

Supplemental Information

Urinary Metal Levels and Coronary Artery Calcification: Longitudinal Evidence in the Multi-Ethnic Study of Atherosclerosis

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Extended Methods

Figure S1. Participant Flowchart

Figure S2. Spearman Correlation of Metal Levels

Figure S3. Percent Difference in CAC-SW Adjusted by Diabetes and Fasting Blood Glucose

Figure S4. BKMR Bivariate Exposure Response Function

Figure S5. Percent Difference in CAC-SW Adjusted by PM2.5

Figure S6. Percent Difference in CAC-SW Adjusted by Water Uranium Levels

Figure S7. Percent Difference in CAC-SW Adjusted by Albumin Creatinine Ratio

Figure S8. Percent Difference in CAC-SW Adjusted by Neighborhood-level Socioeconomic Status

Table S1. Urine Metal Detection Limits

Table S2. Percent Difference in CAC-SW for Traditional CVD Risk Factors

Table S3. Relative Risks of Agatston CAC for Priority Metals

Table S4. Percent Difference in CAC-SW for all other Metals

Table S5. Interactions and Subgroup Analysis of Priority Metals

Table S6. Percent Difference in CAC-SW for time-varying exposure for Priority Metals

Methods

Urinary Metals

Spot urine samples were collected during mid to late morning at baseline exams 1 and 5 using urine cups, aliquoted in small vials, shipped frozen on dry ice to the MESA biorepository, and stored at -80°C. In 2019, 0.8 mL urine aliquots were shipped on dry ice to the Trace Metals Core Laboratory at Columbia University. Detailed information on the analytical protocol to measure metals in MESA have been described elsewhere.¹ Briefly, all metals were analyzed using PerkinElmer NexION 350S Inductively Coupled Plasma Mass Spectrometry with dynamic reaction cell (ICP-DRC-MS).² At least five multi-element standard solutions were used for instrument calibration. The same diluent used for urine sample dilution (1:50) was used for calibration standards. Metal concentrations of the calibration solutions were chosen to cover the expected ranges of urine analyte concentrations. Samples were analyzed, blinded to participants' characteristics, along with sample preparation blanks, and commercially available certified urine reference materials with a broad range of metal concentrations. Approximately 10% of the samples were prepared and measured in duplicate to determine intraday-precision, and ~10% were prepared and measured on different days to determine interday-precision. The intra- and inter-assay coefficient of variation ranged from 2.5% for zinc to 14% for uranium, and from 5.8% for cadmium to 16% for uranium, respectively (Table S1). Samples below the method detection limit (MDL) were replaced with the MDL divided by the $\sqrt{2}$. In most urine samples (>95%), the measured elemental concentrations exceeded the MDL except for uranium (11%) and tungsten (32%), see Table S1. To correct for urine dilution, we divided metal concentration by urine creatinine concentration ($\mu\text{g}/\text{creatinine}$), measured using the Jaffe reaction method.³ 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 good reflection of long-term metal levels.

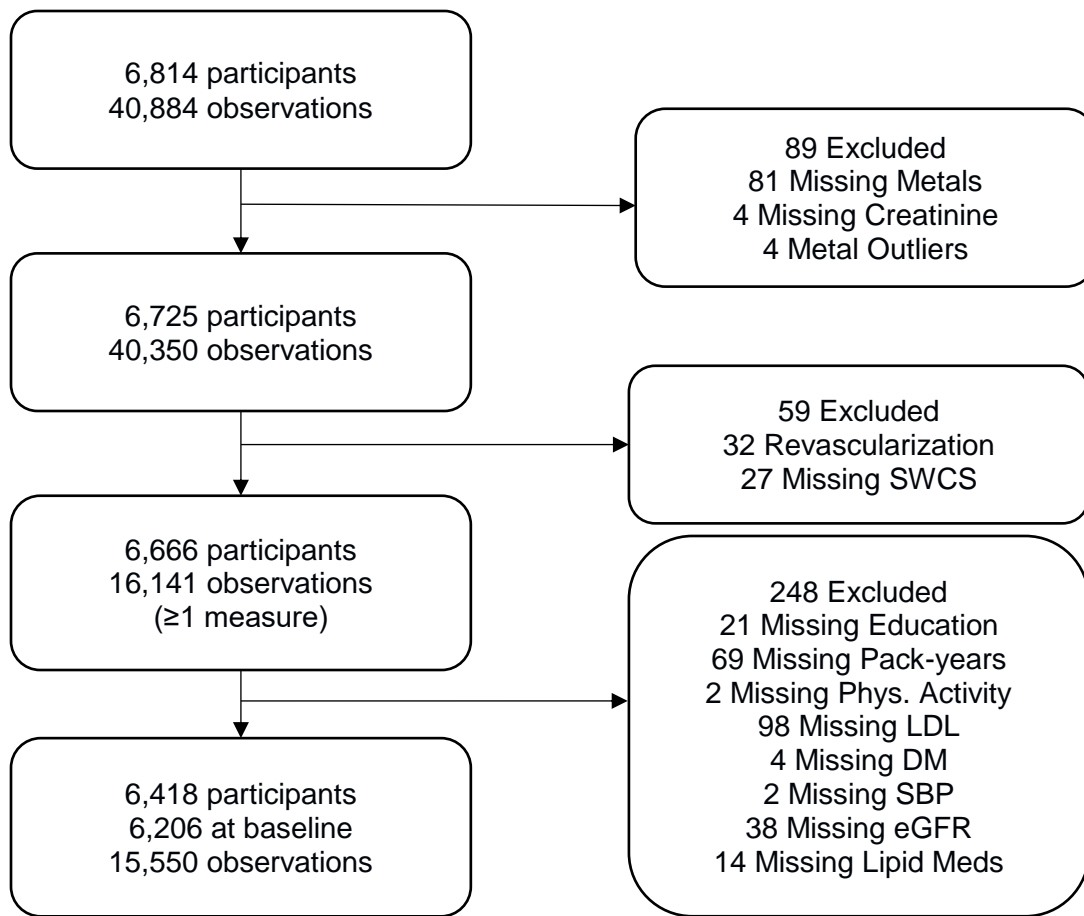
Statistical Analysis

In this model, the baseline association is the coefficient of the main effect for each metal, the annual change is the coefficient of the interaction between each metal and time since baseline CT scan, and the 10-year cumulative change is the follow-up time of 10 years multiplied by the sum of the coefficients. By exponentiating the baseline and 10-year cumulative coefficients, subtracting 1.00 and multiplying by 100, the model estimates the percentage differences.

$$Y_{iv} = [a_0 + X_{i0}a_1 + a_i] + [t_{iv}\beta_0 + t_{iv}m_{i0}\beta_1 + t_{iv}b_i] + [\epsilon_{iv}]$$

This model uses the following definitions: Y_{iv} indicates CAC-SW measurement for participant i at v th follow-up exam; a_0 , average CAC-SW measurement at exam 1 for participants in the reference group; $X_{i0} = (C_{i0}, m_{i0})$, a matrix including the time-invariant cross-sectional covariate matrix C_{i0} and metal of interest m_{i0} at exam 1 for participant i ; a_1 , coefficients for associations between exam 1 CAC-SW measurements and covariates (including each metal); a_i , participant-specific random intercept; t_{iv} , time in years from exam 1 to the v th follow-up exam for participant i ; β_0 , CAC-SW progression (annual rate of change) in average participants in the reference group; m_{i0} , time-invariant cross-sectional vector of the metal of interest; β_1 , coefficient for association between the metal of interest and rate of CAC-SW progression; b_i , participant-specific random slope; ϵ_{iv} , error associated with Y_{iv} .

Figure S1. Participant flowchart and exclusion criteria based on missing data. Tables indicate number of participants at each visit, those with CT scans, and number of participants with 1 or more CT scans.



	N by exam	N by CT Scan	N with CAC-SW	N Scans	N participants	Total Obs
Exam 1	6,814	6,814	6,540	1 Scan	916	916
Exam 2	6,232	2,953	2,825	2 Scans	2,466	4,932
Exam 3	5,939	2,805	2,807	3 Scans	2,442	7,326
Exam 4	5,704	1,406	1,217	4 Scans	594	2,376
Exam 5	4,655	3,305	3,081	Total	6,418	15,550

Figure S3. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) with further adjustment for diabetes (DM) and fasting blood glucose (FPG) at baseline (A) and 10-year cumulative change (B). Model 1 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI. Model 2 was adjusted for systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, and lipid lowering medications. Model 2a was additionally adjusted for diabetes (DM) and fasting blood glucose (FPG).

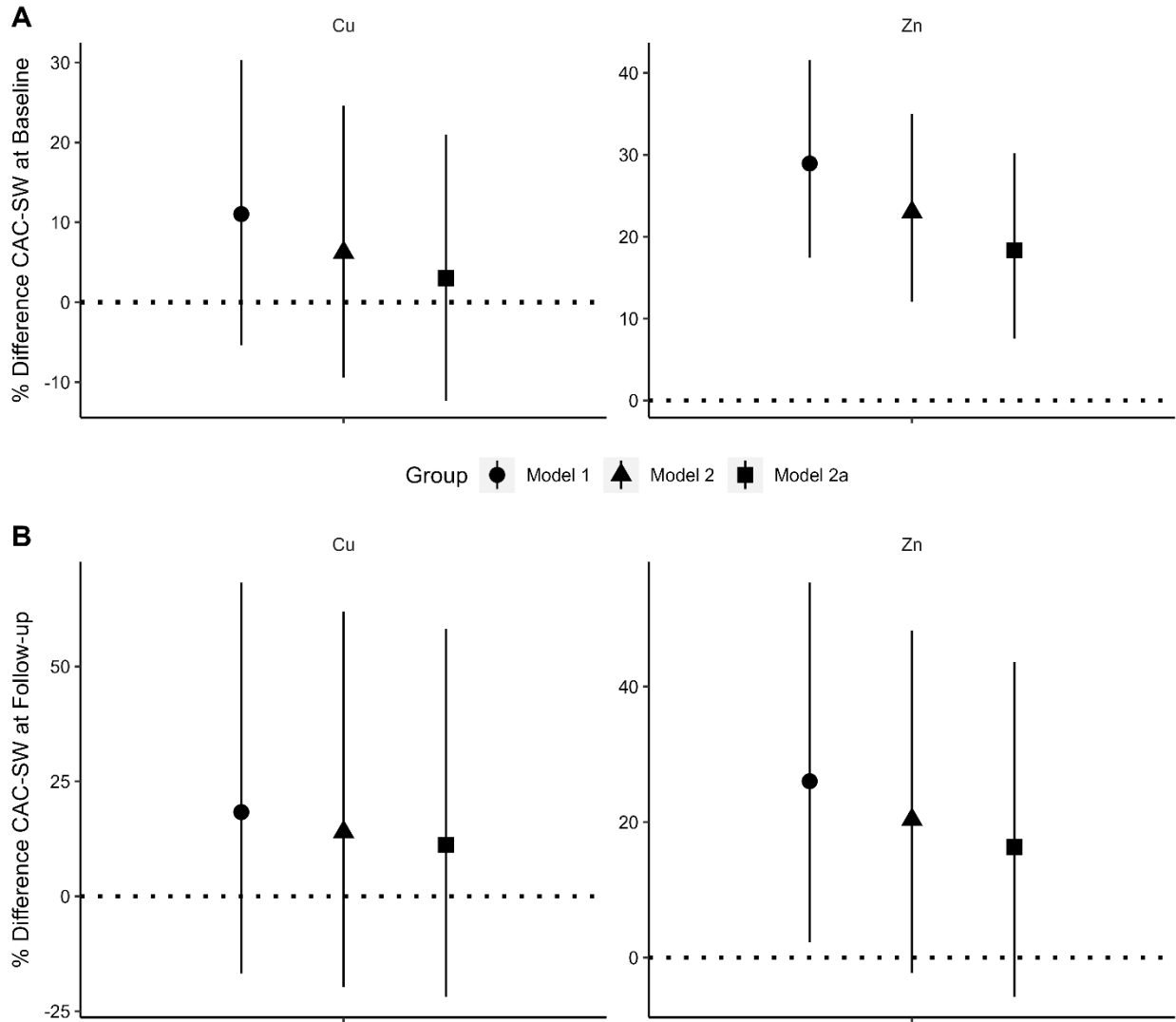


Figure S4. Bivariate exposure-response function for the assessment of interactions. Percent differences (95% credibility intervals) of spatially weighted coronary artery calcification (CAC-SW) for each metal when the other metal is fixed to a particular quartile (25th, 50th, 75th) and all other metals are fixed to the 50th percentile. The metal mixture includes cadmium, tungsten, uranium, cobalt, copper, and zinc. Models were adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status.

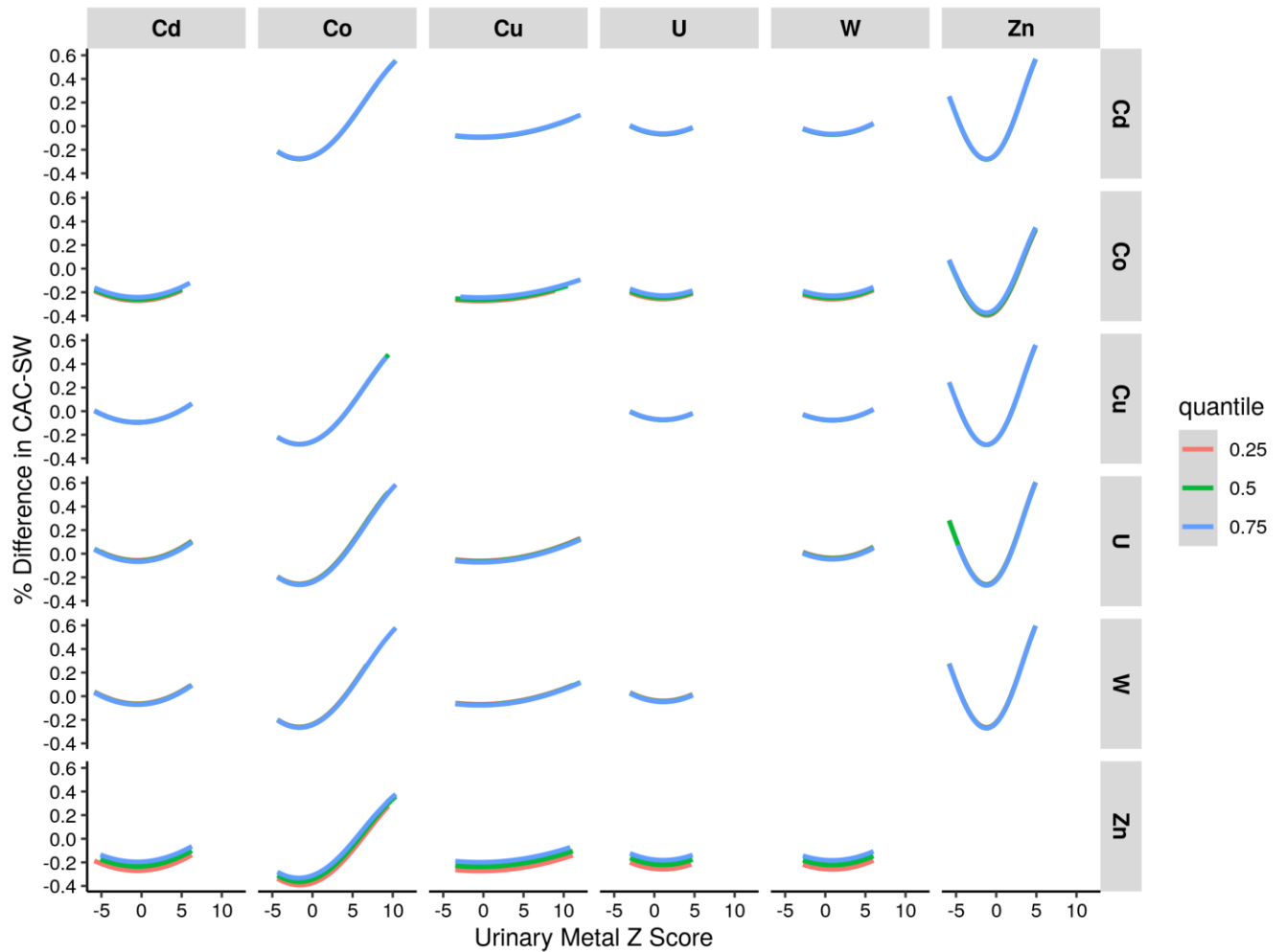


Figure S5. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) with further adjustment for PM2.5 at baseline (A) and 10-year cumulative change (B). Model 2 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, diabetes status (circle, n=6,418). Model 2a was additionally adjusted for PM2.5 (triangle, n=6,152).

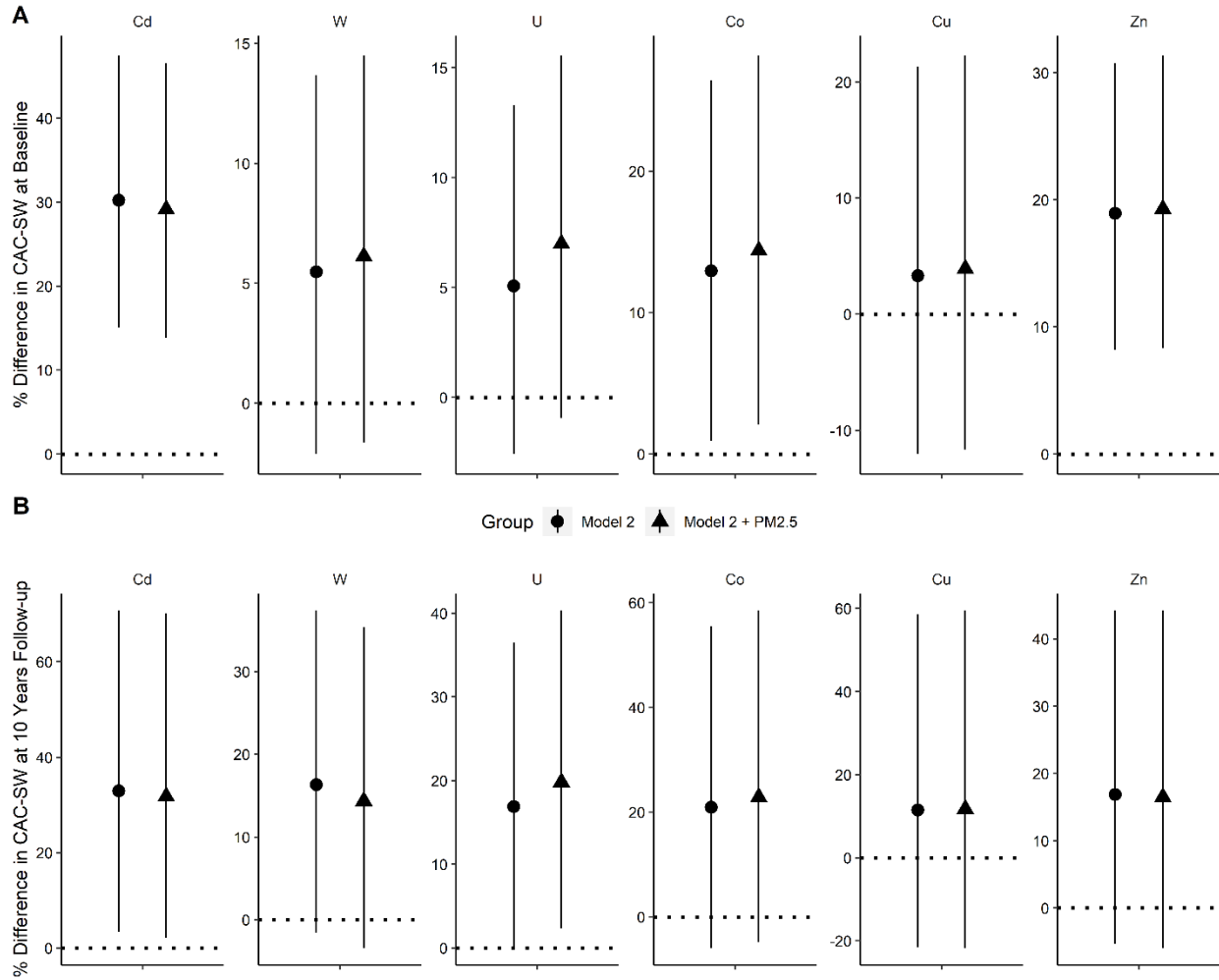


Figure S6. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) with further adjustment for water Uranium measured in community water systems, at baseline (A) and 10-year cumulative change (B). Model 2 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, diabetes status (circle, $n=6,418$). Model 2a was additionally adjusted for water Uranium (triangle, $n=3,395$).

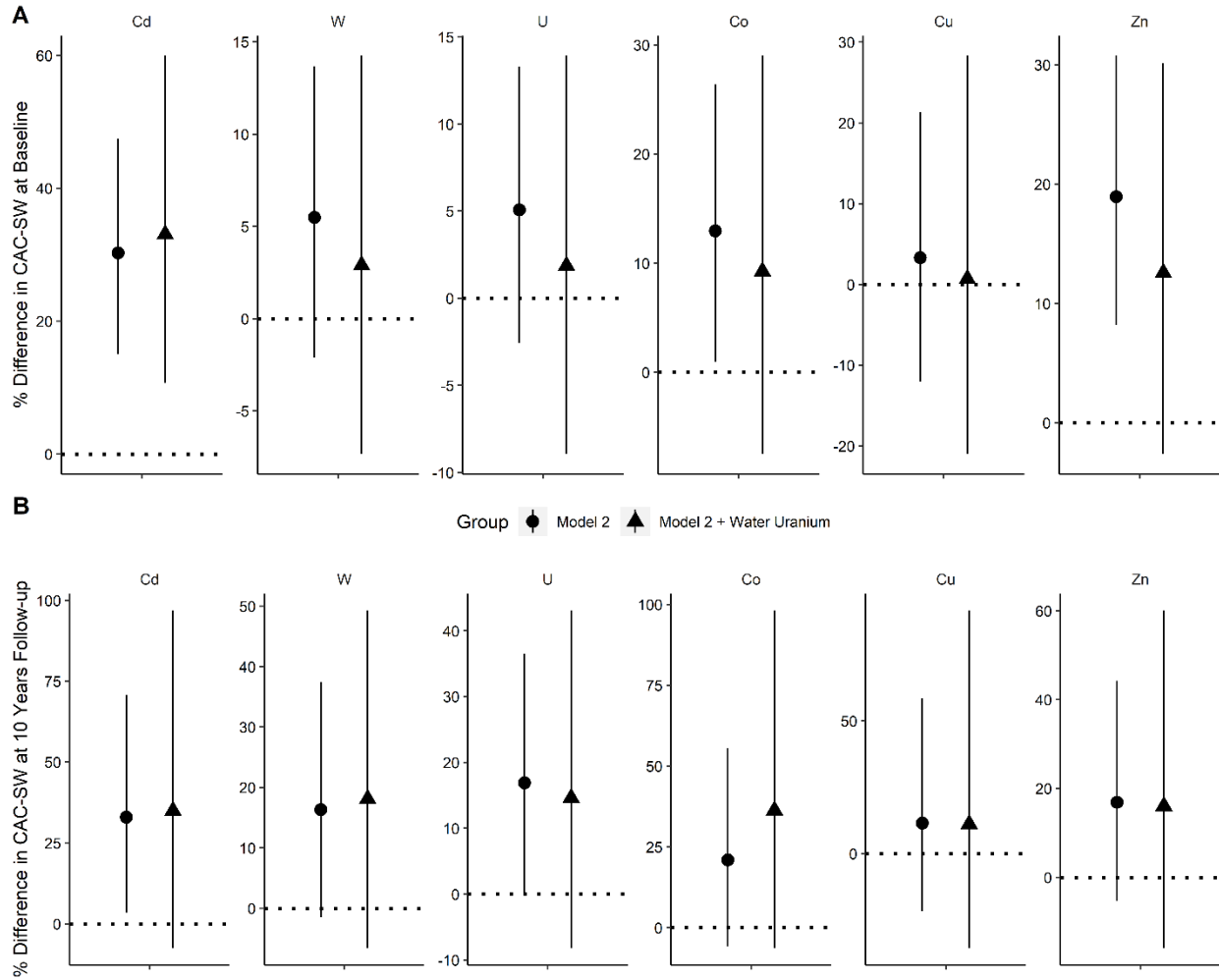


Figure S7. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) with further adjustment for albumin-creatinine ratio at baseline (A) and 10-year cumulative change (B). Model 2 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, diabetes status (circle, $n=6,418$). Model 2a was additionally adjusted for albumin-creatinine ratio (triangle, $n=6,418$).

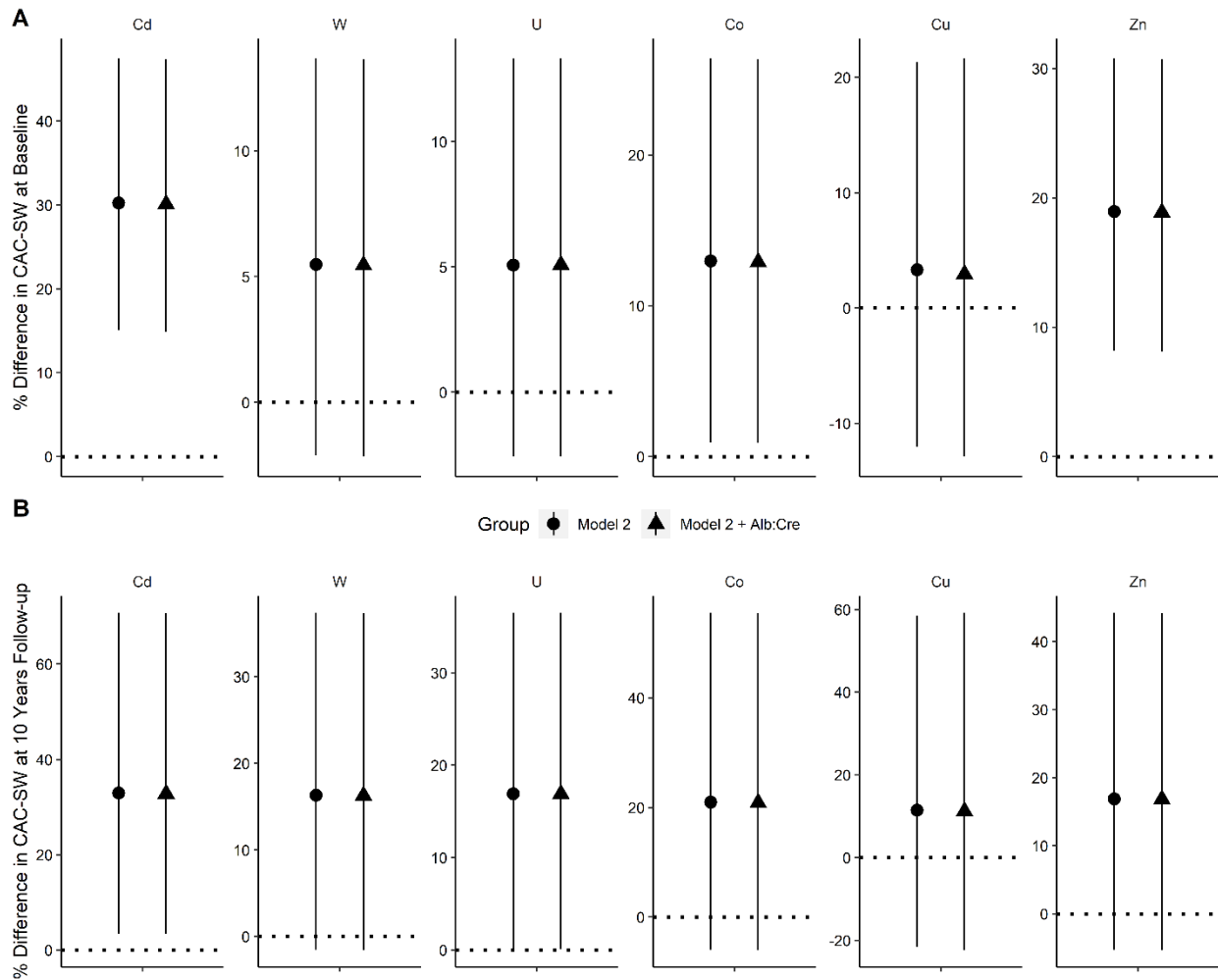


Figure S8. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) with further adjustment for neighborhood problem score at baseline (A) and 10-year cumulative change (B). Neighborhood – level socioeconomic status is derived from American Community Survey 2005 – 2008 census tract estimates . Model 2 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, diabetes status (circle, $n=6,418$). Model 2a was additionally adjusted for neighborhood problem score (triangle, $n=5,880$).

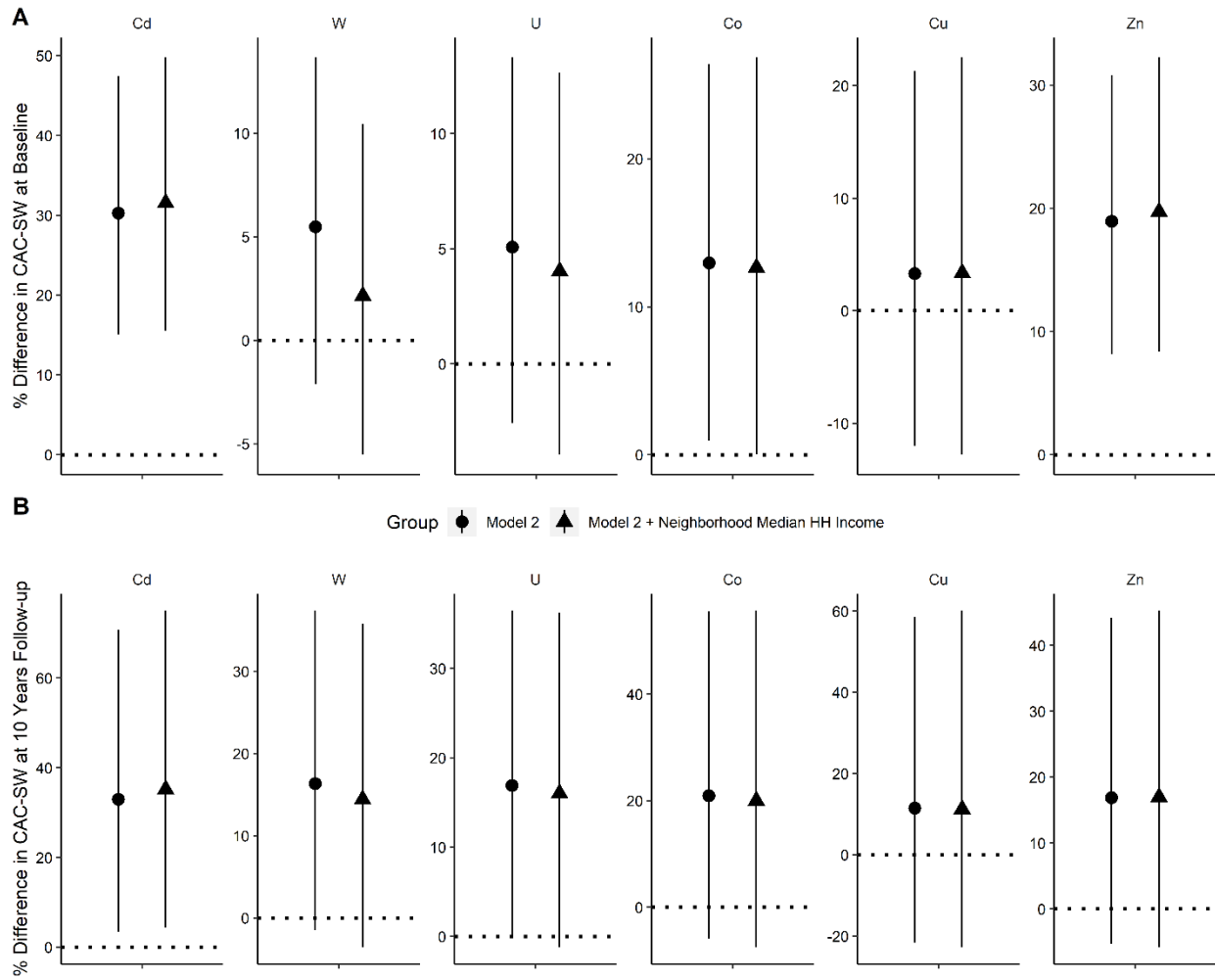


Table S1. Metal names, short names, method detection limit (MDL) values, and percent of observations below MDL (%MDL) at baseline.

Element	Short Name	MDL (µg/L)	%MDL	Intra-assay CV (%)	Inter-assay CV (%)
Non Essential Metals					
Arsenic	As	0.14	0%	1.7	3.8
Barium	Ba	0.11	1%	9.0	9.7
Cadmium	Cd	0.01	0%	3.5	5.8
Cesium	Cs	0.01	0%	1.4	3.2
Lead	Pb	0.05	0%	4.3	6.8
Strontium	Sr	0.13	0%	1.6	3.2
Thallium	Tl	0.0	0%	3.2	4.9
Tungsten	W	0.03	32%	11	13
Uranium	U	0.0	11%	14	16
Essential Metals					
Cobalt	Co	0.02	0%	4.0	6.3
Copper	Cu	0.85	0%	2.9	6.3
Manganese	Mn	0.14	19%	26	19
Molybdenum	Mo	0.53	0%	1.4	3.3
Selenium	Se	1.7	0%	2.2	5.4
Zinc	Zn	6.2	0%	2.5	6.5

Table S2. Percentage difference (95% confidence interval) in spatially weighted coronary artery calcification (CAC-SW) by traditional cardiovascular disease risk factors (smoking status, diabetes status, and low-density lipoprotein (LDL)-cholesterol) measured at exam 1 among MESA participants (n=6,418). Model 1 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity and BMI. Model 2 was additionally adjusted for systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status. Risk factors were removed from model adjustments if they were the predictor in the model.

	N	Baseline %		10-Year Cumulative Change %	
		Model 1	Model 2	Model 1	Model 2
Smoking status					
Never	3,165	0 (referent)	0 (referent)	0 (referent)	0 (referent)
Former	2,248	11 (-5, 28)	14 (-1, 32)	7 (-7, 23)	10 (-5, 26)
Current	793	21 (-2, 50)	27 (3, 57)	51 (30, 75)	59 (37, 84)
Diabetes status					
Normal ^a	4,602	0 (referent)	0 (referent)	0 (referent)	0 (referent)
IFG	849	10 (-8, 32)	1 (-16, 21)	29 (8, 53)	15 (-3, 37)
Yes	755	86 (53, 126)	58 (30, 92)	2.19 (83, 163)	87 (56, 124)
LDL-cholesterol^b					
Per IQR	6,418	13 (5, 22)	19 (10, 29)	12 (-7, 33)	17 (-2, 40)

^aDiabetes status was defined by the 2003 American Diabetes Association as normal (<100 mg/dL blood FPG), impaired fasting glucose – IFG (100-125 mg/dL blood FPG), or untreated and treated diabetes (≥126 mg/dL blood FPG or taking diabetes medications).

^bLDL-cholesterol is a continuous variables and estimates are per interquartile range (IQR) of LDL-cholesterol

Table S3. Relative risks (RR) (95% confidence interval) of coronary artery calcium Agatston scores (CAC-AS \geq 1) per IQR of metal levels (μ g/g creatinine). Model 1 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity and BMI. Model 2 was additionally adjusted for systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status.

Metal	Cases/Controls	Baseline Association		10-Year Cumulative Change	
		Model 1	Model 2	Model 1	Model 2
Cadmium, Cd	3080/3126	1.09 (1.03, 1.16)	1.10 (1.03, 1.16)	1.08 (0.93, 1.25)	1.08 (0.93, 1.26)
Tungsten, W	3080/3126	1.03 (0.99, 1.07)	1.02 (0.99, 1.06)	1.02 (0.92, 1.13)	1.02 (0.92, 1.13)
Uranium, U	3080/3126	1.04 (1.00, 1.07)	1.03 (0.99, 1.06)	1.03 (0.94, 1.13)	1.03 (0.94, 1.13)
Cobalt, Co	3080/3126	1.02 (0.97, 1.07)	1.02 (0.97, 1.07)	1.02 (0.87, 1.19)	1.03 (0.88, 1.20)
Copper, Cu	3080/3126	1.03 (0.96, 1.11)	1.01 (0.94, 1.09)	1.02 (0.83, 1.26)	1.01 (0.82, 1.25)
Zinc, Zn	3080/3126	1.07 (1.02, 1.12)	1.05 (1.00, 1.09)	1.05 (0.92, 1.19)	1.02 (0.90, 1.17)
Risk Factor	Cases/Controls	Model 1	Model 2	Model 1	Model 2
Smoking status					
Never	1400/1765	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Former	1296/952	1.12 (1.05, 1.20)	1.13 (1.06, 1.21)	1.14 (1.07, 1.22)	3.80 (3.50, 4.13)
Current	384/409	1.18 (1.07, 1.31)	1.20 (1.09, 1.33)	1.06 (1.00, 1.12)	1.08 (1.01, 1.14)
Diabetes status					
Normal ^a	2124/2478	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
IFG	483/366	1.05 (0.97, 1.14)	1.02 (0.94, 1.10)	1.06 (0.98, 1.16)	3.41 (3.10, 3.74)
Yes	473/282	1.18 (1.09, 1.29)	1.13 (1.04, 1.23)	1.16 (1.08, 1.25)	1.09 (1.02, 1.17)
LDL-cholesterol ^b					
Per IQR	3080/3126	1.06 (1.03, 1.10)	1.09 (1.05, 1.13)	1.10 (0.86, 1.25)	1.13 (1.10, 1.26)

Table S4. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) per log interquartile range of metal levels ($\mu\text{g/g}$ creatinine). Model 1 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity and BMI. Model 2 was additionally adjusted for systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status.

Metal	N	Baseline Association		10-Year Cumulative Change	
		Model 1	Model 2	Model 1	Model 2
Arsenic, As	6,418	18 (11, 26)	-2 (-2, -2)	-2(-14, 12)	-5 (-16, 9)
Barium, Ba	6,418	1 (-6, 8)	1 (-6, 8)	1 (-14, 18)	2 (-13, 19)
Cesium, Cs	6,418	-5 (-19, 12)	-4 (-18, 12)	-2 (-29, 36)	-1 (-18, 37)
Lead, Pb	6,418	-2 (-13, 9)	-1 (-11, 11)	-7 (0.72, 19)	-5 (-26, 22)
Strontium, Sr	6,418	11 (1, 23)	12 (1, 23)	9 (-12, 35)	10 (-11, 37)
Thallium, Tl	6,418	-2 (-13, 11)	-2 (-13, 10)	3 (-21, 34)	2 (-21, 33)
Manganese, Mn	6,418	5 (-2, 14)	3 (-4, 11)	11 (-7, 32)	9 (-8, 30)
Molybdenum, Mo	6,418	9 (-2, 21)	7 (-4, 19)	10 (-14, 40)	8 (-15, 37)
Selenium, Se	6,418	15 (-3, 37)	11 (-6, 32)	2 (-30, 49)	-1 (-32, 45)

Table S5. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) by metal levels ($\mu\text{g/g}$ creatinine) stratified by participant characteristic and Wald Tests for interaction p-values. Models were adjusted for age, sex, race and ethnicity, education, eGFR, smoking status, pack-years, physical activity, BMI, systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status.

Subgroup	N	Baseline		10-Year Cumulative Change	
		GMR (95%CI)	P-value for interaction	GMR (95%CI)	P-value for interaction
Cadmium, Cd					
Age <55	1,823	29 (6, 57)	0.61	33 (-14, 105)	0.89
Age 55-64	1,772	23 (-3, 55)		35 (-15, 115)	
Age \geq 65	2,823	37 (11, 69)		49 (-1, 123)	
Female	3,390	39 (17, 65)	0.02	42 (-2, 107)	0.77
Male	3,028	19 (-1, 43)		20 (-17, 73)	
Black	1,764	17 (-8, 47)	<0.001	13 (-34, 93)	0.13
Chinese	775	-3 (-35, 44)		20 (-28, 75)	
Hispanic	1,396	7 (-15, 34)		10 (-32, 78)	
White	2,483	63 (32, 102)		39 (-9, 112)	
Never	3,276	21 (2, 44)	0.02	31 (-7, 84)	0.01
Former	2,329	71 (20, 142)		53 (-29, 229)	
Current	813	46 (19, 80)		33 (-13, 104)	
Overall	6,418	30 (15, 47)		33 (3, 71)	
Tungsten, W					
Age <55	1,823	-4 (-15, 7)	0.16	16 (-12, 54)	0.33
Age 55-64	1,772	18 (2, 36)		21 (-10, 65)	
Age \geq 65	2,823	6 (-7, 20)		14 (-13, 50)	
Female	3,390	0 (-10, 11)	0.16	29 (1, 65)	<0.001
Male	3,028	14 (3, 27)		4 (-16, 30)	
Black	1,764	12 (-3, 30)	0.36	18 (-17, 70)	0.54
Chinese	775	8 (-12, 34)		2 (-20, 30)	
Hispanic	1,396	7 (-6, 22)		28 (-4, 72)	
White	2,483	39 (-9, 112)		4 (-22, 40)	
Never	3,276	0 (-10, 11)	0.04	15 (-8, 45)	0.62
Former	2,329	33 (7, 64)		40 (-15, 133)	
Current	813	6 (-7, 21)		13 (-15, 49)	
Overall	6,418	5 (-2, 14)		16 (-2, 37)	
Uranium, U					
Age <55	1,823	-3 (-14, 10)	0.64	25 (-6, 65)	0.26
Age 55-64	1,772	2 (-12, 17)		11 (-16, 46)	
Age \geq 65	2,823	17 (3, 33)		26 (-1, 62)	
Female	3,390	-6 (-15, 5)	0.03	26 (0, 58)	<0.001
Male	3,028	23 (11, 36)		12 (-9, 37)	
Black	1,764	3 (-11, 20)	0.19	0 (-29, 41)	0.02
Chinese	775	3 (-21, 34)		17 (-9, 49)	

Hispanic	1,396	-4 (-16, 10)		42 (9, 86)	
White	2,483	11 (-2, 26)		8 (-18, 42)	
Never	3,276	-3 (-13, 8)	0.04	19 (-4, 47)	0.08
Former	2,329	34 (7, 67)		21 (-24, 93)	
Current	813	13 (-1, 28)		14 (-12, 48)	
Overall	6,418	5 (-3, 13)		17 (0, 37)	

Cobalt, Co

Age <55	1,823	9 (-10, 31)	0.43	24 (-20, 92)	0.74
Age 55-64	1,772	12 (-10, 39)		16 (-28, 86)	
Age >=65	2,823	17 (-3, 41)		24 (-16, 84)	
Female	3,390	8 (-7, 26)	0.13	24 (-14, 79)	0.14
Male	3,028	19 (1, 41)		18 (-18, 68)	
Black	1,764	16 (-6, 44)	0.07	43 (-16, 142)	<0.001
Chinese	775	-4 (-38, 50)		34 (-15, 111)	
Hispanic	1,396	-4 (-21, 16)		27 (-20, 101)	
White	2,483	20 (-1, 44)		4 (-31, 56)	
Never	3,276	8 (-8, 27)	0.05	30 (-9, 86)	0.01
Former	2,329	41 (1, 95)		3 (-52, 121)	
Current	813	12 (-7, 35)		16 (-23, 74)	
Overall	6,418	13 (1, 26)		21 (-6, 56)	

Copper, Cu

Age <55	1,823	-3 (-25, 26)	0.26	13 (-39, 111)	0.72
Age 55-64	1,772	-3 (-29, 32)		4 (-65, 100)	
Age >=65	2,823	11 (-15, 45)		21 (-30, 111)	
Female	3,390	3 (-19, 30)	0.83	20 (-29, 104)	0.03
Male	3,028	5 (-16, 31)		3 (-36, 66)	
Black	1,764	12 (-16, 51)	0.14	7 (-49, 123)	0.05
Chinese	775	7 (-42, 98)		40 (-25, 162)	
Hispanic	1,396	-3 (-28, 30)		19 (-40, 137)	
White	2,483	-1 (-24, 30)		3 (-41, 81)	
Never	3,276	8 (-14, 36)	0.35	25 (-25, 107)	0.24
Former	2,329	7 (-28, 57)		10 (-54, 166)	
Current	813	-4 (-28, 27)		-4 (-48, 75)	
Overall	6,418	3 (-12, 21)		11 (-22, 59)	

Zinc, Zn

Age <55	1,823	4 (-11, 20)	0.48	21 (-16, 75)	0.07
Age 55-64	1,772	22 (1, 49)		8 (-29, 64)	
Age >=65	2,823	25 (8, 46)		29 (-6, 78)	
Female	3,390	20 (5, 36)	0.46	25 (-7, 68)	0.17
Male	3,028	19 (3, 36)		7 (-20, 44)	
Black	1,764	23 (1, 48)	0.25	21 (-24, 91)	0.07
Chinese	775	25 (-11, 75)		21 (-16, 74)	
Hispanic	1,396	12 (-6, 33)		28 (-13, 88)	
White	2,483	22 (5, 42)		3 (-26, 43)	
Never	3,276	26 (10, 43)	0.24	27 (-55, 71)	0.26

Former	2,329	9 (-18 ,46)	25 (-36, 144)
Current	813	14 (-2, 34)	2 (-27, 43)
Overall	6,418	19 (8, 31)	17 (-5, 44)

Table S6. Percentage difference (95% confidence interval) of spatially weighted calcium scores (CAC-SW) per log interquartile range (IQR) of time-varying metal levels ($\mu\text{g/g}$ creatinine) measured at exams 1 and 5 (N=594, no. of observations=1,188). Model 1 was adjusted for age, sex, race and ethnicity, study site, education, eGFR, smoking status, pack-years, physical activity and BMI. Model 2 was additionally adjusted for systolic blood pressure, antihypertensive medication, LDL-cholesterol, HDL-cholesterol, lipid lowering medications, and diabetes status.

Metal	N	Baseline Association		10-Year Cumulative Change	
		Model 1	Model 2	Model 1	Model 2
Cadmium, Cd	594	56 (8, 125)	58 (10, 127)	41 (-30, 184)	44 (-28, 191)
Tungsten, W	594	-3 (-22, 20)	-4 (-22, 19)	17 (-28, 90)	15 (-29, 86)
Uranium, U	594	0 (-21, 26)	-2 (-22, 23)	16 (-27, 85)	13 (-29, 80)
Cobalt, Co	594	0 (-29, 41)	0 (-29, 41)	-4 (-54, 100)	-3 (-53, 100)
Copper, Cu	594	11 (-30, 76)	7 (-32, 69)	12 (-58, 204)	6 (-61, 187)
Zinc, Zn	594	4 (-21, 39)	-2 (-26, 31)	1 (-46, 88)	-8 (-50, 72)

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