SUPPLEMENTAL MATERIAL

Table S1. Beta coefficients[*] of linear terms, squared terms, and pairwise interactions of blood metals for cardiovascular disease mortality in Cox's regression[†] in the testing set.

Covariates	Beta coefficient (95% CI)
Linear term	
Lead	0.74 (0.07, 1.41)
Cadmium	0.32 (-0.16, 0.80)
Mercury	-0.41 (-0.70, -0.12)
Squared term	
Lead	-0.09 (-0.35, 0.17)
Cadmium	0.05 (-0.13, 0.23)
Mercury	0.01 (-0.09, 0.11)
Pairwise interaction	
Lead*cadmium	0.21 (-0.14, 0.56)
Lead*mercury	0.29 (-0.03, 0.42)
Cadmium*mercury	0.01 (-0.18, 0.18)

[*] Beta coefficient (95% confidence interval) per 1-unit increase in each covariate based on log-transformed blood metal concentrations.

[†] All linear terms, squared terms, and pairwise interactions were simultaneously included in the model, adjusting for age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index.

Table S2. Reclassification of participants who died from cardiovascular disease or who were alive when the Environmental Risk Score were added to the established risk factors in the testing Set.

Model with established risk factors*	**Model with established risk factors and environmental risk score†**				
	<5% Risk	5-10% Risk	10-20% Risk	≥20% Risk	Total No.
Participants who died from cardiovascular disease					
<5% Risk	53	10	0	0	63
5-10% Risk	4	63	20	0	87
10-20% Risk	0	15	61	10	86
≥20% Risk	0	0	5	15	20
Total no.	57	88	86	25	256
Participants who did not die					
<5% Risk	5711	151	0	0	5862
5-10% Risk	244	903	143	0	1290
10-20% Risk	0	122	326	59	507
≥20% Risk	0	2	31	37	70
Total no.	5955	1178	500	96	7729

* Established risk factors include age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index.

† The net reclassification improvement equals to 0.07 (95%CI: 0.01, 0.13).

Table S3. C-statistics for Cox's regression models predicting death from cardiovascular disease in the testing set adjusting for additional covariates.

Risk Factors	C-statistics for CVD death (95% CI)
Established risk factors + additional covariates*	0.848 (0.825, 0.872)
Established + additional covariates + blood lead (linear term)	0.851 (0.828, 0.875)
Established + additional covariates + blood cadmium (linear term)	0.854 (0.832, 0.878)
Established + additional covariates + blood mercury (linear term)	0.851 (0.827, 0.875)
Established + additional covariates + 3 linear term + 3 squared term + 3 pairwise interactions of blood lead, cadmium, and mercury	0.856 (0.834, 0.879)
Established + additional covariates + ERS	0.860 (0.837, 0.882)

CVD, cardiovascular disease; ERS, environmental risk score.

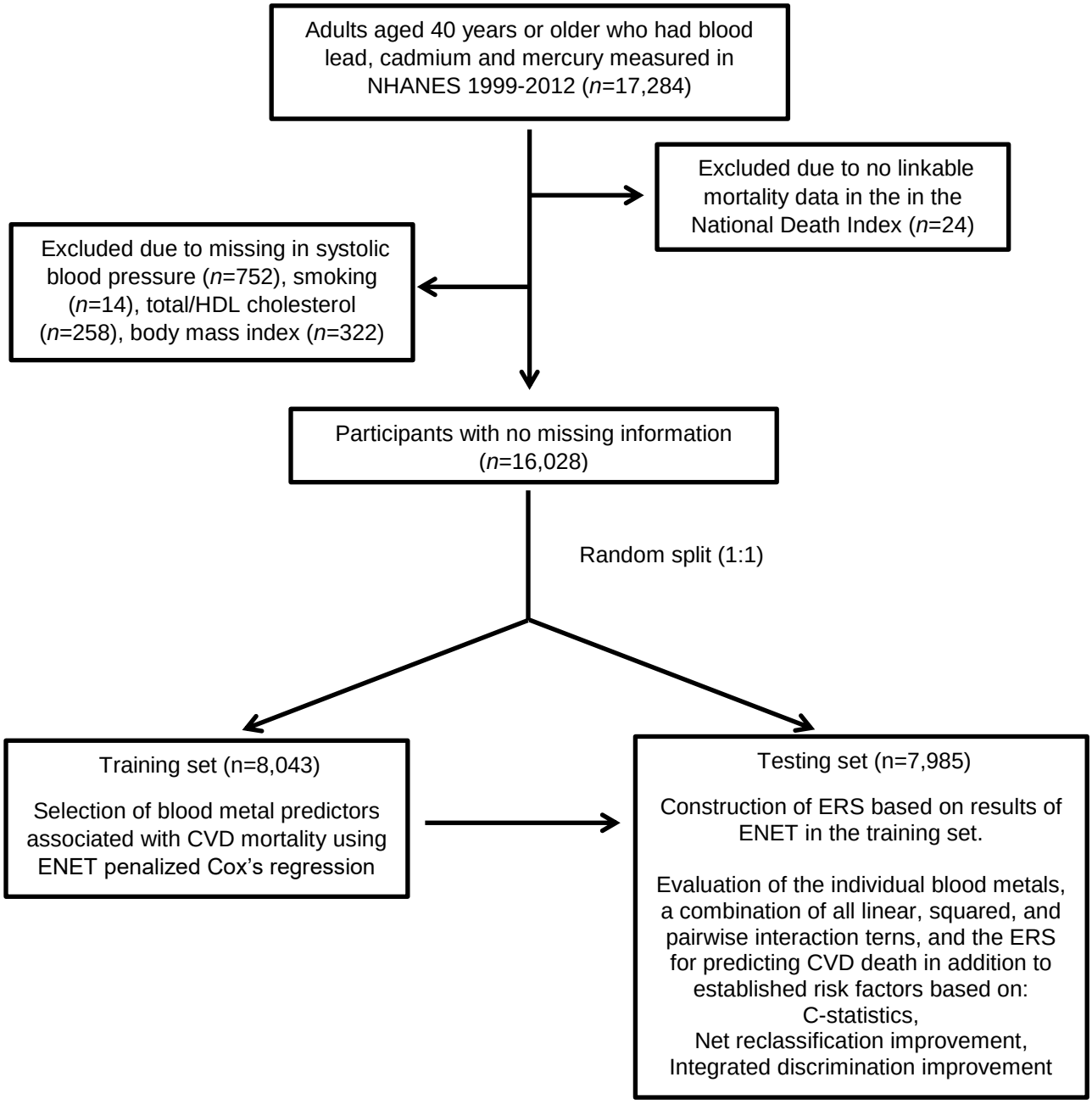
* Established risk factors include age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index. Additional covariates include NHANES survey cycles, serum cotinine, pack-year of cigarette smoking, and omega-3 fatty acids from dietary intake.

Table S4. C-statistics for Cox's regression models predicting death from cardiovascular disease in the subpopulation of testing set[*].

Risk Factors	C-statistics for CVD death (95% CI)
Established risk factors[†]	0.844 (0.820, 0.868)
Established + blood lead (linear term)	0.846 (0.823, 0.870)
Established + blood cadmium (linear term)	0.849 (0.827, 0.873)
Established + blood mercury (linear term)	0.847 (0.823, 0.871)
Established + 3 linear term + 3 squared term + 3 pairwise interactions of blood lead, cadmium, and mercury	0.856 (0.833, 0.880)
Established + ERS	0.854 (0.830, 0.876)
Established + CRP	0.847 (0.824, 0.871)
Established + family history of CVD	0.845 (0.821, 0.869)

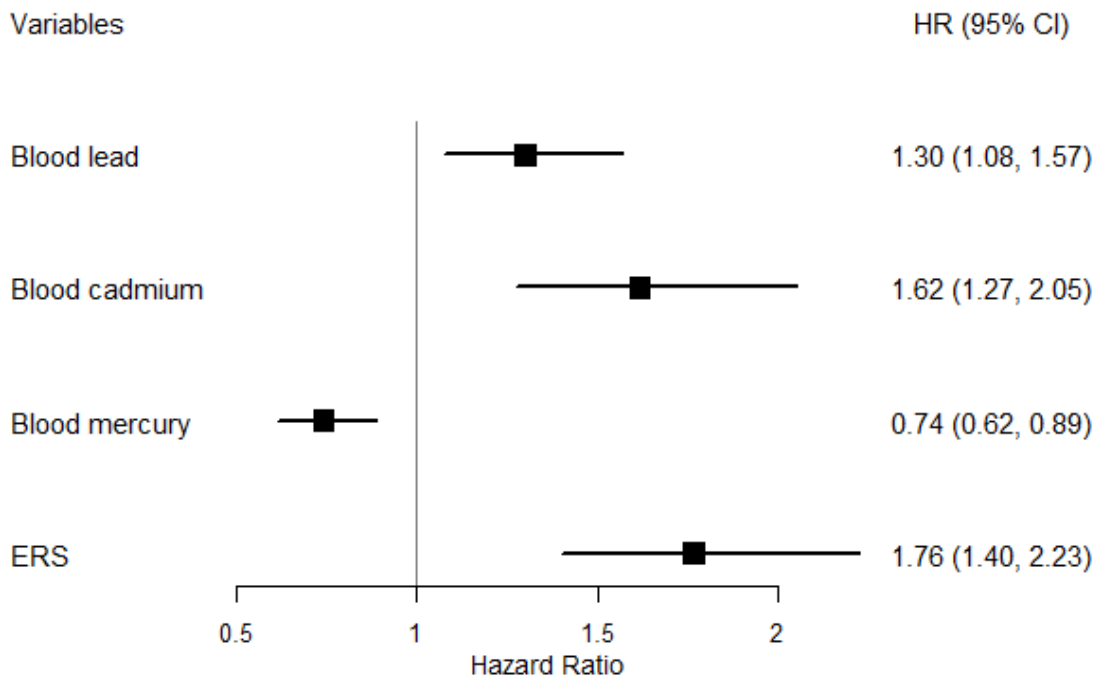
CVD, cardiovascular disease; CRP, C-reactive protein; ERS, environmental risk score.
[*] All models are performed in the testing set excluding the participants enrolled in NHANES 2011-2012 cycle, in which information on CRP is not available.
[†] Established risk factors include age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index.

Figure S1. Schematic diagram of study methodology in NHANES 1999-2012.



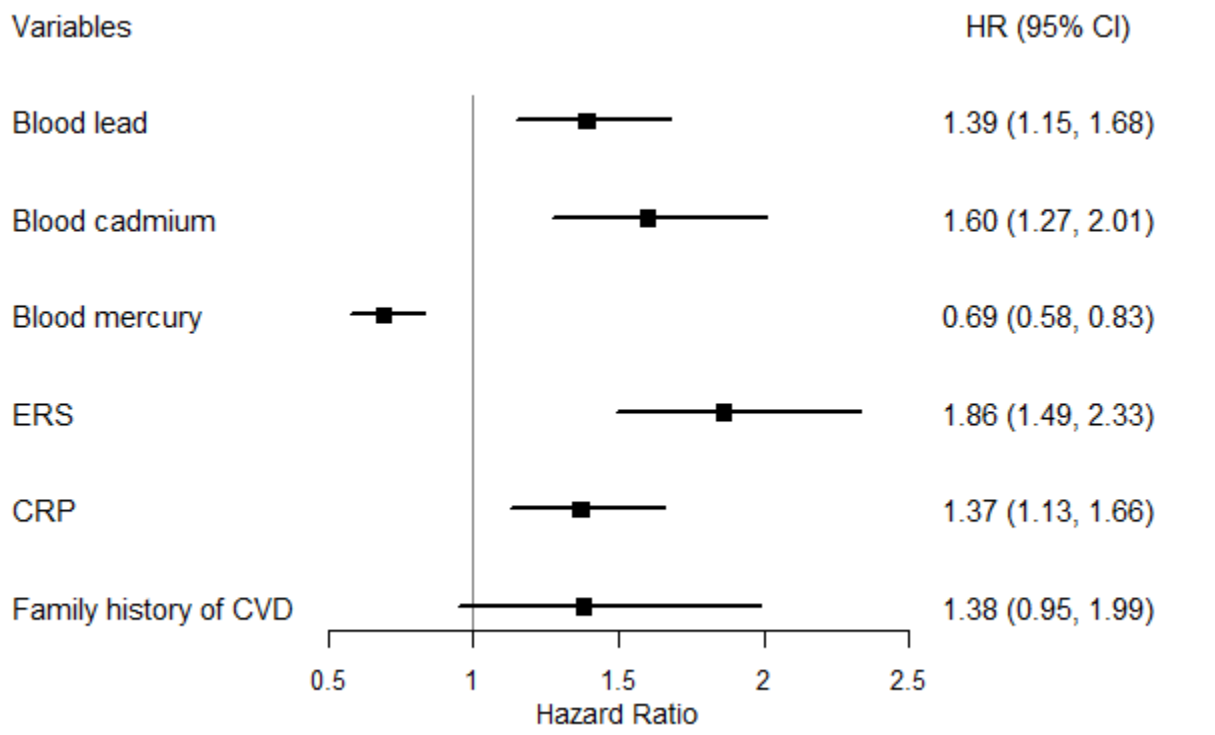
CVD, cardiovascular disease; HDL, high-density lipoprotein; ERS, environmental risk score; ENET, elastic net.

Figure S2. Hazard ratios for death from cardiovascular disease, according to individual blood metal concentrations and the Environmental Risk Score in the testing Set, after adjusting for additional covariates.



ERS, environmental risk score.
* Hazard ratio (95% confidence interval) comparing the 75th vs. the 25th percentile of each variable. Blood lead, blood cadmium, blood mercury were log-transformed. Each variable was included separately in each Cox's model. All models were adjusted age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index, and additionally adjusted NHANES survey cycles, serum cotinine, pack-year of cigarette smoking, and omega-3 fatty acids from dietary intake.

Figure S3. Hazard ratios for death from cardiovascular disease, according to individual blood metal concentration, the Environmental Risk Score, C-reactive protein and family history of cardiovascular disease in the subpopulation of testing set.



CRP, C-reactive protein; ERS, environmental risk score; CVD, cardiovascular disease.
* Hazard ratio (95% confidence interval) comparing the 75th vs. the 25th percentile of each variable, except for family history of CVD (comparing participants with family history of CVD with those without family history). Blood lead, blood cadmium, blood mercury were log-transformed. Each covariates was included separately in each Cox's model. All models were adjusted age, sex, race/ethnicity, current smoking status, systolic blood pressure, use of antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes, and body mass index. All models are performed in the testing set excluding the participants enrolled in NHANES 2011-2012 cycle, in which information on CRP is not available.