See corresponding editorial on page 357.

Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study[1–3]

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ABSTRACT

Background: Recent epidemiologic study results showed that subjects who had high intakes of whole-grain foods had lower risks of death and heart disease than did subjects who had low intakes. However, the findings were inconsistent for fruit and vegetable intake.

Objective: The relations of whole-grain, refined-grain, and fruit and vegetable intakes with the risk of total mortality and the incidence of coronary artery disease (CAD) and ischemic stroke were studied in the Atherosclerosis Risk in Communities (ARIC) cohort (baseline: age 45–64 y, n = 15 792).

Design: Proportional hazards regression analyses were used to assess the relations of whole-grain, refined-grain, and fruit and vegetable intakes with the risk of death and the incidence of CAD and ischemic stroke, with adjustment for age, sex, ethnicity, energy intake, and cardiovascular disease risk factors. Dietary intakes were assessed by using a food-frequency questionnaire.

Results: Over an 11-y follow-up period, whole-grain intake was inversely associated with total mortality and incident CAD. The relative hazards of death for quintiles 2–5 of fruit and vegetable intake were 1.08 (95% CI: 0.88, 1.33), 0.94 (0.75, 1.17), 0.87 (0.68, 1.10), and 0.78 (0.61, 1.01), respectively; P for trend = 0.02. An inverse association between fruit and vegetable intake and CAD was observed among African Americans but not among whites (P for interaction = 0.01). The risk of ischemic stroke was not significantly related to whole-grain, refined-grain, or fruit and vegetable consumption.

Conclusion: These observational findings suggest a beneficial effect of whole-grain and fruit and vegetable consumption on the risks of total mortality and incident CAD but not on the risk of ischemic stroke. *Am J Clin Nutr* 2003;78:383–90.

KEY WORDS Whole grain, fruit and vegetables, coronary artery disease, stroke, all-cause mortality

INTRODUCTION

The 2000 *Dietary Guidelines for Americans* from the US Department of Agriculture provides advice about healthy food choices for the American population aged ≥ 2 y (1). These guidelines recommend that Americans consume ≥ 5 servings of fruit and vegetables/d and 6–11 servings of grain products/d, especially whole grains.

A whole grain consists of 3 botanically defined parts: the bran, the germ, and the endosperm. The bran and germ contain many nutrients and phytochemicals, whereas the endosperm is largely starch and provides mostly energy. A refined grain contains only the endosperm and thus provides fewer nutrients and phytochemicals than does the whole grain. US adults consume on average 5.7 servings of refined grain/d (2). Despite the well-known fact that whole-grain food is more nutrient dense than is refined-grain food, the average consumption of whole-grain foods among US adults is only 1 serving/d, and only 8% of US adults consume 3 servings/d (2). Similar to whole grain, fruit and vegetables are rich in a myriad of nutrients and phytochemicals, including energy, fiber, B vitamins, vitamin C, antioxidants, potassium, flavonoids, and other identified and unidentified food compounds. The median intake of fruit and vegetables among US adults is 3.4 servings/d, and only 23% of US adults consume the recommended 5 servings of fruit and vegetables/d (3).

Clinical studies have shown that increasing the intake of whole-grain foods and fruit and vegetables improves the cardiovascular risk profile. Feeding studies of increased whole grain consumption over 4–8 wk reported significantly reduced fasting insulin and 2-h insulin concentrations (4, 5), total and LDL-cholesterol concentrations (6), and systolic blood pressure (7) and slightly reduced weight and body mass index (BMI; in kg/m^2) (8). The intake of fruit and vegetables may decrease the risks of death, coronary artery disease (CAD), and stroke through modification of platelet activity (9), homocysteine concentrations (10, 11), and blood pressure (12) and replacement of fatty acids in the diet, such as a reduction of saturated fat intake.

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Several prospective studies have shown reduced disease incidence with increased consumption of whole-grain foods (13–17). However, the evidence is inconsistent regarding the health outcomes of refined-grain consumption (14, 15) and fruit and vegetable consumption (18). Most previous studies were conducted among whites. We hypothesized that both whole-grain and fruit and vegetable consumption would be inversely associated with the risks of death and incident CAD and ischemic stroke among white and African American men and women enrolled in the Atherosclerosis Risk in Communities (ARIC) Study. In addition, we hypothesized that refined-grain intake would be positively associated with the risks of all-cause mortality and incident CAD and ischemic stroke.

SUBJECTS AND METHODS

Study design and population

The ARIC Study is a multicenter, population-based prospective investigation of the etiology and natural history of atherosclerotic disease in middle-aged adults (19). A probability sample of 15 792 residents aged 45–64 y was recruited in 1987–1989 from Forsyth County, NC; Jackson, MS; selected suburbs of Minneapolis; and Washington County, MD. Participation rates at baseline were 60% overall, including 42–49% of eligible African American men and women and 67–68% of eligible white men and women (20). Because 2 endpoints of interest were incident CAD and ischemic stroke, study participants were excluded from the analyses if they had prevalent CAD ($n = 766$) or prevalent stroke or transient ischemic attack ($n = 738$). Participants with prevalent diabetes ($n = 1870$) or cancer ($n = 889$) were also excluded because they may have changed their dietary intakes after diagnosis of these conditions. We further excluded 11 subjects with missing dietary information and 282 subjects with an energy intake < 500 or 700 kcal or > 3500 or 4500 kcal for women and men, respectively. These cutoffs approximated the lower and upper 1% of the energy-intake distribution. Forty-eight subjects were excluded from the analyses because they were not white or African American. The analyses consisted of 11 940 participants (4083 white men, 4754 white women, 1188 African American men, and 1915 African American women). The Institutional Review Boards of the 4 participating centers approved the study.

Data collection

Study participants underwent a comprehensive baseline examination for cardiovascular disease risk factors and ≤ 3 triennial reexaminations. Usual dietary intakes were assessed with the use of a 66-item, semiquantitative food-frequency questionnaire, which was administered by an interviewer at baseline and 6 y later (exam 3). The questionnaire was a modified version of the 61-item instrument and was validated by Willett et al (21). Participants were asked to report the frequency of consumption of each food on the basis of 9 categories, ranging from never or < 1 time/mo to ≥ 6 times/d. Interviewers obtained additional information, including the brand name of the breakfast cereal usually consumed.

Foods were grouped into whole grain, refined grain, fruit and vegetables, dairy foods, fish, and meat. The whole- and refined-grain groups were formed according to previously developed procedures (13). The food items that were classified as whole grain were dark bread and whole-grain cold breakfast cereal. Whole-grain cold cereals contained ≥ 25% whole grain or bran by weight [arbitrary cutoff selected by the original scorers (13)] as determined from the package label or from records shared by the cereal manufacturing companies. Food items classified as refined grain included cold breakfast cereals containing < 25% whole grain or bran by weight, cooked cereals (subjects were queried about their consumption of oatmeal, cream of wheat, and cream of rice on a single questionnaire item, and thus the consumption of 1 of these 3 cereals could not be separated from that of the other 2), white bread, bagels, donuts, pastry, muffins, biscuits, cookies, cake, brownies, pasta, and rice (subjects were not queried about their consumption of brown rice and wild rice). Seven categories of fruit (fresh apples or pears, oranges, orange or grapefruit juice, peaches, apricots or plums, bananas, and other fruit) and 15 categories of vegetables (green beans, broccoli, cabbage, cauliflower, Brussel sprouts, carrots, corn, spinach, collards or other greens, peas or lima beans, dark-yellow winter squash, sweet potatoes, beans or lentils, tomatoes, and potatoes, not including French fries) listed on the food-frequency questionnaire were categorized in the fruit and vegetable food group. Vegetables in mixed dishes were not included as a component of the fruit and vegetable group for these analyses.

Ascertainment of events

Study participants were followed for all-cause mortality, incident CAD, and incident ischemic stroke endpoints. Potential events were identified via annual telephone calls, community-wide hospital surveillance, and linkage with local and national death-certificate registries (22, 23). Events were investigated and validated by using hospital records, and deaths were investigated and validated by using physician records and next-of-kin interviews. Incident CAD was defined on the basis of published criteria (22) as the first definite or probable myocardial infarction, silent myocardial infarction by electrocardiography, definite CAD death, or coronary revascularization. Incident ischemic stroke was defined as the first definite or probable cardioembolic or thrombotic brain infarction on the basis of criteria adopted from the National Survey of Stroke (23). Events were classified by a combination of computer algorithm and independent review of medical record abstractions and discharge summaries by 1 or 2 physicians (and adjudication, if necessary) (22, 23).

Statistical analysis

All analyses were conducted by using the statistical software package SAS, version 6.12 (SAS Institute Inc, Cary, NC). Follow-up time was calculated as the time from baseline to an event or the last follow-up contact or through 31 December 1999, whichever occurred first. The whole-grain, refined-grain, and fruit and vegetable food groups were categorized into quintiles. Means or frequencies of demographic, physical, and clinical characteristics and of dietary intakes were computed for each quintile of whole-grain, refined-grain, and fruit and vegetable intake. Cox proportional hazards regression analyses were used to assess the relations of whole-grain, refined-grain, and fruit and vegetable consumption with the risk of all-cause mortality or the incidence of CAD or ischemic stroke, with adjustment for age at baseline, sex, race, energy intake (kilocalories), and selected CAD risk factors. These risk factors included education (≤ high school graduate or > high school graduate), BMI, waist-to-hip ratio (WHR; waist circumference in centimeters divided by hip circumference in centimeters), systolic blood pressure (average of 2 measurements), use of antihypertensive medication (yes or no), current smoking (yes or no), pack-years of cigarette smoking, Baecke

TABLE 1
Baseline characteristics of white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study by quintile (Q) of whole-grain intake[1]

Characteristic	Q1 (0.1; 0–0.2)[2]	Q2 (0.5; 0.3–0.7)	Q3 (1.0; 0.8–1.1)	Q4 (1.5; 1.2–1.9)	Q5 (3.0; 2.0–10.5)	*P* for trend
Age (y)	53.2 ± 0.1[3]	53.3 ± 0.1	53.6 ± 0.1	54.1 ± 0.1	54.3 ± 0.1	<0.001
>High school education (%)	32	43	47	54	54	<0.001
BMI (kg/m^2)	27.2 ± 0.1	27.4 ± 0.1	27.4 ± 0.1	27.1 ± 0.1	27.3 ± 0.1	0.14
Waist-to-hip ratio (×100)	92.8 ± 0.1	92.1 ± 0.1	91.8 ± 0.1	91.5 ± 0.1	91.2 ± 0.1	<0.001
Hypertension (%)	31	31	32	32	28	0.02
Current smoker (%)	35	31	26	19	19	<0.001
Never alcohol drinker (%)	26	24	25	24	24	0.21
Physical activity (%)[4]	50	59	58	65	65	<0.001
Energy intake (kcal/d)	1485 ± 12	1493 ± 12	1560 ± 12	1590 ± 12	1810 ± 12	<0.001
Alcohol intake (g/d)	7.2 ± 0.3	6.8 ± 0.3	6.7 ± 0.3	5.9 ± 0.3	5.3 ± 0.3	<0.001
Hormone replacement in women (%)	30	33	34	38	37	<0.001

[1] n = 11 940. Values were adjusted for age at baseline, sex, race, and baseline energy intake.
[2] $\bar{x}$ and range in parentheses (in servings/d).
[3] $\bar{x}$ ± SE.
[4] Score of >2.0 on the sport index of the Baeke physical activity questionnaire (24).

physical activity (sport index ≤2 or >2) (24), and alcohol intake (grams per day). LDL cholesterol and HDL cholesterol were included in the incident CAD models only. The time-dependent diet variables represent the average cumulative diet from exam 1 and exam 3 (year 6 of follow-up), provided that the participant did not die or was not diagnosed with CAD or stroke before exam 3. For those participants who died or were diagnosed with CAD or stroke by exam 3, only diet information from exam 1 was included in the model (25). The lowest quintile of intake formed the reference category. Tests for linear trends across increasing quintiles of food-group intake used the median value in each quintile as the intake. Two- and 3-way interactions between sex, race, and each food variable were tested.

RESULTS

Among the 11 940 study participants who were free of CAD and stroke at baseline and over an average of 11 y of follow-up, 867 died of all causes, 535 had fatal or nonfatal incident CAD, and 270 sustained a fatal or nonfatal incident stroke, of which 214 were ischemic strokes. Only 2% of the study participants were lost to follow-up. The mean (±SD) ages of the women and the men at baseline were 53.4 ± 5.7 and 54.1 ± 5.7 y, respectively.

Whole-grain intake

The median intake of whole-grain foods in the subjects was 1.0 serving/d. Almost 10% of white men and women reported consuming ≥3 servings of whole-grain foods/d, whereas <5% of African Americans consumed ≥3 servings/d. Mean age varied by ≈1 y across the whole-grain intake quintiles (**Table 1**). As expected, compared with the subjects who consumed less whole grain, those who consumed more completed more years of education and engaged in healthier behaviors (eg, not smoking, physical activity, and lower alcohol consumption at baseline). A high whole-grain intake was also associated with greater energy intake and the consumption of more daily servings of fruit and vegetables, dairy foods, and fish and fewer daily servings of refined-grain foods and red meat (data not shown). Although mean BMI varied little across the whole-grain quintiles, the whole-grain consumers had significantly lower mean WHR values, which suggests that the whole-grain consumers had proportionately less central adiposity and perhaps greater lean mass.

Refined-grain intake

The median intake of refined grains in the subjects was 2.0 servings/d. Consumption of refined grain was unrelated to age (**Table 2**). In contrast with the results for whole-grain intake, greater refined-grain intake was associated with lower educational attainment and with participation in unhealthy behaviors, including smoking, being sedentary, and consuming more meat and fewer whole-grain foods, fruit and vegetables, and dairy foods (data not shown).

Fruit and vegetable intake

The median total intake of fruit and vegetables was 3.5 servings/d. About 25% of the women and men consumed ≥5 servings of fruit and vegetables/d. Compared with a low fruit and vegetable intake, a high intake was associated with older age, higher educational attainment, not smoking, lower WHR, a greater prevalence of hypertension, greater participation in physical activity (**Table 3**), and consumption of more whole-grain foods (data not shown). Similar to the results for whole grain, a high consumption of fruit and vegetables was related to greater intakes of dairy foods and fish and lower intakes of red meat and refined grain (data not shown).

Adjusted associations of plant-based food intake with risks of death, incident CAD, and ischemic stroke

Whole-grain intake

After adjustment for age, sex, race, and total energy intake, inverse dose-response relations for both total mortality and incident CAD were observed across quintiles of whole-grain intake (**Table 4**). Further adjustment for potential confounding factors, including lifestyle factors represented in model 2 and physical and clinical CAD risk characteristics in model 3, attenuated the associations; however, the linear trends remained significant. The subjects in the quintile with a mean intake of 3 servings of whole grain/d had a 23% and 28% lower risk of total mortality and incident CAD, respectively, than did those in the quintile with a mean intake of 0.1 serving/d. The hazard ratios for the relation between

TABLE 2
Baseline characteristics of white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study by quintile (Q) of refined-grain intake[1]

Characteristic	Q1 (0.5; 0–1.01)[2]	Q2 (1.5; 1.02–1.64)	Q3 (2.0; 1.65–2.40)	Q4 (3.0; 2.41–3.60)	Q5 (5.5; 3.61–30.0)	*P* for trend
Age (y)	53.9 ± 0.1[3]	53.5 ± 0.1	53.6 ± 0.1	53.7 ± 0.1	53.8 ± 0.1	0.15
>High school education (%)	54	51	49	41	34	<0.001
BMI (kg/m^2)	27.3 ± 0.1	27.4 ± 0.1	27.3 ± 0.1	27.3 ± 0.1	27.1 ± 0.1	0.49
Waist-to-hip ratio (×100)	91.8 ± 0.1	91.5 ± 0.1	91.9 ± 0.1	91.9 ± 0.1	92.3 ± 0.1	<0.001
Hypertension (%)	30	30	30	32	32	0.75
Current smoker (%)	23	24	24	27	32	<0.001
Never alcohol drinker (%)	22	22	25	28	25	0.001
Physical activity (%)[4]	68	63	59	55	52	<0.001
Energy intake (kcal/d)	1172 ± 10	1339 ± 10	1543 ± 10	1756 ± 10	2148 ± 10	<0.001
Alcohol intake (g/d)	6.2 ± 0.3	6.6 ± 0.3	6.1 ± 0.3	6.0 ± 0.3	6.9 ± 0.3	0.11
Hormone replacement in women (%)	37	34	34	34	32	0.18

[1] n = 11 940. Values were adjusted for age at baseline, sex, race, and baseline energy intake.
[2] $\bar{x}$ and range in parentheses (in servings/d).
[3] $\bar{x}$ ± SE.
[4] Score of >2.0 on the sport index of the Baeke physical activity questionnaire (24).

whole-grain intake and incident ischemic stroke were similar to those for mortality and incident CAD. However, the linear trend did not remain significant after adjustment for potential confounding factors. The point estimates changed very little when refined grain was included in the models.

Refined-grain intake

In contrast with the results for whole-grain intake, positive dose-response relations for total mortality and incident CAD were observed across quintiles of refined-grain intake after adjustment for demographic characteristics and energy intake (**Table 5**). However, after further adjustment for potential confounding factors, the relations were attenuated for both total mortality and incident CAD in models 2 and 3. Compared with the subjects in the quintile with a mean intake of 0.5 servings of refined-grain foods/d, those in the quintile with a mean intake of 2 servings/d showed a trend for an increase in risk; however, the linear trend was not significant after adjustment for potential confounding factors. No relation was observed between risk of incident ischemic stroke and consumption of refined-grain foods. The point estimates changed very little when whole grain was included in the models.

Fruit and vegetable intake

As shown in **Table 6**, consumption of fruit and vegetables was inversely associated with total mortality in all models and with incident CAD in model 1 only. Compared with the subjects in the quintile with a mean intake of 1.5 servings of fruit and vegetables/d, those in the quintile with a mean intake of 7.5 servings/d had a 22% lower risk of total mortality after adjustment for confounding factors and whole- and refined-grain intake. There was no association between the intake of fruit and vegetables and the risk of incident ischemic stroke.

Subgroup analyses by race and sex

Two- and 3-way interactions with race, sex, and each food-group variable were tested, and most were not significant. Associations of consumption of refined grains (*P* for interaction = 0.10) and of fruit and vegetables (*P* for interaction = 0.01) with the risk

TABLE 3
Baseline characteristics of white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study by quintile (Q) of fruit and vegetable intake[1]

Characteristic	Q1 (1.5; 0.1–2.1)[2]	Q2 (2.5; 2.2–3.1)	Q3 (3.5; 3.2–4.1)	Q4 (4.5; 4.2–5.4)	Q5 (7.5; 5.5–60)	*P* for trend
Age (y)	52.7 ± 0.1[3]	53.1 ± 0.1	53.8 ± 0.1	54.3 ± 0.1	54.7 ± 0.1	<0.001
>High school education (%)	35	43	47	51	54	<0.001
BMI (kg/m^2)	27.4 ± 0.1	27.4 ± 0.1	27.1 ± 0.1	27.2 ± 0.1	27.3 ± 0.1	0.21
Waist-to-hip ratio (×100)	92.6 ± 0.1	92.1 ± 0.1	91.6 ± 0.1	91.5 ± 0.1	91.4 ± 0.1	<0.001
Hypertension (%)	28	29	31	32	34	0.001
Current smoker (%)	37	31	23	21	19	<0.001
Never alcohol drinker (%)	22	23	24	26	27	<0.001
Physical activity (%)[4]	46	55	60	65	71	<0.001
Energy intake (kcal/d)	1226 ± 11	1416 ± 11	1567 ± 11	1723 ± 11	2020 ± 11	<0.001
Alcohol intake (g/d)	7.1 ± 0.3	6.6 ± 0.3	5.9 ± 0.3	6.2 ± 0.3	6.0 ± 0.3	<0.001
Hormone replacement in women (%)	29	31	37	37	37	<0.001

[1] n = 11 940. Values were adjusted for age at baseline, sex, race, and baseline energy intake.
[2] $\bar{x}$ and range in parentheses (in servings/d).
[3] $\bar{x}$ ± SE.
[4] Score of >2.0 on the sport index of the Baeke physical acitivity questionnaire (24).

TABLE 4
Multivariate-adjusted hazard rate ratios (and 95% CIs) for death, incident coronary artery disease (CAD), and incident ischemic stroke by quintile (Q) of whole-grain intake in white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study[1]

	Q1 (0.1)[2]	Q2 (0.5)	Q3 (1.0)	Q4 (1.5)	Q5 (3.0)	*P* for trend
All-cause mortality						
Cases	229	197	166	155	120	
Model 1[3]	1	0.84 (0.69, 1.01)	0.66 (0.54, 0.81)	0.63 (0.51, 0.78)	0.52 (0.41, 0.65)	0.001
Model 2[4]	1	0.98 (0.80, 1.19)	0.81 (0.65, 0.99)	0.87 (0.70, 1.07)	0.75 (0.59, 0.95)	0.009
Model 3[5]	1	0.96 (0.79, 1.17)	0.80 (0.65, 0.99)	0.87 (0.70, 1.08)	0.77 (0.61, 0.97)	0.02
Incident CAD						
Cases	154	95	116	96	74	
Model 1	1	0.71 (0.55, 0.91)	0.80 (0.63, 1.02)	0.56 (0.43, 0.73)	0.52 (0.39, 0.69)	0.001
Model 2	1	0.80 (0.61, 1.04)	0.96 (0.75, 1.24)	0.73 (0.55, 0.97)	0.71 (0.53, 0.95)	0.02
Model 3	1	0.76 (0.58, 0.99)	0.93 (0.72, 1.21)	0.73 (0.55, 0.98)	0.72 (0.53, 0.97)	0.05
Incident ischemic stroke						
Cases	59	49	43	33	30	
Model 1	1	1.09 (0.74, 1.60)	0.73 (0.47, 1.11)	0.78 (0.51, 1.19)	0.62 (0.39, 0.99)	0.016
Model 2	1	1.14 (0.77, 1.68)	0.79 (0.51, 1.23)	0.87 (0.57, 1.38)	0.73 (0.45, 1.18)	0.11
Model 3	1	1.11 (0.75, 1.64)	0.79 (0.50, 1.21)	0.89 (0.57, 1.39)	0.75 (0.46, 1.22)	0.15

[1] n = 11 940.
[2] $\bar{x}$ servings/d.
[3] Adjusted for age at baseline, race, sex, and time-dependent energy intake.
[4] Adjusted for model 1 covariates plus education, smoking status, pack-years of smoking, physical activity, alcohol intake, and hormone replacement in women.
[5] Adjusted for model 2 covariates plus BMI, waist-to-hip ratio, systolic blood pressure, and use of antihypertensive medications; HDL and LDL are included in the model for incident CAD.

of incident CAD were stronger among the African Americans than among the whites. After adjustment for age, sex, energy intake, and other confounding factors, the hazard ratios (and 95% CIs) for incident CAD across quintiles of refined-grain intake in the Africans Americans were 1.0 (referent), 0.88 (0.44, 1.76), 1.24 (0.64, 2.37), 1.58 (0.82, 3.04), and 2.05 (1.01, 4.14) (*P* for linear trend = 0.01). Among the whites, the hazard ratios (and 95% CIs) for incident CAD across quintiles of refined-grain intake were 1.0, 0.88 (0.60, 1.29), 1.18 (0.83, 1.68), 1.11 (0.78, 1.59), and 0.98 (0.66, 1.47) (*P* for linear trend = 0.67). Among the African Americans, the multivariate hazard ratios (and 95% CIs) for incident CAD across quintiles of fruit and vegetable intake were 1.0 (referent), 0.96 (0.57, 1.59), 0.70 (0.40, 1.23), 0.75 (0.42, 1.34), and 0.37 (0.17, 0.80) (*P* for linear trend = 0.01). Among the whites, the hazard ratios (and 95% CIs) for incident CAD across quintiles of fruit and vegetable intake were 1.0, 1.11 (0.80, 1.55), 1.48 (1.07, 2.05), 1.21 (0.84, 1.75), and 1.13 (0.75, 1.71) (*P* for linear trend = 0.48).

TABLE 5
Multivariate-adjusted hazard rate ratios (and 95% CIs) for death, incident coronary artery disease (CAD), and incident ischemic stroke by quintile (Q) of refined-grain intake in white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study[1]

	Q1 (0.5)[2]	Q2 (1.5)	Q3 (2.0)	Q4 (3.0)	Q5 (5.0)	*P* for trend
All-cause mortality						
Cases	146	151	166	172	232	
Model 1[3]	1	0.96 (0.76, 1.22)	1.08 (0.85, 1.35)	1.07 (0.85, 1.36)	1.34 (1.04, 1.72)	0.02
Model 2[4]	1	0.94 (0.74, 1.20)	1.03 (0.81, 1.31)	0.96 (0.76, 1.23)	1.09 (0.84, 1.42)	0.51
Model 3[5]	1	0.96 (0.75, 1.23)	1.03 (0.81, 1.31)	0.97 (0.76, 1.23)	1.08 (0.83, 1.40)	0.62
Incident CAD						
Cases	74	77	118	132	134	
Model 1	1	0.92 (0.67, 1.27)	1.25 (0.92, 1.69)	1.53 (1.13, 2.06)	1.54 (1.1, 2.15)	0.001
Model 2	1	0.89 (0.64, 1.24)	1.18 (0.87, 1.61)	1.30 (0.96, 1.78)	1.17 (0.83, 1.65)	0.09
Model 3	1	0.91 (0.65, 1.27)	1.14 (0.83, 1.56)	1.28 (0.93, 1.75)	1.17 (0.82, 1.66)	0.11
Incident ischemic stroke						
Cases	39	49	41	36	49	
Model 1	1	1.12 (0.72, 1.73)	1.06 (0.68, 1.65)	0.76 (0.46, 1.24)	1.01 (0.60, 1.67)	0.53
Model 2	1	1.11 (0.71, 1.72)	1.03 (0.66, 1.62)	0.69 (0.42, 1.14)	0.83 (0.49, 1.41)	0.18
Model 3	1	1.10 (0.71, 1.73)	1.00 (0.63, 1.58)	0.68 (0.41, 1.13)	0.82 (0.48, 1.40)	0.16

[1] n = 11 940.
[2] $\bar{x}$ servings/d.
[3] Adjusted for age at baseline, race, sex, and time-dependent energy intake.
[4] Adjusted for model 1 covariates plus education, smoking status, pack-years of smoking, physical activity, alcohol intake, and hormone replacement in women.
[5] Adjusted for model 2 covariates plus BMI, waist-to-hip ratio, systolic blood pressure, and use of antihypertensive medications; HDL and LDL are included in the model for incident CAD.

TABLE 6
Multivariate-adjusted hazard rate ratios (and 95% CIs) for death, incident coronary artery disease (CAD), and incident ischemic stroke by quintile (Q) of fruit and vegetable intake in white and African American men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study[1]

	Q1 (1.5)[2]	Q2 (2.5)	Q3 (3.5)	Q4 (5.0)	Q5 (7.5)	*P* for trend
All-cause mortality						
Cases	193	204	159	163	148	
Model 1[3]	1	0.97 (0.80, 1.19)	0.76 (0.62, 0.94)	0.64 (0.51, 0.80)	0.53 (0.42, 0.68)	0.001
Model 2[4]	1	1.10 (0.89, 1.35)	0.95 (0.76, 1.18)	0.88 (0.70, 1.11)	0.80 (0.62, 1.04)	0.02
Model 3[5]	1	1.08 (0.88, 1.33)	0.94 (0.75, 1.17)	0.87 (0.68, 1.10)	0.78 (0.61, 1.01)	0.02
Incident CAD						
Cases	117	120	103	108	87	
Model 1	1	0.96 (0.74, 1.25)	1.01 (0.78, 1.32)	0.82 (0.62, 1.09)	0.59 (0.42, 0.81)	0.001
Model 2	1	1.08 (0.82, 1.41)	1.23 (0.93, 1.61)	1.08 (0.80, 1.46)	0.85 (0.60, 1.21)	0.43
Model 3	1	1.10 (0.84, 1.45)	1.21 (0.91, 1.60)	1.06 (0.78, 1.44)	0.82 (0.57, 1.17)	0.29
Incident ischemic stroke						
Cases	43	55	41	39	36	
Model 1	1	1.47 (0.97, 2.23)	1.04 (0.66, 1.62)	0.91 (0.56, 1.45)	0.89 (0.54, 1.48)	0.21
Model 2	1	1.60 (1.05, 2.44)	1.14 (0.72, 1.82)	1.09 (0.67, 1.79)	1.03 (0.59, 1.78)	0.60
Model 3	1	1.55 (1.02, 2.37)	1.10 (0.69, 1.76)	1.04 (0.63, 1.70)	0.94 (0.54, 1.63)	0.40

[1] n = 11 940.
[2] $\bar{x}$ servings/d.
[3] Adjusted for age at baseline, race, sex, and time-dependent energy intake.
[4] Adjusted for model 1 covariates plus education, smoking status, pack-years of smoking, physical activity, alcohol intake, and hormone replacement in women.
[5] Adjusted for model 2 covariates plus BMI, waist-to-hip ratio, systolic blood pressure, and use of antihypertensive medications; HDL and LDL are included in the model for incident CAD.

DISCUSSION

Over an 11-y follow-up period in the African American and white men and women, the intake of whole-grain foods was inversely associated with total mortality and the incidence of CAD, whereas the intake of fruit and vegetables was inversely associated with total mortality. Refined-grain intake was positively related to incident CAD in the African Americans but not in the whites. The incidence of ischemic stroke was not related to consumption of plant-based foods, although the risk decreased nonsignificantly among the habitual whole-grain consumers. While refined-grain consumption is lower among the ARIC Study participants than among the US population, the average consumption of whole-grain foods and fruit and vegetables in the ARIC Study cohort is similar to that in the US population (2, 3).

Consumption of nutrient-dense plant-based foods, including whole-grain foods and fruit and vegetables, is considered to be beneficial to health (26, 27). We found that whole-grain consumers generally reported healthier lifestyle habits, including greater physical activity, not smoking, lower red meat intake, and greater fruit and vegetable intake, and these results were consistent with those of other studies (13–15). Fruit and vegetable intake in the present study was also associated with greater physical activity, not smoking, greater fish intake, and lower alcohol and red meat intakes. In contrast, refined-grain intake was generally associated with a less healthy lifestyle both in the present study and in other prospective studies (13, 15). However, in the Iowa Women's Health Study, refined-grain intake was inversely associated with meat consumption (13).

Among the ARIC Study participants, the risk of all-cause mortality in those who were in the highest quintile of whole-grain intake was 23% lower than that of those who were in the lowest quintile, which is consistent with results of other investigations in mainly white populations. Among postmenopausal women who participated in the Iowa Women's Health Study (14) and among Norwegian men and women (28), subjects in the highest quintile of whole-grain intake had a 15–25% lower risk of death from all causes than did those in the lowest quintile. We observed a moderately strong, 28% lower risk of incident CAD among the men and women in the quintile with a mean intake of 3 servings of whole grain/d than among those in the quintile with a mean intake of 0.5 serving/d, which is consistent with the 26% lower risk among US nurses in the highest intake quintile than in the lowest intake quintile (15). In our study, the association of incident ischemic stroke with whole-grain intake remained inverse but was attenuated after adjustment for several confounding factors. However, Liu et al (16) reported a 31% lower risk of ischemic stroke among nurses in the highest quintile of whole-grain intake than in the lowest quintile, which is not far from our nonsignificant hazard ratio of 0.75. On average, whole-grain consumption in the nurses was similar to that in the ARIC Study participants (≈1 serving/d).

In contrast with studies of whole grain, findings regarding the relations between refined-grain intake and the risks of total mortality and CAD have been inconsistent. Refined-grain foods are typically energy rich and nutrient poor and may consequently increase the risk of atherosclerosis. Compared with the men and women in the present study who were in the lowest quintile of refined-grain intake, those in the highest quintile had a 34% higher risk of total mortality and a 54% higher risk of incident CAD, after adjustment for age, sex, race, and energy intake. However, these associations were attenuated and lost significance after further adjustment for confounding factors. In subgroup analyses, the risk of incident CAD in the African American subjects in the quintile with a mean intake of 5 servings of refined grain/d was 2-fold that in the African American subjects in the quintile with a mean intake of 0.5 serving/d. Compared with the white subjects in the ARIC Study, the African American subjects reported fewer years of education, lower levels of physical activity, and higher blood

pressure. In the Iowa Women's Health Study, women in the highest quintile of refined-grain intake had a 16% greater risk of total mortality than did women in the lowest quintile (14). However, Liu et al (15) found no evidence of an association between refined-grain intake and the risk of CAD among US nurses. Consistent with the results of the Nurses' Health Study (16), no relation between refined-grain intake and the risk of ischemic stroke was observed in the present study. The average refined-grain intake among the nurses, the women who participated in the Iowa Women's Health Study, and the ARIC Study participants was ≈2 servings/d, although African Americans in the ARIC Study reported an intake of ≈2.7 servings/d, including more white bread, refined-grain cereal, and biscuits.

As with whole-grain intake, we found inverse relations between total mortality and consumption of fruit and vegetables in the ARIC Study cohort. Among 9 cohort studies (18, 29, 30), 5 reported inverse associations between fruit and vegetable consumption and the risk of CAD, CAD death, or stroke (29–33). In the present study, the subjects in the highest quintile of fruit and vegetable intake had a 22% lower risk of total mortality than did those in the lowest quintile. Among the African Americans, those who consumed an average of 7.5 servings of fruit and vegetables/d had a 63% lower risk of incident CAD than did those who consumed 1.5 servings/d. Other studies of US nurses and male health professionals reported a 20% lower risk of incident CAD in subjects in quintile 5 than in subjects in quintile 1 (30). In a study of 5133 Finnish men and women, a 34% lower risk of CAD death was reported in those in the highest tertile of vegetable consumption than in those in the lowest tertile (31). Although we found no relation between fruit and vegetable intake and the risk of ischemic stroke, a 24–31% lower risk of stroke was observed in men and women who consumed high amounts of fruit and vegetables than in those who consumed low amounts in the Nurses' Health Study, the Health Professionals Study, the Framingham study, and the first National Health and Nutrition Examination Survey (NHANES) Follow-up Study (29, 32, 33). On average, daily fruit and vegetable intake was higher among the nurses, male health professionals, and men in the Framingham study than among the ARIC Study participants. Interestingly, investigators in the Lyon Diet Heart Study, a randomized secondary prevention trial, showed that a Mediterranean diet, which is characterized by increased intakes of fruit, vegetables, legumes, cereals, and fish, reduced the rate of recurrence among patients who had experienced their first myocardial infarction (34).

An important limitation of the present study is the use of the food-frequency questionnaire to characterize whole-grain intake. The 66-item food-frequency questionnaire was not designed to differentiate whole-grain food items from refined-grain food items in the food list. Some of the foods in the list are combinations of whole-grain and refined-grain foods. For example, the food item "rice," which was classified as a refined grain, includes white rice, brown rice, and wild rice. Another food item classified as a refined grain was "cooked cereals," which include hot breakfast cereals such as oatmeal, cream of wheat, cream of rice, and farina. Oatmeal is a whole-grain cereal, but cream of wheat and cream of rice are refined-grain cereals. Although corn bread is a whole-grain food, it was grouped with a refined-grain food, ie, biscuits; therefore, the "corn bread and biscuits" group was categorized as refined grain. The food-frequency questionnaire potentially misclassifies whole-grain consumption as refined-grain consumption, thereby creating the possibility for attenuation of the true hazard ratio. An alternative explanation for our study results is that whole-grain consumption is a marker for a healthy lifestyle. However, we adjusted the regression models for behaviors, including smoking, alcohol consumption, physical activity, and physical characteristics reflecting healthy behavior, such as BMI and WHR. Another explanation is the "substitution effect" of whole-grain consumption, ie, that whole-grain foods replace other unhealthy foods, such as red or processed meats or high-fat, refined-grain foods, resulting in lower serum cholesterol concentrations. However, we included saturated fat and dietary cholesterol in the model, but no attenuation in risk was observed. Moreover, clinical studies have shown improved glucose metabolism and lipid and blood-pressure effects with increased whole-grain consumption in adults (4–10). It is likely that the biologically active nutrients and food compounds in whole grain act singularly or synergistically to enhance some aspects of health. Residual confounding is always a possible explanation for weak to moderate associations. It is of interest to note that there was little difference between the risk estimates for models 2 and 3; ie, after adjustment for lifestyle factors (model 2), the associations between exposure variables and outcomes were not attenuated further by adding the physical and clinical CAD risk factors to the model (model 3).

A major strength of this prospective study is the large number of white and African American men and women who were studied. Another strength is the second dietary interview to update dietary information in the regression models, because food choices and frequency of intake may change over time.

Our study findings support a protective effect of the consumption of whole-grain foods and fruit and vegetables.

These study conclusions support the US *Dietary Guidelines for Americans* (1): "choose a variety of fruits and vegetables daily" and "choose a variety of grains daily, especially whole grains." Our data specifically suggest that whole-grain foods are more healthful than are refined-grain foods.

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