ORIGINAL RESEARCH

Rice Intake, Arsenic Exposure, and Subclinical Cardiovascular Disease Among US Adults in MESA

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Background—Arsenic-related cardiovascular effects at exposure levels below the US Environmental Protection Agency's standard of 10 μg/L are unclear. For these populations, food, especially rice, is a major source of exposure. We investigated associations of rice intake, a marker of arsenic exposure, with subclinical cardiovascular disease (CVD) markers in a multiethnic population.

Methods and Results—Between 2000 and 2002, MESA (Multi-Ethnic Study of Atherosclerosis) enrolled 6814 adults without clinical CVD. We included 5050 participants with baseline data on rice intake and markers of 3 CVD domains: inflammation (hsCRP [high-sensitivity C-reactive protein], interleukin-6, and fibrinogen), vascular function (aortic distensibility, carotid distensibility, and brachial flow-mediated dilation), and subclinical atherosclerosis at 3 vascular sites (carotid intima-media thickness, coronary artery calcification, and ankle-brachial index). We also evaluated endothelial-related biomarkers previously associated with arsenic. Rice intake was assessed by food frequency questionnaire. Urinary arsenic was measured in 310 participants. A total of 13% of participants consumed ≥1 serving of rice/day. Compared with individuals consuming <1 serving of rice/week, ≥1 serving of rice/day was not associated with subclinical markers after demographic, lifestyle, and CVD risk factor adjustment (eg, geometric mean ratio [95% CI] for hsCRP, 0.98 [0.86–1.11]; aortic distensibility, 0.99 [0.91–1.07]; and carotid intima-media thickness, 0.98 [0.91–1.06]). Associations with urinary arsenic were similar to those for rice intake.

Conclusions—Rice intake was not associated with subclinical CVD markers in a multiethnic US population. Research using urinary arsenic is needed to assess potential CVD effects of low-level arsenic exposure. Understanding the role of low-level arsenic as it relates to subclinical CVD may contribute to CVD prevention and control. **(*J Am Heart Assoc*. 2020;9:e015658. DOI: 10.1161/JAHA.119.015658.)**

Key Words: arsenic • cardiovascular disease • inflammation • rice

Evidence from the United States and other countries supports that arsenic exposure via drinking naturally contaminated groundwater is a risk factor for cardiovascular disease (CVD) at levels >10 μg/L, the US Environmental Protection Agency's maximum contaminant level.[1–6] However, few studies have evaluated arsenic's effect on cardiovascular risk at <10 μg/L. Food, especially rice, represents the major source of exposure for populations with low-level arsenic in drinking water (<10 μg/L).[7] Compared with other staple foods, rice more readily accumulates arsenic because of its high demand for silica and the flooding nature of the agricultural process.[8] Epidemiologic data from the United States and elsewhere confirm that the consumption of rice and rice products is associated with higher urinary arsenic levels.[7,9,10]

A study among pregnant women in the United States found that on the basis of total urinary arsenic levels, consuming approximately half a cup of cooked rice (≈79 g), which is generally considered one serving of rice,[11] was comparable to that of drinking 1 L of water at 10 μg/L.[9] In the United States, rice intake comprises a major source of food for certain population subgroups, including Asian and Hispanic communities. It is unknown whether low-level arsenic exposure, likely from arsenic-contaminated rice, is a risk factor for CVD.

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Accompanying Tables S1 through S8 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015658

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Clinical Perspective

What Is New?

- Rice accumulates arsenic, a metal associated with cardiovascular disease at high exposure levels, yet little is known about the association between rice consumption and arsenic-related health effects.
- This multiethnic, US population-based analysis found that frequent rice intake was not associated with several markers of inflammation, vascular function, or subclinical atherosclerosis; however, 2 markers of inflammation that have been previously associated with arsenic exposure (E-selectin and intercellular adhesion molecule-1) were marginally associated with rice intake, suggesting possible arsenic-specific pathways of cardiovascular disease development. Results in a subset with urinary arsenic were consistent.

What Are the Clinical Implications?

- Because several variables may affect arsenic levels and its bioavailability in rice, urinary arsenic serves as a more robust measurement of dietary arsenic exposure than self-reported rice consumption.
- Understanding the role, or lack thereof, of low-level dietary arsenic as it relates to subclinical cardiovascular disease can contribute to arsenic risk assessment and to cardiovascular disease prevention and control in general populations.

Few studies have evaluated the association between rice intake and CVD, with inconsistent findings. In Japanese adults, rice intake was inversely associated with CVD mortality in men but not in women[12]; however, rice grown in Japan has been found to have lower arsenic levels compared with other countries.[13] In Chinese adults, total carbohydrate intake, most likely from rice, was positively associated with incident coronary heart disease in both men and women.[14] Total carbohydrate intake, however, is a broadly defined exposure category not limited to rice intake, and thus is less likely to be an adequate marker of dietary arsenic exposure. More recently, a pooled-cohort study from 3 US studies found that white or brown rice intake was neither associated with fatal nor nonfatal CVD.[15] This study, however, pooled data from studies among mostly white participants and may not be fully representative of the general US population. Given the heterogeneity of published findings and the cultural importance of rice for several population groups, it is imperative to study possible adverse cardiovascular effects of rice among a multiethnic population. Furthermore, no study has evaluated the association between rice intake and subclinical markers of CVD.

The objective of this study was to investigate the association of rice intake, the main dietary source of arsenic, with markers of subclinical atherosclerosis among a multiethnic US population. We modeled our analysis on previous research that examined the association of known CVD risk factors with markers of subclinical atherosclerosis[16,17] using 3 domains of subclinical CVD: inflammatory markers, vascular function, and 3 distinct vascular sites with subclinical measures of atherosclerosis. We hypothesized that higher rice intake would be associated with increased levels of markers of inflammation, endothelial function, and subclinical atherosclerosis.

Methods

Study Sample

MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter, longitudinal cohort study of community-dwelling adults designed to investigate subclinical CVD.[18] Initial enrollment took place between 2000 and 2002, during which 6814 men and women without a diagnosis of clinical CVD between the ages of 45 and 84 years were enrolled from 6 US cities (Baltimore, MD; Chicago, IL; Los Angeles, CA; St Paul, MN; New York, NY; and Salem, NC). Study details, including exclusion criteria, have been published previously.[18] Participants are white (39%), black (28%), Hispanic (22%), or Chinese/Chinese American (12%). Individual review boards from each field center approved the study, and all MESA participants provided informed consent for their involvement. Additional information, including requests to access the data set from qualified researchers trained in human subject confidentiality protocols, may be found at https://mesa-nhlbi.org.

This study was restricted to the baseline examination (2000–2002). Rice intake was assessed by self-report in the overall population by a food frequency questionnaire at baseline. We excluded 657 participants missing rice intake, 540 participants missing CVD outcomes (hsCRP [high-sensitivity C-reactive protein], interleukin-6, fibrinogen, carotid distensibility, carotid intima-media thickness [CIMT], and ankle-brachial index [ABI]), 437 participants with unreliable caloric intake or missing dietary information, 75 participants missing CVD risk factors (diabetes mellitus, hyperlipidemia, and systolic blood pressure), and 53 participants missing sociodemographic or lifestyle factors (education and pack-years), leaving 5050 participants for most analyses (Figure). The sample sizes for brachial flow-mediated dilation (FMD) and aortic distensibility were limited to a subset selected at baseline (N=2702 with FMD, and N=2759 with aortic distensibility). Urinary arsenic was measured in a random-stratified sample of 310 participants; of those participants, 246 remained after excluding participants missing adjustment variables (142 participants with brachial FMD and 128 participants with aortic distensibility). Intercellular adhesion molecule-1 (ICAM-1), E-selectin, and matrix metallopeptidase

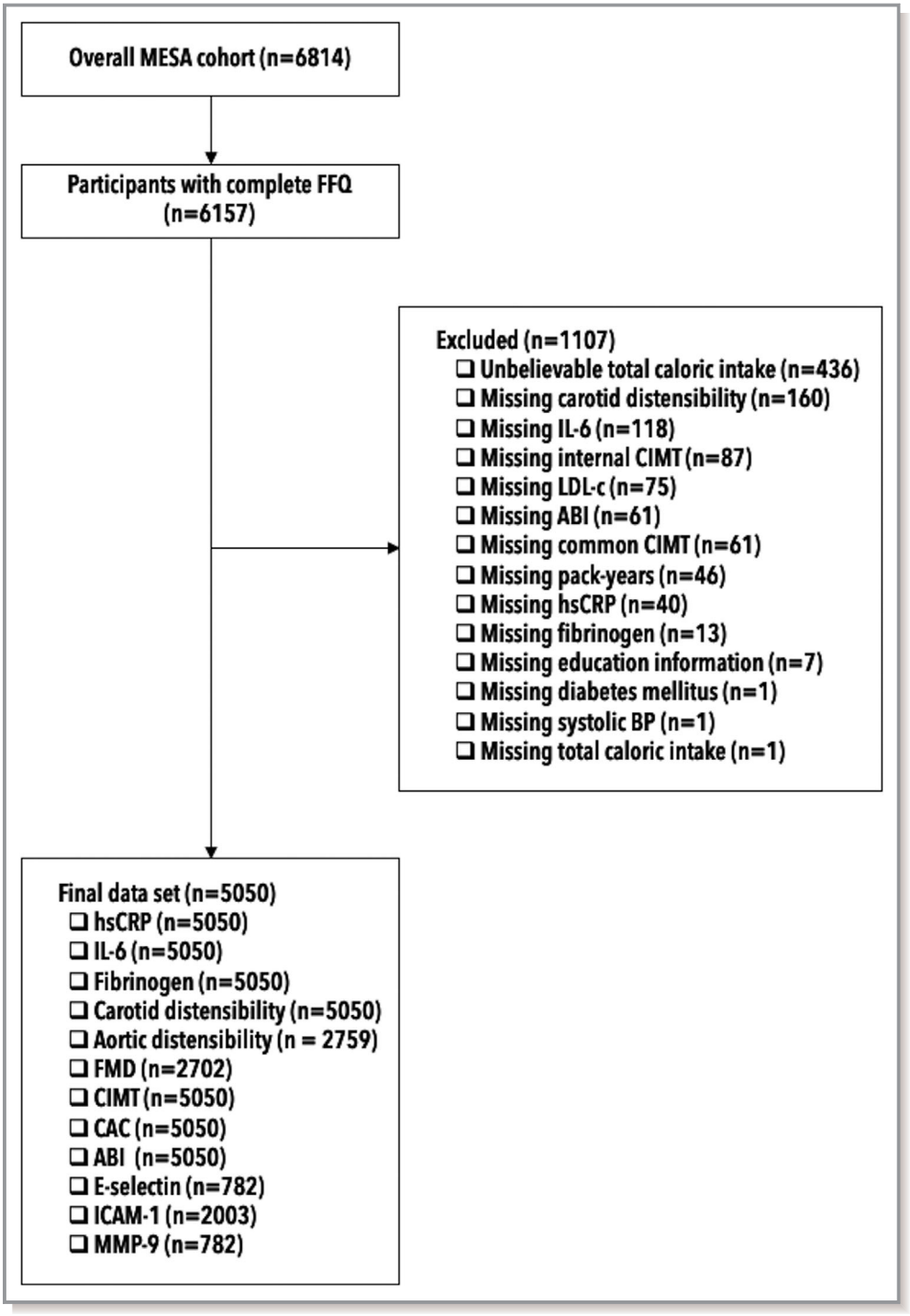

Figure. Study design flow chart. Sample size flow chart for analyses based on rice intake in MESA (Multi-Ethnic Study of Atherosclerosis). A total of 6814 participants were recruited to MESA between 2000 and 2002. Rice intake was assessed via food frequency questionnaire (FFQ) at baseline. Participants with missing rice information (n=658), unreliable dietary information (n=436), or missing adjustment variables (n=670) at baseline were excluded. A subset had brachial flow-mediated dilation measurements (n=2702) and an aortic distensibility assessment (n=2759). Urine arsenic was measured in a stratified random sample of 310 participants at baseline, and 246 remained in our final data set for most outcomes. ABI indicates ankle-brachial index; BP, blood pressure; CAC, coronary artery calcium; CIMT, coronary intima-media thickness; FMD, flow-mediated dilation; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; MMP-9, matrix metallopeptidase 9.

9 (MMP-9) were all available in part in the full study sample; only ICAM-1 was available in the urinary arsenic subset.

Measurements

Rice intake

Usual dietary intake over the past year was assessed using a modified block-style 120-item food frequency questionnaire.[19] We abstracted the 4 variables from the food frequency questionnaire related to rice intake: (1) white rice (including Mexican and sticky rice), (2) brown/wild rice, (3) fried rice, and (4) arroz con pollo. Frequency of these rice variables was collected in MESA in 9 categories: "rare or never," "1 time/month," "2 to 3 times/month," "1 time/week," "2 times/week," "3 to 4 times/week," "5 to 6 times/week," "1 time/day," and "≥2 times/day." Brown rice and mixed rice dishes ("fried rice" and "arroz con pollo") were combined with white rice into one variable of overall rice intake and further categorized into 1 of 3 groups based on how often participants reported eating rice: <1 serving per week, 1 to 6 servings per week, and ≥1 serving per day. These 3 categories are our method of approximating low (<1 serving per week), moderate (1–6 servings per week), and high (≥1 serving per day) arsenic exposure by rice intake. Total caloric intake (kcal/d) was estimated from the food frequency questionnaire. To account for healthy dietary patterns, we used the alternative Healthy Eating Index (aHEI) total score, with adapted scoring methods tailored to the food frequency questionnaire data available in MESA.[20,21] The scores range from 2.5 to 87.5 and reflect assessment of 9 categories, including intake of vegetable, fruits, nuts and soy protein, red meat, cereal fiber, trans fat, and saturated fat, multivitamin use, and alcohol consumption. Because of limitations in the food frequency questionnaire, MESA adapted the aHEI to evaluate vitamin use within the past month rather than vitamin use over the past 5 years. A higher score indicates a greater adherence to the aHEI and, thus, dietary patterns and behaviors associated with lower risk for chronic disease. Participants who provided unreliable dietary information (men with <800 or >4000 kcal/d or women with <500 or >3500 kcal/d) were excluded (N=436).[22]

Urinary arsenic

Baseline urine samples were stored at temperatures <−70°C until analyses. Speciated arsenic concentrations (inorganic arsenic [iAs], methylarsonate, dimethylarsinate, and arsenobetaine) were measured using anion-exchange high-performance liquid chromatography (Agilent 1100; Agilent Technologies, Waldbronn, Germany) coupled with inductively coupled plasma mass spectrometry (Agilent 7700x ICPMS; Agilent Technologies).[23] The limits of detection were 0.1 μg/L for iAs, methylarsonate, dimethylarsinate, and arsenobetaine. The percentages of individuals with urinary concentrations below the limit of detection were 45.8%, 14.2%, 0%, and 3.9% for iAs, methylarsonate, dimethylarsinate, and arsenobetaine, respectively. These participants were assigned a level equal to the limit of detection divided by the square root of 2.[24] To account for the influence nontoxic seafood arsenicals have on toxic arsenicals (iAs, methylarsonate, and dimethylarsinate) at low levels of exposure,[24] urinary concentrations of iAs, methylarsonate, and dimethylarsinate were regressed on arsenobetaine (a nontoxic species used as a marker of overall exposure to seafood arsenicals). The residuals of this model reflect inorganic and methylated arsenic species that are not related to recent seafood intake.[24] To have levels of exposure that are easily communicable and represent arsenic concentrations after removing the impact of seafood, we added the mean concentration of the corresponding arsenic species (iAs, methylarsonate, or dimethylarsinate) among participants with low arsenobetaine (<1 μg/L) to the residuals.[24] Urinary arsenic in this study is the sum of the iAs, methylarsonate, and dimethylarsinate concentrations with the arsenobetaine correction when appropriate.

Markers of inflammation and endothelial function

Inflammatory markers (hsCRP, interleukin-6, and fibrinogen)[24] and endothelial dysfunction and vascular inflammation markers (E-selectin, ICAM-1, and MMP-9)[25] were measured from serum samples collected at baseline using previously described methods. Biomarkers were modeled as continuous variables; however, hsCRP was additionally modeled dichotomously, using a cut point of hsCRP ≥2 mg/L, consistent with the literature.[16,24]

Arterial distensibility

Common carotid arterial distensibility was assessed using ultrasonography conducted at baseline. It is expressed as the ratio of the diameter change over the cardiac cycle to the brachial artery pulse pressure: distensibility=[2 (Ds−Dd)/Ds]/(Ps−Pd), where Ds is systolic carotid artery diameter, Dd is the diastolic carotid diameter, Ps is the systolic blood pressure, and Pd is the diastolic blood pressure.[26] Aortic distensibility was assessed at baseline using cardiac magnetic resonance imaging with automated contour with FLOW software as aortic distensibility=(maximum area−minimum area)/[(minimum area)×ΔP]×100, where ΔP is the pule pressure in mm Hg.[27,28] Blood pressure was measured immediately before and after both the carotid ultrasound and aortic magnetic resonance imaging measurements.

Flow-mediated dilation

Endothelial function using brachial FMD was measured in a nested sample of 3026 participants at baseline and was performed using a blood pressure cuff inflated to 50 mm Hg

above the participant's systolic blood pressure for 5 minutes. Images of the right brachial artery were captured continuously for 30 seconds before cuff inflation and for 2 minutes immediately after cuff deflation to document the vasodilator response; % FMD=[(maximum diameter−baseline diameter)/baseline diameter]×100%.[26]

CIMT and coronary artery calcium

Right and left common and internal carotid arteries were imaged according to an established protocol using B-mode ultrasonography with a GE Logiq 700 machine. The MESA ultrasound reading center (Tufts Medical Center) measured maximal CIMT of the internal and common carotid artery as the mean of the maximum CIMT of the near and far walls on the right and left sides.[16] Coronary artery calcium (CAC) was measured using electron-beam computed tomography or multidetector row computed tomography.[29] CAC was quantified as 2 binary measures: (1) CAC >0 versus CAC=0 and (2) CAC >75th percentile for age, sex, and race in those with any CAC present at baseline versus <75th percentile.[30]

Peripheral arterial disease

ABI measurements were obtained at baseline using a specific protocol to measure systolic blood pressure in each posterior tibial and dorsalis pedis artery in both legs and in the brachial artery in both arms with a continuous-wave Doppler ultrasound probe. For each leg, the ABI was calculated as the higher of the posterior tibial or dorsalis pedis systolic blood pressure measurements in both arms. We used a binary measure (ABI <1 versus ABI ≥1), as low ABI has been associated with CVD.[18]

Other variables

Sociodemographic (age, sex, race/ethnicity, education, and study site), lifestyle (total caloric intake, aHEI, smoking status, exercise, body mass index, and pack-years), and CVD risk factors (diabetes mellitus, hypertension, hyperlipidemia, and estimated glomerular filtration rate) were assessed at baseline using standardized questionnaires and laboratory procedures for collection and assessment. Exercise here is a sum of total light, moderate, and vigorous activities reported in minutes per week. Diabetes mellitus was defined as a fasting blood glucose >126 mg/dL or use of insulin or hypoglycemic medication. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medications for hypertension.

Statistical Analysis

Nonnormally distributed variables were natural log transformed. For categorical rice analyses, <1 serving of rice per week served as the reference category. For log-transformed continuous end points (all except carotid distensibility and FMD), multivariable linear regression models were used to estimate geometric mean ratios (GMRs). For nontransformed continuous end points (carotid distensibility and FMD), multivariable linear regression models were used to estimate mean differences. For dichotomous end points, odds ratios were estimated using multivariable logistic regression. Models were progressively adjusted in a stepwise manner with covariates selected on the basis of past evidence in studies with arsenic exposure and CVD outcomes.[31–34] Model 1 adjusted for sociodemographic information (age, sex, race/ethnicity, education, and study site) and energy intake. Model 2 included model 1 variables plus behavioral information (smoking status, pack-years, and exercise) and body mass index. Model 3 included model 2 variables plus CVD risk factors (diabetes mellitus, hypertension, hyperlipidemia, and estimated glomerular filtration rate). Our main model, model 4, included model 3 variables plus nutritional information (aHEI). For all models, *P* values for trend were obtained across ordered rice groups. In a secondary analysis among a subsample with urinary arsenic available, results are presented per an interquartile increase in urinary arsenic levels. Effect modification was assessed by race/ethnicity, median age groups, sex, smoking status, median aHEI, and site, including an interaction term in the regression models; the β for the interaction term was assessed using the Wald test. Several sensitivity analyses were conducted to test the robustness of the main analyses. Rice intake in MESA was collected in examination 1 (2000–2002) and examination 5 (2010–2012). To better categorize participants with consistent rice intake, we restricted the analysis to participants who consistently reported the same category of rice intake at examination 1 and again at examination 5 (N=2208). We also assessed the consistency of the findings using different rice intake categorizations. Analyses were performed in R (version 3.5.1) with a *P*=0.05 considered significant.

Results

Participant Characteristics

Of participants, 13% reported consuming ≥1 serving of rice/day (Table 1). Frequent rice eaters (≥1 serving/day) were more likely to be Asian and from Los Angeles. Frequent rice eaters were also more likely to have lower body mass index, lower overall caloric intake, a higher HEI, and lower rates of diabetes mellitus and hypertension, and they were less likely to have a family history of myocardial infarctions (Table 1). Sex and age were similar by rice category. Distribution of subclinical end points in the full sample by rice consumption can be found in the accompanying material (Table S1). In the subset with urinary arsenic measurements, median (interquartile range) urinary arsenic levels (μg/g creatinine) increased

Table 1. Baseline Characteristics of MESA Participants by Rice Intake and Urinary Arsenic (2000–2002)

Characteristic	Overall (n=5050)	Rice Intake			*P* Value
		<1 Serving/wk (n=2028)	1–6 Servings/wk (n=2383)	≥1 Serving/d (n=639)	
Men	2331 (46)	896 (44)	1142 (48)	293 (46)	0.045
Age, y	62 (53–70)	64 (55–71)	60 (52–69)	63 (54–71)	<0.001
Race/ethnicity					<0.001
White	2076 (41)	1221 (60)	845 (36)	10 (2)	
Asian	657 (13)	15 (1)	174 (7)	468 (73)	
Black	1222 (24)	571 (28)	620 (26)	31 (5)	
Hispanic	1095 (22)	221 (11)	744 (31)	130 (20)	
Site					<0.001
Salem, NC	804 (16)	459 (23)	343 (14)	2 (0)	
New York, NY	715 (14)	192 (10)	449 (19)	74 (12)	
Baltimore, MD	726 (14)	426 (21)	291 (12)	9 (1)	
St Paul, MN	838 (17)	445 (22)	372 (16)	21 (3)	
Chicago, IL	937 (19)	347 (17)	438 (18)	152 (24)	
Los Angeles, CA	1030 (20)	159 (8)	490 (21)	381 (60)	
Education					<0.001
High school or less	1781 (35)	615 (30)	816 (34)	350 (55)	
Some college	1143 (23)	521 (26)	535 (23)	87 (14)	
College degree or more	2126 (42)	892 (44)	1032 (43)	202 (32)	
BMI, kg/m^2	27 (24–31)	28 (25–31)	28 (25–31)	25 (22–27)	<0.001
Energy intake, kcal	1397 (1031–1881)	1309 (989–1749)	1523 (1117–2030)	1197 (894–1660)	<0.001
Alternate Healthy Eating Index score	42 (34–50)	40 (32–49)	43 (35–52)	44 (38–51)	<0.001
Physical activity, MET	67 (33–124)	72 (37–132)	71 (36–129)	41 (21–84)	<0.001
Hypertension	2177 (43)	934 (46)	982 (41)	261 (41)	0.002
Diabetes mellitus	1224 (24)	460 (23)	587 (25)	177 (28)	0.03
Family history of myocardial infarction	2003 (40)	900 (44)	944 (40)	159 (25)	<0.001
Current cigarette use	607 (12)	271 (13)	285 (12)	51 (8)	<0.001
Pack-years*	17 (6–33)	19 (8–36)	15 (5–30)	14 (5–29)	<0.001
Urine arsenic/creatinine, μg/g†	3.08 (1.96–4.69)	2.34 (1.55–3.09)	3.27 (1.95–4.62)	4.36 (3.14–6.88)	<0.001

Data are presented as number (percentage) or median (interquartile range). BMI indicates body mass index; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent.
*Among ever smokers only.
†Sum of inorganic arsenic, methylarsonate, and dimethylarsinate, corrected for arsenobetaine levels.

with increasing rice intake (<1 serving per week: 2.34 [1.96–4.69]; 1–6 servings per week: 3.27 [1.55–3.09]; and ≥1 serving per day: 4.36 [3.14–6.88]). The subset was similar to the overall study sample (Table S2).

Inflammatory Markers

For brevity and as all results were similar across models, results from models 1 to 3 are shown in Table S3. Rice intake was not associated with hsCRP, interleukin-6, and fibrinogen (Table 2). Results with urinary arsenic were similar. Although not statistically significant, urinary arsenic was positively associated with hsCRP ≥2 mg/L (odds ratio, 1.20 [95% CI, 0.75–1.91]). There was a positive association between increasing rice intake and E-selectin levels for both moderate rice intake (1–6 servings/week) (GMR, 1.11 [95% CI, 1.03–1.19]) and high rice intake (≥1 serving/day) (GMR, 1.11 [95% CI, 0.96–1.28]) compared with infrequent rice intake (<1 serving/week) (Table 2). The corresponding GMRs (95% CI) for the association of moderate and high versus infrequent rice intake with ICAM-1 were 1.00 (0.97–1.03) and 1.02 (0.97–1.07), respectively; however, for an interquartile range

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Table 2. Association of Rice Intake and Urinary Arsenic With Domains of Subclinical CVD in MESA, United States, 2000 to 2002

	Rice Intake							Urinary Arsenic	
	<1 Serving/wk		1–6 Servings/wk		≥1 Serving/d			Per 2.64 μg/g Creatinine	
Variable	n	Value (95% CI)	n	Value (95% CI)	n	Value (95% CI)	*P* Trend	n	Value (95% CI)
Inflammation markers									
hsCRP (mg/L), GMR	2028	1.00 (Reference)	2383	0.97 (0.91 to 1.03)	639	0.98 (0.86 to 1.11)	0.4	246	1.02 (0.84 to 1.23)
hsCRP ≥2 mg/L, OR	1046/982*	1.00 (Reference)	1136/1247*	0.95 (0.82 to 1.09)	183/456*	0.84 (0.62 to 1.13)	0.3	101/145*	1.20 (0.75 to 1.91)
Interleukin-6 (pg/mL), GMR	2028	1.00 (Reference)	2383	0.99 (0.95 to 1.03)	639	0.98 (0.91 to 1.06)	0.6	246	0.99 (0.88 to 1.12)
Fibrinogen (mg/dL), GMR	2028	1.00 (Reference)	2383	1.00 (0.99 to 1.01)	639	1.01 (0.99 to 1.03)	0.5	246	1.00 (0.96 to 1.03)
Arsenic-specific inflammation markers									
E-selectin (ng/mL), GMR	298	1.00 (Reference)	385	1.11 (1.03 to 1.19)	99	1.11 (0.96 to 1.28)	0.02	0	…
ICAM-1 (ng/mL), GMR	779	1.00 (Reference)	992	1.00 (0.97 to 1.03)	232	1.02 (0.97 to 1.07)	0.7	75	1.07 (0.97 to 1.19)
MMP-9 (ng/mL), GMR	298	1.00 (Reference)	385	0.99 (0.91 to 1.08)	99	0.99 (0.85 to 1.17)	0.9	0	…
Vascular function									
FMD, MD	920	0.00 (Reference)	1316	0.06 (−0.19 to 0.32)	466	0.41 (−0.03 to 0.85)	0.1	142	−0.02 (−0.71 to 0.67)
Carotid distensibility (10^{-3} mm Hg), MD	2028	0.00 (Reference)	2383	−0.02 (−0.08 to 0.04)	639	−0.10 (−0.22 to 0.02)	0.2	246	−0.05 (−0.22 to 0.13)
Aortic distensibility (mm Hg^{-1}), GMR	1130	1.00 (Reference)	1334	0.97 (0.93 to 1.01)	295	0.99 (0.91 to 1.07)	0.3	128	0.96 (0.82 to 1.12)
Subclinical atherosclerosis									
CIMT (internal), GMR	2028	1.00 (Reference)	2383	1.01 (0.98 to 1.04)	639	0.97 (0.92 to 1.02)	0.7	246	0.98 (0.91 to 1.06)
CIMT (common), GMR	2028	1.00 (Reference)	2383	1.00 (0.99 to 1.01)	639	0.97 (0.95 to 1.00)	0.3	246	0.99 (0.96 to 1.03)
CAC >0, OR	1105/923*	1.00 (Reference)	1076/1307*	0.93 (0.79 to 1.08)	308/331*	0.94 (0.69 to 1.27)	0.4	117/129*	0.99 (0.61 to 1.60)
CAC >75th percentile, OR	267/838*	1.00 (Reference)	284/792*	0.93 (0.74 to 1.16)	71/237*	0.67 (0.42 to 1.07)	0.2	27/90*	0.99 (0.61 to 1.60)
ABI <1, OR	284/1744*	1.00 (Reference)	219/2164*	0.89 (0.71 to 1.10)	54/585*	0.85 (0.53 to 1.37)	0.3	20/226*	1.01 (0.46 to 2.21)

Models adjusted for age, sex, race/ethnicity, education, education, smoking status, pack-years, exercise, body mass index, diabetes mellitus, hypertension, hyperlipidemia, estimated glomerular filtration rate, energy intake, and alternative Healthy Eating Index. ABI indicates ankle-brachial index; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; FMD, flow-mediated dilation; GMR, geometric mean ratio; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; MD, mean difference; MESA, Multi-Ethnic Study of Atherosclerosis; MMP-9, matrix metallopeptidase 9; OR, odds ratio.
*Number (yes/no).

increase in urinary arsenic, the GMR was 1.07 (95% CI, 0.97–1.19). There was no association with MMP-9.

Vascular Function

There was no association of rice intake with carotid distensibility, aortic distensibility, or FMD (Table 2). The mean difference for carotid distensibility was −0.10 (95% CI, −0.22 to 0.02) 10^{-3} mm Hg comparing high rice versus infrequent rice intake. There was a similar nonsignificant inverse relationship for carotid distensibility for an interquartile range increase in urinary arsenic (mean difference, −0.05 [95% CI, −0.22 to 0.13] 10^{-3} mm Hg).

Subclinical Atherosclerosis

Rice intake was not associated with any of the subclinical atherosclerosis end points studied (CIMT, CAC, and ABI) (Table 2). Urinary arsenic models were generally consistent with the rice intake analysis.

Effect Modification

There was no evidence of effect modification by race/ethnicity, sex, age, smoking status, aHEI, or site for any of the end points studied in this analysis (Table S4).

Sensitivity Analyses

A total of 3363 participants had food frequency questionnaire data at examination 1 and examination 5. Of those participants, 2208 reported consistent rice intake at both examinations (Table S5). Using this subsample, results were generally consistent with the primary analysis (Table S6). There was a stronger positive association between increasing rice intake and E-selectin levels for consistent moderate rice intake (1–6 servings/week versus <1 serving/week) (GMR, 1.13 [95% CI, 1.01–1.27]) and consistent high rice intake (≥1 serving/day versus <1 serving/week) (GMR, 1.31 [95% CI, 1.01–1.71]) compared with our primary analysis using only examination 1 food frequency questionnaire data. When exploring different rice intake categories, using 2 rice categories (split by median category of rice intake), or using 5 categories, the findings were generally consistent with the primary analysis (Tables S7 and S8).

Discussion

This study investigated the association between rice intake, a main source of dietary arsenic, and multiple clinically relevant end points along the atherosclerotic development pathway, from upstream inflammatory markers to changes in vascular elasticity and function, to further manifestations of atherosclerosis, such as decreasing vascular diameters and calcification.

In this multiethnic population of US adults, rice intake was not associated with markers of inflammation, vascular function, or subclinical atherosclerosis at 3 distinct vascular sites after adjustment for potential confounding variables, except potentially with E-selectin and maybe with ICAM-1 (the latter on the basis of the association with urinary arsenic, although it was still nonstatistically significant). We could not confirm the association between urinary arsenic and E-selectin as this biomarker was not available in the subset of participants with urinary arsenic measured.

In experimental and epidemiological studies, drinking water arsenic at moderate to high levels (≥10 μg/L) was associated with subclinical markers of atherosclerosis, including CIMT,[35,36] plaque score,[37] and CVD risk factors, including hypertension,[38–40] diabetes mellitus,[19,41] and electrocardiographic abnormalities (prolonged QT interval).[31,42,43] In an occupational study, aortic distensibility was significantly decreased in male workers exposed to arsenic compared with unexposed; however, this is the only epidemiologic study on arsenic and arterial distensibility.[44] For inflammatory biomarkers, Bangladeshis in arsenic-endemic regions showed a positive dose-response relationship between arsenic in water and hair with CRP (C-reactive protein).[45] In the SHS (Strong Heart Study) in the United States, urinary arsenic was not associated with CRP, but it was associated with increased fibrinogen levels among those with diabetes mellitus.[32] In adults from China, participants with high blood arsenic levels had altered gene expression for several CVD-associated cytokines, including interleukin-6.[46] Biomarkers related to endothelial function and predictive for CVD, such as ICAM-1 and vascular adhesion molecule-1 in plasma, were positively associated with urinary and well water arsenic levels in moderately to highly exposed individuals in Bangladesh.[34,47] In a murine model, exposure to arsenic trioxide lead to increased E-selectin, ICAM-1, and vascular adhesion molecule-1 levels.[48] MMP-9, a matrix metalloproteinase enzyme that may lead to atherosclerotic complications with increased activated expression, was significantly positively associated with arsenic exposure comparing water, hair, and nail arsenic in arsenic-endemic and nonendemic regions in Bangladesh.[49] In southwestern US populations, urinary arsenic was associated with MMP-9 for residents exposed to moderate drinking water arsenic concentrations[50] as well as those with exposure to iAs from food intake with tap water arsenic concentrations <3 μg/L.[51]

Systematic reviews of toxicological and epidemiological evidence of arsenic exposure and CVD end points have indicated several possible mechanisms for arsenic-related CVD.[52,53] Elevated proinflammatory cytokines and markers of

oxidative stress have been observed in mice exposed to arsenic.[54] Murine models have also demonstrated that arsenic exposure interferes with cholesterol homeostasis and macrophage function, increased inflammatory signaling, nuclear factor-κB activation, and inhibition of NO availability.[55–60] These effects can promote proliferation of endothelial cells and smooth muscle, cell adhesion, platelet aggregation, and arterial vasoconstriction.[47,57,61] Furthermore, a murine study exposing mice to 10 000 μg/L water arsenic versus control over 18 weeks found a significant increase in plaque stenosis size in the innominate artery; this increase in plaque size is consistent with pathological features seen in human atherosclerotic plaques.[62] In a meta-analysis of 12 studies on long-term arsenic exposure and incident CVD, the pooled relative risk comparing water arsenic exposure of 20 μg/L versus 10 μg/L, assuming a linear dose-response relationship, was 1.09 (95% CI, 1.03–1.14).[33] This meta-analysis also evaluated the possibility of a nonlinear dose-response between arsenic exposure with CVD mortality, stroke mortality, and coronary heart disease incidence and mortality; however, because much of the epidemiological and toxicological evidence on arsenic exposure and CVD has focused on moderate to high levels of arsenic exposure (>10 μg/L), data were insufficient to assess nonlinearity and the possibility of a threshold at low arsenic exposure levels.[53]

Although a lack of association between low-level dietary arsenic exposure and CVD is possible, the null findings between rice intake and CVD end points in this study could reflect measurement error and that a single food frequency questionnaire may not capture long-term rice intake over time, as well as overall low-level dietary arsenic exposure. However, in our sensitivity analysis restricted to participants who reported consistent rice intake using data from food frequency questionnaires at 2 points in time, the associations were generally similar, confirming the generally null findings, except a positive association with E-selectin, which became stronger in this sensitivity analysis (Table S6).

Furthermore, the use of rice as a marker of arsenic exposure does not allow us to consider how an individual's ability to metabolize arsenic affects toxicity. Arsenic biomarkers, like urinary arsenic, should be used in populations with low-level dietary arsenic exposure. Urinary arsenic, however, was only available in a small subset. The MESA population, from cities and urban areas, likely uses regulated public drinking water. Arsenic exposure in MESA, therefore, comes primarily through the diet, particularly rice. However, because the cooking method,[63,64] rice variety,[65] and rice origin[13,66] are major determinants of the final arsenic level in cooked rice, using the frequency of intake without measuring arsenic levels in rice may have led to nondifferential exposure misclassification in our study, biasing the associations toward the null. Basmati rice, from India, Pakistan, and California, and sushi rice generally have the lowest levels of inorganic arsenic compared with other types of rice, whereas rice from Arkansas, Louisiana, or Texas generally has higher levels.[67] Although we had some information on the types of rice people were consuming (white versus brown), we lacked more detailed information about the rice cultivars (ie, basmati versus jasmine) or the country where rice was produced. We also lacked additional information on other rice-based foods (ie, rice crackers, rice cereal, and rice-based sweeteners). It is possible these associations are confounded by other foods commonly eaten with rice, because we were unable to verify arsenic levels in rice; however, we found a positive association between rice consumption and urinary arsenic (Figure S1), noted also in other studies,[68,69] indicating that rice consumption contributes to arsenic exposure. The 3 categories we used approximate relatively low (<1 serving per week), moderate (1–6 servings per week), and high (≥1 serving per day) arsenic exposure by rice intake, and are relevant to the half-life of urinary arsenic and could be used to inform future public health guidelines. Further sensitivity analyses considering different rice categorizations yielded similar results. The food frequency questionnaire, however, asked multiple questions about rice intake, including specific culturally relevant questions. Other strengths of the study include the multiethnic population with a large sample size, including groups of differing rice intake levels, and the availability of urinary arsenic measurements in a random subset of participants. Although we only used information from the baseline examination from 2000 to 2002, resulting in a cross-sectional snapshot from 20 years ago, our study included excellent and varied measures of subclinical CVD in a population free of clinical CVD at baseline. This cross-sectional approach has been effectively used, for instance, to assess the relevant subclinical CVD pathways associated with active smoking and secondhand smoke exposure.[16,17]

We found no relationship between rice intake and several markers of subclinical CVD in a multiethnic population of US adults, except maybe for E-selectin and ICAM-1, biomarkers that have been associated with arsenic exposure in previous studies.[34,48] Although rice is likely a large contributor to low-level dietary arsenic exposure, we recommend future research using urinary arsenic as a more accurate marker of low-level arsenic exposure. Understanding the role, or lack thereof, of low-level dietary arsenic as it relates to subclinical CVD can contribute to arsenic risk assessment and to CVD prevention and control in general populations.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Subclinical CVD endpoints of MESA participants by rice intake category, 2000-2002.

Endpoint	Overall *n=5050*	< 1 serving per wk *n=2028*	1-6 servings per wk *n=2383*	≥1 servings per day *n=639*	p-value
Inflammation markers					
hsCRP, mg/L	1.81 (0.80, 4.05)	2.10 (0.9, 4.33)	1.85 (0.84, 4.06)	1.08 (0.55, 2.23)	< 0.001
hsCRP ≥ 2, mg/L	2365 (46.8)	1046 (51.6)	1136 (47.7)	183 (28.6)	< 0.001
IL-6, mg/L	1.17 (0.76, 1.83)	1.25 (0.82, 1.88)	1.19 (0.74, 1.84)	0.95 (0.64, 1.49)	< 0.001
Fibrinogen, mg/dL	335 (293, 386)	337 (293, 387)	335 (293, 388)	333 (292, 378)	0.3
Vascular function					
Carotid distensibility, 10^{-3}mmHg	2.38 (1.79, 3.05)	2.38 (1.82, 3.01)	2.41 (1.80, 3.13)	2.28 (1.70, 2.89)	0.006
Aortic distensibility, $mmHg^{-1}$	1.61 (1.08, 2.37)	1.53 (1.07, 2.25)	1.66 (1.07, 2.47)	1.71 (1.15, 2.67)	0.001
Brachial FMD, %	3.9 (2.3, 6.1)	3.7 (2.00, 5.9)	4.00 (2.30, 6.12)	4.20 (2.60, 6.4)	0.018
Subclinical atherosclerosis					
Internal CIMT, mm	0.85 (0.68, 1.27)	0.91 (0.71, 1.39)	0.83 (0.68, 1.22)	0.74 (0.61, 0.98)	< 0.001
Common CIMT, mm	0.84 (0.73, 0.97)	0.86 (0.75, 0.99)	0.84 (0.73, 0.97)	0.81 (0.71, 0.92)	< 0.001
CAC > 0	2489 (49.3)	1105 (54.5)	1076 (45.2)	308 (48.2)	< 0.001
CAC > 75^{th} percentile	622 (12.3)	267 (13.2)	284 (11.9)	71 (11.1)	< 0.001
ABI < 1.0	557 (11)	284 (14)	219 (9.2)	54 (8.5)	< 0.001
As-specific inflammation markers					
n	*782*	*298*	*385*	*99*	
E-selectin, mg/L	50.33 (36.46, 64.56)	46.69 (34.33, 60.23)	52.57 (38.29, 68.89)	51.70 (36.16, 66.71)	0.002
MMP-9, mg/L	204.05 (151.25, 293.6)	204.90 (154.3, 299)	216.00 (156.8, 302.3)	159.80 (114.25, 240.55)	< 0.001
n	*2003*	*779*	*992*	*232*	
ICAM, mg/L	265.88 (228.50, 308.4)	275.37 (237.82, 313.48)	264.95 (228.97, 308.39)	240.11 (209.62, 280.67)	< 0.001

Data presented at n (%) or median (IQR)

Table S2. Baseline characteristics among participants with urinary arsenic, 2000-2002.

	Subset with Urine As *n=246*
Sociodemographic factors	
Male	134 (54.5)
Age	60 (53, 69)
Ethnicity	
White, Caucasian	70 (28.5)
Asian	61 (24.8)
Black, African-American	58 (23.6)
Hispanic	57 (23.2)
Site	
Salem, NC	26 (10.6)
New York, NY	40 (16.3)
Baltimore, MD	23 (9.3)
St Paul, MN	29 (11.8)
Chicago, IL	50 (20.3)
Los Angeles, CA	78 (31.7)
Education	
≤ High school	81 (32.9)
Some college	48 (19.5)
≥ College degree	117 (47.6)
CVD risk factors	
BMI, kg/m2	26.33 (23.38, 30.45)
Energy intake, kcal	1440.76 (1110.37, 1816.09)
Alternate Healthy Eating Index Score	43.45 (35.62, 51.25)
Physical activity, MET	65.50 (32.19, 118.62)
Hypertension	91 (37)
Diabetes Mellitus	61 (24.8)
Family history myocardial infarction	100 (41)
Current cigarette use	35 (14.2)
Pack-years*	14.50 (4.70, 28.88)
Urine arsenic/creatinine, (μg/g)**	3.08 (1.96, 4.69)
Endpoints	
Inflammation markers	
hsCRP, mg/L	1.55 (0.71, 3.74)
hsCRP ≥ 2, mg/L	101 (41.1)
IL-6, pg/mL	1.07 (0.7, 1.90)
Fibrinogen, mg/dL	329.00 (291, 382.75)
Vascular function	
Carotid distensibility, 10^{-3}mmHg	2.53 (1.94, 3.14)
Aortic distensibility, $mmHg^{-1}$	1.66 (1.14, 2.4)
Brachial FMD, %	3.50 (2.4, 5.38)
Subclinical atherosclerosis	
Internal CIMT, mm	0.83 (0.67, 1.20)
Common CIMT, mm	0.80 (0.73, 0.93)
CAC > 0	117 (47.6)
CAC > 75th percentile	129 (52.4)
ABI < 1.0	20 (8.1)
As-specific inflammation markers	
ICAM, ng/L	252.64 (219.12, 288.76)

Data presented at n (%) or median (IQR)

* among ever smokers only

** sum of iAs, MMA, and DMA corrected for arsenobetaine level

Table S3. Associations of rice intake and urinary arsenic with domains of subclinical CVD, MESA, United States, 2000-2002.

Endpoint		Rice Intake				Urinary Arsenic
		<1 serving per wk	1-6 servings per wk	≥1 servings per day		Value per IQR change
		Value (95% CI)	Value (95% CI)	Value (95% CI)	p trend	(2.7 μg/g creatinine)
Inflammation Markers						
hsCRP (mg/L), GMR	***n***	*2028*	*2383*	*639*		*246*
	Model 1	1.00 (ref)	0.91 (0.85, 0.98)	0.90 (0.79, 1.04)	0.02	0.93 (0.76, 1.14)
	Model 2	1.00 (ref)	0.96 (0.90, 1.02)	0.97 (0.85, 1.10)	0.3	1.00 (0.82, 1.21)
	Model 3	1.00 (ref)	0.96 (0.90, 1.02)	0.96 (0.85, 1.10)	0.3	1.01 (0.83, 1.22)
	Model 4	1.00 (ref)	0.97 (0.91, 1.03)	0.98 (0.86, 1.11)	0.4	1.02 (0.84, 1.23)
hsCRP ≥ 2 mg, OR	***n* *(Yes/No)***	*1046/982**	*1136/1247**	*183/456**		*101/145**
	Model 1	1.00 (ref)	0.86 (0.75, 0.99)	0.76 (0.57, 1.00)	0.01	1.00 (0.66, 1.50)
	Model 2	1.00 (ref)	0.93 (0.81, 1.07)	0.83 (0.62, 1.12)	0.2	1.12 (0.72, 1.73)
	Model 3	1.00 (ref)	0.93 (0.81, 1.07)	0.83 (0.61, 1.11)	0.2	1.12 (0.71, 1.77)
	Model 4	1.00 (ref)	0.95 (0.82, 1.09)	0.84 (0.62, 1.13)	0.3	1.20 (0.75, 1.91)
IL-6 (pg/mL), GMR	***n***	*2028*	*2383*	*639*		*246*
	Model 1	1.00 (ref)	0.96 (0.92, 1.00)	0.95 (0.87, 1.03)	0.05	0.95 (0.84, 1.08)
	Model 2	1.00 (ref)	0.99 (0.95, 1.02)	0.98 (0.91, 1.06)	0.4	0.99 (0.88, 1.11)
	Model 3	1.00 (ref)	0.99 (0.95, 1.02)	0.98 (0.91, 1.05)	0.4	0.99 (0.88, 1.11)
	Model 4	1.00 (ref)	0.99 (0.95, 1.03)	0.98 (0.91, 1.06)	0.6	0.99 (0.88, 1.12)
Fibrinogen (mg/dL), GMR	***n***	*2028*	*2383*	*639*		*246*
	Model 1	1.00 (ref)	1.00 (0.98, 1.01)	1.00 (0.98, 1.03)	0.8	0.99 (0.95, 1.02)
	Model 2	1.00 (ref)	1.00 (0.99, 1.01)	1.01 (0.99, 1.03)	0.6	1.00 (0.96, 1.03)
	Model 3	1.00 (ref)	1.00 (0.99, 1.01)	1.01 (0.99, 1.03)	0.6	1.00 (0.96, 1.03)
	Model 4	1.00 (ref)	1.00 (0.99, 1.01)	1.01 (0.99, 1.03)	0.5	1.00 (0.96, 1.03)
Arsenic-Specific Inflammation Markers						
E-Selectin (ng/mL), GMR	***n***	*298*	*385*	*99*		*0*
	Model 1	1.00 (ref)	1.10 (1.02, 1.18)	1.09 (0.94, 1.25)	0.03	-
	Model 2	1.00 (ref)	1.10 (1.02, 1.18)	1.09 (0.95, 1.26)	0.03	-
	Model 3	1.00 (ref)	1.10 (1.02, 1.18)	1.11 (0.96, 1.28)	0.02	-
	Model 4	1.00 (ref)	1.11 (1.03, 1.19)	1.11 (0.96, 1.28)	0.02	-
ICAM (ng/mL), GMR	***n***	*779*	*992*	*232*		*75*
	Model 1	1.00 (ref)	0.99 (0.97, 1.02)	1.01 (0.96, 1.06)	0.9	1.04 (0.94, 1.14)
	Model 2	1.00 (ref)	1.00 (0.97, 1.03)	1.01 (0.96, 1.07)	0.8	1.06 (0.96, 1.17)
	Model 3	1.00 (ref)	1.00 (0.97, 1.02)	1.02 (0.97, 1.07)	0.7	1.08 (0.98, 1.19)

	Model 4	1.00 (ref)	1.00 (0.97, 1.03)	1.02 (0.97, 1.07)	0.7	1.07 (0.97, 1.19)
	n	*298*	*385*	*99*		*0*
	Model 1	1.00 (ref)	0.99 (0.91, 1.07)	1.00 (0.85, 1.18)	0.9	-
MMP-9 (ng/mL), GMR	**Model 2**	1.00 (ref)	0.99 (0.91, 1.08)	1.01 (0.86, 1.19)	0.9	-
	Model 3	1.00 (ref)	0.99 (0.91, 1.07)	0.99 (0.85, 1.17)	0.8	-
	Model 4	1.00 (ref)	0.99 (0.91, 1.08)	0.99 (0.85, 1.17)	0.9	-
Vascular Function						
	n	*2028*	*2383*	*639*		*246*
	Model 1	0.00 (ref)	-0.01 (-0.07, 0.05)	-0.08 (-0.20, 0.04)	0.4	-0.02 (-0.19, 0.15)
Carotid Distensibility (10^{-3}mmHg), MD	**Model 2**	0.00 (ref)	-0.02 (-0.08, 0.04)	-0.10 (-0.23, 0.02)	0.2	-0.05 (-0.22, 0.12)
	Model 3	0.00 (ref)	-0.02 (-0.08, 0.04)	-0.10 (-0.22, 0.02)	0.2	-0.05 (-0.22, 0.12)
	Model 4	0.00 (ref)	-0.02 (-0.08, 0.04)	-0.10 (-0.22, 0.02)	0.2	-0.05 (-0.22, 0.13)
	n	*1130*	*1334*	*295*		*128*
	Model 1	1.00 (ref)	0.96 (0.92, 1.01)	0.98 (0.90, 1.07)	0.2	1.03 (0.88, 1.20)
Aortic Distensibility ($mmHg^{-1}$), GMR	**Model 2**	1.00 (ref)	0.96 (0.92, 1.00)	0.98 (0.90, 1.07)	0.2	1.01 (0.86, 1.17)
	Model 3	1.00 (ref)	0.97 (0.93, 1.01)	0.99 (0.91, 1.07)	0.3	0.98 (0.84, 1.14)
	Model 4	1.00 (ref)	0.97 (0.93, 1.01)	0.99 (0.91, 1.07)	0.3	0.96 (0.82, 1.12)
	n	*920*	*1316*	*466*		*142*
	Model 1	0.00 (ref)	0.10 (-0.16, 0.35)	0.45 (0.02, 0.89)	0.1	-0.09 (-0.74, 0.57)
FMD, MD	**Model 2**	0.00 (ref)	0.08 (-0.17, 0.34)	0.43 (-0.01, 0.87)	0.1	-0.04 (-0.72, 0.64)
	Model 3	0.00 (ref)	0.09 (-0.17, 0.34)	0.43 (-0.01, 0.86)	0.1	-0.02 (-0.71, 0.66)
	Model 4	0.00 (ref)	0.06 (-0.19, 0.32)	0.41 (-0.03, 0.85)	0.1	-0.02 (-0.71, 0.67)
Subclinical Atherosclerosis						
	n	*2028*	*2383*	*639*		*246*
	Model 1	1.00 (ref)	1.00 (0.97, 1.02)	0.95 (0.90, 1.00)	0.2	0.96 (0.89, 1.04)
CIMT-Internal, GMR	**Model 2**	1.00 (ref)	1.01 (0.98, 1.04)	0.96 (0.91, 1.02)	0.7	0.98 (0.91, 1.06)
	Model 3	1.00 (ref)	1.01 (0.98, 1.04)	0.97 (0.92, 1.02)	0.7	0.98 (0.91, 1.06)
	Model 4	1.00 (ref)	1.01 (0.98, 1.04)	0.97 (0.92, 1.02)	0.7	0.98 (0.91, 1.06)
	n	*2028*	*2383*	*639*		*246*
	Model 1	1.00 (ref)	1.00 (0.98, 1.01)	0.96 (0.94, 0.99)	0.02	0.98 (0.95, 1.02)
CIMT-Common, GMR	**Model 2**	1.00 (ref)	1.00 (0.99, 1.01)	0.97 (0.95, 0.99)	0.2	0.99 (0.96, 1.03)
	Model 3	1.00 (ref)	1.00 (0.99, 1.01)	0.97 (0.95, 0.99)	0.2	1.00 (0.96, 1.03)
	Model 4	1.00 (ref)	1.00 (0.99, 1.01)	0.97 (0.95, 1.00)	0.3	0.99 (0.96, 1.03)
CAC > 0, OR	***n* *(Yes/No)***	*1105/923**	*1076/1307**	*308/331**		*117/129**

	Model 1	1.00 (ref)	0.88 (0.76, 1.02)	0.85 (0.63, 1.14)	0.1	0.97 (0.62, 1.54)
	Model 2	1.00 (ref)	0.94 (0.81, 1.09)	0.94 (0.69, 1.26)	0.4	0.98 (0.61, 1.56)
	Model 3	1.00 (ref)	0.93 (0.80, 1.08)	0.94 (0.70, 1.28)	0.4	0.99 (0.61, 1.60)
	Model 4	1.00 (ref)	0.93 (0.79, 1.08)	0.94 (0.69, 1.27)	0.4	0.99 (0.61, 1.60)
CAC > 75th, OR	***n (Yes/No)***	*267/838**	*284/792**	*71/237**		*27/90**
	Model 1	1.00 (ref)	0.91 (0.73, 1.13)	0.65 (0.41, 1.04)	0.1	1.23 (0.59, 2.57)
	Model 2	1.00 (ref)	0.94 (0.75, 1.17)	0.67 (0.42, 1.06)	0.2	1.29 (0.60, 2.75)
	Model 3	1.00 (ref)	0.93 (0.74, 1.17)	0.67 (0.42, 1.07)	0.2	1.27 (0.59, 2.74)
	Model 4	1.00 (ref)	0.93 (0.74, 1.16)	0.67 (0.42, 1.07)	0.2	0.99 (0.61, 1.60)
ABI < 1, OR	***n (Yes/No)***	*284/1744**	*219/2164**	*54/585**		*20/226**
	Model 1	1.00 (ref)	0.85 (0.68, 1.05)	0.90 (0.56, 1.44)	0.2	1.01 (0.48, 2.10)
	Model 2	1.00 (ref)	0.87 (0.70, 1.07)	0.86 (0.53, 1.39)	0.2	0.96 (0.45, 2.02)
	Model 3	1.00 (ref)	0.87 (0.70, 1.09)	0.84 (0.52, 1.36)	0.2	1.01 (0.46, 2.20)
	Model 4	1.00 (ref)	0.89 (0.71, 1.10)	0.85 (0.53, 1.37)	0.3	1.01 (0.46, 2.21)

* n (yes/no)

Model 1: Adjusted for age, sex, race, education, site, energy intake
Model 2: Further adjusted for smoking status, pack-years, exercise, BMI
Model 3: Further adjusted for diabetes, hypertension, hyperlipidemia, estimated glomerular filtration rate
Model 4: Further adjusted for alternative healthy eating index

GMR, geometric mean ratio; MD, mean difference; OR, odds ratio; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; ICAM, intercellular adhesion molecule-1; MMP-9, matrix metallopeptidase 9; FMD, flow-mediated dilation; CIMT, carotid intima-media thickness; CAC, coronary artery calcium; ABI, ankle-brachial index.

Table S4. Evaluation of effect modification of associations with demographic variables by subclinical CVD domain.

	INFLAMMATION					
	hsCRP			hsCRP ≥ 2		
	≥1 per day vs < 1 per week		p-interaction	≥1 per day vs < 1 per week		p-interaction
	n	GMR (95%CI)		n (Y/N)	OR (95%CI)	
Overall	*639 vs 2028*	*0.98 (0.86, 1.11)*	*0.4*	*183/456 vs 1046/982*	*0.84 (0.62, 1.13)*	*0.3*
Race			0.6			0.3
White, Caucasian	10 vs 1221	1.1 (0.58, 2.06)		5/5 vs 587/634	1.43 (0.35, 5.79)	
Asian	468 vs 15	0.94 (0.56, 1.57)		94/374 vs 5/10	0.59 (0.19, 1.85)	
Black, African-American	31 vs 571	0.78 (0.54, 1.13)		16/15 vs 337/234	0.88 (0.39, 1.96)	
Hispanic	130 vs 221	1.16 (0.93, 1.45)		68/62 vs 117/104	1.14 (0.71, 1.85)	
Age			0.1			0.2
< 62 y/o	285 vs 885	1.01 (0.86, 1.19)		84/201 vs 454/431	0.96 (0.66, 1.41)	
≥ 62 y/o	354 vs 1143	0.94 (0.81, 1.10)		99/255 vs 592/551	0.74 (0.52, 1.06)	
Sex			0.1			0.1
Female	346 vs 1132	0.88 (0.76, 1.03)		112/234 vs 690/442	0.69 (0.49, 0.98)	
Male	293 vs 896	1.1 (0.93, 1.29)		71/222 vs 356/540	1.08 (0.74, 1.57)	
aHEI score			0.6			0.8
< 42	260/1145	0.93 (0.79, 1.09)		83/177 vs 631/514	0.83 (0.57, 1.20)	
> 42	379/883	1.02 (0.87, 1.2)		100/279 vs 415/668	0.86 (0.6, 1.24)	
Smoking Status			0.3			0.3
Never	456 vs 898	0.95 (0.81, 1.1)		126/330 vs 457/441	0.83 (0.58, 1.18)	
Former	132 vs 859	1.08 (0.88, 1.33)		39/93 vs 429/430	1.04 (0.64, 1.70)	
Current	51 vs 271	0.83 (0.61, 1.13)		18/33 vs 160/111	0.50 (0.25, 1.02)	

	INFLAMMATION					
	Fibrinogen			IL-6		
	≥1 per day vs < 1 per week		p-interaction	≥1 per day vs < 1 per week		p-interaction
	n	GMR (95%CI)		n	GMR (95%CI)	
Overall	*639 vs 2028*	*1.01 (0.99, 1.03)*	*0.5*	*639 vs 2028*	*0.98 (0.91, 1.06)*	*0.6*
Race			0.9			0.4
White, Caucasian	10 vs 1221	1.01 (0.9, 1.14)		10 vs 1221	1.27 (0.88, 1.83)	
Asian	468 vs 15	1.03 (0.93, 1.13)		468 vs 15	1.00 (0.74, 1.35)	
Black, African-American	31 vs 571	1.00 (0.93, 1.07)		31 vs 571	0.84 (0.68, 1.04)	
Hispanic	130 vs 221	0.99 (0.95, 1.04)		130 vs 221	1.03 (0.91, 1.18)	
Age			0.4			0.05
< 62 y/o	285 vs 885	1.02 (0.99, 1.05)		285 vs 885	1.01 (0.92, 1.11)	
≥ 62 y/o	354 vs 1143	1.00 (0.97, 1.03)		354 vs 1143	0.94 (0.86, 1.03)	
Sex			0.1			0.2
Female	346 vs 1132	1.03 (1, 1.06)		346 vs 1132	0.95 (0.86, 1.04)	
Male	293 vs 896	0.99 (0.96, 1.02)		293 vs 896	1.03 (0.93, 1.13)	
aHEI score			0.5			0.1
< 42	260/1145	1.02 (0.99, 1.05)		260/1145	1.02 (0.93, 1.12)	
> 42	379/883	1.00 (0.98, 1.03)		379/883	0.96 (0.87, 1.05)	
Smoking Status			0.6			0.2
Never	456 vs 898	1.01 (0.98, 1.04)		456 vs 898	0.98 (0.9, 1.07)	
Former	132 vs 859	1.02 (0.98, 1.06)		132 vs 859	1.02 (0.9, 1.15)	
Current	51 vs 271	0.98 (0.92, 1.03)		51 vs 271	0.87 (0.73, 1.05)	

	VASCULAR FUNCTION								
	Carotid distensibility			Aortic distensibility			Brachial FMD		
	≥1 per day vs < 1 per week		p-interaction	≥1 per day vs < 1 per week		p-interaction	≥1 per day vs < 1 per week		p-interaction
	n	MD (95%CI)		n	GMR (95%CI)		n	MD (95%CI)	
Overall	*639 vs 2028*	*-0.10 (-0.22, 0.02)*	*0.2*	*295 vs 1130*	*0.99 (0.91, 1.07)*	*0.3*	466 vs 920	*0.41 (-0.03, 0.85)*	*0.1*
Race			0.1			0.8			0.7
White, Caucasian	10 vs 1221	0.5 (-0.08, 1.07)		10 vs 1221	1.21 (0.87, 1.69)		10 vs 1221	1.71 (-0.48, 3.91)	
Asian	468 vs 15	0.05 (-0.43, 0.52)		468 vs 15	1 (0.71, 1.4)		468 vs 15	-0.23 (-1.74, 1.28)	
Black, African-American	31 vs 571	-0.13 (-0.23, -0.02)		31 vs 571	0.95 (0.76, 1.18)		31 vs 571	0.04 (-1.35, 1.43)	
Hispanic	130 vs 221	0.02 (-0.12, 0.16)		130 vs 221	0.95 (0.81, 1.12)		130 vs 221	0.63 (-0.15, 1.41)	
Age			0.2			0.0003			0.6
< 62 y/o	285 vs 885	0.00 (-0.15, 0.16)		285 vs 885	1.13 (1.01, 1.25)		285 vs 885	0.34 (-0.21, 0.89)	
≥ 62 y/o	354 vs 1143	-0.13 (-0.27, 0.02)		354 vs 1143	0.88 (0.78, 0.98)		354 vs 1143	0.65 (0.12, 1.18)	
Sex			0.6			0.6			0.6
Female	346 vs 1132	-0.11 (-0.25, 0.03)		346 vs 1132	0.98 (0.88, 1.08)		346 vs 1132	0.44 (-0.08, 0.97)	
Male	293 vs 896	-0.09 (-0.24, 0.06)		293 vs 896	0.99 (0.89, 1.11)		293 vs 896	0.37 (-0.17, 0.91)	
aHEI score			0.8			0.5			1.0
< 42	260/1145	-0.12 (-0.26, 0.03)		260/1145	0.95 (0.86, 1.06)		260/1145	0.37 (-0.18, 0.92)	
> 42	379/883	-0.10 (-0.24, 0.05)		379/883	1.02 (0.92, 1.13)		379/883	0.44 (-0.09, 0.97)	
Smoking Status			0.9			0.3			0.1
Never	456 vs 898	-0.12 (-0.26, 0.02)		456 vs 898	0.97 (0.88, 1.07)		456 vs 898	0.42 (-0.09, 0.93)	
Former	132 vs 859	-0.12 (-0.31, 0.07)		132 vs 859	1 (0.87, 1.16)		132 vs 859	0.21 (-0.47, 0.9)	
Current	51 vs 271	0.00 (-0.29, 0.28)		51 vs 271	1.07 (0.87, 1.32)		51 vs 271	1.44 (0.35, 2.54)	

	SUBCLINICAL ATHEROSCLEROSIS								
	CIMT - Internal			CIMT - Common			CAC > 0		
	1+ per day vs < 1 per week		p-interaction	1+ per day vs < 1 per week		p-interaction	1+ per day vs < 1 per week		p-interaction
	n	GMR (95%CI)		n	GMR (95%CI)		n (Y/N)	OR (95%CI)	
Overall	639 vs 2028	*0.97 (0.92, 1.02)*	*0.7*	639 vs 2028	*0.97 (0.95, 1.00)*	*0.3*	308/331 vs 1105/923	*0.94 (0.69, 1.27)*	*0.4*
Race			0.3			0.5			0.4
White, Caucasian	10 vs 1221	1.12 (0.86, 1.44)		10 vs 1221	0.91 (0.82, 1.02)		3/7 vs 736/485	0.26 (0.05, 1.48)	
Asian	468 vs 15	1.01 (0.82, 1.25)		468 vs 15	1.00 (0.91, 1.09)		229/239 vs 7/8	1.03 (0.29, 3.61)	
Black, African-American	31 vs 571	0.99 (0.85, 1.15)		31 vs 571	1.01 (0.94, 1.07)		17/14 vs 253/318	1.69 (0.72, 3.97)	
Hispanic	130 vs 221	1.00 (0.91, 1.09)		130 vs 221	0.96 (0.93, 1)		59/71 vs 109/112	0.96 (0.57, 1.6)	
Age			0.0007			0.05			0.9
< 62 y/o	285 vs 885	1.04 (0.97, 1.11)		285 vs 885	0.99 (0.96, 1.01)		82/203 vs 304/581	0.92 (0.63, 1.33)	
≥ 62 y/o	354 vs 1143	0.90 (0.84, 0.96)		354 vs 1143	0.95 (0.93, 0.98)		226/128 vs 801/342	0.84 (0.6, 1.19)	
Sex			0.5			0.2			0.2
Female	346 vs 1132	0.97 (0.91, 1.04)		346 vs 1132	0.99 (0.96, 1.01)		144/202 vs 497/635	1.12 (0.78, 1.61)	
Male	293 vs 896	0.96 (0.90, 1.03)		293 vs 896	0.96 (0.93, 0.99)		164/129 vs 608/288	0.76 (0.52, 1.11)	
aHEI score			0.5			0.6			0.5
< 42	260/1145	0.97 (0.91, 1.04)		260/1145	0.97 (0.94, 0.99)		125/135 vs 595/550	1.07 (0.74, 1.56)	
> 42	379/883	0.96 (0.90, 1.03)		379/883	0.98 (0.95, 1.01)		183/196 vs 510/373	0.82 (0.57, 1.19)	
Smoking Status			0.7			0.02			0.4
Never	456 vs 898	0.98 (0.92, 1.04)		456 vs 898	0.99 (0.97, 1.02)		206/250 vs 442/456	1.08 (0.76, 1.54)	
Former	132 vs 859	0.98 (0.90, 1.07)		132 vs 859	0.95 (0.91, 0.98)		75/57 vs 522/337	0.68 (0.42, 1.1)	
Current	51 vs 271	0.91 (0.80, 1.04)		51 vs 271	0.97 (0.91, 1.02)		27/24 vs 141/130	0.84 (0.4, 1.76)	

	SUBCLINICAL ATHEROSCLEROSIS					
	CAC > 75th percentile			ABI > 1		
	1+ per day vs < 1 per week		p-interaction	1+ per day vs < 1 per week		p-interaction
	n (Y/N)	OR (95%CI)		n (Y/N)	OR (95%CI)	
Overall	71/237 vs 267/838	*0.67 (0.42, 1.07)*	*0.2*	*54/585 vs 284/1744*	*0.85 (0.53, 1.37)*	*0.3*
Race			0.02			0.1
White, Caucasian	0/3 vs 155/581	NA		1/9 vs 144/1077	1.46 (0.16, 13.63)	
Asian	49/180 vs 1/6	1.25 (0.14, 10.96)		38/430 vs 1/14	1.12 (0.13, 9.35)	
Black, African-American	7/10 vs 80/173	2.07 (0.69, 6.25)		9/22 vs 126/445	2.16 (0.9, 5.15)	
Hispanic	15/44 vs 31/78	1.00 (0.46, 2.15)		6/124 vs 13/208	0.74 (0.26, 2.08)	
Age			0.6			0.8
< 62 y/o	29/53 vs 116/188	0.62 (0.33, 1.16)		13/272 vs 78/807	0.83 (0.41, 1.68)	
≥ 62 y/o	42/184 vs 151/650	0.73 (0.44, 1.21)		41/313 vs 206/937	0.85 (0.51, 1.42)	
Sex			0.4			0.2
Female	42/102 vs 144/353	0.74 (0.42, 1.3)		41/305 vs 203/929	0.95 (0.56, 1.61)	
Male	29/135 vs 123/485	0.61 (0.35, 1.09)		13/280 vs 81/815	0.66 (0.32, 1.34)	
aHEI score			0.2			0.2
< 42	32/93 vs 159/436	0.65 (0.37, 1.14)		24/236 vs 180/965	0.85 (0.48, 1.51)	
> 42	39/144 vs 108/402	0.72 (0.41, 1.27)		30/349 vs 104/779	0.89 (0.5, 1.61)	
Smoking Status			0.1			0.9
Never	51/155 vs 94/348	0.78 (0.44, 1.36)		41/415 vs 111/787	0.92 (0.53, 1.60)	
Former	17/58 vs 121/401	0.90 (0.45, 1.78)		9/123 vs 121/738	0.74 (0.33, 1.66)	
Current	3/24 vs 52/89	0.18 (0.05, 0.65)		4/1 vs 52/219	0.62 (0.20, 1.94)	

Table S5. Frequency of rice intake at Exam 1 (2000-2002) and Exam 5 (2010-2012) among study participants in the main analyses (n=5050). A total of 2208 participants reported consistent rice intake frequency at both Exams 1 and 5.

		Exam 1			Total
		<1/wk	**1-6/wk**	**≥1/day**	
Exam 5	**<1/wk**	**1004**	515	34	1553
	1-6/wk	346	**988**	133	1467
	≥1/day	10	117	**216**	343
	Missing	668	763	256	1687
Total		2028	2383	639	5050

Table S6. Association of Rice Intake and Domains of Subclinical CVD among participants with consistent rice intake at Exam 1 (2000-2002) and Exam 5 (2010-2012).

	Consistent Rice Intake						
	<1 serving per week		1-6 servings per week		≥1 servings per day		
	n	Value (95% CI)	*n*	Value (95% CI)	*n*	Value (95% CI)	p-trend
Inflammation Markers							
hsCRP (mg/L), GMR	*1004*	1.00 (ref)	*988*	0.94 (0.85, 1.04)	*216*	1.18 (0.93, 1.51)	0.9
hsCRP ≥ 2 mg, OR	*499/505**	1.00 (ref)	*433/555**	0.87 (0.70, 1.10)	*54/162**	1.10 (0.62, 1.96)	0.5
IL-6 (pg/mL), GMR	*1004*	1.00 (ref)	*988*	0.96 (0.91, 1.02)	*216*	0.98 (0.85, 1.13)	0.3
Fibrinogen (mg/dL), GMR	*1004*	1.00 (ref)	*988*	0.99 (0.97, 1.01)	*216*	1.00 (0.95, 1.04)	0.4
Arsenic-Specific Inflammation Markers							
E-Selectin (ng/mL), GMR	*152*	1.00 (ref)	*167*	1.13 (1.01, 1.27)	*31*	1.31 (1.01, 1.71)	0.01
ICAM (ng/mL), GMR	*403*	1.00 (ref)	*421*	0.99 (0.95, 1.03)	*83*	1.06 (0.97, 1.16)	0.9
MMP-9 (ng/mL), GMR	*152*	1.00 (ref)	*167*	1.01 (0.89, 1.14)	*31*	0.88 (0.66, 1.16)	0.7
Vascular Function							
FMD, MD	*522*	0.00 (ref)	*620*	0.09 (-0.31, 0.49)	*185*	1.06 (0.28, 1.83)	0.1
Carotid Distensibility (10^{-3}mmHg), MD	*1004*	0.00 (ref)	*988*	-0.06 (-0.16, 0.03)	*216*	-0.21 (-0.42, 0.01)	0.1
Aortic Distensibility ($mmHg^{-1}$), GMR	565	1.00 (ref)	*596*	0.97 (0.91, 1.03)	111	1.05 (0.91, 1.22)	0.8
Subclinical Atherosclerosis							
CIMT-Internal, GMR	*1004*	1.00 (ref)	*988*	1.00 (0.96, 1.04)	*216*	0.91 (0.83, 1.00)	0.4
CIMT-Common, GMR	*1004*	1.00 (ref)	*988*	1.00 (0.98, 1.01)	*216*	0.97 (0.93, 1.01)	0.3
CAC > 0, OR	*501/503**	1.00 (ref)	*376/612**	0.82 (0.65, 1.04)	*93/123**	0.81 (0.46, 1.43)	0.1
CAC > 75^{th} %ile, OR	*125/376**	1.00 (ref)	*101/275**	0.76 (0.51, 1.12)	*54/162**	0.35 (0.12, 0.99)	0.1
ABI < 1, OR	*104/900**	1.00 (ref)	*74/914**	1.26 (0.86, 1.85)	*54/162**	0.50 (0.18, 1.40)	0.7

* n (yes/no)

Models adjusted for age, sex, race/ethnicity, education, education, smoking status, pack-years, exercise, BMI, diabetes, hypertension, hyperlipidemia, estimated glomerular filtration rate, energy intake, and alternative healthy eating index.

Table S7. Association of Rice Intake (2 categories) and Domains of Subclinical CVD.

	Rice Intake				
	≤ 1 serving per week		≥ 2 servings per week		
	n	Value (95% CI)	*n*	Value (95% CI)	p trend
Inflammation Markers					
hsCRP (mg/L), GMR	*2817*	1.00 (ref)	*2233*	1.00 (0.94, 1.07)	0.9
hsCRP ≥ 2 mg, OR	*1410/1407**	1.00 (ref)	*955/1278**	1.00 (0.79, 1.26)	1.0
IL-6 (pg/mL), GMR	*2817*	1.00 (ref)	*2233*	1.01 (0.97, 1.05)	0.5
Fibrinogen (mg/dL), GMR	*2817*	1.00 (ref)	*2233*	1.00 (0.99, 1.02)	0.6
Arsenic-Specific Inflammation Markers					
E-Selectin (ng/mL), GMR	*418*	1.00 (ref)	*364*	1.04 (0.97, 1.13)	0.3
ICAM (ng/mL), GMR	*1116*	1.00 (ref)	*887*	1.00 (0.97, 1.03)	0.9
MMP-9 (ng/mL), GMR	*418*	1.00 (ref)	*364*	1.04 (0.96, 1.14)	0.3
Vascular Function					
FMD, MD	*1307*	0.00 (ref)	*1395*	0.04 (-0.23, 0.30)	0.8
Carotid Distensibility (10^{-3}mmHg), MD	*2817*	0.00 (ref)	*2233*	-0.02 (-0.09, 0.04)	0.5
Aortic Distensibility ($mmHg^{-1}$), GMR	*1561*	1.00 (ref)	*1198*	0.98 (0.94, 1.02)	0.3
Subclinical Atherosclerosis					
CIMT-Internal, GMR	*2817*	1.00 (ref)	*2233*	1.01 (0.99, 1.04)	0.3
CIMT-Common, GMR	*2817*	1.00 (ref)	*2233*	1.00 (0.99, 1.02)	0.5
CAC > 0, OR	*1486/1331**	1.00 (ref)	*1003/1230**	0.76 (0.60, 0.98)	0.03
CAC > 75^{th} %ile, OR	*1131/1331**	1.00 (ref)	*736/1230**	0.90 (0.59, 1.37)	0.6
ABI < 1, OR	*353/2464**	1.00 (ref)	*204/2029**	1.40 (0.93, 2.11)	0.1

* n (yes/no)

Models adjusted for age, sex, race/ethnicity, education, education, smoking status, pack-years, exercise, BMI, diabetes, hypertension, hyperlipidemia, estimated glomerular filtration rate, energy intake, and alternative healthy eating index.

Table S8. Association of Rice Intake (5 categories) and Domains of Subclinical CVD.

	Rice Intake										
	Rare or Never		1-3 servings per month		1-2 servings per week		3-6 servings per week		≥1 servings per day		
	n	Value (95% CI)	*n*	Value (95% CI)	*n*	Value (95% CI)	*n*	Value (95% CI)	*n*	Value (95% CI)	p-trend
Inflammation Markers											
hsCRP (mg/L), GMR	*363*	1.00 (ref)	*1665*	1.07 (0.95, 1.20)	*1500*	1.01 (0.90, 1.14)	*883*	1.06 (0.93, 1.22)	*639*	1.05 (0.89, 1.24)	0.9
hsCRP ≥ 2 mg, OR	*185/178**	1.00 (ref)	*861/804**	1.10 (0.76, 1.58)	*712/788**	0.91 (0.61, 1.35)	*424/459**	1.04 (0.67, 1.62)	*183/456**	1.05 (0.57, 1.95)	0.7
IL-6 (pg/mL), GMR	*363*	1.00 (ref)	*1665*	0.98 (0.92, 1.05)	*1500*	0.98 (0.91, 1.05)	*883*	0.99 (0.91, 1.07)	*639*	0.97 (0.89, 1.07)	0.7
Fibrinogen (mg/dL), GMR	*363*	1.00 (ref)	*1665*	0.99 (0.97, 1.01)	*1500*	0.99 (0.97, 1.02)	*883*	1.00 (0.97, 1.02)	*639*	1.00 (0.97, 1.03)	0.7
Arsenic-Specific Inflammation Markers											
E-Selectin (ng/mL), GMR	*51*	1.00 (ref)	*247*	1.08 (0.95, 1.24)	*237*	1.21 (1.05, 1.39)	*148*	1.13 (0.97, 1.32)	*99*	1.16 (0.96, 1.39)	0.05
ICAM (ng/mL), GMR	*130*	1.00 (ref)	*649*	0.99 (0.95, 1.04)	*632*	0.99 (0.95, 1.04)	*360*	0.99 (0.94, 1.05)	*232*	1.01 (0.95, 1.08)	0.9
MMP-9 (ng/mL), GMR	*51*	1.00 (ref)	*247*	1.00 (0.86, 1.17)	*237*	0.98 (0.84, 1.15)	*148*	1.01 (0.85, 1.21)	*99*	1.01 (0.81, 1.24)	0.9
Vascular Function											
FMD, MD	*150*	0.00 (ref)	*770*	0.18 (-0.30, 0.66)	*765*	0.28 (-0.20, 0.77)	*551*	0.05 (-0.48, 0.58)	*466*	0.47 (-0.14, 1.08)	0.3
Carotid Distensibility (10^{-3}mmHg), MD	*363*	0.00 (ref)	*1665*	0.03 (-0.07, 0.14)	*1500*	0.01 (-0.10, 0.12)	*883*	-0.00 (-0.13, 0.12)	*639*	-0.08 (-0.23, 0.07)	0.2
Aortic Distensibility ($mmHg^{-1}$), GMR	*192*	1.00 (ref)	*938*	0.97 (0.90, 1.04)	*831*	0.94 (0.87, 1.01)	*503*	0.96 (0.88, 1.04)	*295*	0.97 (0.87, 1.08)	0.3
Subclinical Atherosclerosis											
CIMT-Internal, GMR	*363*	1.00 (ref)	*1665*	0.99 (0.95, 1.04)	*1500*	0.99 (0.95, 1.04)	*883*	1.03 (0.98, 1.09)	*639*	0.97 (0.91, 1.04)	0.7
CIMT-Common, GMR	*363*	1.00 (ref)	*1665*	1.01 (0.99, 1.03)	*1500*	1.01 (0.99, 1.03)	*883*	1.01 (0.99, 1.03)	*639*	0.98 (0.95, 1.01)	0.5
CAC > 0, OR	*219/144**	1.00 (ref)	*886/779**	1.09 (0.75, 1.59)	*715/785**	0.86 (0.58, 1.29)	*361/522**	0.89 (0.57, 1.40)	*308/331**	0.92 (0.50, 1.71)	0.3
CAC > 75^{th}%ile, OR	*160/144**	1.00 (ref)	*678/779**	0.61 (0.35, 1.07)	*548/785**	0.43 (0.23, 0.81)	*244/522**	0.68 (0.33, 1.39)	*237/331**	0.31 (0.11, 0.90)	0.1
ABI < 1, OR	*66/297**	1.00 (ref)	*218/1447**	1.20 (0.69, 2.08)	*137/1363**	1.22 (0.66, 2.27)	*82/801**	2.40 (1.19, 4.81)	*54/585**	0.90 (0.31, 2.56)	0.1

* n (yes/no)

Models adjusted for age, sex, race/ethnicity, education, education, smoking status, pack-years, exercise, BMI, diabetes, hypertension, hyperlipidemia, estimated glomerular filtration rate, energy intake, and alternative healthy eating index.

Figure S1. Distributions of urinary arsenic levels by rice intake category of MESA participants, 2000-2002 (n=246).