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### **Supplemental Material**

#### **Plasma Metal Concentrations and Incident Coronary Heart Disease in Chinese Adults: The Dongfeng-Tongji Cohort**

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**Table S1. Limits of detection, percentages of samples below detection limits, intra-assay and inter-assay coefficients of variation (n = 3242).**

Plasma metals (µg/L)	LOD	Total No. (%) < LOD <sup>a</sup>	Cases < LOD <sup>a</sup>	Controls < LOD <sup>a</sup>	Intra-assay CV%	Inter-assay CV%
Aluminum	0.2534	6 (0.19)	2 (0.12)	4 (0.25)	3.65	5.74
Antimony	0.0030	378 (11.66)	196 (12.09)	182 (11.23)	2.44	6.67
Arsenic	0.0141	6 (0.19)	1 (0.06)	5 (0.31)	2.36	3.28
Barium	0.0277	0 (0.00)	0 (0.00)	0 (0.00)	2.75	1.46
Cadmium	0.0037	136 (4.19)	77 (4.75)	59 (3.64)	1.82	7.91
Chromium	0.0321	3 (0.09)	0 (0.00)	3 (0.19)	4.00	5.29
Cobalt	0.0039	147 (4.53)	80 (4.94)	67 (4.13)	4.09	7.17
Copper	0.1276	2 (0.06)	0 (0.00)	2 (0.12)	1.16	2.47
Iron	0.4088	0 (0.00)	0 (0.00)	0 (0.00)	2.57	2.29
Lead	0.0064	0 (0.00)	0 (0.00)	0 (0.00)	3.12	5.91
Manganese	0.0595	25 (0.77)	13 (0.80)	12 (0.74)	5.01	4.86
Molybdenum	0.0330	110 (3.39)	50 (3.08)	60 (3.70)	5.80	7.67
Nickel	0.0364	16 (0.49)	10 (0.62)	6 (0.37)	1.60	2.82
Rubidium	0.0272	2 (0.06)	0 (0.00)	2 (0.12)	2.01	1.65
Selenium	0.0466	1 (0.03)	0 (0.00)	1 (0.06)	3.62	1.01
Strontium	0.0663	2 (0.06)	0 (0.00)	2 (0.12)	4.38	1.82
Thallium	0.0026	102 (3.15)	12 (0.74)	90 (5.55)	4.59	6.55
Tin	0.0198	2599 (80.17)	1288 (79.46)	1311 (80.88)	5.71	6.33
Titanium	0.1758	1 (0.03)	0 (0.00)	1 (0.06)	4.10	2.57
Tungsten	0.0548	3186 (98.27)	1588 (97.96)	1598 (98.58)	7.92	8.8
Uranium	0.0018	1752 (54.04)	890 (54.90)	862 (53.18)	6.28	7.15
Vanadium	0.0046	2 (0.06)	0 (0.00)	2 (0.12)	2.02	5.16
Zinc	0.4992	0 (0.00)	0 (0.00)	0 (0.00)	1.11	3.21

Abbreviations: LOD, limit of detection; CV, coefficient of variation.

<sup>a</sup> Number and percentage of samples below LOD.

**Table S2. Correlations between plasma metals among the case-control participants (n = 3242).**

	Al	As	Ba	Cd	Co	Cr	Cu	Fe	Mn	Mo	Ni	Pb	Rb	Sb	Se	Sr	Ti	Tl	V	Zn
Al	1.00	0.58*	0.62*	0.45*	0.23*	0.40*	-0.01	0.27*	0.66*	0.21*	0.32*	0.58*	0.13*	0.33*	-0.01	0.35*	0.30*	0.19*	0.72*	0.66*
As		1.00	0.71*	0.24*	0.21*	0.29*	0.00	0.24*	0.39*	0.18*	0.16*	0.45*	0.15*	0.21*	0.05*	0.31*	0.22*	0.23*	0.50*	0.55*
Ba			1.00	0.34*	0.12*	0.37*	0.01	0.27*	0.41*	0.19*	0.27*	0.59*	0.14*	0.10*	0.02	0.32*	0.23*	0.11*	0.54*	0.64*
Cd				1.00	0.23*	0.34*	-0.02	0.15*	0.39*	0.20*	0.21*	0.54*	0.05*	0.36*	0.01	0.26*	0.20*	0.19*	0.44*	0.35*
Co					1.00	0.15*	0.01	0.08*	0.33*	0.22*	0.14*	0.14*	0.10*	0.46*	0.00	0.18*	0.14*	0.41*	0.31*	0.13*
Cr						1.00	0.08*	0.23*	0.36*	0.19*	0.26*	0.37*	0.17*	0.16*	0.18*	0.25*	0.34*	0.14*	0.50*	0.41*
Cu							1.00	-0.12*	-0.02	0.09*	0.09*	-0.03	-0.02	-0.07*	0.16*	0.13*	0.08*	-0.07*	-0.03	0.02
Fe								1.00	0.21*	-0.06*	0.12*	0.22*	0.31*	0.06*	0.14*	0.12*	0.13*	0.13*	0.26*	0.33*
Mn									1.00	0.18*	0.36*	0.52*	0.06*	0.50*	0.01	0.30*	0.32*	0.29*	0.59*	0.38*
Mo										1.00	0.10*	0.18*	-0.01	0.14*	0.03	0.21*	0.10*	0.10*	0.26*	0.18*
Ni											1.00	0.23*	0.02	0.13*	0.12*	0.19*	0.08*	0.02	0.20*	0.21*
Pb												1.00	0.09*	0.27*	-0.05*	0.31*	0.25*	0.18*	0.55*	0.62*
Rb													1.00	0.03	0.21*	0.08*	0.14*	0.23*	0.20*	0.31*
Sb														1.00	-0.08*	0.14*	0.14*	0.47*	0.35*	0.13*
Se															1.00	0.06*	0.20*	0.00	0.05 <sup>#</sup>	0.08*
Sr																1.00	0.21*	0.12*	0.36*	0.32*
Ti																	1.00	0.09*	0.45*	0.30*
Tl																		1.00	0.25*	0.14*
V																			1.00	0.69*
Zn																				1.00

Abbreviations: Al, Aluminum; As, Arsenic; Ba, Barium; Cd, Cadmium; Co, Cobalt; Cr, Chromium; Cu, Copper; Fe, Iron; Mn, Manganese; Mo, Molybdenum; Ni, Nickel; Pb, Lead; Rb, Rubidium; Sb, Antimony; Se, Selenium; Sr, Strontium; Ti, Titanium; Tl, Thallium; V, Vanadium; Zn, Zinc.

Plasma tungsten, tin, and uranium concentrations were excluded from analysis because of many samples < LOD (98.3%, 80.2%, and 54.0%, respectively).

Samples < LOD were imputed before correlations were derived.

Spearman's rank correlation coefficients were shown in the table. \* $p < 0.01$  # $p < 0.05$

**Table S3. Basic characteristics of the study participants in the Metals Correlation Study at baseline (n = 94).**

<b>Variables</b>	<b>Participants (n = 94)</b>
Age (years)	43.8 ± 9.7
Male sex, No. (%)	53 (56.4)
BMI (kg/m <sup>2</sup> )	24.6 ± 3.35
Smoking status, No. (%)	
Current smoker	23 (24.5)
Former smoker	4 (4.3)
Never smoker	67 (71.3)
Alcohol intake status, No. (%)	
Current drinker	40 (42.6)
Former drinker	2 (2.1)
Never drinker	52 (55.3)
Hypertension, No. (%) <sup>a</sup>	19 (19.4)
Hyperlipidemia, No. (%) <sup>b</sup>	14 (14.9)
Diabetes, No. (%) <sup>c</sup>	3 (3.1)

Abbreviations: BMI, body mass index.

Data are presented as mean ± SD, or number (percentage).

<sup>a</sup> Hypertension were defined as measured values ≥ 140 mmHg for SBP or ≥ 90 mmHg for DBP, self-reported physician diagnosis, or reported use of anti-hypertensive medication.

<sup>b</sup> Hyperlipidemia were defined as total cholesterol ≥ 5.72 mmol/L, triglycerides ≥ 1.70 mmol/L, or a self-reported physician diagnosis, or anti-hyperlipidemia medication use.

<sup>c</sup> Diabetes was defined as fasting glucose ≥ 7.0 mmol/L, self-reported physician diagnosis, or anti-diabetic medication use (insulin or oral hypoglycemic agents).

**Table S4. Metal concentrations and correlations between plasma, whole blood and urine samples in the Metals Correlation Study (n = 94).**

Metals	Median concentration (IQR)			Correlation $r_s$ , <sup>b</sup> ( <i>p</i> -Value)	
	Plasma $\mu\text{g/L}$	Whole blood $\mu\text{g/L}$	Urine <sup>a</sup> $\mu\text{g/g}$	Plasma-whole blood	Plasma-urine
Aluminum	128.68 (21.68, 155.85)	103.35 (56.19, 137.29)	6.98 (4.19, 11.98)	0.73 (< 0.001)	-0.06 (0.6)
Antimony	0.13 (0.10, 0.22)	0.09 (0.09, 0.18)	0.03 (0.02, 0.04)	0.19 (0.07)	0.04 (0.74)
Arsenic	3.32 (2.41, 4.01)	2.46 (1.89, 3.30)	5.95 (4.02, 9.14)	0.68 (< 0.001)	0.34 (0.001)
Barium	39.27 (32.03, 50.94)	20.46 (13.80, 25.17)	2.16 (1.27, 4.06)	0.59 (< 0.001)	0.07 (0.52)
Cadmium	0.11 (0.04, 0.18)	0.66 (0.43, 1.58)	0.20 (0.13, 0.29)	0.11 (0.28)	0.07 (0.5)
Chromium	3.20 (2.86, 3.60)	4.59 (3.43, 5.43)	0.28 (0.21, 0.38)	-0.09 (0.41)	0.1 (0.36)
Cobalt	0.17 (0.11, 0.24)	0.14 (0.10, 0.20)	0.08 (0.06, 0.13)	0.45 (< 0.001)	0.42 (< 0.001)
Copper	954.34 (837.75, 1066.19)	752.93 (677.84, 836.52)	2.25 (1.86, 2.94)	0.75 (< 0.001)	0.05 (0.64)
Iron	1393.33 (1026.80, 1687.59)	4.44×10 <sup>5</sup> (3.93×10 <sup>5</sup> , 4.91×10 <sup>5</sup> )	8.31 (5.28, 14.39)	0.17 (0.11)	0.02 (0.88)
Lead	7.28 (6.44, 8.54)	28.23 (22.92, 37.77)	0.60 (0.45, 0.84)	0.23 (0.03)	0.03 (0.77)
Manganese	6.13 (2.16, 6.84)	11.89 (9.97, 13.83)	0.33 (0.18, 0.55)	0.38 (< 0.001)	-0.19 (0.06)
Molybdenum	1.16 (0.94, 1.41)	0.66 (0.53, 0.85)	13.94 (9.68, 23.97)	0.73 (< 0.001)	0.53 (< 0.001)
Nickel	1.54 (0.41, 2.00)	3.50 (2.34, 5.49)	0.53 (0.37, 0.82)	0.18 (0.09)	-0.05 (0.61)
Rubidium	309.43 (251.65, 349.13)	2143.40 (1888.54, 2431.04)	502.42 (378.00, 676.71)	0.64 (< 0.001)	0.03 (0.77)
Selenium	83.64 (68.38, 96.18)	83.26 (74.68, 96.27)	3.78 (2.83, 5.14)	0.52 (< 0.001)	0.64 (< 0.001)
Strontium	36.88 (31.24, 42.03)	20.07 (17.51, 24.36)	36.20 (22.40, 57.47)	0.71 (< 0.001)	0.29 (0.005)
Thallium	0.29 (0.19, 0.41)	0.18 (0.12, 0.23)	0.16 (0.12, 0.24)	0.73 (< 0.001)	0.13 (0.22)
Titanium	41.15 (37.14, 45.41)	73.00 (63.43, 81.92)	35.41 (24.27, 46.20)	0.12 (0.25)	0.32 (0.002)
Vanadium	0.98 (0.89, 1.07)	0.62 (0.49, 0.74)	0.32 (0.26, 0.46)	0.23 (0.03)	0.26 (0.01)
Zinc	909.94 (822.04, 1010.45)	5184.98 (4747.69, 5877.37)	72.56 (50.56, 97.90)	0.14 (0.19)	0.23 (0.03)

<sup>a</sup> Urine metals are creatinine-standardized  $\mu\text{g/g}$ .

<sup>b</sup> Spearman correlation coefficients.

Tin, tungsten, and uranium were excluded because of many samples < LOD.

**Table S5. Adjusted odds ratios (95% CI) for incident CHD according to quartiles of exposure for plasma metals included in the single-metal model. <sup>a</sup>**

Plasma metals	Quartiles of plasma metals ( $\mu\text{g/L}$ ) <sup>b</sup>				<i>p</i> -Trend <sup>c</sup>	<i>FDR</i> <sup>d</sup>
	Q1	Q2	Q3	Q4		
Aluminum	< 31.03	31.03–48.95	48.95–97.15	> 97.15		
N (case/control)	358/405	349/405	395/405	519/406		
Odds ratio (95% CI)	1.00	0.93 (0.74, 1.16)	1.05 (0.83, 1.32)	1.33 (1.07, 1.65)	0.001	0.009
Antimony	< 0.09	0.09–0.14	0.14–0.22	> 0.22		
N (case/control)	404/405	428/405	427/405	362/406		
Odds ratio (95% CI)	1.00	1.06 (0.85, 1.31)	1.00 (0.80, 1.26)	0.88 (0.70, 1.12)	0.25	0.38
Arsenic	< 1.28	1.28–1.96	1.96–3.49	> 3.49		
N (case/control)	323/405	357/405	369/405	572/406		
Odds ratio (95% CI)	1.00	1.17 (0.93, 1.48)	1.12 (0.89, 1.40)	1.68 (1.35, 2.09)	< 0.001	< 0.001
Barium	< 23.26	23.26–35.48	35.48–62.52	> 62.52		
N (case/control)	328/405	375/405	424/405	494/406		
Odds ratio (95% CI)	1.00	1.21 (0.96, 1.53)	1.25 (1.00, 1.56)	1.44 (1.15, 1.79)	0.002	0.011
Cobalt	< 0.12	0.12–0.15	0.15–0.20	> 0.20		
N (case/control)	420/405	386/405	438/405	377/406		
Odds ratio (95% CI)	1.00	0.88 (0.71, 1.10)	0.99 (0.79, 1.24)	0.88 (0.70, 1.10)	0.39	0.55
Copper	< 856.11	856.11–962.14	962.148–1072.48	> 1072.48		
N (case/control)	373/405	389/405	388/405	471/406		
Odds ratio (95% CI)	1.00	1.02 (0.82, 1.27)	0.99 (0.79, 1.24)	1.20 (0.95, 1.50)	0.16	0.29
Lead	< 8.84	8.84–13.12	13.12–20.70	> 20.70		
N (case/control)	329/405	424/405	413/405	455/406		
Odds ratio (95% CI)	1.00	1.34 (1.07, 1.68)	1.31 (1.04, 1.65)	1.30 (1.03, 1.63)	0.15	0.29
Manganese	< 2.97	2.97–4.05	4.05–5.72	> 5.72		
N (case/control)	327/405	433/405	450/405	411/406		
Odds ratio (95% CI)	1.00	1.27 (1.01, 1.58)	1.38 (1.10, 1.72)	1.18 (0.94, 1.48)	0.17	0.29
Molybdenum	< 1.09	1.09–1.36	1.36–1.74	> 1.74		
N (case/control)	400/405	408/405	378/405	435/406		
Odds ratio (95% CI)	1.00	1.10 (0.89, 1.37)	1.05 (0.84, 1.30)	1.08 (0.87, 1.35)	0.59	0.66
Nickel	< 2.17	2.17–3.03	3.03–4.54	> 4.54		
N (case/control)	380/405	410/405	409/405	422/406		
Odds ratio (95% CI)	1.00	0.98 (0.79, 1.22)	1.06 (0.85, 1.33)	0.97 (0.76, 1.22)	0.87	0.87
Rubidium	< 318.27	318.27–357.09	357.09–399.29	> 399.29		
N (case/control)	426/405	411/405	375/405	409/406		
Odds ratio (95% CI)	1.00	0.98 (0.78, 1.22)	0.77 (0.62, 0.96)	0.84 (0.67, 1.05)	0.05	0.14
Selenium	< 57.69	57.69–67.48	67.48–78.66	> 78.66		
N (case/control)	438/405	437/405	392/406	354/405		
Odds ratio (95% CI)	1.00	0.97 (0.79, 1.19)	0.88 (0.71, 1.10)	0.72 (0.57, 0.91)	0.007	0.03
Strontium	< 30.13	30.13–35.91	35.91–42.30	> 42.30		
N (case/control)	368/405	388/405	387/405	478/406		
Odds ratio (95% CI)	1.00	1.03 (0.83, 1.28)	0.99 (0.79, 1.23)	1.10 (0.89, 1.37)	0.42	0.55
Thallium	< 0.10	0.10–0.13	0.13–0.18	> 0.18		
N (case/control)	394/405	357/405	416/405	454/406		
Odds ratio (95% CI)	1.00	0.84 (0.68, 1.05)	1.01 (0.81, 1.26)	1.15 (0.91, 1.44)	0.10	0.24

(continued)

Plasma metals	Quartiles of plasma metals ( $\mu\text{g/L}$ ) <sup>b</sup>				<i>p</i> -Trend <sup>c</sup>	FDR <sup>d</sup>
	Q1	Q2	Q3	Q4		
Titanium	< 24.42	24.42–29.14	29.14–35.70	> 35.70		
N (case/control)	319/405	396/405	441/405	465/406		
Odds ratio (95% CI)	1.00	1.28 (1.02, 1.61)	1.35 (1.07, 1.69)	1.37 (1.09, 1.73)	0.010	0.03
Vanadium	< 0.53	0.53–0.67	0.67–0.99	> 0.99		
N (case/control)	368/405	415/405	425/405	413/406		
Odds ratio (95% CI)	1.00	1.24 (0.98, 1.56)	1.20 (0.96, 1.50)	1.05 (0.84, 1.32)	0.79	0.84
Zinc	< 1015.20	1015.20–1193.53	1193.53–2623.42	> 2623.42		
N (case/control)	340/405	379/405	462/405	440/406		
Odds ratio (95% CI)	1.00	1.02 (0.81, 1.29)	1.27 (1.01, 1.59)	1.13 (0.91, 1.41)	0.47	0.57

<sup>a</sup> Metals were included in the conditional logistic regression models separately (single-metal model), and adjusted for BMI, smoking status, pack year, alcohol intake status, education, physical activity, hypertension, hyperlipidemia, CHD family history, diabetes, and eGFR.

<sup>b</sup> Plasma metal concentration was presented as raw data.

<sup>c</sup> *p*-Trend across quartiles of metals were obtained by including the median of each quartile (natural log-transformed) as a continuous variable in logistic regression models.

<sup>d</sup> False Discovery Rate (FDR) adjusted *p*-Values [using software published by Pike (2011)].



**Table S6. Adjusted odds ratios (95% CI) for incident CHD according to quartiles of exposure for plasma metals included in the multiple-metal model.**

Plasma Metals	Quartiles of plasma metals ( $\mu\text{g/L}$ ) <sup>a</sup>				<i>p</i> -Trend <sup>b</sup>
	Q1	Q2	Q3	Q4	
Aluminum	< 31.03	31.03–48.95	48.95–97.15	> 97.15	
N (case/control)	358/405	349/405	395/405	519/406	
Model 1 <sup>c</sup>	1.00	0.85 (0.67, 1.08)	0.90 (0.70, 1.15)	0.94 (0.71, 1.25)	0.83
Model 2 <sup>d</sup>	1.00	0.85 (0.67, 1.08)	0.89 (0.70, 1.14)	0.94 (0.71, 1.24)	0.86
Model 3 <sup>e</sup>	1.00	0.85 (0.67, 1.08)	0.90 (0.70, 1.15)	0.94 (0.71, 1.24)	0.87
Arsenic	< 1.28	1.28–1.96	1.96–3.49	> 3.49	
N (case/control)	323/405	357/405	369/405	572/406	
Model 1	1.00	1.17 (0.91, 1.50)	1.15 (0.88, 1.50)	1.78 (1.29, 2.46)	0.001
Model 2	1.00	1.16 (0.91, 1.50)	1.14 (0.87, 1.49)	1.74 (1.26, 2.41)	0.001
Model 3	1.00	1.16 (0.90, 1.49)	1.13 (0.86, 1.47)	1.74 (1.26, 2.41)	0.002
Barium	< 23.26	23.26–35.48	35.48–62.52	> 62.52	
N (case/control)	328/405	375/405	424/405	494/406	
Model 1	1.00	1.15 (0.90, 1.47)	1.03 (0.79, 1.34)	0.91 (0.66, 1.25)	0.41
Model 2	1.00	1.14 (0.89, 1.45)	1.03 (0.79, 1.35)	0.91 (0.66, 1.25)	0.44
Model 3	1.00	1.13 (0.89, 1.45)	1.03 (0.79, 1.35)	0.92 (0.66, 1.26)	0.46
Selenium	< 57.69	57.69–67.48	67.48–78.66	> 78.66	
N (case/control)	438/405	437/405	392/406	354/405	
Model 1	1.00	0.92 (0.74, 1.14)	0.80 (0.64, 1.00)	0.67 (0.52, 0.85)	0.001
Model 2	1.00	0.93 (0.75, 1.15)	0.80 (0.64, 1.01)	0.67 (0.52, 0.85)	0.001
Model 3	1.00	0.93 (0.75, 1.16)	0.80 (0.63, 1.00)	0.67 (0.52, 0.85)	0.001
Titanium	< 24.42	24.42–29.14	29.14–35.70	> 35.70	
N (case/control)	319/405	396/405	441/405	465/406	
Model 1	1.00	1.28 (1.01, 1.62)	1.33 (1.05, 1.69)	1.32 (1.03, 1.69)	0.04
Model 2	1.00	1.28 (1.01, 1.63)	1.35 (1.06, 1.71)	1.33 (1.04, 1.71)	0.03
Model 3	1.00	1.29 (1.02, 1.64)	1.36 (1.07, 1.73)	1.33 (1.04, 1.71)	0.03

<sup>a</sup> Plasma metal concentration was presented as raw data.

<sup>b</sup> *p*-Trend across quartiles of metals were obtained by including the median of each quartile (natural log-transformed) as a continuous variable in logistic regression models.

<sup>c</sup> Model 1 Metals that were significant in the single-metal model (FDR < 0.05) were included in the conditional logistic regression model simultaneously (multiple-metals model) and adjusted for BMI, smoking status, pack year, alcohol intake status, education, physical activity, hypertension, hyperlipidemia, family history of coronary heart disease, diabetes, eGFR.

<sup>d</sup> Model 2 Further adjusted for occupational categories (six categories).

<sup>e</sup> Model 3 Further adjusted for occupational categories (six categories) and consumption habit (yes or no) of meat, fish or seafood, milk or dairy products, beans or soy foods, fruits or vegetables. If the participant reported eating the food five or more times per week, the response would be 'yes'.

**Table S7. Adjusted odds ratios (95% CI) for incident CHD in subgroups stratified by age, sex, body mass index, smoking status, hypertension, diabetes, and renal function.<sup>a</sup>**

<b>Variables</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>p-Trend<sup>b</sup></b>
<b>Arsenic</b>					
<b>Age &lt; 65 (n = 1546)</b>					
N (case/control)	163/210	171/192	164/181	275/190	
OR (95% CI)	1.00	1.10 (0.80, 1.53)	1.13 (0.79, 1.61)	1.68 (1.09, 2.58)	0.03
<b>Age ≥ 65 (n = 1696)</b>					
N (case/control)	160/195	186/213	205/224	297/216	
OR (95% CI)	1.00	1.04 (0.75, 1.44)	0.99 (0.70, 1.40)	1.53 (1.01, 2.30)	0.05
<b>Men (n = 1578)</b>					
N (case/control)	161/179	181/211	196/221	251/178	
OR (95% CI)	1.00	0.86 (0.62, 1.18)	0.87 (0.62, 1.22)	1.33 (0.87, 2.02)	0.20
<b>Women (n = 1664)</b>					
N (case/control)	162/226	176/194	173/184	321/228	
OR (95% CI)	1.00	1.38 (0.99, 1.92)	1.29 (0.90, 1.85)	1.98 (1.30, 3.03)	0.003
<b>BMI &lt; 25 (n = 1841)</b>					
N (case/control)	175/255	168/241	196/254	307/245	
OR (95% CI)	1.00	0.96 (0.70, 1.30)	1.03 (0.74, 1.43)	1.53 (1.04, 2.26)	0.03
<b>BMI ≥ 25 (n = 1401)</b>					
N (case/control)	148/150	189/164	173/151	265/161	
OR (95% CI)	1.00	1.17 (0.82, 1.66)	1.06 (0.72, 1.55)	1.71 (1.08, 2.72)	0.04
<b>Never-smokers (n = 2211)</b>					
N (case/control)	205/289	235/277	242/277	392/294	
OR (95% CI)	1.00	1.20 (0.90, 1.59)	1.17 (0.86, 1.59)	1.78 (1.23, 2.56)	0.003
<b>Ever-smokers<sup>c</sup> (n = 1031)</b>					
N (case/control)	118/116	122/128	127/128	180/112	
OR (95% CI)	1.00	0.88 (0.59, 1.31)	0.86 (0.56, 1.32)	1.26 (0.75, 2.12)	0.38
<b>Hypertension (n = 1773)</b>					
N (case/control)	200/154	220/149	256/179	398/217	
OR (95% CI)	1.00	1.15 (0.83, 1.59)	1.18 (0.83, 1.67)	1.62 (1.07, 2.45)	0.02
<b>No Hypertension (n = 1469)</b>					
N (case/control)	123/251	137/256	113/226	174/189	
OR (95% CI)	1.00	1.04 (0.75, 1.44)	0.97 (0.68, 1.39)	1.69 (1.09, 2.61)	0.05
<b>Diabetes (n = 554)</b>					
N (case/control)	75/38	92/38	95/47	121/48	
OR (95% CI)	1.00	1.61 (0.85, 3.02)	1.54 (0.79, 3.01)	2.23 (0.99, 4.99)	0.07
<b>No Diabetes (n = 2688)</b>					
N (case/control)	248/367	265/367	274/358	451/358	
OR (95% CI)	1.00	1.02 (0.80, 1.31)	1.03 (0.79, 1.35)	1.54 (1.12, 2.12)	0.012
<b>eGFR &lt; 90 (n = 2041)</b>					
N (case/control)	192/223	218/246	243/239	415/265	
OR (95% CI)	1.00	0.97 (0.72, 1.30)	0.98 (0.71, 1.35)	1.59 (1.09, 2.32)	0.009
<b>eGFR ≥ 90 (n = 1201)</b>					
N (case/control)	131/182	139/159	126/166	157/141	
OR (95% CI)	1.00	1.35 (0.94, 1.94)	1.20 (0.81, 1.78)	1.60 (0.97, 2.62)	0.11

(continued)

Variables	Q1	Q2	Q3	Q4	p-Trend <sup>b</sup>
<b>Selenium</b>					
<b>Age &lt; 65 (n = 1546)</b>					
N (case/control)	218/197	219/188	179/205	157/183	
OR (95% CI)	1.00	1.07 (0.80, 1.43)	0.75 (0.55, 1.03)	0.71 (0.52, 0.98)	0.012
<b>Age ≥ 65 (n = 1696)</b>					
N (case/control)	220/208	218/217	213/201	197/222	
OR (95% CI)	1.00	0.87 (0.65, 1.16)	0.98 (0.73, 1.32)	0.78 (0.57, 1.05)	0.20
<b>Men (n = 1578)</b>					
N (case/control)	239/221	221/194	185/180	144/194	
OR (95% CI)	1.00	0.99 (0.74, 1.31)	0.91 (0.67, 1.23)	0.61 (0.45, 0.83)	0.004
<b>Women (n = 1664)</b>					
N (case/control)	199/184	216/211	207/226	210/211	
OR (95% CI)	1.00	0.97 (0.72, 1.32)	0.81 (0.60, 1.11)	0.89 (0.65, 1.21)	0.35
<b>BMI &lt; 25 (n = 1841)</b>					
N (case/control)	234/258	226/244	198/238	188/255	
OR (95% CI)	1.00	0.95 (0.72, 1.25)	0.90 (0.67, 1.19)	0.71 (0.52, 0.95)	0.03
<b>BMI ≥ 25 (n = 1401)</b>					
N (case/control)	204/147	211/161	194/168	166/150	
OR (95% CI)	1.00	0.98 (0.71, 1.34)	0.81 (0.59, 1.12)	0.78 (0.56, 1.09)	0.08
<b>Never-smokers (n = 2211)</b>					
N (case/control)	259/247	281/276	277/310	257/304	
OR (95% CI)	1.00	0.94 (0.73, 1.23)	0.79 (0.60, 1.02)	0.71 (0.54, 0.93)	0.007
<b>Ever-smokers<sup>c</sup> (n = 1031)</b>					
N (case/control)	179/158	156/129	115/96	97/101	
OR (95% CI)	1.00	1.06 (0.75, 1.48)	1.03 (0.71, 1.50)	0.80 (0.54, 1.18)	0.39
<b>Hypertension (n = 1773)</b>					
N (case/control)	311/185	282/183	250/167	231/164	
OR (95% CI)	1.00	0.85 (0.65, 1.12)	0.81 (0.61, 1.09)	0.74 (0.55, 1.00)	0.07
<b>No Hypertension (n = 1469)</b>					
N (case/control)	127/220	155/222	142/239	123/241	
OR (95% CI)	1.00	1.12 (0.81, 1.53)	0.87 (0.63, 1.21)	0.71 (0.51, 1.01)	0.018
<b>Diabetes (n = 554)</b>					
N (case/control)	88/33	96/39	103/42	96/57	
OR (95% CI)	1.00	1.00 (0.56, 1.79)	0.91 (0.51, 1.63)	0.63 (0.36, 1.12)	0.08
<b>No Diabetes (n = 2688)</b>					
N (case/control)	350/372	341/366	289/364	258/348	
OR (95% CI)	1.00	0.96 (0.77, 1.19)	0.82 (0.65, 1.03)	0.76 (0.59, 0.96)	0.019
<b>eGFR &lt; 90 (n = 2041)</b>					
N (case/control)	296/255	283/249	263/234	226/235	
OR (95% CI)	1.00	0.94 (0.73, 1.22)	0.91 (0.70, 1.20)	0.77 (0.58, 1.01)	0.10
<b>eGFR ≥ 90 (n = 1201)</b>					
N (case/control)	142/150	154/156	129/172	128/170	
OR (95% CI)	1.00	1.01 (0.72, 1.43)	0.76 (0.53, 1.09)	0.75 (0.52, 1.09)	0.03

(continued)

Variables	Q1	Q2	Q3	Q4	<i>p</i> -Trend <sup>b</sup>
<b>Titanium</b>					
<b>Age &lt; 65 (n = 1546)</b>					
N (case/control)	163/195	193/196	205/189	212/193	
OR (95% CI)	1.00	1.21 (0.88, 1.65)	1.24 (0.90, 1.70)	1.15 (0.83, 1.60)	0.52
<b>Age ≥ 65 (n = 1696)</b>					
N (case/control)	156/210	203/209	236/216	253/213	
OR (95% CI)	1.00	1.38 (1.01, 1.88)	1.42 (1.04, 1.94)	1.45 (1.06, 1.99)	0.05
<b>Men (n = 1578)</b>					
N (case/control)	176/228	196/203	204/182	213/176	
OR (95% CI)	1.00	1.36 (1.01, 1.85)	1.45 (1.07, 1.97)	1.48 (1.07, 2.04)	0.02
<b>Women (n = 1664)</b>					
N (case/control)	143/177	200/202	237/223	252/230	
OR (95% CI)	1.00	1.24 (0.90, 1.72)	1.19 (0.86, 1.64)	1.13 (0.82, 1.59)	0.71
<b>BMI &lt; 25 (n = 1841)</b>					
N (case/control)	152/250	209/255	237/257	248/233	
OR (95% CI)	1.00	1.39 (1.03, 1.86)	1.40 (1.04, 1.89)	1.49 (1.08, 2.03)	0.02
<b>BMI ≥ 25 (n = 1401)</b>					
N (case/control)	167/155	187/150	204/148	217/173	
OR (95% CI)	1.00	1.18 (0.85, 1.65)	1.24 (0.89, 1.74)	1.09 (0.77, 1.52)	0.80
<b>Never-smokers (n = 2211)</b>					
N (case/control)	199/252	261/295	303/291	311/299	
OR (95% CI)	1.00	1.11 (0.85, 1.46)	1.21 (0.91, 1.59)	1.13 (0.85, 1.50)	0.47
<b>Ever-smokers<sup>c</sup> (n = 1031)</b>					
N (case/control)	120/153	135/110	138/114	154/107	
OR (95% CI)	1.00	1.65 (1.14, 2.40)	1.49 (1.02, 2.16)	1.64 (1.11, 2.42)	0.03
<b>Hypertension (n = 1773)</b>					
N (case/control)	214/164	249/161	303/181	308/193	
OR (95% CI)	1.00	1.22 (0.90, 1.65)	1.26 (0.93, 1.69)	1.22 (0.90, 1.65)	0.36
<b>No Hypertension (n = 1469)</b>					
N (case/control)	105/241	147/244	138/224	157/213	
OR (95% CI)	1.00	1.41 (1.01, 1.95)	1.39 (0.99, 1.95)	1.48 (1.05, 2.09)	0.04
<b>Diabetes (n = 554)</b>					
N (case/control)	90/32	81/41	110/47	102/51	
OR (95% CI)	1.00	0.72 (0.39, 1.32)	0.84 (0.47, 1.52)	0.72 (0.40, 1.30)	0.38
<b>No Diabetes (n = 2688)</b>					
N (case/control)	229/373	315/364	331/358	363/355	
OR (95% CI)	1.00	1.42 (1.12, 1.81)	1.42 (1.11, 1.81)	1.46 (1.14, 1.87)	0.013
<b>eGFR &lt; 90 (n = 2041)</b>					
N (case/control)	204/248	261/243	293/238	310/244	
OR (95% CI)	1.00	1.28 (0.97, 1.69)	1.37 (1.03, 1.80)	1.37 (1.03, 1.83)	0.06
<b>eGFR ≥ 90 (n = 1201)</b>					
N (case/control)	115/157	135/162	148/167	155/162	
OR (95% CI)	1.00	1.29 (0.89, 1.86)	1.25 (0.87, 1.81)	1.24 (0.85, 1.81)	0.34

Quartiles for each metal were defined as shown in Table 2. <sup>a</sup> Unconditional logistic regression models were used in the subgroup analysis. All stratified models included metals left in the multiple-metals model, and adjusted for age, sex, BMI, smoking status, pack year, alcohol intake status, education, physical activity, hypertension, hyperlipidemia, family history of coronary heart disease, diabetes, and eGFR (except for the corresponding stratified variable). <sup>b</sup> *p*-Trend across quartiles of metals were obtained by including the median of each quartile (natural log-transformed) as a continuous variable in logistic regression models. <sup>c</sup> Ever-smokers included current and former smokers.

**Table S8. Comparison of baseline basic characteristics of the study participants in the case-control study (n = 1621) and Metals Variability Study (n = 138).**

<b>Variables</b>	<b>Controls in the nested case-control study (n = 1621)</b>	<b>Participants in the metals variability study (n = 138)</b>	<b>p-Value <sup>a</sup></b>
Age (years)	65.6 ± 7.4	62.0 ± 6.9	< 0.001
Male sex, No. (%)	789 (48.7)	58 (42.0)	0.13
BMI (kg/m <sup>2</sup> )	24.23± 3.3	24.1 ± 3.4	0.66
Smoking status, No. (%)			
Current smoker	305 (18.8)	24 (17.4)	
Former smoker	179 (11.0)	11 (8.0)	0.45
Never smoker	1137 (70.1)	103 (74.6)	
Alcohol intake status, No. (%)			
Current drinker	360 (22.2)	32 (23.2)	
Former drinker	78 (4.8)	7 (5.1)	0.95
Never drinker	1183 (73.0)	99 (71.7)	
Education level, No. (%)			
Primary school or below	512 (31.6)	44 (31.9)	
Middle school	563 (34.7)	46 (33.3)	0.94
High school or beyond	546 (33.7)	48 (34.8)	
Physical activity, No. (yes, %) <sup>b</sup>	1466 (90.4)	124 (89.9)	0.82
CHD family history, No. (%)	77 (4.8)	11 (8.0)	0.10
Hypertension, No. (%) <sup>c</sup>	699 (43.1)	47 (34.1)	0.039
Hyperlipidemia, No. (%) <sup>c</sup>	711 (43.9)	57 (41.3)	0.56
Diabetes, No. (%) <sup>c</sup>	171 (10.5)	2 (1.4)	0.002
eGFR (ml/min/1.73 m <sup>2</sup> )	88.00 ± 21.06	88.21 ± 20.98	0.15

Data are presented as mean ± SD, or number (percentage).

<sup>a</sup> p-Values are derived from Student's t tests for continuous variables, and Chi-square tests for the category variables.

<sup>b</sup> Physical activity was defined as exercise for more than twenty minutes per week for more than half a year.

<sup>c</sup> Hypertension, hyperlipidemia and diabetes were defined as shown in Table 1.

**Table S9. Variance and correlations between plasma metal concentrations measured in samples collected in 2003 and 2008 from participants in the Metals Variability Study (n = 138).**

<b>Metal <sup>a</sup></b>	<b>Between person <math>\sigma^2</math></b>	<b>Within person <math>\sigma^2</math></b>	<b>ICC</b>	<b>r<sup>b</sup> (p-Value)</b>
Aluminum	0.08	0.53	0.13	-0.01 (0.91)
Antimony	0.03	0.39	0.07	0.35 (< 0.001)
Arsenic	0.09	0.29	0.25	0.003 (0.97)
Barium	0.16	0.10	0.63	0.08 (0.37)
Cobalt	0.04	0.12	0.25	0.43 (< 0.001)
Copper	0.02	0.01	0.74	0.72 (< 0.001)
Lead	0.18	0.22	0.45	-0.01 (0.90)
Manganese	0.04	0.08	0.36	0.08 (0.34)
Molybdenum	0.05	0.21	0.18	0.46 (< 0.001)
Nickel	0.02	0.25	0.09	0.19 (0.02)
Rubidium	0.02	0.01	0.65	0.51 (< 0.001)
Selenium	0.03	0.02	0.64	0.73 (< 0.001)
Strontium	0.04	0.02	0.61	0.52 (< 0.001)
Thallium	0.08	0.21	0.26	0.55 (< 0.001)
Titanium	0.01	0.01	0.56	0.52 (< 0.001)
Vanadium	0.04	0.11	0.28	0.28 (0.001)
Zinc	0.03	0.36	0.08	-0.11 (0.19)

Metals were log-transformed in the analysis.

Abbreviations: ICC, intra-class correlation coefficient.

<sup>a</sup> Plasma tungsten, tin, and uranium concentrations were excluded from further analysis because of many samples < LOD (98.3%, 80.2%, and 54.0%, respectively). Plasma cadmium, chromium, and iron were excluded from further analyses because of concerns about the use of plasma concentrations as a biomarker.

<sup>b</sup> Pearson correlation coefficients.

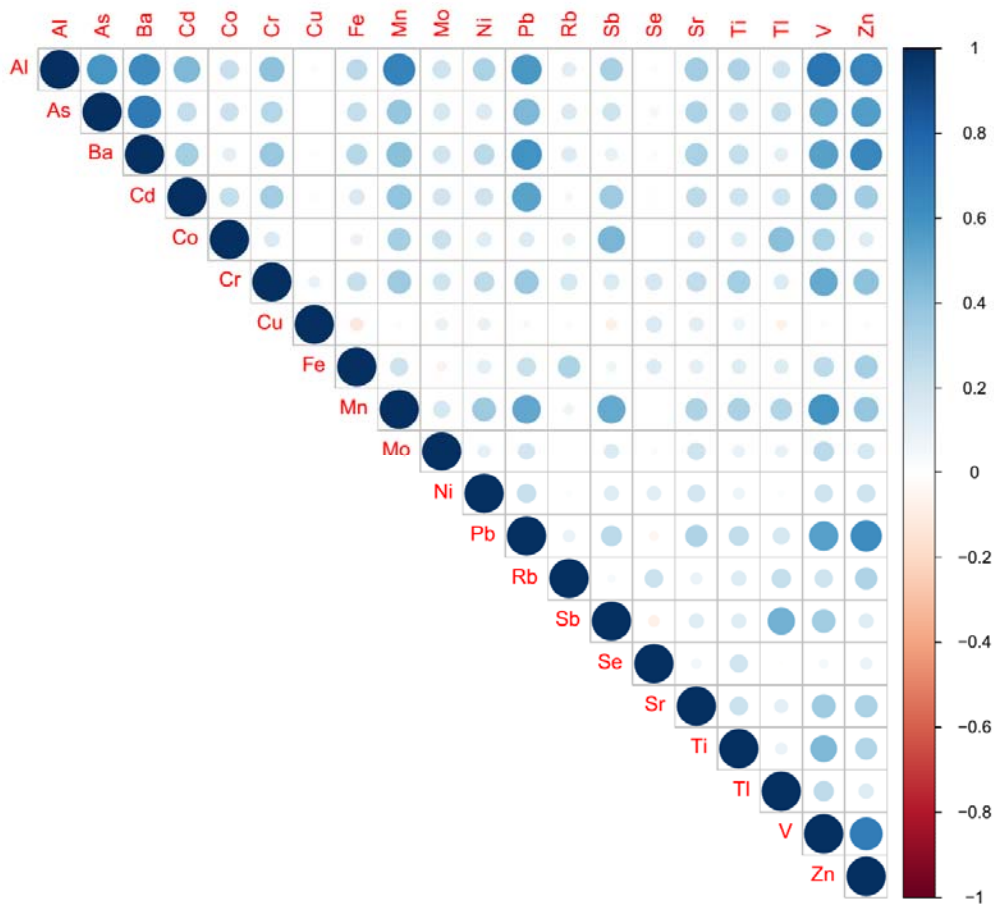
**Table S10. Basic characteristics of case-control study participants according to quartiles of plasma titanium (n = 3242).**

Variables	Quartiles of Plasma Titanium				p-Value <sup>a</sup>
	Q1 (n = 724)	Q2 (n = 801)	Q3 (n = 846)	Q4 (n = 871)	
Age (years)	65.7 ± 7.0	65.8 ± 7.7	65.6 ± 7.4	65.6 ± 7.3	0.84
Male sex, No. (%)	404 (55.8)	399 (49.8)	386 (45.6)	389 (44.7)	< 0.001
BMI (kg/m <sup>2</sup> )	24.70 ± 3.24	24.33 ± 3.25	24.45 ± 3.32	24.61 ± 3.34	0.87
Smoking status, No. (%)					
Current smoker	173 (23.9)	152 (19.0)	164 (19.4)	160 (18.4)	
Former smoker	100 (13.8)	93 (11.6)	88 (10.4)	101 (11.6)	0.01
Never smoker	451 (62.3)	556 (69.4)	594 (70.2)	610 (70.0)	
Alcohol intake status, No. (%)					
Current drinker	172 (23.8)	189 (23.6)	170 (20.1)	190 (21.8)	
Former drinker	43 (5.9)	33 (4.1)	36 (4.3)	36 (4.1)	0.18
Never drinker	509 (70.3)	579 (72.3)	640 (75.7)	645 (74.1)	
Education level, No. (%)					
Primary school or below	233 (32.2)	255 (31.8)	289 (34.2)	278 (31.9)	
Middle school	275 (38.0)	299 (37.3)	273 (32.3)	313 (35.9)	0.29
High school or beyond	216 (29.8)	247 (30.8)	284 (33.6)	280 (32.1)	
Physical activity, No. (yes, %)	674 (89.4)	719 (89.8)	754 (89.1)	783 (89.8)	0.95
CHD family history, No. (%)	31 (4.3)	42 (5.2)	38 (4.5)	44 (5.1)	0.79
Hypertension, No. (%) <sup>b</sup>	378 (52.2)	410 (51.2)	484 (57.2)	501 (57.5)	0.013
Hyperlipidemia, No. (%) <sup>b</sup>	295 (40.7)	414 (51.7)	451 (53.3)	544 (62.5)	< 0.001
Diabetes, No. (%) <sup>b</sup>	122 (16.9)	122 (15.2)	157 (18.6)	153 (17.6)	0.23
eGFR (ml/min/1.73 m <sup>2</sup> )	86.67 ± 20.43	87.19 ± 21.03	86.00 ± 20.31	85.88 ± 20.77	0.26

Data are presented as mean ± SD, or number (percentage).

<sup>a</sup> p-Values of continuous variables were calculated with linear regression without adjustments, and category variables were calculated with Chi-square tests.

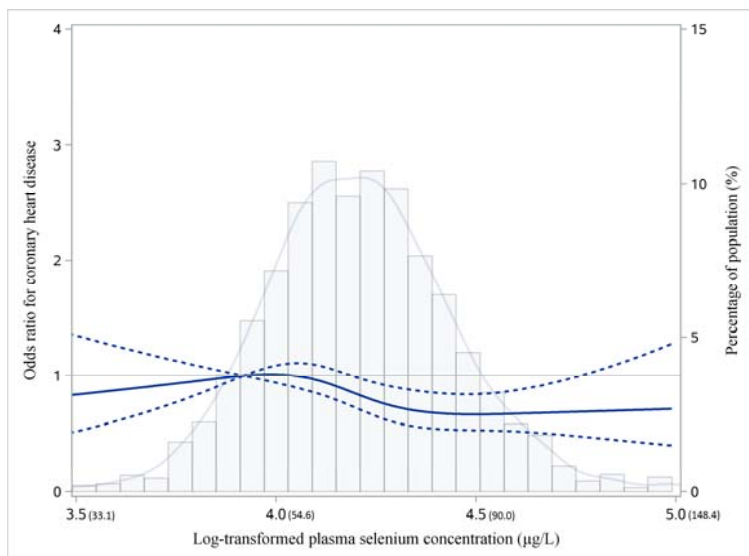
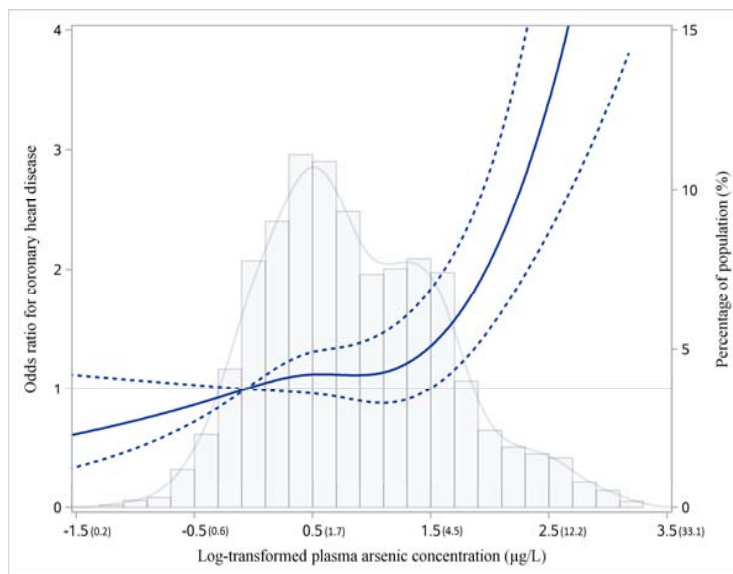
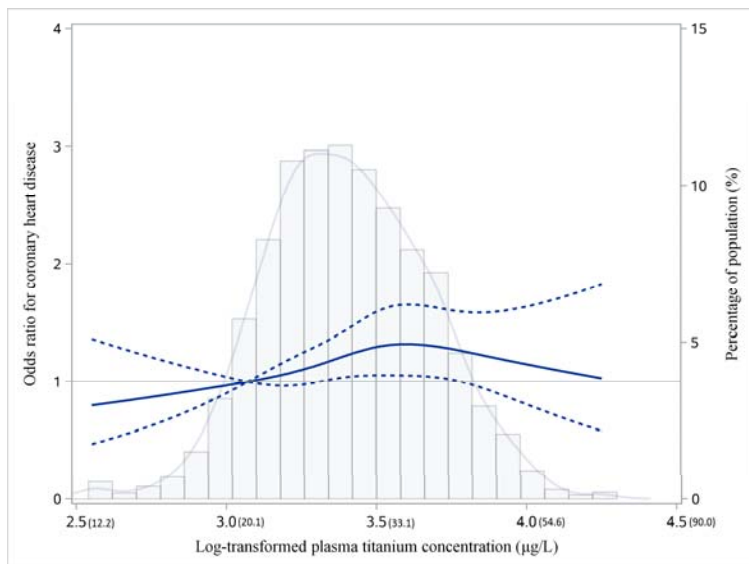
<sup>b</sup> Hypertension, hyperlipidemia and diabetes were defined as shown in Table 1.



**Figure S1. Correlation matrix of plasma metals among the case-control study participants. Spearman's rank correlation coefficients are presented.**

Abbreviations: Al, Aluminum; As, Arsenic; Ba, Barium; Cd, Cadmium; Co, Cobalt; Cr, Chromium; Cu, Copper; Fe, Iron; Mn, Manganese; Mo, Molybdenum; Ni, Nickel; Pb, Lead; Rb, Rubidium; Sb, Antimony; Se, Selenium; Sr, Strontium; Tl, Titanium; Tl, Thallium; V, Vanadium; Zn, Zinc.





**Figure S2. The restricted cubic spline for the association between plasma metals and incident CHD.**

The lines represent adjusted odds ratios based on restricted cubic splines for the log-transformed levels of plasma titanium, arsenic, and selenium in the multiple-metals conditional regression model.

Knots were placed at 5<sup>th</sup>, 35<sup>th</sup>, 65<sup>th</sup>, and 95<sup>th</sup> percentiles. Adjustment factors were the same as multiple-metal model. The bars represent histograms of plasma metal distribution among the total population.

The model included barium and aluminum as well.