regression models but was not related to log CRP or fibrinogen in any of the models (Table 4). After adjustment for demographic and lifestyle variables, there was a strong positive relationship between refined grain intake and log PAI-1 ($\beta = 0.113$; SEM = 0.032; $P = 0.0005$). This was attenuated by additional adjustment for dietary confounders, which included whole grain intake, but the association remained significant ($\beta = 0.076$; SEM = 0.034; $P = 0.0251$). Additionally adjusting for potential metabolic intermediates did not affect the relationship ($\beta = 0.083$; SEM = 0.031; $P = 0.0078$). The β from model 2 corresponds to a 1.16- $\mu\text{g/L}$ increase in PAI-1 associated with an increase in refined grain consumption of 2 servings/d when all other variables in the model are held constant.

There were no significant interactions found between grain intakes and ethnicity, sex, glucose tolerance, or smoking status. A quantitative interaction term was found for refined grain tertile with waist circumference group for PAI-1 ($P = 0.0064$). The relationship between refined grain intake and log PAI-1 appeared stronger among participants in the "at risk" waist circumference group and remained significant even after adjustment for S_1 and 2-h postload glucose (Table 5; $\beta = 0.103$; SEM = 0.049; $P = 0.0359$). Adjusting for dietary confounders had a large attenuating effect on the β coefficient among participants

TABLE 3 Multiple regression analyses for whole grain intake with inflammatory protein concentrations

Outcome variable	n	Whole grain intake, ¹ servings/d		
		β	SEM	P
Log PAI-1				
Model 1 ²	1005	-0.167	0.035	<0.0001
Model 2 ³	1005	-0.102	0.038	0.0077
Model 3 ⁴	959	-0.049	0.036	0.166
Log CRP				
Model 1 ²	932	-0.103	0.044	0.0181
Model 2 ³	932	-0.102	0.048	0.0340
Model 3 ⁴	890	-0.036	0.044	0.4203
Fibrinogen				
Model 1 ²	1005	-0.522	2.439	0.8305
Model 2 ³	1005	-1.660	2.685	0.5367
Model 3 ⁴	959	1.185	2.637	0.6532

¹ One serving corresponds to a participant-identified, medium-sized serving of FFQ line items comparable to servings consumed by men or women of the same age.

² Adjusted for, age, sex, ethnicity, total energy intake, smoking status, total estimated energy expenditure, and alcohol consumption category.

³ Adjusted for variables in the previous models as well as the opposing grain variable, vegetable intake, fruit intake, percent energy from oleic acid, PUFA, and saturated fat intake.

⁴ Adjusted for variables in the previous model as well as waist circumference, S_1 , and 2-h glucose.

TABLE 4 Multiple regression analyses for refined grain intake with inflammatory protein concentrations

Outcome variable	n	Refined grain intake, ¹ servings/d		
		β	SEM	P
Log PAI-1				
Model 1 ²	1005	0.113	0.032	0.0005
Model 2 ³	1005	0.076	0.034	0.0251
Model 3 ⁴	959	0.083	0.031	0.0078
Log CRP				
Model 1 ²	932	0.024	0.041	0.5518
Model 2 ³	932	-0.021	0.041	0.6222
Model 3 ⁴	890	-0.009	0.039	0.8172
Fibrinogen				
Model 1 ²	1005	-2.084	2.230	0.3501
Model 2 ³	1005	-2.893	2.364	0.2214
Model 3 ⁴	959	-3.252	2.303	0.1582

¹ One serving corresponds to a participant-identified, medium-sized serving of FFQ line items comparable to servings consumed by men or women of the same age.

² Adjusted for, age, sex, ethnicity, total energy intake, smoking status, total estimated energy expenditure, and alcohol consumption category.

³ Adjusted for variables in the previous models as well as the opposing grain variable, vegetable intake, fruit intake, percent energy from oleic acid, PUFA, and saturated fat intake.

⁴ Adjusted for variables in the previous model as well as waist circumference, S_1 , and 2-h glucose.

TABLE 5 Multiple regression analysis of refined grain intake with PAI-1 stratified by waist circumference¹

Log PAI-1	Refined grain intake, ² servings/d							
	≤Waist circumference cutpoint				>Waist circumference cutpoint			
	<i>n</i>	β	SEM	<i>P</i>	<i>n</i>	β	SEM	<i>P</i>
Model 1 ³	693	0.099	0.040	0.0131	310	0.122	0.047	0.0108
Model 2 ⁴	668	0.063	0.041	0.1237	293	0.099	0.051	0.0528
Model 3 ⁵	668	0.075	0.039	0.0577	293	0.103	0.049	0.0359

¹ Waist circumference stratified into above and below sex-specific at risk cutpoints: >88 cm for women, >102 cm for men.

² One serving corresponds to a participant-identified, medium-sized serving of FFQ line items comparable to servings consumed by men or women of the same age.

³ Adjusted for age, sex, ethnicity, total energy intake, smoking status, total estimated energy expenditure, and alcohol consumption.

⁴ Adjusted for variables in the previous models as well as whole grain intake, vegetable intake, fruit intake, percent energy from oleic acid, PUFA, and saturated fat intake.

⁵ Adjusted for variables in the previous model as well as S₁ and 2-h glucose.

below the at risk waist circumference cutpoints ($\beta = 0.063$; SEM = 0.041; $P = 0.1237$), although the magnitudes of the β coefficients remained comparable to those observed for refined grain in relation to log PAI-1 in the whole study population.

Discussion

In this nondiabetic population of African American, non-Hispanic White, and Hispanic adults from the IRAS, whole grain intake was significantly inversely related to log PAI-1 and log CRP, independent of demographic, lifestyle, and dietary variables. The attenuation of these relationships when S₁, waist circumference, and 2-h postload glucose were added to the models suggested that these variables could partially mediate the inverse relationships observed between whole grain intake and PAI-1 and CRP. In contrast, refined grain intake was positively related to log PAI-1, independent of demographic, lifestyle, and dietary variables. Interestingly, the additional adjustment for S₁, waist circumference, and 2-h postload glucose did not affect the relationship observed, which suggested that the relationship between refined grain intake and PAI-1 was not mediated by an effect of refined grain intake on these variables, which themselves are related to PAI-1. There was no evidence of a relationship between whole grain intake and fibrinogen nor between refined grain intake and CRP or fibrinogen.

To the best of our knowledge, the relationships between whole and refined grain intakes and PAI-1 concentration have not been examined in the context of a large observational study. A limited number of intervention studies have investigated how PAI-1 concentrations or PAI-1 activity change in response to interventions of whole or refined grain diets, although due to the short duration of the trials, it is difficult to compare their outcomes to the present study, which looked at the association between regular consumption of whole and refined grains and PAI-1 concentrations (38,39). Finding whole grain to be inversely and refined grain positively associated with PAI-1 levels adds to the body of evidence suggesting the health-promoting effects of whole grain intake and possibly detrimental effects of refined grain intake, as plasma PAI-1 concentrations have been significantly associated with an increased risk of type 2 diabetes (8,9).

The findings that whole grain intake was not related to fibrinogen concentration but was inversely related to CRP concentration are consistent with findings from the Nurses' Health Study II and Health Professionals Follow-up Study (17). The inverse relationship observed between whole grain intake

and log CRP in the current study is also consistent with findings from the Multi-Ethnic Study of Atherosclerosis study (18). When Jensen et al. (17) added lifestyle factors and BMI to their demographic model, however, the inverse association between whole grain intake and CRP was attenuated to nonsignificance. Due to the concurrent addition of lifestyle factors and BMI, it is difficult to compare these results with the findings from the current analysis in which the relationship between whole grain intake and CRP remained significant with adjustment for lifestyle factors (smoking, physical activity, and alcohol intake) but did not when waist circumference was added to the model. The results from the current study are consistent with those from the Multi-Ethnic Study of Atherosclerosis, which followed a similar multiple regression modeling strategy (18). The authors also found that additional adjustment for dietary factors, including fat subtypes, refined grain intake, and fruit and vegetable intakes, did not attenuate the relationship between whole grain intake and CRP but that additional adjustment for BMI and fasting insulin in their mechanistic model had an attenuating effect (18).

Central adiposity, glucose control, and S₁ are likely mediators of the relationships between whole grain consumption and inflammation. Observational studies have shown an inverse relationship between whole grain intake and BMI, waist circumference, and risk of weight gain (40) and refined grain intake has been related to a higher waist:hip ratio and increased risk of weight gain (40). Body weight, central adiposity in particular, has been strongly associated with plasma inflammatory protein concentrations, including CRP, fibrinogen, and PAI-1, and visceral adipose tissue is known to secrete a number of proinflammatory adipokines, including tumor necrosis factor α , interleukin-6, and PAI-1 (41). Thus, it is possible that whole grain intake could be related to lower inflammatory protein concentrations by preventing weight gain, promoting weight maintenance, and reducing visceral adiposity.

Whole grain consumption could also reduce the time spent in postprandial hyperglycemic states, because intact whole grain structure is thought to decrease the rate of gastric emptying and decrease macronutrient absorption (42). Lower postprandial glucose responses could lead to decreased plasma inflammatory protein concentrations by reducing the formation of advanced glycation end products that can induce oxidative stress and inflammation (43). Additionally, whole grain intake has been associated with lower fasting insulin concentrations and insulin resistance (17,18,31) and higher S₁ (31). The importance of S₁ in relation to inflammation relates to the emerging hypothesis that

insulin is an antiinflammatory hormone as evidenced by studies that have shown it to have downregulatory effects on proinflammatory transcription factors (44), and it is hypothesized that in an insulin-resistant state, there is a decrease in the downregulatory action of insulin on inflammatory transcription factor activity (44). Observational studies have shown strong positive associations between insulin resistance and plasma inflammatory protein concentrations (45) and, interestingly, insulin-sensitizing agents have been found to decrease concentrations of CRP and PAI-1 (45).

One limitation of this study is the cross-sectional analysis, making the temporal sequence of diet in relation to plasma inflammatory protein concentrations impossible to evaluate and causal relationships cannot be assumed. Additionally, although potential confounding variables were carefully considered, it is possible that residual confounding could have occurred due to other factors. However, the quality of metabolic and anthropometric measurements obtained at IRAS study visits, including waist circumference for a measure of visceral adiposity and a frequently sampled i.v. glucose tolerance test for a measure of S_1 , allowed for the adjustment of these variables with a high degree of precision, potentially providing insight to the pathway by which whole grain consumption could influence plasma inflammatory protein concentrations. Other studies of similar exposure and outcome measures have not included these specific measurements (17,18). Additionally, other indicators of a healthy lifestyle such as physical activity, smoking status, and fruit and vegetable intakes, were adjusted for in this analysis, reducing the potential for residual confounding.

The analysis of the relationship between grain intakes and inflammation in this study was limited due to the restricted number of plasma inflammatory protein measures available. Given the emerging interest in the relationship between antiinflammatory cytokines and dietary fiber (46) and the complex interplay between diet, cytokines, and inflammatory proteins (47), this study would have been enriched had a more complete panel of both inflammatory and antiinflammatory measures been available for this study population.

The FFQ used in this analysis was limited in its ability to accurately classify whole and refined grain intakes due to lack of specificity of some of the FFQ item lines, as the FFQ was not designed to distinguish between whole and refined grain intakes. Notwithstanding, the current findings of strong relationships between both whole and refined grain intakes and PAI-1 and the opposing directionality of these associations suggest that the grain variables used in this study adequately differentiated between high and low whole and refined grain consumers, as any misclassification error would have likely been nondifferential and would have tended to bias results toward the null.

One strength of the FFQ used was that it was modified to include food items that were reported to be regularly consumed by Hispanic and African American residents in the study center areas, which was especially important for measuring grain intakes in ethnic groups, as the foods added to the questionnaire included refined grain products (e.g. corn tortillas, burritos).

In conclusion, whole grain consumption may be related to lower circulating plasma concentrations of PAI-1 and CRP, which in turn could lower the risk of type 2 diabetes and cardiovascular disease. These findings suggest that the protectiveness of whole grains in relation to type 2 diabetes and cardiovascular disease may be due to an effect on plasma inflammatory protein concentrations and reinforces the public health recommendations that whole grains be consumed daily as part of a healthy diet. Refined grain intakes were positively associated with PAI-1 con-

centrations, indicating that refined grain intake could have proinflammatory effects. The novelty of this finding warrants further investigation into the potential effects of refined grain consumption on metabolic and inflammatory measures.

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