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Whole-grain intake and carotid artery atherosclerosis in a multiethnic cohort: the Insulin Resistance Atherosclerosis Study[1–3]

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ABSTRACT

Background: Whole-grain intake has been shown to be inversely associated with cardiovascular events, but an association with atherosclerosis is less well established.

Objective: We sought to evaluate the association of whole-grain intake with carotid intimal medial thickness (IMT) and IMT progression in a multiethnic cohort.

Design: This study evaluated 1178 participants in the Insulin Resistance Atherosclerosis Study. Baseline whole-grain intake was estimated on the basis of intake of dark breads, cooked cereals, and high-fiber cereals assessed with a validated food-frequency questionnaire. Bilateral carotid IMT was evaluated ultrasonographically, yielding 16 IMT measures at baseline and year 5. Multivariate models evaluated the independent association of whole-grain intake with common carotid artery (CCA) and internal carotid artery (ICA) IMT and IMT progression.

Results: The cohort had a mean (±SD) age of 55.2 ± 8.4 y and was 56% female. The baseline median whole-grain intake was 0.79 servings/d. Whole-grain intake was inversely associated with CCA IMT ($\beta \pm$ SE: -0.043 ± 0.013, $P = 0.005$) and IMT progression ($\beta \pm$ SE: -0.019 ± 0.011, $P = 0.09$) in models adjusted for demographics, energy intake, energy expenditure, cardiovascular disease risk factors, and medication use. This association was less significant for ICA IMT ($\beta \pm$ SE: -0.049 ± 0.023, $P = 0.05$) and not significant for ICA IMT progression ($\beta \pm$ SE: -0.013 ± 0.014, $P = 0.35$). The relation between whole-grain intake and CCA IMT remained significant after adjustment for mediating pathways (lipids, adiposity, and insulin resistance), nutrient constituents, and a principal components–derived healthy dietary pattern.

Conclusions: Whole-grain intake is inversely associated with CCA IMT, and this relation is not attributable to individual risk intermediates, single nutrient constituents, or larger dietary patterns. *Am J Clin Nutr* 2007;85:1495–502.

KEY WORDS Atherosclerosis, cereals, diet, ethnic groups, cohort studies, Doppler ultrasound

INTRODUCTION

The concurrent pandemics of type 2 diabetes (T2DM) and cardiovascular disease (CVD) (1) have followed a shift in population dietary patterns from whole to refined carbohydrate sources (2). Current guidelines propose that grains should lie at the foundation of a healthy diet, with whole grains being preferred over refined grains (3). Despite these recommendations, whole-grain intake in the United States falls far short of the recommended 3 servings/d (4). Numerous studies have found that higher whole-grain intakes are associated with a lower incidence of T2DM (5) and CVD (6–8). This protective effect has been attributed, in part, to the association between whole-grain intake and improved insulin sensitivity (9, 10), a cardioprotective lipid profile (11), and improved endothelial function (12). These beneficial characteristics of whole grains reflect a unique constellation of constituents and nutrients (13), such as fiber, magnesium, vitamin E, and phytonutrients, which are removed in the refining process.

Although the epidemiologic association between whole-grain intake and decreased cardiovascular disease risk has been widely replicated, the relation between whole-grain intake and atherosclerosis is less well established. One study in predominantly white postmenopausal women with preexisting heart disease found that women with a whole-grain intake above the median had less angiographic coronary atherosclerotic progression (14). However, it is unclear whether these findings are generalizable to a population that is more diverse with respect to demographic characteristics and cardiovascular disease risk profile. Carotid intimal medial thickness (IMT) is a noninvasive marker of systemic atherosclerosis, and IMT progression has been associated with subsequent cardiovascular events (15). We sought to evaluate the relation of whole-grain intake with carotid IMT and IMT progression in a multiethnic cohort. Furthermore, we evaluated the association between dietary patterns and IMT to determine whether any observed associations with whole-grain intake could be attributed to a broader pattern of dietary intake.

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SUBJECTS AND METHODS

Study population

The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, observational study to evaluate the relations between insulin resistance, cardiovascular disease risk factors, and atherosclerosis in a multiethnic cohort (16). The study sample was selected to obtain comparable representation of participants across age, sex, ethnicity (African American, Hispanic, and non-Hispanic white), and glucose tolerance [based on World Health Organization criteria (17)] strata, drawing from 4 US field centers (Los Angeles, CA; Oakland, CA; San Luis Valley, CO; and San Antonio, TX). From October 1992 to April 1994, 1625 participants aged 40–69 y underwent a baseline history (including dietary history), physical exam, laboratory measures, and diagnostic imaging. The study protocol was approved by local institutional review boards, and all participants provided written informed consent.

Five years after the baseline examination, all participants were invited to return for a follow-up examination, at which time all measures were repeated under an identical protocol. The response rate to this solicitation was 81%, and those who attended the follow-up examination were similar to those who did not attend in terms of ethnicity, sex, baseline glucose tolerance status, and body mass index (BMI; in kg/m^2) ($P > 0.32$ for all comparisons). The current study included 1178 participants who had baseline carotid ultrasonography and dietary data as well as follow-up carotid sonograms.

Dietary measures and independent variables

Information on usual dietary intake was assessed by using a 1-y, semiquantitative, 114-item food-frequency questionnaire (FFQ). Based on the National Cancer Institute Health History and Habits Questionnaire, the dietary instrument was modified to include regional and ethnic food choices and was validated in a sample of the cohort (18). Participants recalled their usual intakes of foods and beverages over the previous year, with responses ranging from "never or <1 time/mo" to "≥2 times/d" for foods and from "never or <1 time/mo" to "≥ 6 times/d" for beverages. Participants reported serving size as small, medium, or large compared with other men or women about the participant's age. Diet interviews were conducted in a standardized manner by interviewers who were centrally trained and certified, and audiotapes of the interviews were reviewed quarterly. The nutrient database HHHQ-DIETSYS (version 3.0; NCI, Bethesda, MD) was expanded to reflect the inclusion of additional food items and additional nutrients of interest.

Daily whole-grain intake was estimated on the basis of 3 FFQ lines worded as follows: *1*) "dark bread (including whole wheat, rye, pumpernickel, other high-fiber bread)"; *2*) "high-fiber bran or granola cereals, shredded wheat"; and *3*) "cooked cereal (including oatmeal, cream of wheat, grits)." Whole grain was calculated in servings per day by weighting the intake frequency with a factor based on the serving size (small: 0.5; medium: 1.0; large: 1.5).

Additionally, glycemic index (GI) and glycemic load (GL) were estimated as described previously (19). Briefly, each line item from the IRAS FFQ was assigned a mean GI value based on the white bread standard. In the case of multiple foods per FFQ line, each food was assigned a GI value, and the GI of the line item was estimated by using the weighted average of GI values based on the relative estimated population consumption of those items. Average dietary GI was determined by summing the products of the digestible carbohydrate content (total carbohydrate minus dietary fiber) per serving for each item, multiplied by the average number of servings of that food per day, multiplied by the item's GI. This value was then divided by the total amount of daily digestible carbohydrate intake (20). The method for determining average dietary GL was the same as for determining GI, but the summary value was not divided by the total digestible carbohydrate intake. For ease of interpretation, average dietary GI and GL values were converted to the glucose = 100 scale by multiplication with the factor 0.7. For additional analyses on dietary patterns, the FFQ and alcohol questionnaire items were condensed into 33 food groups on the basis of similarities in food and nutrient composition, and the daily intake of these food groups was computed (21).

The baseline interview also included a medical history and medication use. Participants were classified as current smokers, past smokers, or never smokers. Information on physical activity over the prior year was obtained by using a validated instrument (22), modified to include activities common among study participants (23). Annual energy expenditure was estimated from the frequency and duration of light, moderate, and vigorous physical activities. Anthropometric measures included height and weight measured in duplicate and recorded to the nearest 0.5 cm and 0.1 kg, respectively. Measurements of adiposity included BMI as well as minimum waist circumference measured with a flexible-steel tape measure and recorded to the nearest 0.5 cm. Seated blood pressure was obtained in a standardized manner with a mercury sphygmomanometer, averaging the second and third of 3 measures. Hypertension was defined by the current use of antihypertensive medications, systolic blood pressure (SBP) ≥140 mm Hg, or diastolic blood pressure (DBP) ≥90 mm Hg.

Participants were examined over a 2-d period to determine glucose tolerance status and insulin sensitivity. Both visits occurred after a 12-h fast, and participants were asked to abstain from heavy alcohol for 24 h before and refrain from smoking the morning of each visit. During the first visit, participants underwent a 2-h oral-glucose-tolerance test (Orange-dex; Custom Laboratories, Baltimore, MD). For these analyses, participants were classified by using American Diabetes Association criteria (24) as follows: T2DM—current hypoglycemic medication use, fasting glucose ≥126 mg/dL, or 2-h glucose ≥200 mg/dL; prediabetes—fasting glucose 100–125 mg/dL or 2-h glucose 140–199 mg/dL; normal glucose tolerance—fasting glucose <100 mg/dL and 2-h glucose <140 mg/dL. On a second visit, insulin sensitivity was assessed by using the frequently sampled intravenous-glucose-tolerance test (25) with minimal model analysis (26). The protocol was modified to use insulin rather than tolbutamide (27) and used a reduced number of plasma samples (from 30 to 12) (28). Details on the modeling methods were published previously (29).

Carotid ultrasonography

Participants underwent high-resolution B-mode carotid ultrasonography at baseline and at a 5-y follow-up with the use of identical scanning protocols and equipment. The protocol included bilateral assessment of wall thickness for the common carotid artery (CCA) and internal carotid artery (ICA). The ICA measurements were taken at the site of maximal thickness between the dilatation of the carotid bulb and the ICA, 1 cm distal

to the tip of the flow divider. Measures were taken of the near and far walls at 3 angles (proximal, lateral, and anterior). For the CCA, measures were taken 1 cm proximal to the dilatation of the carotid bulb at a single (lateral) angle. At follow-up, the sonographer sought the site of maximal IMT, independent of its location at baseline. This protocol resulted in a maximum of 8 measurements in each of the right and left arteries for each participant at baseline and follow-up. Ultrasound images were recorded on super-VHS tape and read at a central facility after completion of the follow-up examination by a single reader blinded to participant, participant characteristics, and examination. A subset of 43 participants was rescanned at baseline to assess intrasonographer variability, and the Pearson correlation coefficient between scans was 0.86 and 0.75 for the CCA and ICA IMTs, respectively. Similarly, in 64 scans reread to assess intrareader variability, the Pearson correlation coefficients between scans were 0.95 and 0.94 for the CCA and ICA IMTs, respectively.

Statistical analysis

For baseline characteristics, the cohort was stratified by median whole-grain intake. Comparisons of continuous variables between strata of whole-grain intake were made by using *t* tests, and categorical variables were compared by using chi-square statistics.

The primary outcome was composed of 32 planned IMT measurements (16 walls each at baseline and follow-up) per participant. To account for repeated measures of IMT within subjects over time (30), we used multivariate Laird-Ware linear models (31) to pool measures across visits. This has been shown to be an efficient approach to increase statistical power in evaluating IMT while allowing for heterogeneity among sites (30). In these models, individual wall segments were viewed as nested within subjects, and a compound symmetry covariance structure was assumed. The log-transformed IMT measurement Y_{ghijkl} from subject g, visit h (baseline/follow-up), and site defined by i = segment (common/internal), j = angle (proximal/lateral/anterior), k = side (left/right), and l = wall (near/far) was assumed to be normally distributed. Because there was evidence of a visit by segment by whole-grain intake interaction ($P < 0.0001$), all analyses were stratified by segment (CCA and ICA). All models included terms that allowed for different progression rates among sites (visit × wall × side). Multivariate analyses modeled the variable main effects (reflecting the association of variable and IMT at baseline and follow-up). Additionally, these analyses modeled IMT progression using variable × visit interaction terms: if the relation between a predictor and IMT varied by visit (significant variable × visit interaction), then it was significantly associated with IMT progression. Interactions for whole-grain intake and demographic characteristics (sex and ethnicity) were examined and were not significant ($P > 0.1$). Model 1 was fitted with adjustment for demographic factors (age, sex, clinical site, and ethnicity). Model 2 included the covariates in model 1 and covariates that reflected energy balance (total energy intake and total energy expenditure) and smoking status. Model 3 adjusted for covariates in model 2 and for cardiovascular disease risk factors (hypertension and diabetes status). Model 4 included covariates in model 3 and the use of lipid-lowering, hypoglycemic, and antihypertensive medications. β Coefficients are reported for the main effects of whole grain and the whole grain × visit interaction; negative values represented an inverse association between whole-grain intake and IMT or IMT progression. Exploratory models evaluated nutrient components and dietary characteristics (fiber, magnesium, B vitamins, vitamin E, GI, and GL) that could account for beneficial effects of whole-grain consumption. Additional exploratory models examined potential intermediate pathways whereby whole-grain intake may influence atherosclerosis, including adiposity (BMI and waist circumference), insulin sensitivity, and lipid variables (LDL cholesterol, LDL particle size, and total:HDL cholesterol ratio). For these analyses, the individual covariate was added to the fully adjusted model (model 4) to determine whether the association of whole grain and whole grain × visit with IMT persisted after these covariates were accounted for.

To evaluate the hypothesis that whole-grain intake was a marker of a healthy dietary profile, principal component factor analyses were performed with the use of the FACTOR procedure in SAS, and factor scores were generated with varimax rotation to create uncorrelated factors. The number of factors for inclusion was determined after examination of eigenvalues, the scree plot, and the interpretability of the factor solutions, evaluating solutions ranging from 2 to 6 factors. A factor score for each study participant was then calculated from the sum of the servings/d from all food groups and was multiplied by the respective factor loadings using the NFACT and OUT options in the FACTOR procedure. These factors were then modeled simultaneously in the fully adjusted multivariate model described above (model 4). Additionally, to compare the effect of whole-grain intake and a whole grain-associated dietary pattern, whole-grain intake was modeled after adjustment for the factor most closely associated with whole grains. All analyses were performed by using SAS version 9.1 (SAS Institute, Cary, NC), and all statistical tests were 2-tailed with an α level of 0.05.

RESULTS

At the baseline visit, the cohort was 55.8% female and had a mean (±SD) age of 55.2 ± 8.4 y (**Table 1**). The cohort had a median whole-grain intake of 0.79 servings/d, largely consisting of dark-bread whole-grain foods. Individuals with whole-grain intakes above the median were older, and there was a higher percentage of white participants in this group. Hypertension and medication use were more prevalent in individuals with a whole-grain intake above the median, and the prevalence of current smoking was lower in this group.

When whole-grain intake was modeled as a continuous variable, there was a strong, inverse association between whole-grain intake and CCA IMT in models 1–4 (**Table 2**). With respect to IMT progression, there was an inverse association with whole-grain intake that was marginally significant in the fully adjusted model. For the ICA, there was an inverse association between whole-grain intake and IMT in the fully adjusted model. Although the direction of the association was the same for ICA IMT progression, this inverse association was not significant.

The observed association between whole-grain intake and CCA IMT persisted in exploratory models that included nutritional factors that might account for this association (**Table 3**). Furthermore, in a model that included multiple nutrients or dietary characteristics as covariates (magnesium, thiamine, vitamin B-6, fiber, vitamin E, and GI), the relation between whole-grain intake and CCA IMT persisted: whole grain ($\beta \pm$ SE: -0.043 ± 0.015, $P = 0.005$) and whole grain × visit ($\beta \pm$ SE: -0.010 ± 0.013, $P = 0.43$). Additional exploratory models included potential mediating pathways for the beneficial effect of

TABLE 1
Baseline characteristics of the Insulin Resistance Atherosclerosis Study cohort (n = 1178), stratified by median whole-grain intake[1]

Characteristic	Whole-grain intake		P[2]
	<0.79 servings/d	≥0.79 servings/d	
Age (y)	54.1 ± 8.4	56.3 ± 8.2	< 0.0001
Female (%)	58.2	53.4	0.09
Ethnicity (%)			0.003
African American	29.1	29.8	
Hispanic	34.3	28.0	
White	36.6	42.3	
Diabetes status (%)			0.18
Normal	46.6	46.6	
Prediabetes	24.7	20.7	
T2DM	28.8	32.7	
S_I ($min^{-1} \cdot \mu U^{-1} \cdot mL^{-1} \cdot 10^{-4}$)	1.66 ± 1.87	1.72 ± 1.84	0.60
Hypertension (%)	34.1	40.7	0.02
LDL cholesterol (mg/dL)	141 ± 36	140 ± 33	0.60
LDL size (Å)	259.7 ± 9.3	259.9 ± 10.2	0.72
Total:HDL cholesterol ratio	5.26 ± 2.50	5.07 ± 2.01	0.14
BMI (kg/m^2)	29.4 ± 6.1	29.2 ± 5.5	0.46
Waist circumference (cm)	92.8 ± 13.6	92.6 ± 12.7	0.81
Lipid-lowering medication (%)	5.3	10.1	0.002
Hypoglycemic medication (%)	12.2	16.7	0.03
Antihypertensive (%)	24.3	30.5	0.02
Current smoking (%)	16.8	11.6	0.02
Total energy expenditure ($kcal \cdot kg^{-1} \cdot y^{-1}$)	14577 ± 2512	14580 ± 2586	0.99
Whole-grain intake (servings/d)	0.31 ± 0.23	1.51 ± 0.68	< 0.0001
Dark bread (servings/d)	0.18 ± 0.19	0.96 ± 0.63	< 0.0001
High-fiber cereal (servings/d)	0.06 ± 0.12	0.29 ± 0.37	< 0.0001
Hot cereal (servings/d)	0.07 ± 0.11	0.26 ± 0.33	< 0.0001
Total energy intake (kcal/d)	1803 ± 815	2029 ± 820	< 0.0001
Dietary fiber (g/d)	13.8 ± 6.8	19.2 ± 7.6	< 0.0001
Dietary magnesium (mg/d)	337 ± 221	493 ± 289	< 0.0001
Dietary vitamin E (mg/d)	10.4 ± 5.9	11.9 ± 5.9	< 0.0001
Glycemic index	82.8 ± 6.4	81.3 ± 5.9	< 0.0001
Glycemic load	162 ± 76	188 ± 77	< 0.0001

[1] S_I, insulin sensitivity; T2DM, type 2 diabetes mellitus.
[2] For comparison across median whole-grain intakes with the use of t tests or chi-square statistics.

whole grains (Table 3). In a model that evaluated multiple pathways simultaneously (insulin sensitivity, total:HDL cholesterol ratio, LDL particle size, and waist circumference), whole-grain intake remained inversely associated with CCA IMT: whole grain ($\beta \pm$ SE: -0.39 ± 0.021, $P = 0.02$) and whole grain × visit ($\beta \pm$ SE: -0.014 ± 0.012, $P = 0.08$).

TABLE 2
Whole-gain intake, carotid intimal medial thickness (IMT), and IMT progression in the Insulin Resistance Atherosclerosis Study cohort (n = 1178)

	Whole-grain main effect		Whole-grain × visit	
	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Common carotid artery				
Model 1[1]	−0.046 ± 0.013	0.003	−0.022 ± 0.011	0.05
Model 2[2]	−0.041 ± 0.013	0.01	−0.021 ± 0.011	0.07
Model 3[3]	0.042 ± 0.013	0.006	−0.021 ± 0.011	0.07
Model 4[4]	−0.043 ± 0.013	0.005	−0.019 ± 0.011	0.09
Internal carotid artery				
Model 1[1]	−0.050 ± 0.023	0.08	−0.023 ± 0.013	0.08
Model 2[2]	−0.039 ± 0.023	0.12	−0.010 ± 0.013	0.48
Model 3[3]	−0.043 ± 0.023	0.1	−0.012 ± 0.014	0.36
Mode 4[4]	−0.049 ± 0.023	0.05	−0.013 ± 0.014	0.35

[1] Multivariate Laird-Ware model, adjusted for age, sex, ethnicity, clinical site, vessel side, wall, angle, visit, and variable × visit interaction terms for all covariates.
[2] Adjusted for covariates in model 1 + total energy intake, total energy expenditure, smoking status, and variable × visit interaction terms for all covariates.
[3] Adjusted for covariates in model 2 + diabetes, hypertension, and variable × visit interaction terms for all covariates.
[4] Adjusted for covariates in model 3 + hypoglycemic, antihypertensive, and lipid-lowering medication use and variable × visit interaction terms for all covariates.

TABLE 3
Whole-grain intake, common carotid artery (CCA) intimal medial thickness (IMT), and CCA IMT progression in the Insulin Resistance Atherosclerosis Study cohort ($n = 1178$), adjusted for dietary factors or mediating pathways

	Whole-grain main effect		Whole-grain × visit	
Model	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Model 4[1]	−0.043 ± 0.013	0.005	−0.019 ± 0.011	0.09
Nutrients and dietary characteristics				
Model 4 + fiber	−0.045 ± 0.015	0.03	−0.012 ± 0.013	0.36
Model 4 + PUFAs[2]	−0.042 ± 0.013	0.005	−0.019 ± 0.011	0.10
Model 4 + magnesium	−0.032 ± 0.014	0.03	−0.011 ± 0.012	0.38
Model 4 + zinc	−0.039 ± 0.013	0.01	−0.017 ± 0.012	0.13
Model 4 + thiamine	−0.039 ± 0.014	0.01	−0.018 ± 0.012	0.14
Model 4 + riboflavin	−0.037 ± 0.013	0.02	−0.016 ± 0.012	0.16
Model 4 + niacin	−0.041 ± 0.013	0.009	−0.019 ± 0.012	0.11
Model 4 + vitamin B-6	−0.039 ± 0014	0.009	−0.015 ± 0.012	0.21
Model 4 + vitamin E	−0.040 ± 0.013	0.008	−0.018 ± 0.011	0.12
Model 4 + glycemic index	−0.042 ± 0.013	0.006	−0.018 ± 0.012	0.13
Model 4 + glycemic load	−0.042 ± 0.013	0.007	−0.021 ± 0.012	0.08
Mediating pathways				
Model 4 + BMI	−0.040 ± 0.013	0.01	−0.020 ± 0.011	0.08
Model 4 + waist circumference	−0.039 ± 0.013	0.01	−0.019 ± 0.011	0.10
Model 4 + insulin sensitivity[3]	−0.038 ± 0.014	0.02	−0.018 ± 0.012	0.12
Model 4 + total:HDL ratio	−0.043 ± 0.013	0.007	−0.020 ± 0.012	0.09
Model 4 + LDL	−0.043 ± 0.013	0.008	−0.023 ± 0.012	0.05
Model 4 + LDL particle size	−0.042 ± 0.013	0.008	−0.021 ± 0.012	0.08

[1] Multivariate Laird-Ware model, adjusted for measurement (visit, side, wall, and angle), demographic (age, sex, ethnicity, and clinical site), energy balance (total energy intake, and total energy expenditure), risk factor (diabetes, hypertension, and current smoking), and medication use (hypoglycemic, antihypertensive, and lipid-lowering) covariates, and for variable × visit interaction terms for all covariates.
[2] PUFAs, polyunsaturated fatty acids.
[3] Determined from a frequently sampled intravenous glucose tolerance test.

To examine the hypothesis that a dietary pattern associated with whole grains accounts for the observed association, principal-components factor analyses were performed. After factor solutions ranging from 2 to 6 factors were examined, a 3-factor solution was selected, and dietary patterns were named based on food groups that loaded heavily on the respective factors (**Table 4**). Groups that loaded heavily on the first factor, "Healthy," included whole grains, fruit, vegetables, fish, and poultry. A second factor, "Meat and Starch," included meat (beef and pork), refined grains, beans, and French fried potatoes. A third factor, "Snacks and Sweets," had high loadings for pastries, sweets, nuts, and salty snacks. These 3 factors accounted for 26% of the variance in food group intake (variance explained by varimax rotated dietary patterns: Healthy, 10.5%; Meat and Starch, 9.7%; and Snacks and Sweets, 6.2%). When these 3 patterns, along with the pattern × visit interactions, were modeled simultaneously to predict CCA IMT, the Healthy dietary pattern was not associated with CCA IMT or IMT progression (**Table 5**). There was a trend toward higher IMT, but not greater IMT progression, with greater intake of the Meat and Starch dietary pattern. When the Healthy dietary pattern was modeled simultaneously with whole-grain intake in fully adjusted models (model 4), the association between whole-grain intake and CCA IMT persisted: whole grain ($\beta \pm$ SE: -0.039 ± 0.014, $P = 0.01$) and whole grain × visit ($\beta \pm$ SE: -0.017 ± 0.012, $P = 0.16$).

DISCUSSION

In this multiethnic cohort of middle-aged men and women, whole-grain intake was inversely and independently associated with CCA IMT and IMT progression. This confirms and extends the findings of one prior study, which found that a high whole-grain intake was associated with less atherosclerotic progression in postmenopausal women with established heart disease (14). However, unlike the cohort examined by Erkkila et al, most of the participants in the IRAS cohort were not white (62%). Longitudinal studies have consistently found higher intakes of whole grains to be associated with lower cardiovascular disease risk, with a risk reduction of ≈25% when the high and low quintiles of intake were compared (6–8). Of the prior studies, only the Atherosclerosis Risk in Communities cohort had a significant ethnic minority (26%). Although our study was not powered to compare this association across ethnic groups, it does suggest that the favorable relation between whole-grain intake and atherosclerosis or cardiovascular disease risk is broadly applicable to individuals of different ethnicities and cardiovascular disease risk profiles.

There are multiple plausible mechanisms through which whole grains could be cardioprotective. Whole grains consist of endosperm, bran, and germ layers, the latter 2 components of which are removed during the refining process. The bran and germ layers are nutritionally complex and rich in fiber (soluble and insoluble), resistant starches, antioxidants, minerals, phytonutrients, and antinutrients (13). In turn, these constituents influence multiple factors associated with cardiovascular disease risk, including insulin resistance (9, 10), adiposity (32), LDL-cholesterol concentrations (11, 33) and particle size (34), endothelial function (12), and oxidative stress (13). In our study, the inverse association between whole-grain intake and CCA IMT

TABLE 4
Factor loadings for dietary patterns in the Insulin Resistance Atherosclerosis Study cohort

	Dietary pattern[1]		
Food groups	Healthy diet	Meat and starch	Snacks and sweets
Whole-grain bread, cereal	0.38	−0.30	0.26
Refined bread, cereal	—	0.75	—
Rice, pasta	0.63	0.14	—
Pastry	—	0.26	0.49
Vegetable, tomato	0.54	0.44	—
Vegetable, cruciferous	0.63	0.14	—
Vegetable, others	0.73	0.17	—
Potatoes	0.31	0.11	0.27
French fries, fried potatoes	−0.21	0.49	0.18
Fruit	0.57	—	0.15
Fruit juice	0.27	—	—
Cottage cheese	0.26	—	0.22
Cheese (Cheddar, American, etc)	0.22	0.35	0.37
Milk, yogurt (≤2% fat)	0.32	−0.27	0.29
Milk, yogurt (whole milk)	0.32	0.27	0.13
Ice cream, frozen yogurt	0.12	—	0.40
Fish	0.59	—	—
Dried beans	0.21	0.70	−0.14
Eggs	—	0.59	—
Meat	—	0.74	0.25
Poultry	0.51	—	—
Tofu, tempeh	0.13	—	—
Meal replacements	—	—	0.16
Nuts and seeds	—	—	0.50
Fats and oils	0.16	0.32	0.37
Sweets and sugars	−0.13	0.29	0.49
Salty snacks	—	0.10	0.51
Coffee and tea	—	0.22	0.21
Soft drinks and lemonades	—	0.29	—
Diet soft drinks and water	0.35	—	—
Beer	—	0.31	−0.17
Alcohol from mixed drinks	—	—	—
Wine	0.13	−0.13	—

[1] Derived by using principal components analyses with varimax rotation. Absolute factor loadings < 0.10 not presented for the sake of clarity.

persisted in all exploratory models, which reflects the complex and pleotropic benefits of whole grains.

One limitation of observational nutritional investigations is the possibility of residual confounding, because significant associations may be attributable to other dietary factors that are correlated to the exposure of interest. To address this, we evaluated empirically derived dietary patterns as an alternative hypothesis to explain the inverse association between whole-grain intake and atherosclerosis. In these analyses, whole grains loaded heavily on a Healthy pattern, which is consistent with previous studies of empirically derived dietary patterns. This pattern, which also includes fish, vegetables, and fruit, is comparable with the prudent (35, 36) or Mediterranean (37) diet. Previous factor analyses identifying this pattern associated it with a decreased risk of heart disease (35, 38) and cardiovascular or all-cause mortality (36). Although the Healthy factor was the dietary pattern with the highest factor loading for whole grains in our study, this pattern was not associated with CCA IMT or IMT

TABLE 5
Dietary patterns with respect to common carotid artery (CCA) intimal medial thickness (IMT) and CCA IMT progression in the Insulin Resistance Atherosclerosis Study cohort (n = 1178)[1]

	Pattern main effect		Pattern × visit	
Dietary pattern	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Healthy	0.011 ± 0.009	0.12	−0.003 ± 0.008	0.72
Meat and starch	0.023 ± 0.014	0.06	0.00 ± 0.12	0.97
Snacks and sweets	0.003 ± 0.010	0.26	−0.012 ± 0.009	0.15

[1] Modeled simultaneously in multivariate Laird-Ware models adjusted for measurement (visit, side, wall, and angle), demographic (age, sex, ethnicity, and clinical site), energy balance (total energy intake and total energy expenditure), risk factor (diabetes, hypertension, and current smoking), and medication-use (hypoglycemic, antihypertensive, and lipid-lowering) covariates and variable × visit interaction terms for all covariates.

progression. Furthermore, when whole-grain intake was adjusted for the score for the Healthy dietary pattern, the association between whole-grain intake and CCA IMT persisted. This finding suggests that the association of whole grains observed in the current study was attributable to whole grains themselves, rather than other dietary exposures in isolation or in synergy with whole grains (39).

Although these analyses noted a significant association of whole grain with CCA IMT and IMT progression, this association was not significant for the ICA measures. There are several potential explanations for these results. In a previous analysis from this cohort, Espeland et al (30) found that CCA and ICA IMT progression were not strongly correlated, noting that progression at one arterial site may induce remodeling at distal sites (40). This was supported by the observation that the correlation between CCA and ICA progression diminished with worsening glucose tolerance status (and the associated acceleration of progression). In our analyses, the β coefficients for the main effects were comparable when modeling CCA and ICA IMT, although the β coefficients for IMT progression were smaller for the ICA than for the CCA. This could indicate that the association between whole-grain intake and atherosclerotic progression varies by site.

Strengths of the current study include the study population and measures obtained. The IRAS cohort included a large number of African American and Hispanic participants, which allowed us to extend previous observations to nonwhite groups. A variety of historical, physical, laboratory, and diagnostic imaging measures were obtained in a standardized manner, which increased the capacity to adjust for confounders. The outcome of interest was a prospectively ascertained measure of subclinical atherosclerosis—carotid IMT—that was obtained using standardized techniques. Furthermore, carotid IMT is a validated measure of atherosclerosis that is predictive of subsequent myocardial infarction, coronary artery disease, and death due to ischemic heart disease (15). These factors rendered this cohort uniquely well suited to address questions regarding the relation between dietary factors and subclinical atherosclerosis.

There are several potential limitations to this investigation. The IRAS cohort was recruited to specifically address questions regarding insulin sensitivity and atherosclerosis and was thus enriched for individuals with T2DM or prediabetes. These findings may not be broadly applicable to lower-risk general populations. However, the association between whole-grain intake and a reduced risk of incident cardiovascular disease has been noted in healthy adults as well (8). Despite this enriched sample, annualized CCA IMT progression was lower in the IRAS (4.7 μm/y) than in the population-based Atherosclerosis Risk in Communities cohort (6.5 to 10.1 μm/y) (41). This lower rate of progression may be one reason why we did not detect a significant effect of whole-grain intake on CCA IMT progression.

Additionally, the use of a food-frequency questionnaire to evaluate this association may increase the opportunity for misclassification. Although designed for cross-ethnic applicability and validated in a sample of the cohort (18), the IRAS FFQ was not specifically designed to address hypotheses related to whole-grain intake. Thus, some foods classified as whole grains in previous studies (ie, popcorn and brown rice) (6) would have been included in line items that were dominated by refined products (salty snacks and rice) and were thus excluded from our whole-grain variable. This sort of misclassification is ubiquitous among investigations pertaining to dietary exposures and subclinical or clinical outcomes and would be expected to bias results toward the null. Additionally, dietary grains, like other foods, may be subject to underreporting (42). However, any observational investigation of dietary hypotheses would be subject to these limitations, and our results support and extend previous findings of the role of whole-grain intake in cardiovascular health.

In conclusion, whole-grain food intake was inversely associated with common carotid intimal medial thickness in this middle-aged, multiethnic cohort, and this was not attributable to individual risk intermediates, single nutrient constituents, or larger dietary patterns. These findings provide further support for the potential beneficial role of whole grains in reducing atherosclerotic cardiovascular disease.

The authors' responsibilities were as follows—PBM: study conception and manuscript preparation; PBM, ADL, and DMH: study design; PBM, ADL, JAT, and LEW: data analysis; PBM and JAT: statistical analysis; ADL, JAT, MZV, LEW, and DMH: editorial input. None of the authors had a conflict of interest to disclose

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