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Supplemental Material

Urinary Metals and Heart Rate Variability: A Cross-Sectional Study of Urban Adults in Wuhan, China

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Table S1. Basic characteristics and HRV indices of original cohort population and source population in Wuhan city.

Variable (unit)	Original cohort population (n=3053)	Source population (n=2004)	*P*
Age (year)	53.75 (28.67-74.86)	51.83 (26.83-72.86)	< 0.001
Gender: male/female (%)	35.6/64.6	36.2/63.8	0.593
Body mass index (kg/m^2)	23.92 (19.05-30.12)	23.85 (19.00-29.94)	0.801
Smokers: never/former/current (%)	74.7/5.7/19.6	74.3/5.2/20.5	0.590
Pack years, mean ± SD	26.80 ± 22.81	26.48 ± 22.67	0.795
HRV indices			
SDNN (msec)	34.60 (18.90-63.38)	35.00 (18.90-63.13)	0.320
r-MSSD (msec)	22.50 (13.20-46.88)	22.65 (13.20-46.10)	0.626
Low frequency (ms^2)	219.12 (39.85-1134.55)	232.57 (43.11-1137.06)	0.086
High frequency (ms^2)	125.93 (22.26-801.44)	127.85 (24.34-781.73)	0.513
Total power (ms^2)	819.36 (204.86-3250.73)	855.04 (208.21-3109.79)	0.168

Abbreviations: SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals. Data were presented as median (5–95% percentiles). Chi-square test and Mann Whitney U test were performed for comparison of the categorical and continuous variables respectively.

Table S2. The distributions of urinary metals in the community-dwelling population (n=2004).

Urinary metals	Geometric mean	Percentile 5th	Percentile 25th	Percentile 50th	Percentile 75th	Percentile 95th	N (%) < LOQ
Unstandardized for urinary creatinine (μg/L)							
Aluminium	33.80	12.77	21.99	32.02	49.15	113.05	0 (0.00)
Titanium	41.96	10.68	25.23	44.42	73.53	140.60	0 (0.00)
Vanadium	0.51	0.19	0.35	0.50	0.75	1.34	0 (0.00)
Chromium	1.45	0.50	0.93	1.46	2.24	4.35	3 (0.15)
Manganese	2.56	0.88	1.67	2.53	3.84	7.66	0 (0.00)
Iron	85.27	22.48	46.53	80.08	146.72	378.07	0 (0.00)
Cobalt	0.27	0.08	0.16	0.25	0.43	1.28	2 (0.10)
Nickel	2.36	0.76	1.50	2.35	3.65	7.90	5 (0.25)
Copper	7.70	2.85	5.26	7.59	11.23	20.62	0 (0.00)
Zinc	276.94	84.09	171.15	278.92	446.40	912.32	0 (0.00)
Arsenic	28.02	6.50	17.25	29.51	48.50	92.37	0 (0.00)
Selenium	7.28	1.93	4.51	7.65	12.19	23.54	0 (0.00)
Rubidium	1856.88	431.25	1212.60	2067.03	3191.14	5236.96	0 (0.00)
Strontium	117.35	35.10	76.79	125.40	186.47	319.81	0 (0.00)
Molybdenum	45.37	10.49	27.35	47.46	80.51	159.89	0 (0.00)
Cadmium	0.87	0.23	0.53	0.91	1.48	2.97	0 (0.00)
Tin	0.25	< LOQ	< LOQ	0.28	0.41	0.76	744 (37.13)
Antimony	0.16	0.06	0.11	0.16	0.24	0.42	0 (0.00)
Barium	4.01	1.53	2.64	3.91	5.92	11.29	0 (0.00)
Tungsten	0.12	0.03	0.07	0.12	0.22	0.75	43 (2.15)
Thallium	0.52	0.13	0.34	0.57	0.89	1.52	0 (0.00)
Lead	3.08	0.45	2.19	3.31	4.67	8.94	108 (5.39)
Uranium	0.03	0.01	0.02	0.03	0.05	0.08	9 (0.45)
Urinary creatinine-standardized (μg/mmol creatinine)							
Aluminium	2.90	0.90	1.65	2.63	4.61	13.74	0 (0.00)
Titanium	3.60	1.07	2.16	3.74	6.11	10.57	0 (0.00)
Vanadium	0.04	0.02	0.03	0.04	0.07	0.13	0 (0.00)
Chromium	0.12	0.04	0.07	0.12	0.21	0.49	3 (0.15)
Manganese	0.22	0.06	0.13	0.21	0.36	0.96	0 (0.00)
Iron	7.31	1.78	3.75	6.76	13.10	38.09	0 (0.00)
Cobalt	0.02	0.01	0.01	0.02	0.04	0.11	2 (0.10)
Nickel	0.20	0.07	0.12	0.19	0.32	0.72	5 (0.25)
Copper	0.66	0.28	0.44	0.62	0.91	1.85	0 (0.00)
Zinc	23.75	8.70	16.24	23.43	35.23	64.32	0 (0.00)
Arsenic	2.40	0.89	1.68	2.42	3.45	6.43	0 (0.00)
Selenium	0.62	0.25	0.43	0.62	0.91	1.50	0 (0.00)
Rubidium	159.24	61.70	114.27	164.71	230.54	358.77	0 (0.00)
Strontium	10.06	3.26	6.66	10.55	15.63	28.35	0 (0.00)
Molybdenum	3.89	1.29	2.58	3.99	5.95	10.87	0 (0.00)
Cadmium	0.08	0.03	0.05	0.08	0.11	0.22	0 (0.00)
Tin	0.02	< LOQ	< LOQ	0.02	0.03	0.08	744 (37.13)
Antimony	0.01	0.01	0.01	0.01	0.02	0.04	0 (0.00)
Barium	0.34	0.11	0.20	0.33	0.56	1.37	0 (0.00)
Tungsten	0.01	0.00	0.01	0.01	0.02	0.06	43 (2.15)
Thallium	0.05	0.02	0.03	0.05	0.07	0.12	0 (0.00)
Lead	0.26	0.08	0.18	0.26	0.41	0.87	108 (5.39)
Uranium	0.00	0.00	0.00	0.00	0.00	0.01	9 (0.45)

Abbreviations: LOQ, limits of quantification.

Table S3. Associations between urinary metals (Spearman's rank correlation coefficients, all $p < 0.001$).

	Al	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	As	Se	Rb	Sr	Mo	Cd	Sn	Sb	Ba	W	Tl	Pb	U
Al	1.00	0.19	0.29	0.34	0.69	0.34	0.25	0.27	0.29	0.25	0.14	0.19	0.16	0.20	0.15	0.21	0.37	0.37	0.51	0.31	0.19	0.46	0.42
Ti		1.00	0.65	0.52	0.09	0.10	0.36	0.34	0.29	0.30	0.46	0.70	0.50	0.37	0.39	0.40	0.44	0.36	0.14	0.27	0.48	0.36	0.24
V			1.00	0.79	0.28	0.23	0.38	0.39	0.45	0.33	0.45	0.58	0.49	0.39	0.42	0.38	0.45	0.46	0.31	0.34	0.49	0.48	0.37
Cr				1.00	0.34	0.23	0.26	0.35	0.36	0.20	0.23	0.37	0.27	0.21	0.20	0.21	0.37	0.28	0.32	0.21	0.31	0.41	0.26
Mn					1.00	0.70	0.32	0.30	0.34	0.32	0.20	0.16	0.19	0.17	0.19	0.22	0.35	0.38	0.46	0.28	0.17	0.44	0.35
Fe						1.00	0.32	0.23	0.30	0.34	0.29	0.23	0.26	0.17	0.26	0.25	0.28	0.32	0.24	0.21	0.19	0.30	0.22
Co							1.00	0.58	0.43	0.41	0.52	0.50	0.52	0.41	0.52	0.54	0.41	0.49	0.21	0.36	0.50	0.40	0.25
Ni								1.00	0.54	0.45	0.45	0.44	0.40	0.30	0.45	0.46	0.34	0.50	0.23	0.32	0.33	0.39	0.32
Cu									1.00	0.58	0.54	0.46	0.47	0.32	0.49	0.54	0.37	0.58	0.30	0.36	0.40	0.45	0.48
Zn										1.00	0.59	0.57	0.51	0.40	0.54	0.53	0.37	0.56	0.22	0.38	0.41	0.43	0.39
As											1.00	0.77	0.76	0.55	0.74	0.64	0.44	0.66	0.16	0.43	0.61	0.41	0.42
Se												1.00	0.78	0.54	0.67	0.60	0.54	0.62	0.17	0.45	0.65	0.45	0.38
Rb													1.00	0.42	0.63	0.65	0.46	0.60	0.11	0.37	0.83	0.42	0.35
Sr														1.00	0.51	0.44	0.37	0.48	0.47	0.42	0.48	0.47	0.36
Mo															1.00	0.57	0.40	0.62	0.13	0.50	0.53	0.40	0.39
Cd																1.00	0.40	0.56	0.20	0.36	0.56	0.44	0.41
Sn																	1.00	0.53	0.27	0.41	0.43	0.49	0.37
Sb																		1.00	0.34	0.55	0.47	0.53	0.63
Ba																			1.00	0.26	0.21	0.41	0.43
W																				1.00	0.36	0.41	0.44
Tl																					1.00	0.47	0.30
Pb																						1.00	0.40
U																							1.00

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

Table S4. Estimated percent difference in HRV parameters (95% CI) in association with a 10-fold increase in creatinine-standardized urine metal concentrations based on multiple-metal models.

Variable	β (95% CIs)	*p*
SDNN		
Titanium	12.24 (5.50, 19.41)	< 0.001
Selenium	-9.73 (-18.07, -0.54)	0.038
Rubidium	8.06 (-0.86, 17.79)	0.078
Strontium	5.44 (-0.62, 11.87)	0.079
Cadmium	-7.88 (-14.12, -1.19)	0.022
r-MSSD		
Titanium	13.95 (5.96, 22.53)	< 0.001
Selenium	-8.67 (-16.87, 0.34)	0.059
Strontium	7.18 (-0.31, 15.24)	0.061
Lead	-6.41 (-12.04, -0.43)	0.036
Low frequency		
Titanium	31.61 (14.37, 51.44)	< 0.001
Manganese	16.41 (2.28, 32.51)	0.021
Arsenic	-21.24 (-35.07, -4.46)	0.015
Rubidium	25.01 (-0.16, 56.53)	0.052
Cadmium	-18.61 (-32.45, -1.94)	0.030
Lead	-13.49 (-25.66, 0.68)	0.061
High frequency		
Titanium	28.46 (6.79, 54.53)	0.008
Vanadium	19.78 (-2.02, 46.44)	0.078
Cadmium	-21.11 (-34.76, -4.61)	0.014
Total power		
Aluminium	11.92 (-0.04, 25.32)	0.051
Titanium	28.09 (14.02, 43.90)	< 0.001
Cadmium	-13.45 (-24.98, -0.15)	0.048
Lead	-11.14 (-21.79, 0.96)	0.070

Abbreviations: SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals.

Metals (natural log-transformed) were selected by backward elimination in multivariate linear regression models (alpha = 0.10) with adjustment for age, gender, smoking status, pack year, BMI, hypertension, hyperlipidemia and diabetes, respectively.

Table S5. Percent difference (95% CI) in HRV parameters according to age, gender and smoking status.

Variable	Age (≤ 52 yrs, n=1003)	Age (> 52 yrs, n=1001)	*p* for interaction	Male (n=725)	Female (n=1279)	*p* for interaction	Non-smokers (n=1594)*	Current smokers (n=410)	*p* for interaction
SDNN									
Titanium	2.49 (-4.05, 9.48)	9.93 (1.92, 18.56)	0.417	10.52 (1.38, 20.48)	5.11 (-0.96, 11.54)	0.233	6.67 (0.97, 12.69)	7.24 (-3.88, 19.64)	0.179
Copper	-5.40 (-13.69, 3.69)	-11.61 (-19.68, -2.73)	0.518	-7.52 (-17.76, 4.00)	-9.00 (-15.84, -1.61)	0.854	-8.70 (-14.96, -1.98)	-10.04 (-23.25, 5.45)	0.101
r-MSSD									
Titanium	5.02 (-2.73, 13.39)	10.80 (0.88, 21.69)	0.363	12.49 (1.63, 24.51)	5.88 (-1.79, 14.16)	0.305	7.42 (0.21, 15.16)	9.24 (-3.16, 23.43)	0.542
Cadmium	-14.08 (-21.23, -6.27)	4.20 (-7.13, 16.92)	0.041	-0.71 (-12.98, 13.29)	-8.99 (-16.36, -0.97)	0.273	-5.63 (-12.81, 2.14)	-10.88 (-23.89, 4.36)	0.074
Lead	-0.45 (-7.97, 7.67)	-16.48 (-24.23, -7.95)	0.146	-12.36 (-21.38, -2.31)	-5.90 (-12.82, 1.57)	0.665	-7.30 (-13.49, -0.67)	-14.08 (-25.89, -0.40)	0.888
Low frequency									
Titanium	15.08 (-4.88, 39.23)	37.55 (10.10, 71.83)	0.163	30.20 (3.37, 63.98)	22.43 (2.22, 46.64)	0.619	29.93 (10.24, 53.15)	11.83 (-15.52, 48.04)	0.460
Arsenic	-34.58 (-49.62, -15.04)	-18.67 (-40.00, 10.22)	0.239	-19.47 (-42.26, 12.32)	-19.22 (-36.62, 2.96)	0.828	-21.51 (-36.97, -2.27)	-14.15 (-43.95, 31.47)	0.530
Rubidium	48.25 (11.85, 96.49)	10.39 (-23.15, 58.56)	0.616	49.89 (3.38, 117.33)	8.55 (-17.27, 42.43)	0.640	13.06 (-11.69, 44.75)	61.35 (0.09, 160.10)	0.536
Cadmium	-32.18 (-46.37, -14.24)	-8.11 (-32.30, 24.71)	0.024	-38.45 (-55.84, -14.22)	-8.36 (-26.42, 14.13)	0.244	-11.71 (-27.89, 8.11)	-45.99 (-64.00, -18.97)	0.055
High frequency									
Titanium	21.18 (-1.78, 49.49)	37.97 (9.24, 74.25)	0.584	32.76 (2.31, 72.28)	29.37 (6.48, 57.16)	0.901	31.40 (9.88, 57.12)	27.00 (-7.74, 74.82)	0.546
Iron	-10.11 (-23.86, 6.12)	-15.14 (-29.32, 1.87)	0.417	-8.88 (-27.67, 14.79)	-13.89 (-25.45, -0.53)	0.625	-12.46 (-23.56, 0.25)	-9.50 (-32.38, 21.12)	0.520
Cadmium	-33.43 (-47.60, -15.42)	0.53 (-24.54, 33.92)	0.152	-7.35 (-34.13, 30.34)	-23.92 (-38.86, -5.32)	0.304	-17.54 (-32.73, 1.08)	-22.21 (-48.89, 18.38)	0.533
Lead	6.81 (-14.20, 32.96)	-32.59 (-47.29, -13.80)	0.067	-25.97 (-44.20, -1.77)	-6.22 (-23.33, 14.71)	0.378	-12.90 (-27.30, 4.36)	-22.48 (-47.79, 15.10)	0.780
Total power									
Titanium	14.31 (-2.08, 33.44)	35.94 (13.52, 62.79)	0.129	33.68 (9.39, 63.35)	19.46 (3.62, 37.73)	0.533	26.03 (10.48, 43.79)	19.24 (-7.02, 52.91)	0.823
Cadmium	-30.42 (-41.62, -17.07)	8.37 (-13.15, 35.22)	0.006	-20.79 (-38.95, 2.77)	-7.17 (-20.87, 8.91)	0.412	-9.22 (-21.85, 5.46)	-26.24 (-46.63, 1.94)	0.049
Lead	-3.01 (-17.21, 13.64)	-24.30 (-37.21, -8.73)	0.555	-15.56 (-31.86, 4.64)	-10.91 (-22.89, 2.94)	0.659	-11.18 (-22.08, 1.24)	-22.44 (-42.72, 5.02)	0.465

Abbreviations: SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals. Each interaction model included one metal-risk factor interaction term and covariates (age, gender, smoking status, pack-years, BMI, hypertension, diabetes, and urinary creatinine), and other metals that were included in the corresponding multiple-metal models. Interaction p-values represent the p-value for the interaction term. All stratified models were adjusted for other confounders and metals included in the corresponding multiple-metal models. *Non-smokers include never and ex-smokers. Data were presented as estimated percent changes in HRV parameters associated with a ten-fold increase in each urinary metal.

Table S6. Percent difference (95% CI) in HRV parameters according to BMI, hypertension and hyperlipidemia.

Variable	BMI (< 25 kg/m^2, n=1260)	BMI (≥ 25 kg/m^2, n=744)	*p* for interaction	Subjects without hypertension (n=1283)	Subjects with hypertension (n=721)	*p* for interaction	Subjects without hyperlipidemia (n=1168)	Subjects with hyperlipidemia (n=836)	*p* for interaction
SDNN									
Titanium	7.48 (1.09, 14.26)	4.97 (-3.28, 13.92)	0.841	6.22 (0.07, 12.75)	8.17 (-0.58, 17.70)	0.833	2.40 (-3.97, 9.19)	11.64 (3.51, 20.39)	0.225
Copper	-7.58 (-14.62, 0.04)	-9.50 (-19.22, 1.40)	0.803	-8.76 (-15.76, -1.19)	-8.71 (-18.23, 1.92)	0.669	-5.24 (-12.99, 3.21)	-10.29 (-18.78, -0.92)	0.499
r-MSSD									
Titanium	12.84 (4.54, 21.79)	1.68 (-7.87, 12.23)	0.554	6.11 (-1.41, 14.19)	11.89 (0.82, 24.16)	0.373	7.64 (-0.62, 16.59)	7.07 (-2.42, 17.48)	0.812
Cadmium	-9.74 (-17.48, -1.26)	-0.94 (-11.85, 11.32)	0.049	-8.56 (-16.03, -0.42)	2.17 (-9.88, 15.82)	0.054	-5.22 (-13.42, 3.76)	-5.23 (-15.52, 6.32)	0.371
Lead	-8.15 (-14.87, -0.91)	-8.37 (-17.77, 2.12)	0.600	-7.05 (-13.57, -0.04)	-12.04 (-21.69, -1.21)	0.974	-10.25 (-17.00, -2.96)	-5.05 (-14.32, 5.22)	0.326
Low frequency									
Titanium	31.87 (10.52, 57.34)	11.93 (-11.73, 41.94)	0.099	20.71 (1.63, 43.37)	33.57 (4.33, 71.02)	0.958	16.33 (-2.76, 39.18)	33.17 (5.89, 67.48)	0.657
Arsenic	-15.82 (-33.16, 6.01)	-28.06 (-50.03, 3.56)	0.145	-22.12 (-37.98, -2.21)	-19.23 (-44.07, 16.64)	0.829	-19.42 (-37.18, 3.37)	-20.92 (-42.00, 7.82)	0.900
Rubidium	28.99 (-1.35, 68.67)	13.16 (-22.91, 66.11)	0.183	24.13 (-3.65, 59.92)	21.43 (-20.40, 85.22)	0.655	25.01 (-4.60, 63.80)	18.83 (-17.77, 71.73)	0.944
Cadmium	-29.04 (-43.54, -10.82)	-0.37 (-26.51, 35.09)	0.863	-13.71 (-30.60, 7.28)	-25.18 (-46.33, 4.30)	0.500	-21.57 (-37.31, -1.88)	-11.57 (-35.11, 20.51)	0.647
High frequency									
Titanium	40.28 (15.52, 70.33)	18.49 (-8.79, 53.92)	0.472	26.64 (4.97, 52.79)	38.69 (5.49, 82.34)	0.905	25.67 (2.17, 54.57)	34.11 (5.48, 70.51)	0.711
Iron	-9.31 (-22.01, 5.44)	-17.14 (-32.99, 2.47)	0.545	-12.66 (-24.46, 0.97)	-10.88 (-28.82, 11.59)	0.989	-10.47 (-23.50, 4.79)	-15.06 (-30.32, 3.54)	0.867
Cadmium	-24.61 (-40.04, -5.20)	-9.85 (-33.85, 22.87)	0.401	-19.22 (-35.10, 0.54)	-7.11 (-33.19, 29.15)	0.571	-20.75 (-37.31, 0.19)	-9.67 (-32.95, 21.71)	0.520
Lead	-11.61 (-27.42, 7.65)	-18.48 (-39.03, 8.98)	0.631	-5.48 (-21.76, 14.20)	-32.36 (-50.39, -7.77)	0.114	-14.35 (-30.22, 5.13)	-13.08 (-33.75, 14.05)	0.908
Total power									
Titanium	30.50 (12.76, 51.04)	14.30 (-5.75, 38.60)	0.398	18.76 (3.28, 36.56)	35.77 (10.54, 66.76)	0.571	14.79 (-1.28, 33.48)	37.02 (14.09, 64.56)	0.241
Cadmium	13.42 (-27.07, 2.80)	-9.35 (-27.82, 13.85)	0.835	-13.14 (-26.14, 2.14)	-5.29 (-26.07, 21.33)	0.722	-8.46 (-22.84, 8.60)	-15.12 (-32.35, 6.50)	0.899
Lead	-13.85 (-25.50, -0.38)	-10.67 (-27.71, 10.38)	0.881	-9.54 (-21.22, 3.87)	-20.11 (-36.48, 0.49)	0.384	-16.25 (-27.74, -2.94)	-3.92 (-21.54, 17.67)	0.365

Abbreviations: SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals. Each interaction model included one metal-risk factor interaction term and covariates (age, gender, smoking status, pack-years, BMI, hypertension, diabetes, and urinary creatinine), and other metals that were included in the corresponding multiple-metal models. Interaction p-values represent the p-value for the interaction term. All stratified models were adjusted for other confounders and metals included in the corresponding multiple-metal models. Data were presented as estimated percent changes in HRV parameters associated with a ten-fold increase in each urinary metal.

Table S7. Percent difference (95% CI) in HRV parameters according to diabetes and FRS.

Variable	Subjects without diabetes (n=1840)	Subjects with diabetes (n=164)	*p* for interaction	Subjects with low-risk FRS (≤ 5%, n=960)	Subjects with high-risk FRS (> 5%, n=835)	*p* for interaction
SDNN						
Titanium	6.56 (1.36, 12.04)	12.96 (-9.27, 40.63)	0.225	2.00 (-4.83, 9.32)	13.79 (4.72, 23.65)	0.195
Copper	-6.49 (-12.51, -0.05)	-24.30 (-41.74, -1.63)	0.046	-12.32 (-20.08, -3.82)	-10.43 (-19.49, -0.34)	0.813
r-MSSD						
Titanium	8.25 (1.65, 15.27)	6.69 (-15.61, 34.88)	0.586	3.20 (-4.96, 12.05)	13.65 (3.15, 25.21)	0.131
Cadmium	-5.73 (-12.45, 1.50)	-12.00 (-32.30, 14.40)	0.483	-14.06 (-21.28, -6.19)	-0.93 (-11.50, 1.90)	0.127
Lead	-7.99 (-13.78, -1.82)	-10.96 (-28.81, 11.36)	0.504	-4.07 (-11.33, 3.79)	-11.59 (-20.71, -1.43)	0.747
Low frequency						
Titanium	19.97 (3.66, 38.84)	116.66 (20.43, 289.80)	0.271	26.17 (1.60, 56.69)	47.69 (17.37, 85.83)	0.858
Arsenic	-15.67 (-30.91, 2.93)	-59.39 (-82.92, -3.49)	0.085	-35.26 (-50.67, -15.02)	-39.88 (-56.98, -15.97)	0.257
Rubidium	20.33 (-3.85, 50.60)	36.68 (-49.11, 267.07)	0.536	51.75 (10.85, 107.74)	41.59 (-3.50, 107.75)	0.299
Cadmium	-17.73 (-31.78, -0.78)	-25.52 (-64.99, 58.45)	0.557	-38.81 (-52.43, -21.28)	-37.21 (-53.18, -15.81)	0.429
High frequency						
Titanium	30.92 (11.33, 53.95)	41.45 (-21.95, 156.35)	0.555	23.44 (-1.16, 54.18)	37.89 (7.60, 76.71)	0.411
Iron	-9.51 (-20.39, 2.85)	-38.33 (-60.45, -3.83)	0.072	-4.80 (-19.34, 12.37)	-26.94 (-41.00, -9.54)	0.065
Cadmium	-19.05 (-33.15, -1.99)	-9.23 (-53.35, 76.60)	0.741	-36.06 (-49.59, -18.89)	-7.60 (-30.82, 23.42)	0.176
Lead	-11.48 (-25.33, 4.95)	-33.65 (-62.98, 18.91)	0.120	-3.73 (-22.55, 19.66)	-16.50 (37.07, 10.81)	0.593
Total power						
Titanium	23.77 (9.77, 39.55)	48.26 (-8.99, 141.52)	0.718	19.59 (1.42, 41.01)	41.78 (16.60, 72.39)	0.416
Cadmium	-11.54 (-23.18, 1.88)	-25.72 (-56.97, 28.22)	0.843	-28.84 (-40.30, -15.19)	-22.78 (-38.49, -3.05)	0.937
Lead	-12.51 (-22.72, -0.96)	-7.99 (-42.24, 46.58)	0.951	-8.37 (-21.73, 7.28)	-8.51 (-26.54, 13.93)	0.958

Abbreviations: FRS, Framingham risk score; SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals. Each interaction model included one metal-risk factor interaction term and covariates (age, gender, smoking status, pack-years, BMI, hypertension, diabetes, and urinary creatinine), and other metals that were included in the corresponding multiple-metal models. Interaction p-values represent the p-value for the interaction term. All stratified models were adjusted for other confounders and metals included in the corresponding multiple-metal models. Data were presented as estimated percent changes in HRV parameters associated with a ten-fold increase in each urinary metal.

Figure S1. Distribution of natural log-transformed HRV parameters. Abbreviations: lnSDNN, natural log-transformed standard deviation of the normal-to-normal intervals; lnr-MSSD, natural log-transformed square root of the mean squared difference between adjacent normal-to-normal intervals; lnLF, natural log-transformed low frequency; lnHF, natural log-transformed high frequency; lnTP, natural log-transformed total power. p-values were derived from Kolmogorov-Smimov test.

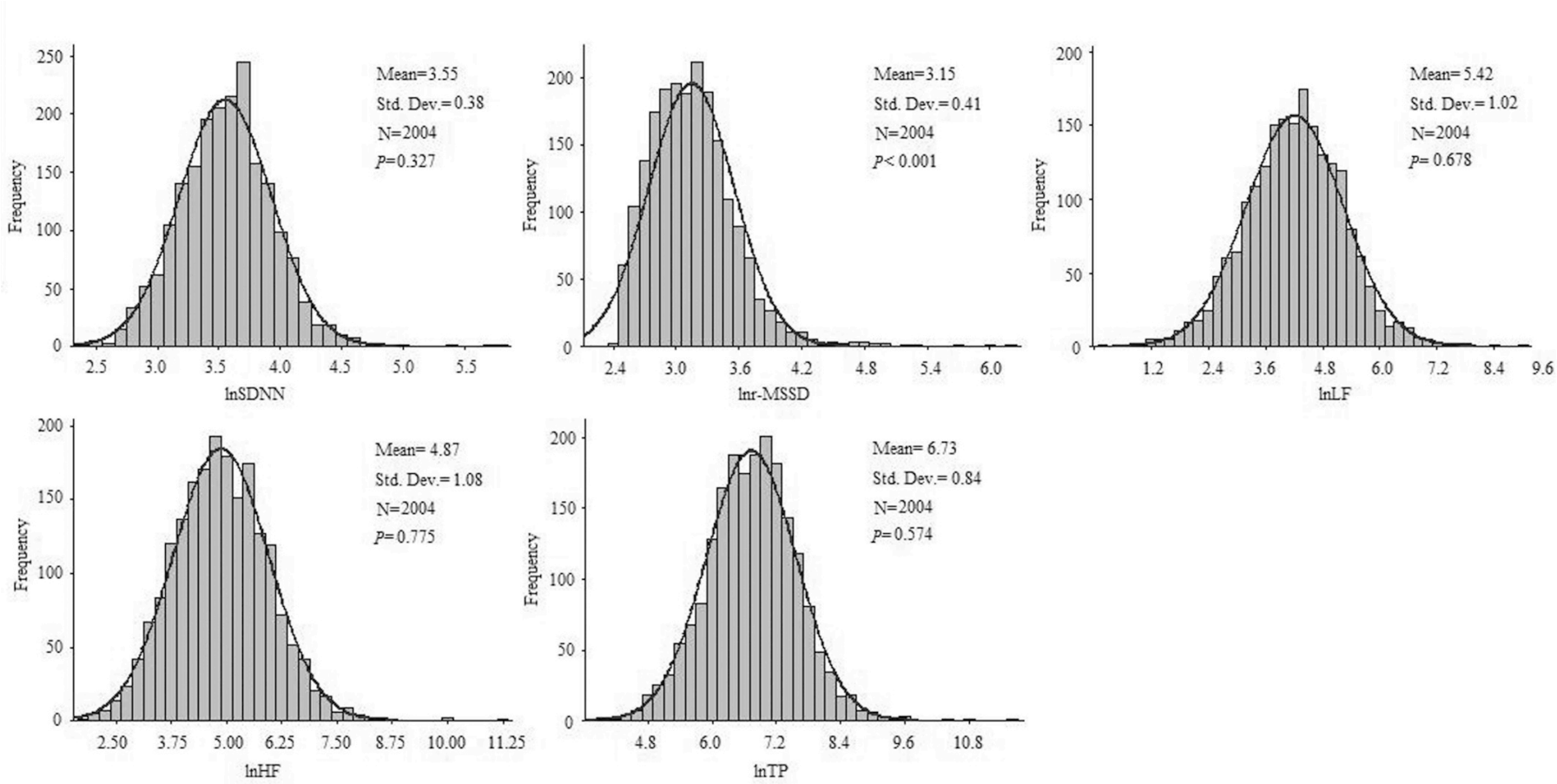

Figure S2. Estimated percent difference (95%CI) in HRV indices with a 10-fold increase in creatinine-standardized urine metal concentrations based on single-metal linear regression models adjusted for age, gender, smoking status, pack-years, BMI, hypertension, hyperlipidemia and diabetes. *FDR-adjusted $p < 0.05$. Abbreviations: FDR, false discovery rate; SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals.