

Supplementary Material

Specification-Dependent Associations of Blood Lead, Cadmium, and Mercury with Cognitive Performance in Older U.S. Adults: A Specification Curve Analysis of NHANES 2011–2014

Sewon Jung

List of supplementary items

Supplementary Table S1. Covariate sets used in the specification-curve analysis.

Supplementary Table S2. Weighted geometric means...

Supplementary Table S3. Specification-curve summaries across cognitive outcomes.

Supplementary Table S4. Cycle-stratified lead–DSST regression estimates.

Supplementary Table S5. Sensitivity of specification-curve robustness summaries to handling specifications with unavailable p-values.

Supplementary Figure S1. Joint influence of covariate set and exposure parameterization on statistically significant metal–DSST associations.

Supplementary Table S1. Covariate sets used in the specification curve

Nested adjustment sets evaluated as one specification dimension

Covariate set	Variables included	Purpose
Minimal	Age, sex, race/ethnicity	Baseline demographic adjustment
Standard	Minimal set + education, poverty income ratio, smoking status	Socioeconomic and smoking adjustment
Extended	Standard set + body mass index, diabetes, hypertension, fish/shellfish consumption, alcohol drinks per drinking day	Cardiometabolic, dietary, and behavioral adjustment

Supplementary Table S1. Covariate sets used in the specification-curve analysis. The minimal set included age, sex, and race/ethnicity. The standard set added educational attainment, family poverty income ratio, and smoking status. The extended set added body mass index, self-reported diabetes, self-reported hypertension, past-30-day fish/shellfish consumption, and average alcoholic drinks per drinking day. These nested sets were interpreted as sensitivity structures rather than a single definitive causal adjustment set (Section 2.4).

Supplementary Table S2. Weighted geometric means of blood metals

NHANES 2011-2014 adults aged 60+ years with non-zero blood metal survey weights

Metal	Unit	Unweighted n	Geometric mean (95% CI)
Pb	µg/dL	2439	1.46 (1.39, 1.54)
Cd	µg/L	2439	0.37 (0.35, 0.39)
Hg	µg/L	2439	0.96 (0.85, 1.07)

Values use survey weights; confidence intervals are shown for geometric means.

Supplementary Table S2. Weighted geometric means of blood lead, cadmium, and total mercury concentrations in the metal-weighted analytic sample (N = 2,536). Geometric means and 95% confidence intervals were estimated using the NHANES complex survey design and the four-year blood metal analytic weight (WT_metal_4YR). Lead is reported in µg/dL; cadmium and total mercury are reported in µg/L.

Supplementary Table S3. Specification-curve summary across cognitive outcomes

Each outcome used the same 864-specification grid per metal

Outcome	Metal	Specifications	Negative %	Sig. negative %	Sig. positive %
DSST (main)	Cd	864	97.0	46.8	0.0
AFT	Cd	864	82.2	19.0	0.0
CERAD_imm	Cd	864	85.1	16.9	0.0
CERAD_del	Cd	864	74.4	8.3	0.0
Global_z	Cd	864	99.4	43.4	0.0
DSST (main)	Hg	864	20.7	0.1	33.3
AFT	Hg	864	8.6	0.0	36.3
CERAD_imm	Hg	864	11.3	0.0	24.1
CERAD_del	Hg	864	30.6	0.0	20.8
Global_z	Hg	864	13.4	0.0	40.0
DSST (main)	Pb	864	68.4	5.4	0.8
AFT	Pb	864	13.1	0.0	2.7
CERAD_imm	Pb	864	92.8	9.8	0.0
CERAD_del	Pb	864	67.0	2.5	0.2
Global_z	Pb	864	62.0	2.7	0.0

Sig. = statistically significant at two-sided $p < 0.05$ within each individual specification.

Supplementary Table S3. Specification-curve summaries across the primary and four secondary cognitive outcomes. Outcomes are the Digit Symbol Substitution Test (DSST; primary), Animal Fluency Test, CERAD immediate recall, CERAD delayed recall, and the global cognitive composite z-score. Each row summarizes 864 specifications for one metal–outcome pair. Percentages indicate the proportion of specifications yielding negative point estimates, statistically significant negative estimates, or statistically significant positive estimates at two-sided $p < 0.05$ within each individual specification. Because the four secondary outcomes are correlated, these proportions are descriptive cross-outcome consistency indicators and are not multiple-testing-adjusted inferential probabilities.

Supplementary Table S4. Cycle-stratified lead regression results

Primary standard-covariate single-metal model fitted separately by NHANES cycle

Analysis	N	Beta per ln-unit (95% CI)	Beta per doubling (95% CI)	p-value
2011-2012 only	1234	0.38 (-3.05, 3.82)	0.27 (-2.11, 2.65)	0.772
2013-2014 only	710	-0.45 (-5.56, 4.66)	-0.31 (-3.85, 3.23)	0.742
Combined (main)	1944	0.05 (-1.72, 1.81)	0.03 (-1.19, 1.26)	0.956

Cycle-specific analyses used the appropriate two-year weight for each cycle.

Supplementary Table S4. Cycle-stratified lead–DSST regression estimates. The primary standard-covariate lead–DSST model was estimated separately in the 2011–2012 cycle (using WTMEC2YR), the 2013–2014 cycle (using WTSH2YR), and the combined 2011–2014 sample (using the four-year blood metal analytic weight WT_metal_4YR). Estimates are shown per ln-unit increase in blood lead, with 95% confidence intervals, p-values, and analytic sample sizes. These analyses evaluated whether the pooled lead estimate was influenced by cycle-specific heterogeneity.

Supplementary Table S5, Panel A. Weighted-only and p-value-availability diagnostics

Overall, survey-weighted, unweighted, and survey-weighted p-value-available summaries

Metal	Subset	Specifications	Unavailable p-values	Unavailable p-values %	Negative %	Sig. negative %	Sig. positive %
Cd	All specifications	864	132	15.3	97.0	46.8	0.0
Cd	Survey-weighted only	432	132	30.6	95.8	27.1	0.0
Cd	Unweighted only	432	0	0.0	98.1	66.4	0.0
Cd	Survey-weighted, p-value available	300	0	0.0	97.0	39.0	0.0
Hg	All specifications	864	132	15.3	20.7	0.1	33.3
Hg	Survey-weighted only	432	132	30.6	17.1	0.0	35.2
Hg	Unweighted only	432	0	0.0	24.3	0.2	31.5
Hg	Survey-weighted, p-value available	300	0	0.0	7.3	0.0	50.7
Pb	All specifications	864	132	15.3	68.4	5.4	0.8
Pb	Survey-weighted only	432	132	30.6	76.4	4.9	0.0
Pb	Unweighted only	432	0	0.0	60.4	6.0	1.6
Pb	Survey-weighted, p-value available	300	0	0.0	75.7	7.0	0.0

Percentages use the displayed subset as the denominator. Specifications with unavailable p-values were retained in denominators and counted as non-significant in the primary all-specification summaries.

Supplementary Table S5, Panel B. Unavailable p-values by specification dimension level: Hg

Counts and percentages of specifications with unavailable focal-metal p-values

Metal	Dimension	Level	Specifications	Unavailable p-values	Unavailable p-values %
Hg	Exposure parameterization	log_continuous	288	44	15.3
Hg	Exposure parameterization	quartile	288	44	15.3
Hg	Exposure parameterization	z_continuous	288	44	15.3
Hg	Metal modeling strategy	mutual	432	84	19.4
Hg	Metal modeling strategy	single	432	48	11.1
Hg	Covariate set	extended	288	96	33.3
Hg	Covariate set	minimal	288	0	0.0
Hg	Covariate set	standard	288	36	12.5
Hg	Outlier handling	none	432	66	15.3
Hg	Outlier handling	winsor99	432	66	15.3
Hg	Missing-data handling	complete_case	432	60	13.9
Hg	Missing-data handling	missing_indicator	432	72	16.7
Hg	Survey weighting	unweighted	432	0	0.0
Hg	Survey weighting	weighted	432	132	30.6
Hg	Age threshold	60	432	66	15.3
Hg	Age threshold	65	432	66	15.3
Hg	Survey cycle	2011_only	288	60	20.8
Hg	Survey cycle	2013_only	288	72	25.0
Hg	Survey cycle	combined	288	0	0.0

Unavailable p-values occurred only in survey-weighted, cycle-specific specifications.

Supplementary Table S5, Panel B. Unavailable p-values by specification dimension level: Cd

Counts and percentages of specifications with unavailable focal-metal p-values

Metal	Dimension	Level	Specifications	Unavailable p-values	Unavailable p-values %
Cd	Exposure parameterization	log_continuous	288	44	15.3
Cd	Exposure parameterization	quartile	288	44	15.3
Cd	Exposure parameterization	z_continuous	288	44	15.3
Cd	Metal modeling strategy	mutual	432	84	19.4
Cd	Metal modeling strategy	single	432	48	11.1
Cd	Covariate set	extended	288	96	33.3
Cd	Covariate set	minimal	288	0	0.0
Cd	Covariate set	standard	288	36	12.5
Cd	Outlier handling	none	432	66	15.3
Cd	Outlier handling	winsor99	432	66	15.3
Cd	Missing-data handling	complete_case	432	60	13.9
Cd	Missing-data handling	missing_indicator	432	72	16.7
Cd	Survey weighting	unweighted	432	0	0.0
Cd	Survey weighting	weighted	432	132	30.6
Cd	Age threshold	60	432	66	15.3
Cd	Age threshold	65	432	66	15.3
Cd	Survey cycle	2011_only	288	60	20.8
Cd	Survey cycle	2013_only	288	72	25.0
Cd	Survey cycle	combined	288	0	0.0

Unavailable p-values occurred only in survey-weighted, cycle-specific specifications.

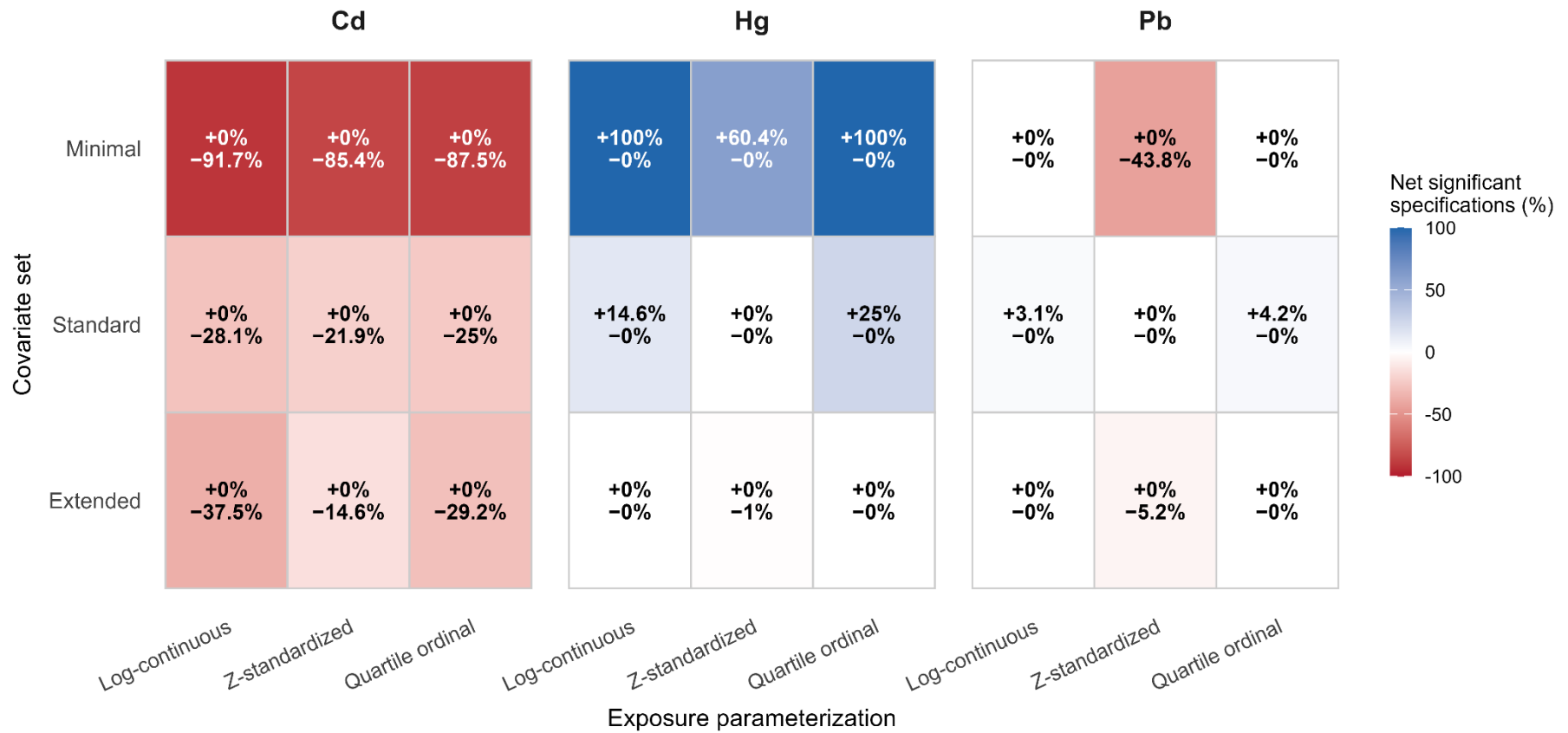
Supplementary Table S5, Panel B. Unavailable p-values by specification dimension level: Pb

Counts and percentages of specifications with unavailable focal-metal p-values

Metal	Dimension	Level	Specifications	Unavailable p-values	Unavailable p-values %
Pb	Exposure parameterization	log_continuous	288	44	15.3
Pb	Exposure parameterization	quartile	288	44	15.3
Pb	Exposure parameterization	z_continuous	288	44	15.3
Pb	Metal modeling strategy	mutual	432	84	19.4
Pb	Metal modeling strategy	single	432	48	11.1
Pb	Covariate set	extended	288	96	33.3
Pb	Covariate set	minimal	288	0	0.0
Pb	Covariate set	standard	288	36	12.5
Pb	Outlier handling	none	432	66	15.3
Pb	Outlier handling	winsor99	432	66	15.3
Pb	Missing-data handling	complete_case	432	60	13.9
Pb	Missing-data handling	missing_indicator	432	72	16.7
Pb	Survey weighting	unweighted	432	0	0.0
Pb	Survey weighting	weighted	432	132	30.6
Pb	Age threshold	60	432	66	15.3
Pb	Age threshold	65	432	66	15.3
Pb	Survey cycle	2011_only	288	60	20.8
Pb	Survey cycle	2013_only	288	72	25.0
Pb	Survey cycle	combined	288	0	0.0

Unavailable p-values occurred only in survey-weighted, cycle-specific specifications.

Supplementary Table S5. Weighted-only and p-value-availability diagnostics for DSST specification summaries. Panel A compares overall, survey-weighted, unweighted, and survey-weighted p-value-available subsets. Panel B summarizes unavailable p-values across specification-dimension levels. Specifications with unavailable p-values were retained in denominators and counted as non-significant in the primary summaries.



Supplementary Figure S1. Joint influence of covariate set and exposure parameterization on statistically significant metal–DSST associations. Each cell summarizes specifications within a given metal, covariate set, and exposure-parameterization stratum. Cell labels report the percentage of specifications yielding statistically significant positive (+) and negative (–) associations at $p < 0.05$. Tile color represents the net difference between significant positive and significant negative percentages; blue indicates positive-dominant strata, red indicates negative-dominant strata, and white indicates little net imbalance. This figure complements the marginal summaries in Figure 3 by showing the joint pattern for two specification dimensions that strongly influenced the results.