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Urinary Metal Levels and Coronary Artery Calcification

Longitudinal Evidence in the Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

BACKGROUND Exposure to metals, a newly recognized risk factor for cardiovascular disease (CVD), could be related to atherosclerosis progression.

OBJECTIVES The authors hypothesized that higher urinary levels of nonessential (cadmium, tungsten, uranium) and essential (cobalt, copper, zinc) metals previously associated with CVD would be associated with baseline and rate of change of coronary artery calcium (CAC) progression, a subclinical marker of CVD in MESA (Multi-Ethnic Study of Atherosclerosis).

METHODS We analyzed data from 6,418 MESA participants with spot urinary metal levels at baseline (2000-2002) and 1 to 4 repeated, continuous measures of CAC over a 10-year period. We used linear mixed-effect models to assess the association of baseline urinary metal levels with baseline CAC and cumulative change in CAC over a 10-year period. Urinary metals (μg/g creatinine) and CAC were log transformed. Models were adjusted for baseline sociodemographic factors, estimated glomerular filtration rate, lifestyle factors, and clinical factors.

RESULTS At baseline, the median CAC was 6.3 (Q1-Q3: 0.7-58.2). Comparing the highest to lowest quartile of urinary cadmium, CAC levels were 51% (95% CI: 32%, 74%) higher at baseline and 75% (95% CI: 47%, 107%) higher over the 10-year period. For urinary tungsten, uranium, and cobalt, the corresponding CAC levels over the 10-year period were 45% (95% CI: 23%, 71%), 39% (95% CI: 17%, 64%), and 47% (95% CI: 25%, 74%) higher, respectively, with no difference for models with and without adjustment for clinical factors. For copper and zinc, the corresponding estimates dropped from 55% to 33% and from 85% to 57%, respectively, after adjustment for clinical factors. The associations of metals with CAC were comparable in magnitude to those for classical CVD risk factors.

CONCLUSIONS Exposure to metals was generally associated with extent of coronary calcification at baseline and follow-up. These findings support that metals are associated with the progression of atherosclerosis, potentially providing a novel strategy for the prevention and treatment of atherosclerosis progression. (JACC. 2024;84:1545-1557)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAC = coronary artery calcification

CAC-AS = coronary artery calcification Agatston method

CAC-SW = spatially weighted coronary artery calcification

Cd = cadmium

CHD = coronary heart disease

Co = cobalt

CT = computed tomography

Cu = copper

CVD = cardiovascular disease

DM = diabetes mellitus

eGFR = estimated glomerular filtration rate

FPG = fasting blood glucose

HDL = high-density lipoprotein

LDL = low-density lipoprotein

MDL = method detection limit

U = uranium

W = Tungsten

Zn = Zinc

Environmental contaminants are increasingly recognized as major risk factors for cardiovascular disease (CVD) despite the relative paucity of research compared to traditional risk factors.[1,2] In 2023, supported by epidemiologic and experimental evidence, the American Heart Association concluded that exposure to arsenic, cadmium, and lead constitutes a CVD risk factor.[3] Other metals may also promote atherosclerosis,[4-6] an inflammatory process underlying the most common forms of CVD. In the coronary arteries, atherosclerosis induces calcification, which can be measured noninvasively. Coronary artery calcification (CAC) is highly predictive of coronary heart disease events.[7] However, the association of metals with CAC is largely unknown.

Metals arise from anthropogenic and natural sources and vary geographically. Some are essential for biological processes whereas nonessential metals have no function in humans. Metals differ in redox activity and, thus, on the potential toxicity mechanisms.[8] Cobalt and copper, both essential elements, are examples of redox active metals capable of directly inducing reactive oxygen species, a precursor to the development of CVD.[9] Conversely, the nonessential metal cadmium binds sulfhydryl groups and depletes glutathione, a protective antioxidant.[10] Several metals additionally disrupt the endocrine system[11] and target the vascular system,[12] supporting that metals are atherogenic through multiple pathways.

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This study investigated the longitudinal association of urinary metal levels, biomarkers of metal exposure and internal dose, with changes in CAC in a multi-ethnic and geographically diverse study of adults in the United States. We used a novel, continuous measure of CAC that measures low levels of calcification that do not meet the traditional Agatston scoring criteria, the spatially weighted CAC score (CAC-SW).[13] We prioritized nonessential (cadmium, tungsten, uranium) and essential (cobalt, copper, zinc) metals that are relevant in U.S. populations and have been previously associated with CVD outcomes.[4,5] Other metals that are difficult to interpret in urine (eg, lead) or in populations with high levels of seafood intake (eg, arsenic) or for which there is limited evidence of an association with CVD outcomes (eg, cesium, strontium, manganese) were reported in secondary analyses.

METHODS

STUDY POPULATION. MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter, prospective cohort study of subclinical to clinical CVD.[14] Between July 2000 and August 2002, MESA recruited 6,814 participants using community-based strategies at 6 U.S. study sites in Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; New York, New York; St Paul, Minnesota; and Winston Salem, North Carolina. Participants were free of clinical CVD, men and women 45 to 84 years of age from 4 race and ethnic groups (White, Black, Hispanic/Latino, and Chinese). Data were analyzed for follow-up through MESA exam 5. Participants completed up to 5 clinical visits (exam 1 in 2000-2002 [n = 6,814], exam 2 in 2002-2004 [n = 6,232], exam 3 in 2004-2006 [n = 5,939], exam 4 in 2005-2007 [n = 5,704], and exam 5 in 2010-2012 [n = 4,655]). Participants who met enrollment criteria gave written informed consent. The Institutional Review Board at each study site approved the study.

Of the 6,814 MESA participants, 6,729 had metals and creatinine measured in urine at baseline (Supplemental Figure 1). We excluded 4 participants with extreme metal values (3 observations for cobalt, 1 for copper, 2 for uranium), as the levels for these participants were 100 times higher than the other highest values in the study. We excluded 32 participants who had a coronary revascularization procedure after exam 1 and 27 participants missing CAC-SW scores, the measure of CAC used in this study. We excluded participants missing data on education (n = 21), cigarette pack years (n = 69), physical activity (n = 2), low-density lipoprotein (LDL) cholesterol (n = 98), diabetes status (n = 4), systolic blood pressure (n = 2), estimated glomerular filtration rate (eGFR) (n = 38), and lipid-lowering and blood pressure medications (n = 14). The final sample size included 6,418 unique participants with one or more repeated measures of CAC

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for 15,550 observations, including 6,206 observations at baseline.

URINARY METALS. Morning spot urine samples were shipped frozen on dry ice to the MESA biorepository. In 2019, aliquots of 0.8 mL urine were shipped on dry ice to the Trace Metals Core Laboratory at Columbia University. Metals were analyzed using inductively coupled plasma mass spectrometry with dynamic reaction cell.[15] Approximately 10% of the samples were prepared and measured in duplicate to determine intraprecision, and ~10% were prepared and measured on different days to determine interprecision. The intra-assay and interassay coefficient of variation ranged from 2.5% for zinc to 14% for uranium, and from 5.8% for cadmium to 16% for uranium, respectively (Supplemental Table 1). Samples below the method detection limit (MDL) were replaced with the MDL/√2. In most urine samples (>95%), the measured elemental concentrations exceeded the MDL except for uranium (11%) and tungsten (32%) (Supplemental Table 1). To correct for urine dilution, we divided metal concentration by urine creatinine concentration (μg/creatinine), measured using the Jaffe reaction method.[16] For participants with metals analyzed at exams 1 and 5 (n = 594), the intraclass correlation coefficient ranged from 0.50 to 0.72 for cobalt and uranium, respectively, supporting that a single baseline metal measure is a moderate to good reflection of long-term metal levels.

CARDIAC COMPUTED TOMOGRAPHY SCANNING AND CORONARY ARTERY CALCIFICATION. All participants at baseline exam 1 received a cardiac computed tomography (CT) scan (n = 6,814). At exam 2, one-half of baseline MESA participants were randomly chosen for a repeat measure of coronary calcification (n = 2,914); the remaining one-half had the repeat measure of coronary calcification at exam 3 (n = 2,925). At exam 4, participants without exam 3 scans were prioritized for CT scans (n = 1,349). At exam 5, participants were preferentially included if they had scans from exam 3 and/or exam 4 (n = 3,304).[17] All CT measurements taken after a cardiac revascularization were removed from analysis (Supplemental Figure 1).

After arterial trajectories across the surface of the heart were determined within 8 mm and a phantom-based adjustment was applied, candidate calcified plaques were identified by software with the criteria that each plaque be composed of at least 4 contiguous voxels with an attenuation level of ≥130 HU. A radiologist or cardiologist scored all CT scans using an interactive scoring system at the Harbor-UCLA Los Angeles Biomedical Research Institute by the Agatston method.[18] The coronary artery calcification Agatston score (CAC-AS) reproducibly quantitates CAC from CT images and is highly predictive of coronary heart disease (CHD) and CVD events.[19] CAC-AS is a continuous measure that is dichotomized as 0 and 1, respectively, where 0 is no measured calcification and 1 is any measured calcification per the Agatston scoring criteria.

The traditional Agatston score, CAC-AS, uses a specific but conservative algorithm for lesion detection ignoring available information in the CT scan and the presence of accurately measurable calcification below the threshold classifying as CAC-AS = 0 participants who are early in the calcification progression stages.[13,20] The CAC-SW score is a semiautomated threshold-free CAC scoring method that assigns weights to each image voxel to calibrate and weight according to the phantom and neighboring voxels to maximize the CT scan information.[20] The detailed algorithm for calculating the CAC-SW is published.[20] CAC-SW is a continuous measure of calcification that provides a quantifiable CAC level even when CAC-AS = 0, and that is very similar to CAC-AS when it is ≥1. CAC-SW predicts incident CHD events even among participants with CAC-AS = 0, supporting it is an accurate measure of extent of atherosclerosis and atherosclerotic CVD risk throughout the entire range of disease.[20]

COVARIATES. Age, sex, race and ethnicity, education, smoking status, physical activity, and use of lipid-lowering and hypertension medications were collected by questionnaire during exam 1. Race and ethnicity were self-reported and categorized as White, Black, Hispanic/Latino, and Chinese. Study sites included Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; New York, New York; St Paul, Minnesota; and Winston Salem, North Carolina. Cigarette smoking status was classified as never, former, and current. Participants who had not smoked 100 cigarettes in their lifetime were classified as never smokers. Participants who answered yes were classified as current smokers if they had smoked in the last 30 days or classified as former smokers if they had not smoked in the last 30 days. Cigarette pack-years were calculated by multiplying the intensity in packs per day by duration in years. Physical activity was defined as the total moderate and high physical activity in hours per week, Monday to Sunday.

At exam 1, height and weight were measured to calculate body mass index (BMI) (kg/m^2). Resting systolic and diastolic blood pressure were measured 3 times in the seated position using a Dinamap model

Pro 100 automated oscillometric sphygmomanometer with the last 2 measurements averaged for analysis. LDL and high-density lipoprotein (HDL) cholesterol (mg/dL blood), and calibrated fasting plasma glucose (FPG) (mg/dL blood), were assessed using standard laboratory techniques. Diabetes mellitus (DM) was defined by the 2003 American Diabetes Association fasting criteria and categorized by normal (<100 mg/dL blood FPG), impaired fasting glucose (100-125 mg/dL blood FPG), untreated, and treated diabetes (≥126 mg/dL blood FPG or taking diabetes medications). Participants with untreated and treated diabetes were grouped together for analysis. Estimated glomerular filtration rate (eGFR) was calculated using the new creatinine and cyastin-C -based Chronic Kidney Disease Epidemiology Collaboration equation without accounting for race and ethnicity.[21] The eGFR can influence metal excretion in urine and was therefore used for adjustment in our models.

STATISTICAL ANALYSIS. We conducted descriptive analyses overall and by participant characteristics at baseline for continuous CAC-SW, dichotomous CAC-AS, and urinary metal levels. Urinary metal levels and CAC-SW were right-skewed and log-transformed for analysis. We performed Spearman correlation tests for log-transformed urinary metals (μg/g creatinine).

We used mixed-effect models on log-transformed repeated CAC-SW measures by baseline urinary metal levels with a random intercept on the participant and random slope on the time since baseline cardiac CT scan. The model estimates the percentage difference in CAC-SW levels at baseline and 10-year cumulative change by metal levels in the average participant after exponentiating the beta estimate, subtracting 1, and multiplying by 100. Urinary metal levels were modeled as: 1) quartiles (to compare each of the quartiles to the reference quartile, ie, the lowest quartile); 2) per interquartile range (IQR) on log-transformed levels (to compare Q3 to Q1); and 3) per IQR on log-transformed concentrations with restricted quadratic splines (to evaluate the flexible dose-response relationship).[22] We also evaluated the association of baseline metal levels with dichotomous CAC-AS score to estimate the relative risk of incident CAC-AS ≥1 among participants with CAC-AS = 0 at baseline. We specified a generalized linear mixed model to estimate baseline and 10-year cumulative change using a modified Poisson regression with log link function and robust standard errors.[23]

Model 1 was adjusted for baseline sociodemographic (age, sex, race and ethnicity, study site, education, eGFR) and lifestyle factors (smoking status, pack-years, physical activity, and BMI). Model 2 was additionally adjusted for baseline physiopathological risk factors (systolic blood pressure, antihypertensive medications, LDL-cholesterol, HDL-cholesterol, lipid-lowering medications, and diabetes status). Because urinary metals levels were measured at baseline, all adjustments were time-invariant covariates acquired at baseline. For the dose-response figures, we only show the results for model 2.

To assess the clinical relevance of the association of metal levels with CAC-SW, we performed mixed-effect models on log-transformed repeated CAC-SW by baseline smoking status, diabetes status, and LDL-cholesterol after adjusting for the same covariates as in our main models. We used Wald tests and conducted subgroup analysis to assess moderation of the associations by subgroups of age, sex, race and ethnicity, smoking status, and diabetes status for baseline and 10-year cumulative change. Finally, we used a flexible approach for estimating the health effects of mixtures, Bayesian kernel machine regression,[24] to assess the overall risk of the total metal mixture (cadmium, tungsten, uranium, cobalt, copper, and zinc) on CAC-SW at baseline, as well as to assess potential interactions between metals in an exploratory analysis.

SENSITIVITY ANALYSES. We conducted several sensitivity analyses. Because diabetes status can impact urinary zinc levels,[25] we further adjusted for FPG levels. To account for potential confounding factors related to environmental copollutants, we adjusted for particulate matter of diameter ≤2.5 $\mu g/m^3$, a source of metal exposure in air, and we adjusted for water uranium levels in community water systems when these data were available.[26,27] Because albumin and preexisting microalbuminuria are markers of kidney damage that could influence urinary metal excretion,[28] we further adjusted models for albumin to creatinine ratio. Because exposure to metals may be a proxy for distressed neighborhoods, we adjusted for the neighborhood socioeconomic status derived from American Community Survey 2005-2008 census tract estimates.[29-32] Finally, in a small subset of participants with repeated metal data available (n = 594), we investigated the relationship between time varying urinary metal levels at exams 1 and 5 with repeated measures of CAC-SW at exams 1 and 5.

RESULTS

The median of CAC-SW score was 6.3 (Q1-Q3: 0.7-58.2) and CAC-AS >0 occurred in approximately 50% participants at baseline (**Table 1**). Median CAC-SW and positive CAC-AS increased with age and were higher

TABLE 1 Baseline Participant Characteristics, Spatially Weighted CAC, and Agatston CAC

	N	CAC-SW	CAC-AS ≥1
Overall	6,206	6.3 (0.7-58.2)	3,080 (49.6)
Age, y			
<55	1,758	1.5 (0.3-7.1)	429 (24.4)
55-64	1,716	4.4 (0.6-31.7)	759 (44.2)
≥65	2,732	30.2 (2.9-162.4)	1,892 (69.3)
Sex			
Female	3,284	2.9 (0.4-23.8)	1,302 (39.6)
Male	2,922	17.1 (2-117.9)	1,778 (60.8)
Race and ethnicity			
White	2,375	8.8 (0.7-102.3)	1,349 (56.8)
Black	1,706	5.6 (0.8-36.2)	741 (43.4)
Hispanic/Latino	1,360	6 (1.4-45)	609 (44.8)
Chinese	765	3.1 (0.3-45.9)	381 (49.8)
Study site			
Salem, NC	960	2.1 (0.1-50)	489 (50.9)
New York, NY	994	6.7 (1.3-35.7)	412 (41.4)
Baltimore, MD	955	10.2 (1.3-89.3)	532 (55.7)
St Paul, MN	972	5.7 (1.6-76.4)	496 (51)
Chicago, IL	1,112	6.2 (0.5-52.4)	534 (48)
Los Angeles, CA	1,213	8.7 (0.8-56.8)	617 (50.9)
Education			
High school or less	2,226	8.1 (1.2-65.9)	1,169 (52.5)
Some college	1,450	6.5 (0.8-57.8)	702 (48.4)
College degree or more	2,530	4.8 (0.5-49.7)	1,209 (47.8)
Smoking status			
Never	3,165	4.3 (0.5-37.4)	1,400 (44.2)
Former	2,248	12.1 (1.3-92.4)	1,296 (57.7)
Current	793	4.7 (0.7-51.9)	384 (48.4)
Pack-years			
0	3,250	4.3 (0.5-37.1)	1,431 (44)
1-10	1,084	5.8 (0.9-52.5)	515 (47.5)
11-20	604	8.9 (1-63.7)	322 (53.3)
>20	1,268	18.3 (1.5-141.8)	812 (64)
BMI, kg/m^2			
<25	1,810	2.2 (0.2-51.2)	862 (47.6)
25 to 30	2,432	5.6 (0.8-62.2)	1,252 (51.5)
≥30	1,964	11.3 (2.3-58.8)	966 (49.2)
Physical activity, MET-h/wk			
≤34	1,625	9 (0.9-62.9)	846 (52.1)
35-69	1,563	6.9 (0.7-65.5)	816 (52.2)
70-139	1,691	6.1 (0.7-60.4)	830 (49.1)
≥140	1,327	4.5 (0.6-37)	588 (44.3)
LDL cholesterol, mg/dL			
<100	1,794	5.6 (0.6-60)	865 (48.2)
100-129	2,414	6.5 (0.7-56.3)	1,183 (49)
130-159	1,435	6.3 (0.8-58.6)	725 (50.5)
≥160	563	7.3 (1.1-62.2)	307 (54.5)
HDL cholesterol, mg/dL			
<50	3,238	10 (1.3-71.2)	1,750 (54)
50-69	2,287	4.5 (0.5-43.3)	1,047 (45.8)
70-99	625	2 (0.2-31.5)	256 (41)
≥100	56	3.8 (0.3-51.6)	27 (48.2)
eGFR, mL/min/1.73 m^2			
<45	55	81.5 (20-230.6)	44 (80)
45-59	140	55.8 (4.9-293.2)	107 (76.4)
60-89	1,739	23.1 (2.6-134.8)	1,141 (65.6)
>90	4,272	3.6 (0.5-30.1)	1,788 (41.9)
Diabetes mellitus, %			
Normal	4,602	4.3 (0.5, 43.3)	2,124 (46.2)
IFG	849	12.6 (1.9, 84.1)	483 (56.9)
DM	755	22.1 (3.4, 151.6)	473 (62.6)
Hypertension			
No	3,415	3 (0.4-27.2)	1,398 (40.9)
Yes	2,791	17.2 (1.9-110.5)	1,682 (60.3)
BP medications			
No	3,897	3.6 (0.5-32.6)	1,681 (43.1)
Yes	2,309	18.1 (2-113.7)	1,399 (60.6)
Lipid medications			
No	5,186	5 (0.6-45.8)	2,400 (46.3)
Yes	1,020	23 (2-144.7)	680 (66.7)

Values are N, median (Q1-Q3), or n (%).

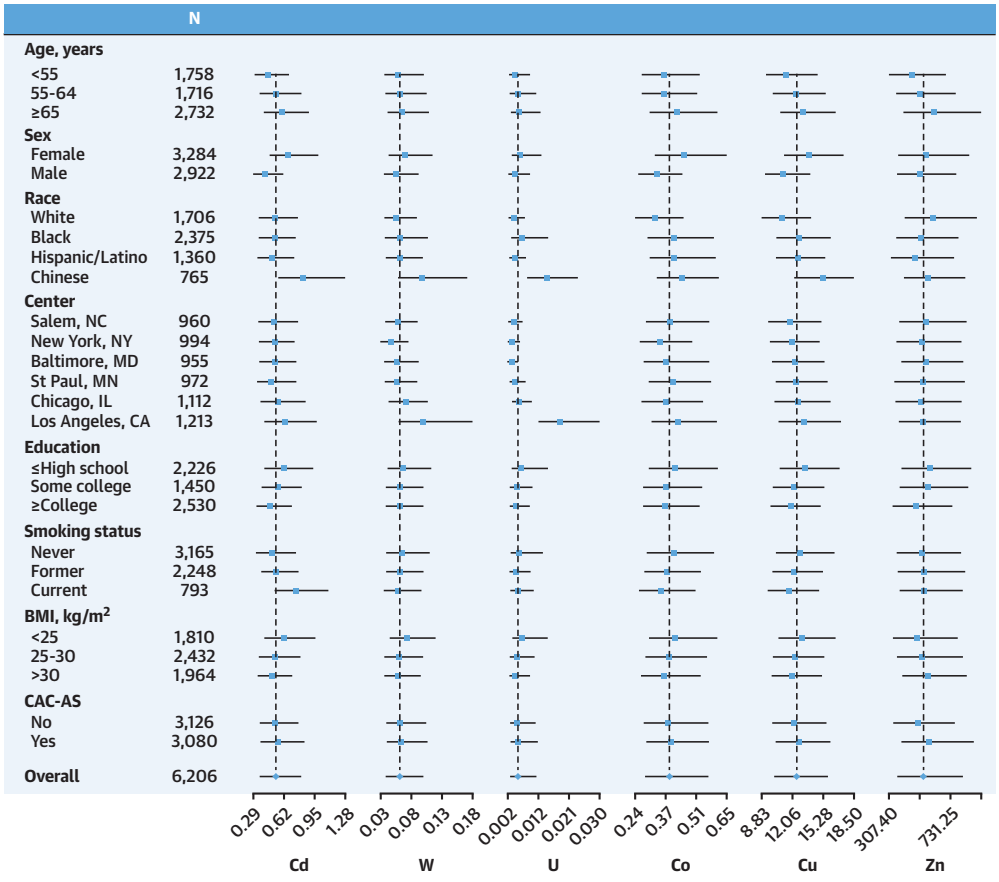
BMI = body mass index; BP = blood pressure; CAC = coronary artery calcification; CAC-SW = specially weighted coronary artery calcification score; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metabolic equivalent.

among males, White participants, and those with high school education or less. Participants who formerly smoked and those who had DM and hypertension had higher median CAC-SW and frequency of positive CAC-AS.

Nonessential and essential urinary metal levels varied by participant characteristic (**Figure 1**). Urinary metal levels (μg/g creatinine) tended to be higher among females, older participants, Chinese participants, and those with less education. Participants from Los Angeles had markedly higher urinary tungsten and uranium levels, and somewhat higher cadmium, cobalt, and copper levels. Cadmium levels were higher among current smokers; the essential metals cobalt and copper were lower among current smokers. Spearman correlation values between urinary metal levels are reported in Supplemental Figure 2.

Comparing the highest to lowest urinary cadmium quartiles, CAC-SW levels were 51% (95% CI: 32%, 74%) higher at baseline and 75% (95% CI: 47%, 107%) higher for 10-year cumulative change CAC-SW (**Table 2**). The nonlinear association apparent in the quartile models was also observed with the restricted quadratic spline models, with clear positive dose-response relationships with CAC observed for urinary cadmium above 0.5 μg/g creatinine both at baseline and at 10 years of follow-up (**Figure 2**). The corresponding percentage higher CAC-SW comparing the highest to lowest quartiles of tungsten and uranium were 13% (95% CI: 0%, 27%) and 17% (95% CI: 4%, 33%) at baseline and

FIGURE 1 Urinary Metal Level Distributions by Participant Characteristics



Median (Q1-Q3) of urinary metal levels (μg/g creatinine) among MESA (Multi-Ethnic Study of Atherosclerosis) participants (n = 6,418) by participant characteristic for nonessential metals cadmium (Cd), tungsten (W), and uranium (U), and essential metals cobalt (Co), copper (Cu), and zinc (Zn). Points represent the median urine metal level and lines correspond to the IQR overall and for each subgroup at baseline. The n for each group is on the y-axis. The dotted line represents the overall median urine metal level. BMI = body mass index; CAC = coronary artery calcification.

45% (95% CI: 23%, 71%) and 39% (95% CI: 17%, 64%) at 10-year cumulative change. The flexible spline models were consistent with a linear dose-response for 10-year cumulative change.

For the essential metals, comparing the highest to lowest quartiles, CAC-SW levels at baseline and at 10 years were 29% (95% CI: 14%, 47%) and 47% (95% CI: 25%, 74%) higher for cobalt, 15% (95% CI: 1%, 31%) and 33% (95% CI: 12%, 58%) higher for copper, and 54% (95% CI: 36%, 74%) and 57% (95% CI: 33%, 85%) higher for zinc. For the 3 essential metals, the dose-responses tended to be flat at lower levels and positive at higher levels, especially at 10 years (**Figure 2**). For copper and zinc, there was a marked decline in the association with CAC-SW both at baseline and 10-year cumulative change after adjusting for clinical risk factors (model 2) compared to model 1. In a post hoc analysis, this attenuation was largely due to adjustment for diabetes status and FPG (Supplemental Figure 3) and not to the other variables.

In the adjusted models for the traditional risk factors, CAC-SW at baseline and 10-year follow-up was 27% (95% CI: 3%, 57%) and 59% (95% CI: 37%, 84%) higher, respectively, comparing current smokers to never smokers, 58% (95% CI: 30%, 92%) and 87% (95% CI: 1.56%, 2.24%) higher, respectively, comparing participants with diabetes mellitus to those with normal fasting glucose, and 19% (95% CI: 10%, 29%) and 17% (95% CI: −2%, 40%) higher,

TABLE 2 Percentage Difference in CAC-SW by Urinary Metal Levels

Level of Metals, μg/g	N	Baseline %		10-Year Cumulative Change %	
		Model 1	Model 2	Model 1	Model 2
Nonessential					
Cadmium					
Q1 (0.02-0.35)	1,606	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (0.35-0.53)	1,611	−6 (−21, 12)	−4 (−19, 15)	−6 (−20, 12)	−2 (−17, 15)
Q3 (0.53-0.79)	1,600	20 (0, 45)	22 (1, 47)	6 (−10, 27)	7 (−9, 27)
Q4 (0.79-24.29)	1,601	50 (30, 73)	51 (32, 74)	71 (44, 104)	75 (47, 107)
Per IQR	6,418	29 (14, 47)	30 (15, 47)	32 (2, 70)	33 (3, 71)
Tungsten					
Q1 (0.01-0.04)	1,604	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (0.04-0.06)	1,598	12 (−6, 33)	8 (−9, 29)	22 (4, 44)	19 (1, 40)
Q3 (0.06-0.10)	1,610	4 (−12, 24)	0 (−16, 19)	22 (3, 44)	18 (0, 40)
Q4 (0.10-10.73)	1,606	20 (6, 36)	13 (0, 27)	53 (29, 81)	45 (23, 71)
Per IQR	6,418	8 (0, 16)	5 (−2, 14)	18 (0, 40)	16 (−2, 37)
Uranium					
Q1 (0.0003-0.003)	1,606	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (0.003-0.005)	1,602	10 (−7, 31)	9 (−8, 29)	10 (−6, 30)	8 (−8, 27)
Q3 (0.005-0.011)	1,607	2 (−15, 22)	−1 (−7, 18)	27 (7, 50)	24 (5, 46)
Q4 (0.011-0.654)	1,603	23 (8, 40)	17 (4, 33)	43 (21, 70)	39 (17, 64)
Per IQR	6,418	8 (0, 16)	5 (−3, 13)	19 (2, 39)	17 (0, 37)
Essential metals					
Cobalt					
Q1 (0.03-0.28)	1,596	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (0.28-0.39)	1,607	1 (−15, 20)	1 (−15, 20)	10 (−7, 30)	12 (−5, 31)
Q3 (0.39-0.56)	1,606	26 (5, 50)	23 (3, 46)	34 (13, 59)	33 (13, 57)
Q4 (0.56-151.89)	1,609	31 (15, 49)	29 (14, 47)	46 (24, 73)	47 (25, 74)
Per IQR	6,418	13 (1, 27)	13 (1, 26)	20 (−7, 55)	21 (−6, 56)
Copper					
Q1 (3.14-9.99)	1,605	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (9.99-12.37)	1,608	15 (−4, 37)	13 (−5, 34)	−3 (−18, 14)	−6 (−20, 11)
Q3 (12.37-15.66)	1,624	22 (1, 46)	14 (−5, 36)	6 (−11, 26)	−1 (−16, 17)
Q4 (15.66-1,733.75)	1,581	36 (20, 55)	15 (1, 31)	55 (30, 84)	33 (12, 58)
Per IQR	6,418	11 (−5, 30)	3 (−12, 21)	18 (−17, 68)	11 (−22, 59)
Zinc					
Q1 (11.1-358)	1,620	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Q2 (358-532)	1,613	20 (1, 43)	16 (−2, 38)	24 (6, 46)	21 (3, 42)
Q3 (532-802)	1,599	31 (10, 56)	16 (−2, 38)	28 (8, 51)	14 (−3, 35)
Q4 (802-14,700)	1,586	84 (62, 108)	54 (36, 74)	85 (56, 119)	57 (33, 85)
Per IQR	6,418	29 (17, 42)	19 (8, 31)	26 (2, 55)	17 (−5, 44)

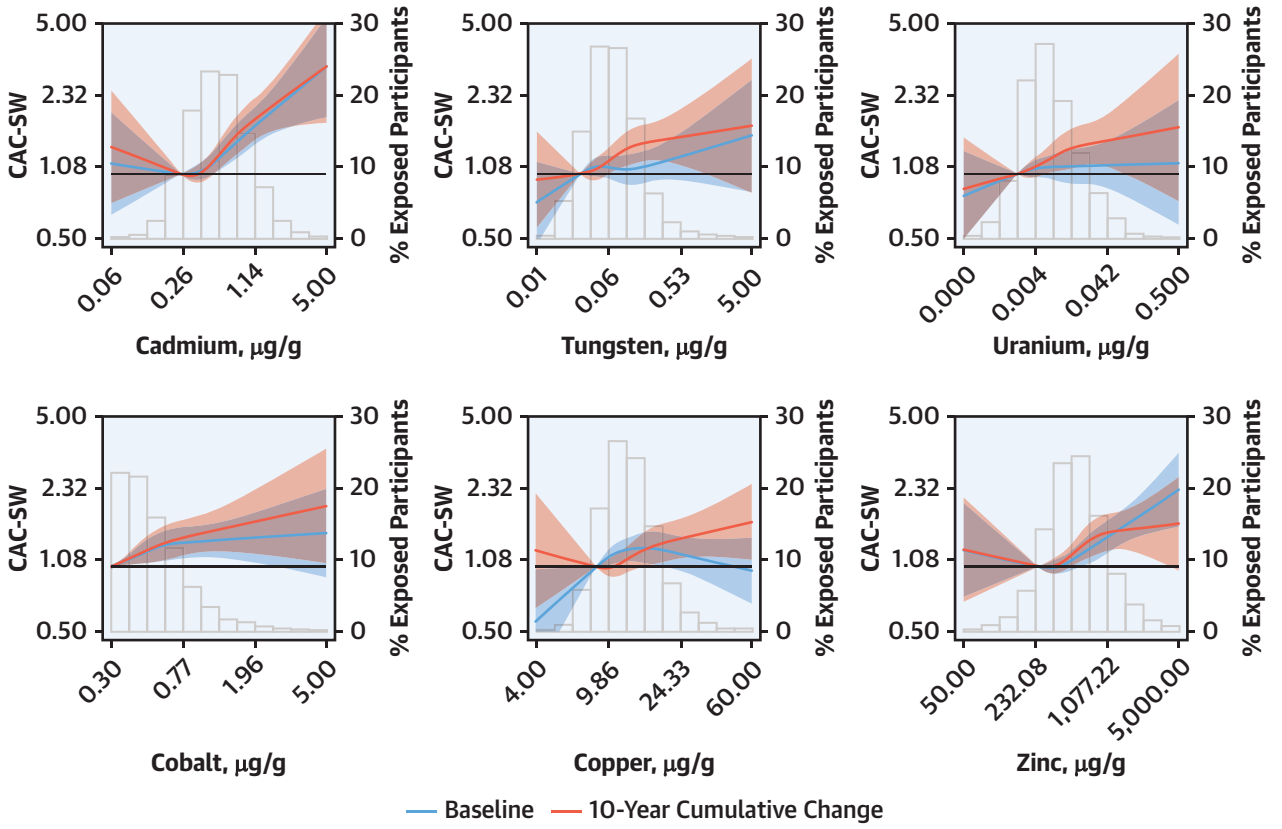
Values are % difference (95% CI), unless otherwise indicated.
Abbreviation as in Table 1.

respectively, comparing an IQR of LDL cholesterol (Supplemental Table 2).

Using incident CAC-AS ≥1 over the follow-up as the study outcome instead of CAC-SW resulted in consistent associations with nonessential (cadmium, tungsten, uranium) and essential (cobalt, copper, zinc) metals (Supplemental Table 3). Models 1 and 2 for the association with CAC-SW of other nonessential (arsenic, barium, cesium, lead, strontium, thallium) and essential (manganese, molybdenum, selenium) elements measured in urine from MESA participants are reported in Supplemental Table 4.

In stratified models by participant subgroups for the association of the priority metals with CAC-SW at baseline and 10-year cumulative change, the associations remained similar by age group and no consistent patterns were observed by race and ethnicity (Supplemental Table 5). By sex, the association for cadmium was stronger in women both at baseline and 10-year cumulative change (*P* value for interaction only significant at baseline), whereas for the other metals, the patterns by sex were inconsistent. By smoking status, the association for cadmium, tungsten, and uranium were stronger for former smokers

FIGURE 2 Flexible Dose-Response of Urinary Metal Levels and CAC



Geometric mean ratios (GMRs) (95% CI) of baseline estimates (blue lines and shaded areas) and 10-year cumulative changes (orange lines and shaded areas) in spatially weighted coronary artery calcium (CAC-SW) scores by log-transformed urinary metal levels (μg/g creatinine) among MESA participants (n = 6,418), modeled as restricted quadratic splines with knots at the 10th (reference), 50th, and 90th percentiles. The histograms represent the distribution of each metal at baseline. Models were adjusted for age, sex, race and ethnicity, study site, education, estimated glomerular filtration rate, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, and diabetes status. [a]GMRs correspond to exponentiating the coefficient obtained from the splines in the regression model. Percent differences in **Table 2** can be obtained by subtracting one from the GMR and multiplying it by 100. Abbreviations as in **Figure 1**.

at baseline only; patterns for other metals were inconsistent.

To better ascertain the association of the joint metal mixture and CAC-SW, we used Bayesian kernel machine regression in an exploratory analysis at baseline. When comparing the 95th to the 25th percentile of the joint metal distribution, we found a strong positive and significant association of a 43.8% (95% credibility intervals: 20.2, 72.1) higher overall risk in CAC-SW for the metal mixture (**Figure 3**). We found no interaction among metals or confounding by metals in the metal mixture (Supplemental Figure 4).

In sensitivity analyses, we found no significant changes in effect estimates after adjusting for particulate matter of diameter ≤2.5 μg/m^3 (Supplemental Figure 5). We found attenuated estimates for uranium and tungsten after adjusting for water uranium levels (Supplemental Figure 6), although the sample size was smaller (n = 3,395). Additionally, we found no change after adjustment for albumin to creatinine ratio (Supplemental Figure 7), or after adjustment for neighborhood-level socioeconomic status (Supplemental Figure 8). In the subset of participants with exposure measures at 2 time points (n = 594), the associations were significant and even stronger compared to the models based on exam 1 data for urinary cadmium (Supplemental Table 6), consistent but not significant

for tungsten and uranium at 10-year cumulative change and for copper at baseline and 10-year cumulative change, and inconsistent but not significant for cobalt and zinc.

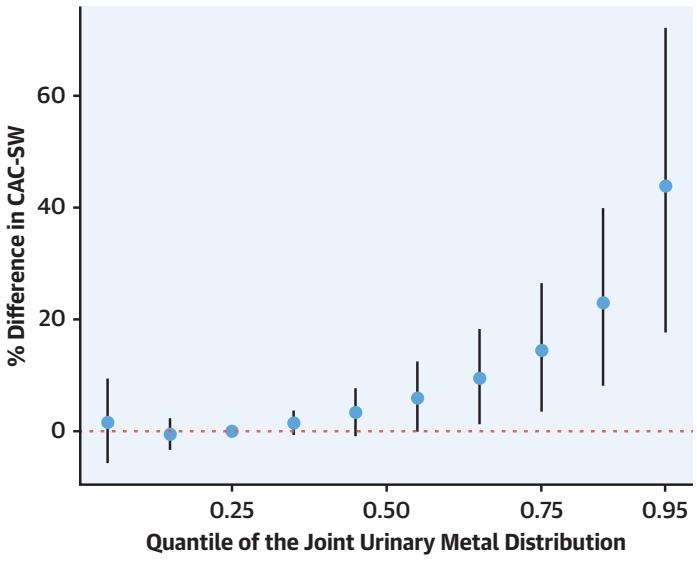
DISCUSSION

In this longitudinal study of coronary atherosclerosis progression among multi-ethnic adults from 6 urban areas in the United States, the highest to the lowest quartiles of baseline urinary levels of the nonessential metals cadmium, tungsten, and uranium, and essential metals cobalt, copper, and zinc were associated with baseline and 10-year cumulative change in CAC, an established subclinical marker of CVD risk. For instance, a 51% increase comparing the highest to lowest cadmium quartiles, would correspond to geometric means of CAC-SW of 9.5 vs 6.3, respectively. These results support that metal exposure and/or metabolism, as reflected in urine, may be associated with the progression of atherosclerosis by increasing coronary calcification in diverse U.S. adults (**Central Illustration**).

CAC is a dynamic process indicative of atherosclerosis.[33] Baseline CAC is highly predictive of CHD events compared to other traditional risk factors.[34] Studies suggest CAC progression is a more accurate predictor of future cardiac risk.[35,36] Likewise, CAC-SW is a more sensitive measure of CAC progression because it quantifies calcification below Agatston scoring criteria.[13] Among MESA participants, CAC-SW was significantly associated with CHD events (HR: 1.23; 95% CI: 1.16-1.30) per doubling of CAC-SW, and was predictive of CHD events even among participants with CAC-AS = 0.[20] In this study, we assessed baseline urinary metal levels and CAC progression using repeated measures of CAC-SW. We found that nonessential metals cadmium, tungsten, and uranium, and essential metals cobalt, copper, and zinc were all associated with baseline and 10-year cumulative change in CAC. Tungsten and uranium were significantly associated with a 10-year cumulative change in CAC. When we assessed the association between traditional CVD risk factors (smoking, diabetes, and LDL cholesterol) and CAC progression, the magnitude of the associations was highly comparable to those for metals, supporting that metals are relevant CVD risk factors.

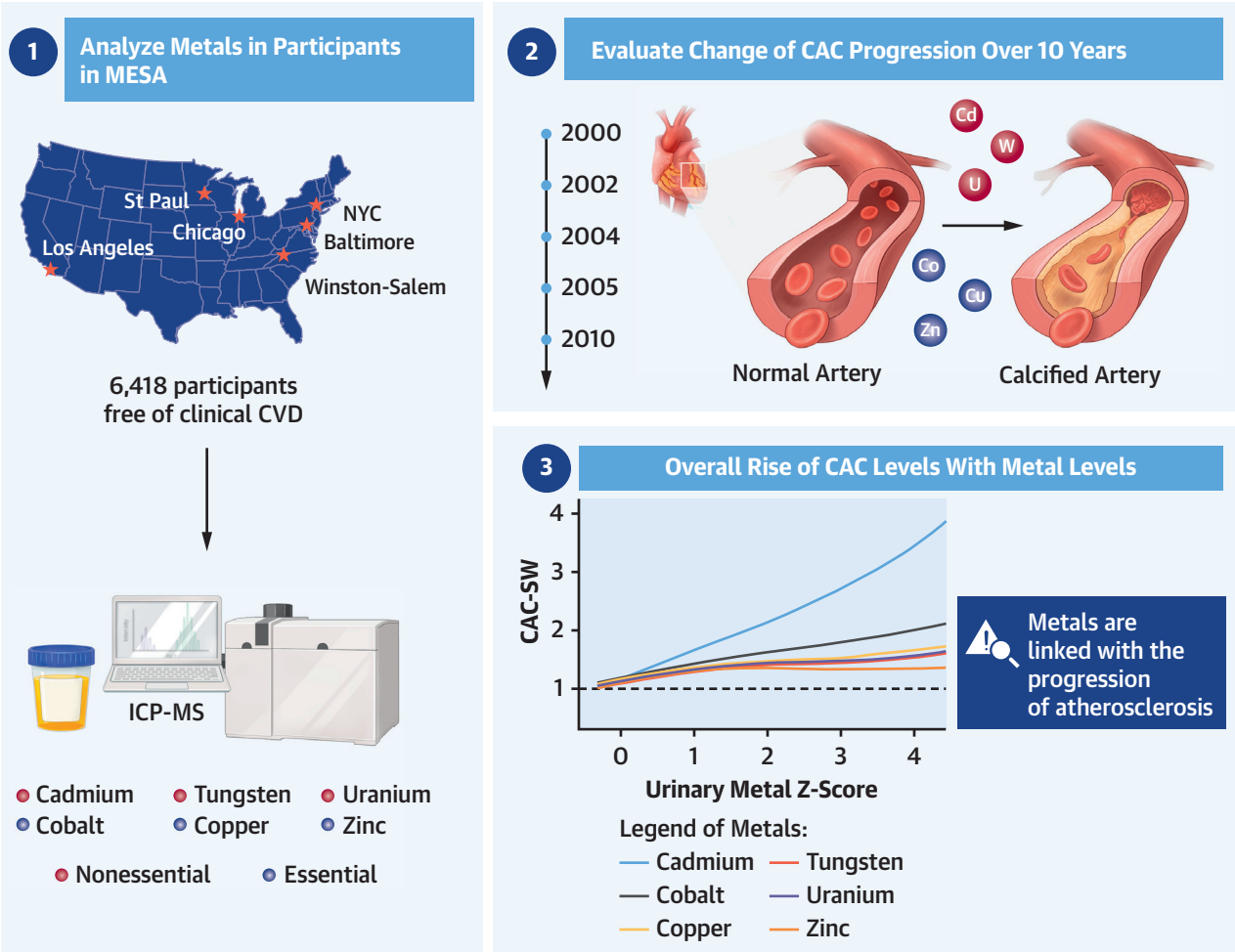
Pollution is the greatest environmental risk to cardiovascular health.[1] Widespread cadmium, tungsten, uranium, cobalt, copper, and zinc pollution occurs from agricultural and industrial uses such as fertilizers, batteries, oil production, welding, mining, and nuclear energy production.[37-39] Tobacco smoke is the main source of cadmium exposure. Two large studies have assessed cross-sectional associations between cadmium levels and CAC. Blood cadmium levels were associated with higher prevalence of CAC-AS ≥1 (prevalence ratio: 1.25; 95% CI: 1.13, 1.38) in Swedish adults (n = 5,627),[40] and urine cadmium levels were associated with greater odds of CAC-AS ≥1 (OR: 1.28; 95% CI: 0.98, 1.67) in the Aragon Workers Health Study (n = 1,873).[4] No other investigations have reported the association of other metals and CAC either cross-sectionally or prospectively. In our study, we found no consistent moderation of the association between metals and CAC by other factors, except for cadmium, by sex and smoking status. Likewise, previous studies do not report effect modification by sex or smoking status. Some studies, however, show that metal levels are associated with clinical CVD events. A meta-analysis of 12 prospective studies comparing the highest to lowest cadmium exposure categories and clinical CVD reported a pooled relative risk of 1.36 (95% CI: 1.11, 1.66) for urine.[41] Another meta-analysis of 35 studies comparing the highest to lowest blood copper tertiles

FIGURE 3 Association Between the Metal Mixture and CAC



The percent difference (95% credibility intervals) of the overall association between the urinary metal mixture (cadmium, tungsten, uranium, cobalt, copper, and zinc) and CAC-SW. The overall association compares the value of the exposure response function when all metals are at a particular percentile (25th to 95th, by 5) as compared to when all predictors are at their 25th percentile. Models were adjusted for age, sex, race and ethnicity, study site, education, estimated glomerular filtration rate, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, and diabetes status. Other abbreviations as in **Figures 1 and 2**.

CENTRAL ILLUSTRATION **Urinary Metals and Repeated Measures of Coronary Artery Calcification in the Multi-Ethnic Study of Atherosclerosis**



McGraw KE, et al. JACC. 2024;84(16):1545-1557.

In a longitudinal study design in MESA (Multi-Ethnic Study of Atherosclerosis), linear mixed-effect models were used to assess baseline metal exposure, as measured in urine using inductively coupled plasma mass spectrometry (ICP-MS), and repeated measures of coronary artery calcification (CAC) over a 10-year follow-up period among 6,418 participants free of clinical cardiovascular disease at baseline (panel 1). Metal exposure may contribute to calcification in the arteries over time through inflammation, oxidative stress, endothelial dysfunction, or lipid metabolism (panel 2). The flexible dose response curves show geometric mean ratios of 10-year cumulative changes in spatially weighted coronary artery calcium (CAC-SW) scores by urinary metal level z-scores modeled as restricted quadratic splines with knots at the 10th, 50th, and 90th percentiles; the reference value was set at the 10th percentile (panel 3). Models were adjusted for age, sex, race and ethnicity, study site, education, estimated glomerular filtration rate, smoking status, pack-years, physical activity, body mass index, systolic blood pressure, antihypertensive medication, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, and diabetes status. Illustrations © by Biotic Artlab, 2024.

reported a pooled relative risk of 1.81 (95% CI: 1.05, 3.11) for incident CVD and 2.22 (95% CI: 1.31, 3.74) for incident CHD.[42] Urinary tungsten levels were associated with higher stroke prevalence[43] and self-reported CVD[44,45] in the National Health and Nutrition Examination Survey; but baseline urinary tungsten was not associated with incident CVD in the Strong Heart Study (n = 2,726).[46] There are limited investigations of cobalt and uranium and clinical CVD. Zinc deficiency in serum and increased urinary zinc levels have been proposed as indicators of the development of CVD and diabetes,[25] and urinary zinc levels have been associated with CVD incidence in the Hortega Study.[47]

Our findings suggest that metals, both essential and nonessential, are related to the development of CVD at least in part through increased arterial calcification and comparable to traditional CVD risk factors. Some evidence from clinical trials supports that metal chelation can improve CVD outcomes in populations with CVD, which could be explained by the role of chelating agents reducing nonessential metal accumulation and improving homeostasis of essential metals in the body.[48,49] Given the importance of metal exposure in CVD outcomes, which is comparable to traditional risk factors, as supported in this study, further investigation in large, longitudinal studies with repeated measures of metals and CAC is necessary to further characterize this association across multiple populations, in particular, to evaluate potential gene-environment interactions, characterize associations for subgroups, and inform relevant interventions. These findings provide additional support for the need of large-scale public health action to lower acceptable limits of metals in air and water and improve enforcement of metal pollution reduction, particularly in communities experiencing disproportionate metal exposures.[3] Public health interventions to reduce metal exposure may contribute to reducing CVD mortality, the leading cause of death across the globe, as supported by previous studies on the impact of lead reductions in reduced CVD incident rates in the United States.[50]

STUDY LIMITATIONS. Although exposure to metals may contribute to plaque calcification via increased inflammation, transition measures of plaque are not yet available in MESA. Urinary cadmium is a robust measure of long-term exposure with low variability over time. However, other metals measured in urine such as cobalt, copper, tungsten, and uranium can be variable depending on changes in exposure sources and other factors[51,52] and may contribute to exposure misclassification. Although urinary metal levels were measured in 10% of participants at both exams 1 and 5, we used urinary metal levels measured at baseline to increase power in our primary analysis and because levels across both exams supported that a single metal measure reflects long-term exposure and internal dose (intraclass correlation coefficient >50%). In an exploratory analysis of the participants with time varying exposure measured at exams 1 and 5 (n = 594), results were largely consistent although not significant, likely due to reduced power. Although we used multiple sensitivity analyses to account for confounding, residual and unknown confounding remain possible. Additionally, we were unable to longitudinally assess the role of metal mixtures (ie, evaluating all the metals simultaneously in a joint model) using repeated measures of CAC due to not yet developed methods for longitudinal data analysis of mixtures. As an important strength, we used CAC-SW, a more sensitive and continuous marker of calcification to maximize the available data in a longitudinal setting.[13]

CONCLUSIONS

This large, longitudinal study among diverse U.S. adults presents new evidence of the association between urinary biomarkers of cadmium and less studied tungsten, uranium, cobalt, copper, and zinc and CAC progression using repeated measures of CAC, which assesses the association with calcification over time.

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KEY WORDS cadmium, cardiovascular disease, cobalt, copper, coronary artery calcification, longitudinal, metals, mixed models, prospective, tungsten, uranium, zinc

APPENDIX For supplemental text, tables, and figures, please see the online version of this paper.