Supplementary Online Content

Metal Mixture and Serum Lipid Levels in Childhood: The Rhea Mother-Child Cohort in Greece

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Figure S39. Joint associations of the metals with triglycerides at 4 years of age among children not exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=153)

Figure S1. Flow chart showing selection of the study population

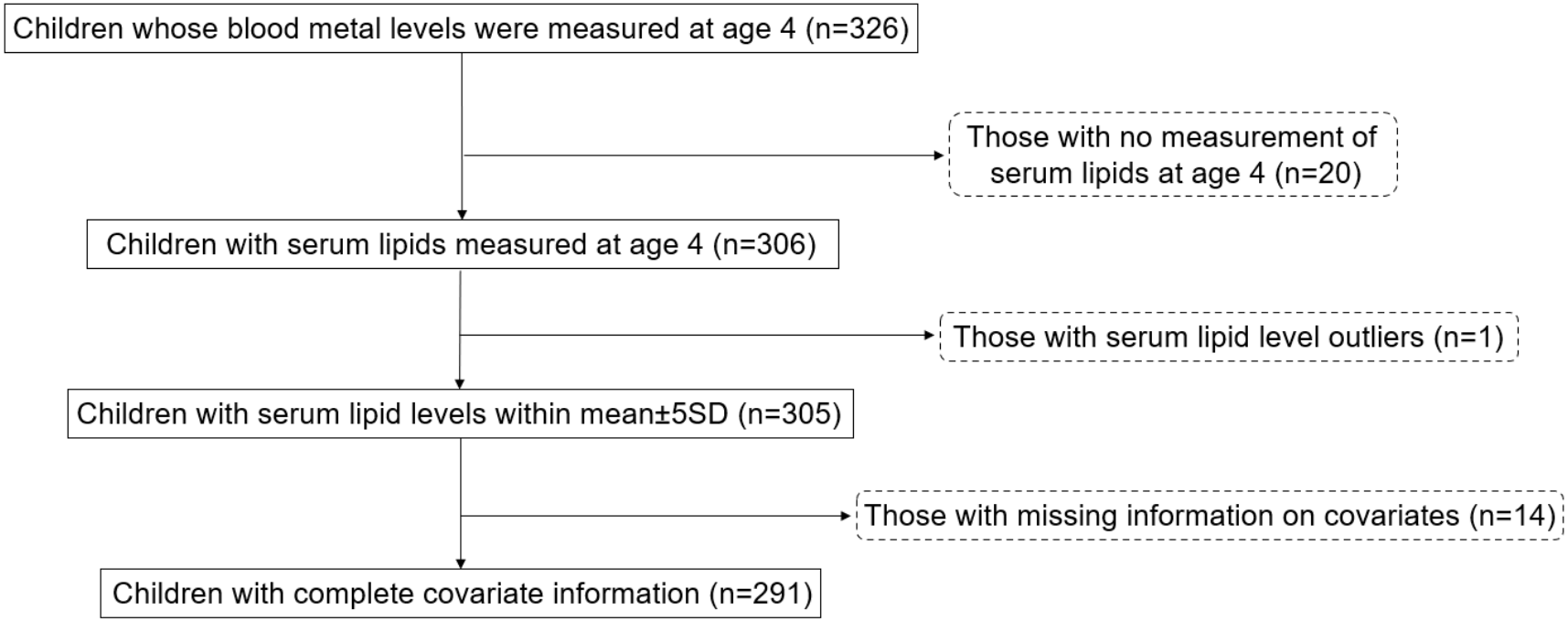
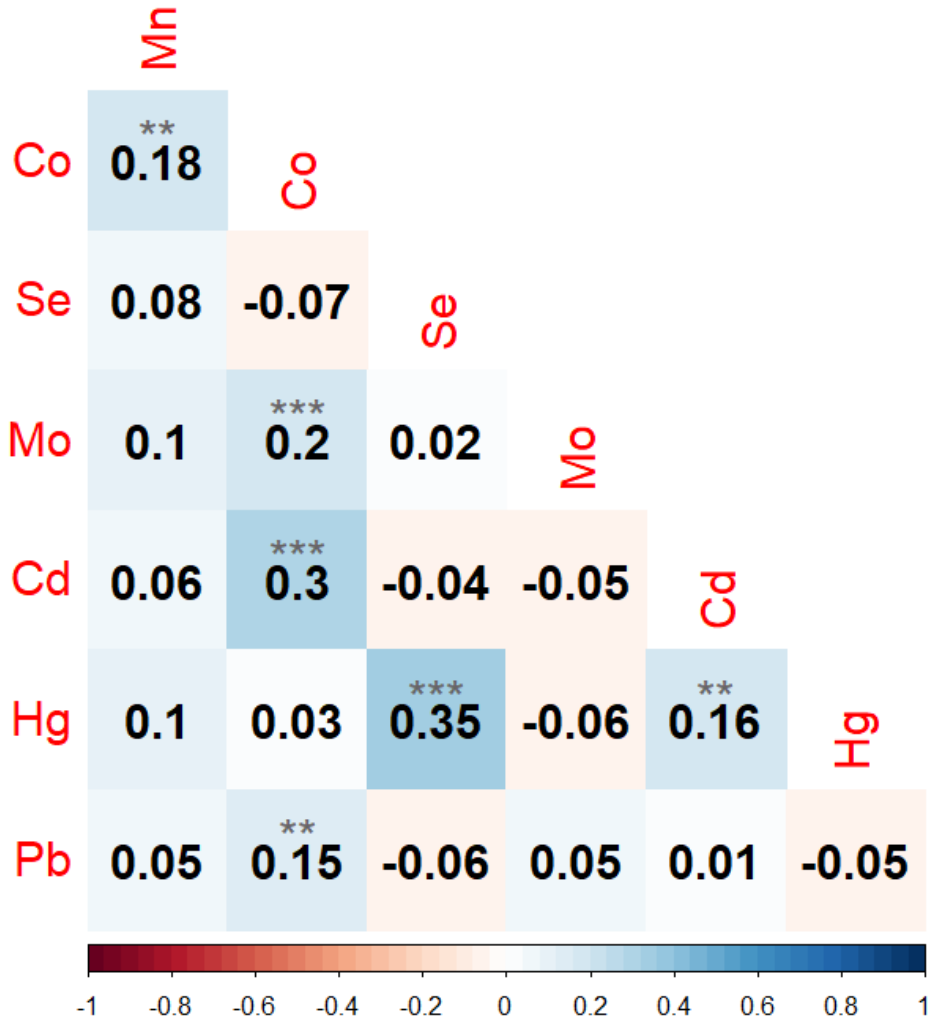


Table S1. References values and obtained values of seven metals in two reference materials included in all analyses for quality control as well as the limit of detection (LOD) for each metal (calculated as three times the SD of the blank concentrations)

Metal/trace element	Seronorm™ Trace Elements Whole blood 1406263 (n=20)		Seronorm™ Trace Elements blood L-2 whole blood 1406264 (n=21)		LOD
	Reference value	Obtained value	Reference value	Obtained value	
Manganese (µg/L)	18.4±3.7	19.6±0.6	31.4±6.3	33.2±2.2	0.1
Cobalt (µg/L)	0.20±0.08	0.21±0.03	5.18±1.04	5.18±0.28	0.01
Selenium (µg/L)	60±12	63.4±3.2	161±32	170±3.9	0.03
Molybdenum (µg/L)	0.51±0.1	0.56±0.11	5.31±1.07	5.00±0.79	0.03
Cadmium (µg/L)	0.28±0.11	0.30±0.04	5.01±1.01	5.05±0.42	0.002
Mercury (µg/L)	1.48±0.3	1.49±0.18	17.0±3.4	17.2±0.99	0.02
Lead (µg/L)	9.9±2.0	10.1±1.4	337±68	287±23	0.3

Figure S2. Spearman correlations between blood metal pairs (n=291)



Positive correlations are marked by blue shades, whereas negative correlations are marked by red shades as shown in the key. The correlations with an asterisk indicate a p-value < 0.05, two asterisks a p-value < 0.01, and three asterisks a p-value < 0.001. Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead.

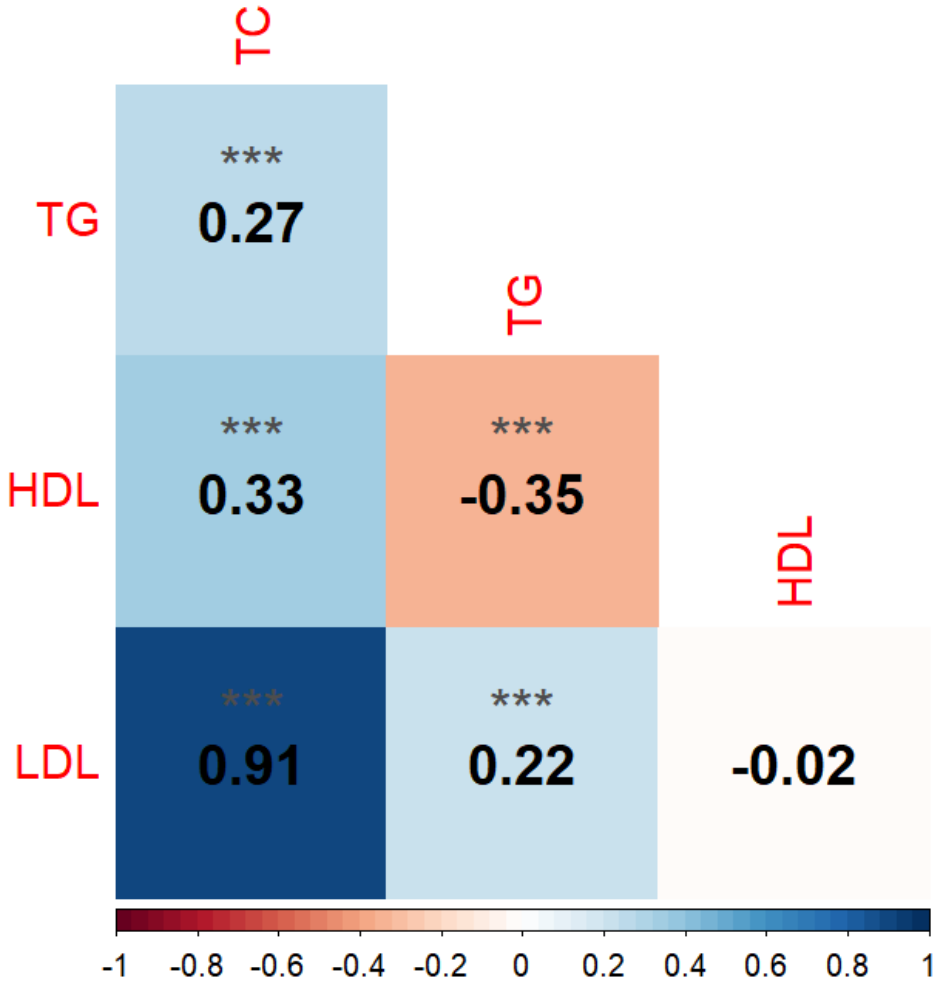
Table S2. Key characteristics of the Rhea cohort participants included and excluded from the analysis

Characteristic	Original population (N=1,363)	Included in the analysis (n=291)	Excluded from the analysis (n=1,072)	*P*
Maternal characteristics				
Maternal age at delivery (years)	29.3±5.1	30.1±5.1	29.1±5.0	0.002
Missing	19 (1.4)	0 (0.0)	19 (1.8)	
Maternal educational attainment				0.001
< 9 years	278 (20.4)	39 (13.4)	239 (22.3)	
9-12 years	661 (48.5)	158 (54.3)	503 (46.9)	
> 12 years	370 (27.1)	94 (32.3)	276 (25.7)	
Missing	54 (4.0)	0 (0.0)	54 (5.0)	
Parity				0.788
Nulliparous	561 (41.2)	123 (42.3)	438 (40.9)	
Parous	745 (54.7)	168 (57.7)	577 (53.8)	
Missing	57 (4.2)	0 (0.0)	57 (5.3)	
Smoking during pregnancy				0.407
None	807 (59.2)	189 (64.9)	618 (57.6)	
During early pregnancy only	165 (12.1)	31 (10.7)	134 (12.5)	
Throughout pregnancy	236 (17.3)	56 (19.2)	180 (16.8)	
Missing	155 (11.4)	15 (5.2)	140 (13.1)	
Child characteristics				
Sex				0.118
Male	694 (50.9)	160 (55.0)	534 (49.8)	
Female	669 (49.1)	131 (45.0)	538 (50.2)	
Gestational age at birth (weeks)	38.2±1.6	38.2±1.6	38.2±1.6	0.659
Missing	20 (1.5)	1 (0.3)	19 (1.8)	
Secondhand tobacco smoke exposure at 4 years				0.469
Yes	427 (31.3)	153 (52.6)	274 (25.6)	
No	360 (26.4)	138 (47.4)	222 (20.7)	
Missing	576 (42.3)	0 (0.0)	576 (53.7)	
Regular fish/seafood intake at 4 years				0.029
Consumed fish/seafood ≥ 2 times per week	861 (63.2)	240 (82.5)	621 (57.9)	
Consumed fish/seafood < 2 times per week	138 (10.1)	51 (17.5)	87 (8.1)	
Missing	364 (26.7)	0 (0.0)	364 (34.0)	
Red meat consumption (times per week)	2.5 ±1.3	2.5±1.2	2.5 ±1.4	0.644
Missing	989 (72.6)	11 (3.8)	709 (66.1)	
Egg intake (times per week)	2.3 (1.8)	2.4±1.8	2.3 (1.8)	0.784
Missing	988 (72.5)	11 (3.8)	708 (66.0)	

Dairy intake (times per week)	27.2 ±11.2	27.6±12.1	27.1 ±10.8	0.503
Missing	989 (72.6)	11 (3.8)	709 (66.1)	
Supplement use	54 (4.0)	20 (6.9)	34 (3.2)	0.151
Missing	379 (27.8)	11 (3.8)	368 (34.3)	
Total cholesterol (mg/dL)	156.8±28.5	157.0±26.7	156.7±29.8	0.902
Missing	674 (49.4)	0 (0.0)	674 (62.9)	
Low-density lipoprotein (mg/dL)	93.2±24.6	93.5±23.3	93.1±25.4	0.848
Missing	674(49.4)	0 (0.0)	674 (62.9)	
High-density lipoprotein (mg/dL)	49.4±11.3	49.3±11.4	49.5±11.2	0.843
Missing	674(49.4)	0 (0.0)	674 (62.9)	
Triglycerides (mg/dL)	70.9±27.7	71.1±29.4	70.8±26.4	0.889
Missing	674(49.4)	0 (0.0)	674 (62.9)	

Mean ± SD for continuous variables and N (%) for categorical variables.

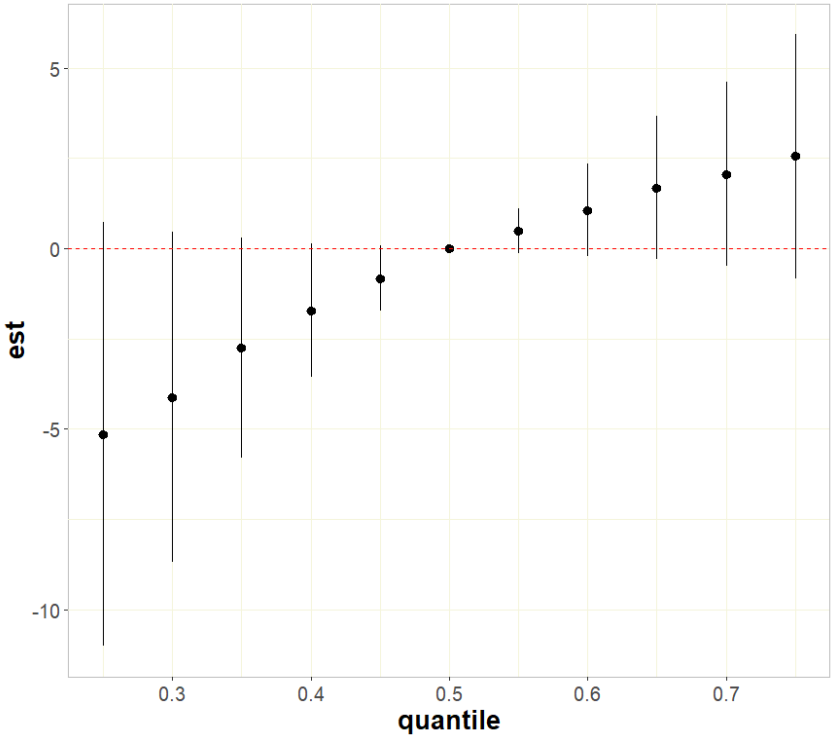
Figure S3. Pearson correlation coefficients between serum lipid measures (n=291)



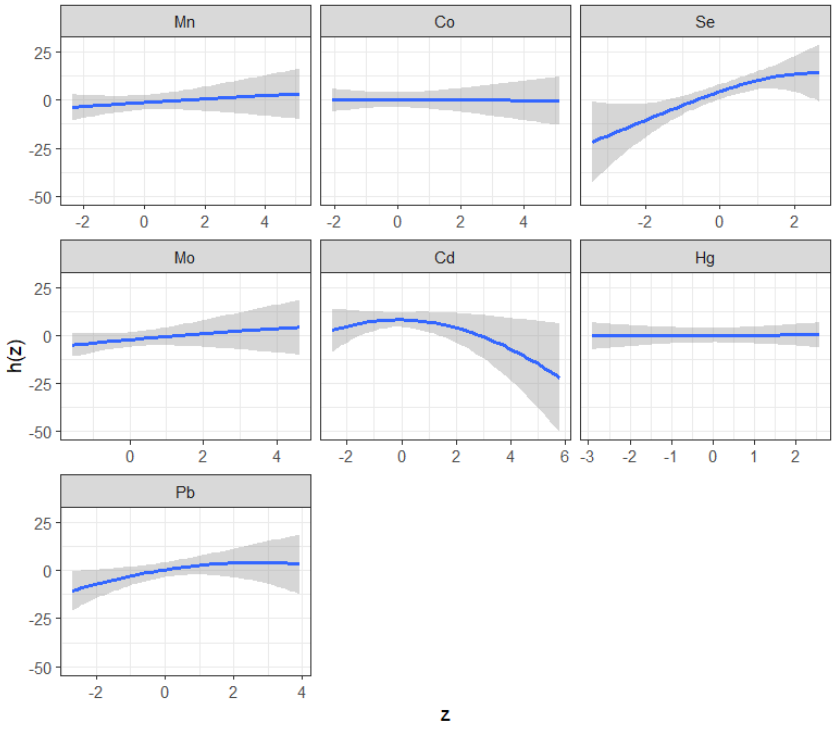
Positive correlations are marked by blue shades, whereas negative correlations are marked by red shades as shown in the key. The correlations with an asterisk indicate a p-value < 0.05, two asterisks a p-value < 0.01, and three asterisks a p-value < 0.001. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

Figure S4. Joint associations of the metals with total cholesterol at 4 years of age estimated by BKMR (n=291)

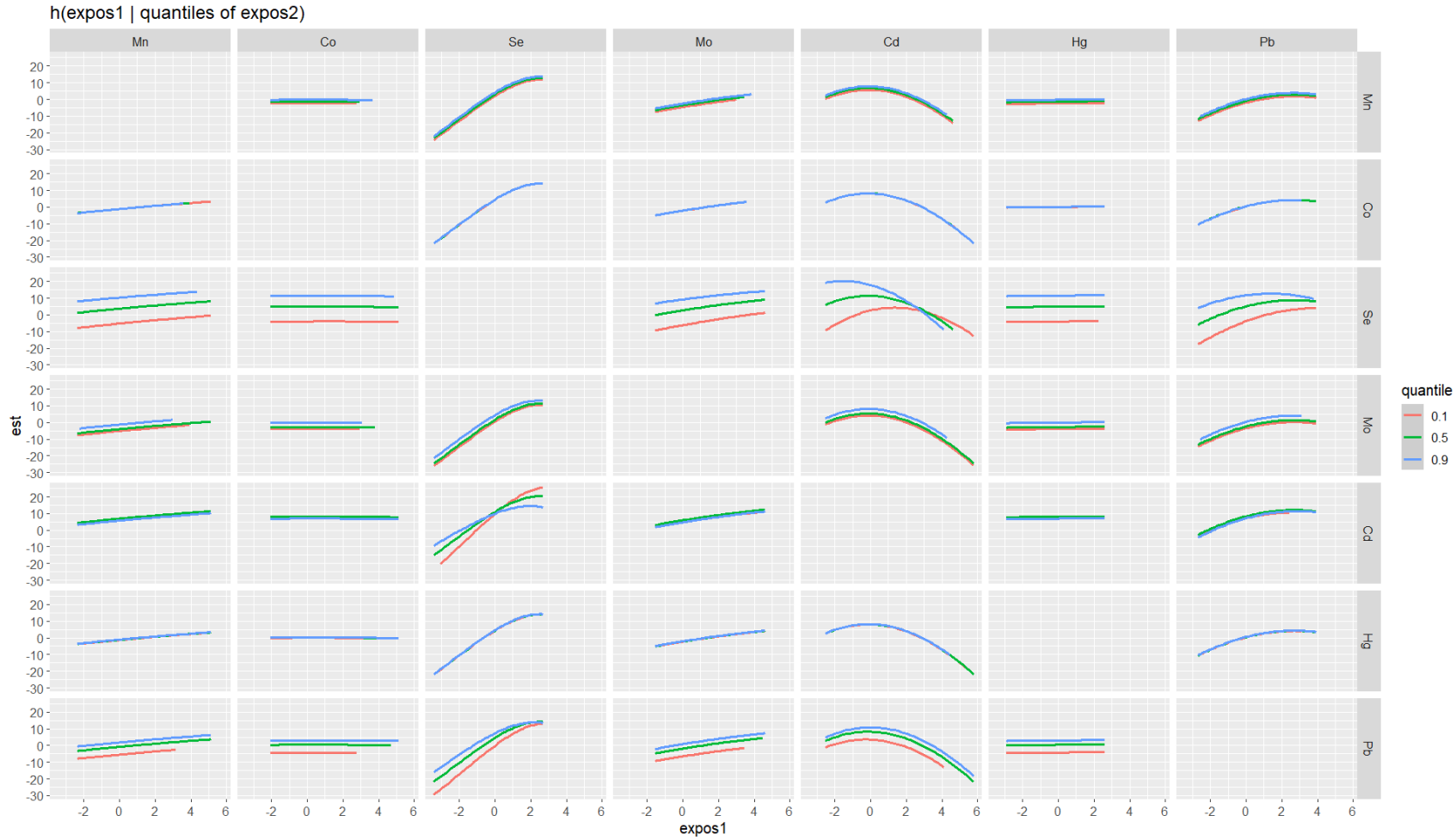
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



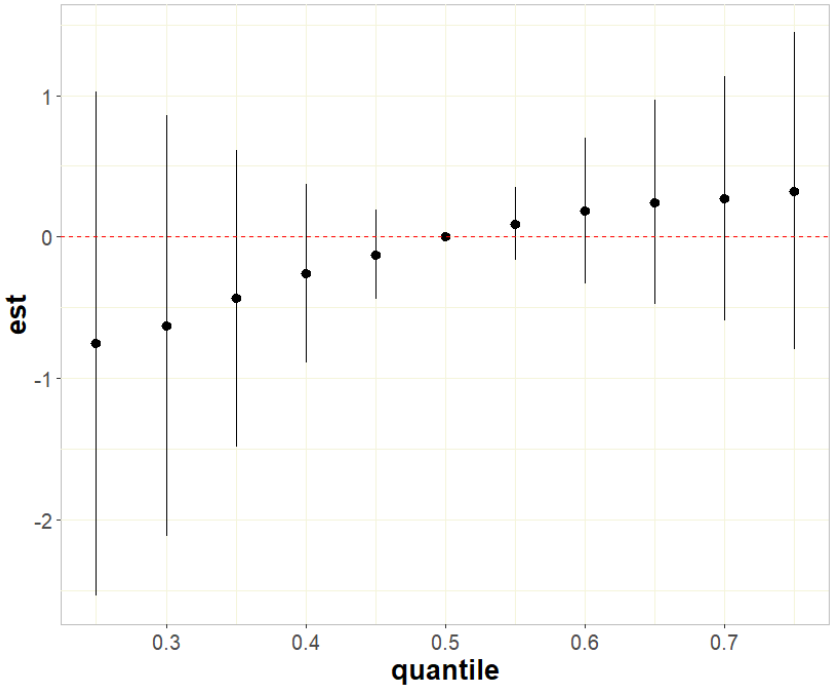
c. Bivariate exposure-response function of each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, holding the other metal exposures at their 50th percentiles



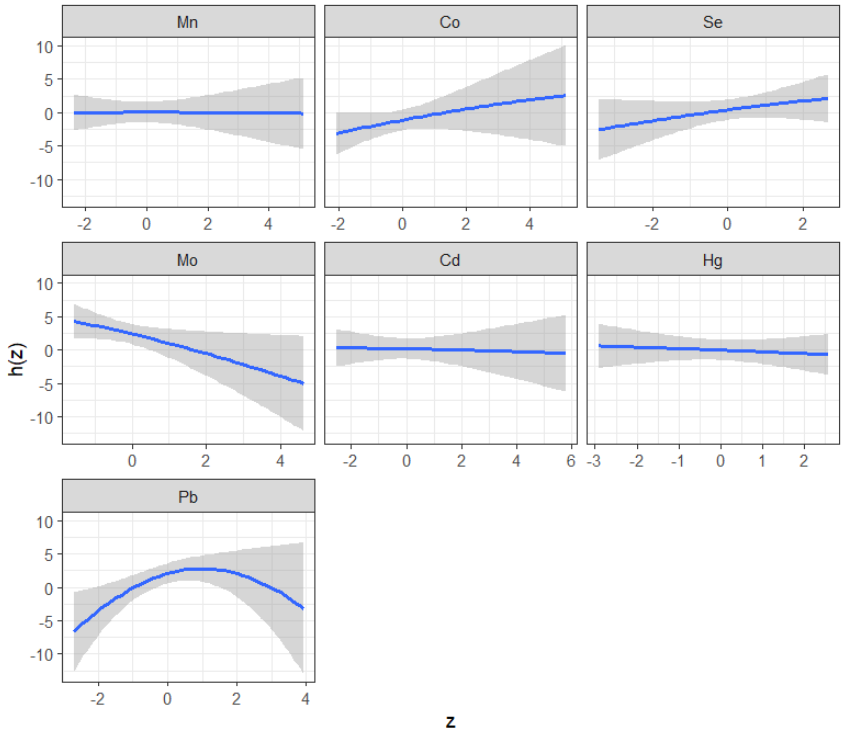
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S5. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age, estimated by BKMR (n=291)

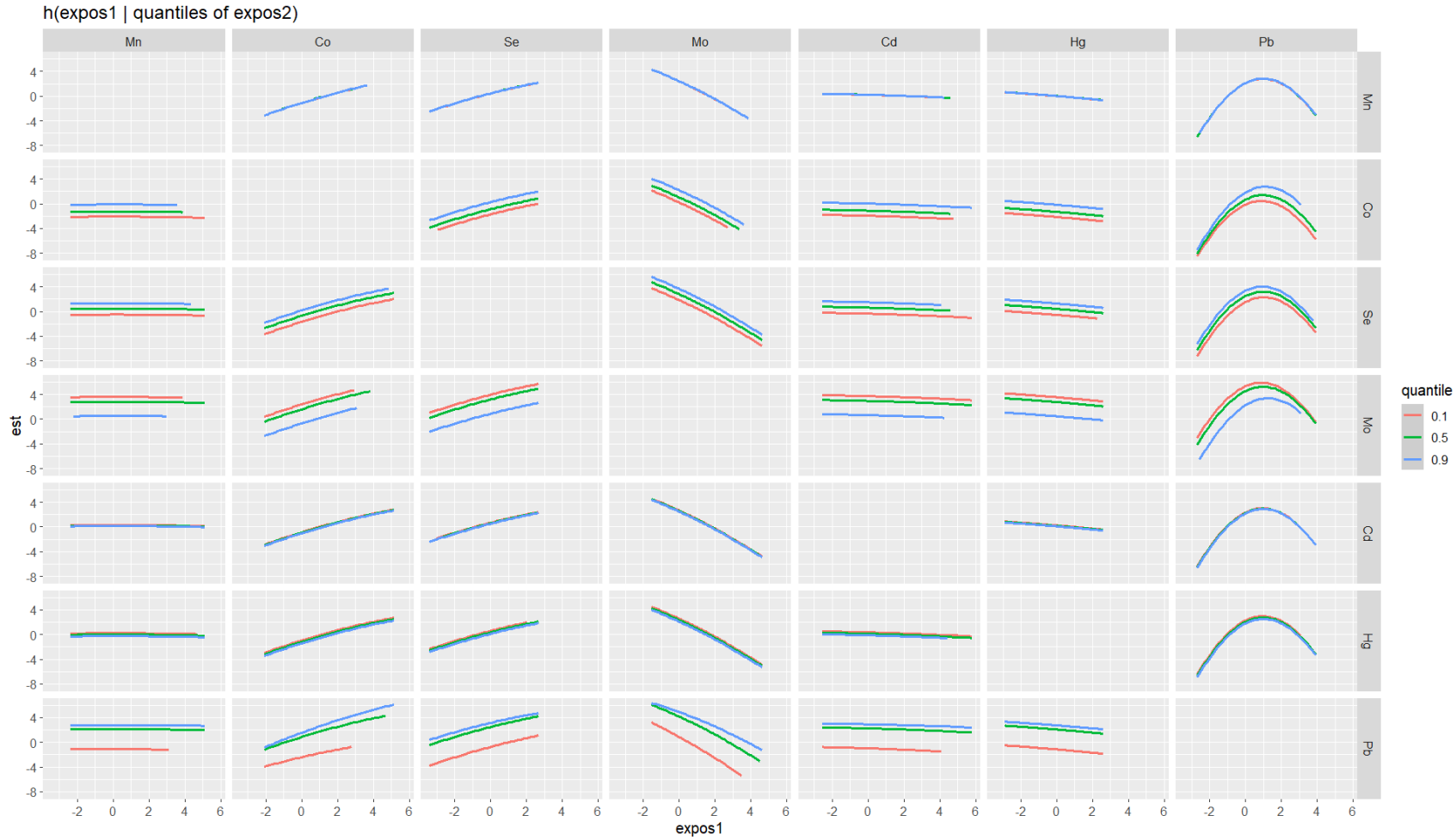
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



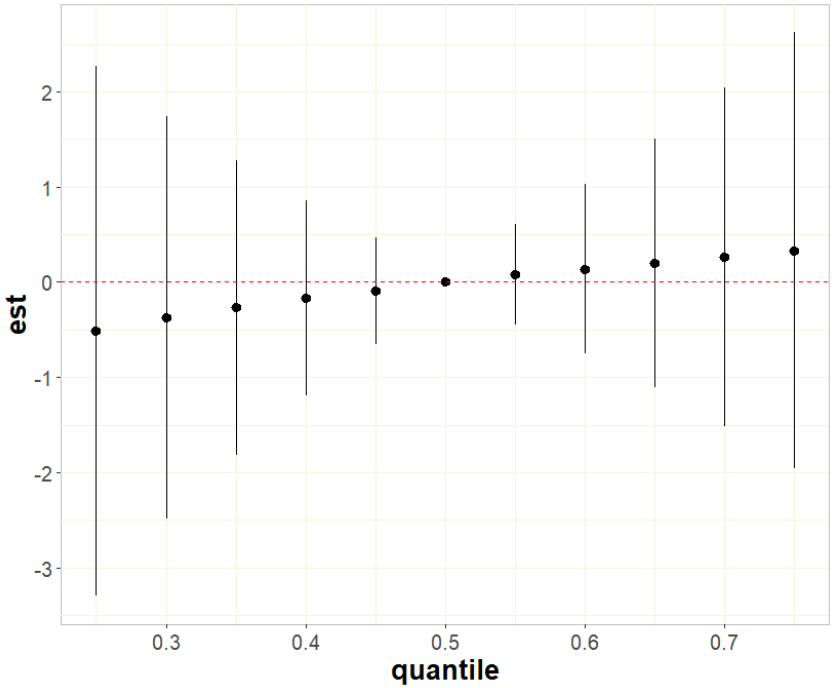
c. Exposure-response function for each metal (column) setting a second metal (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



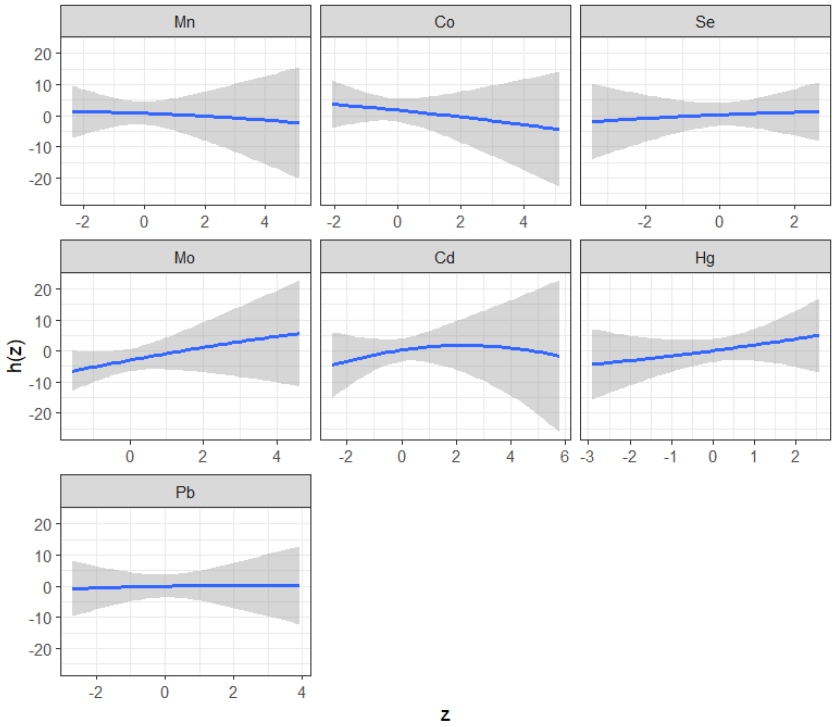
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S6. Joint associations of the metals with triglycerides at 4 years of age, estimated by BKMR (n=291)

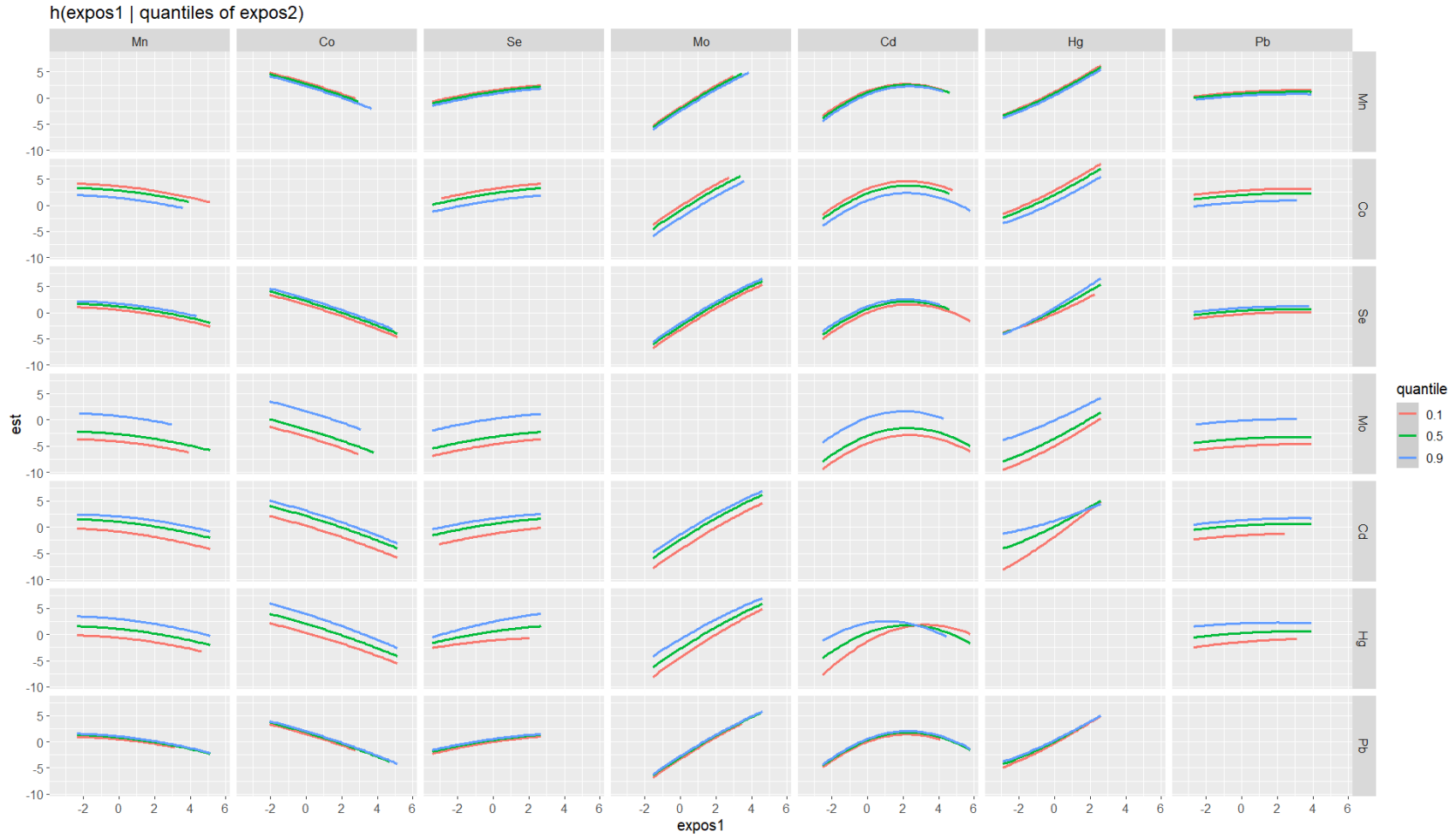
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions for each metal and corresponding 95% credible intervals while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal (column) setting a second metal exposure (row) at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Table S3. Quantile g-computation estimates (psi and 95% confidence bounds) for the difference in each lipid measure at age 4 for a simultaneous decile increase in all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb; n=291)

Total cholesterol (mg/dL)	**Low-density lipoprotein cholesterol** (mg/dL)	**High-density lipoprotein cholesterol** (mg/dL)	**Triglycerides** (mg/dL)
3.79 (1.45, 6.14)	3.19 (1.13, 5.24)	0.27 (-0.66, 1.19)	1.69 (-0.67, 4.05)

Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

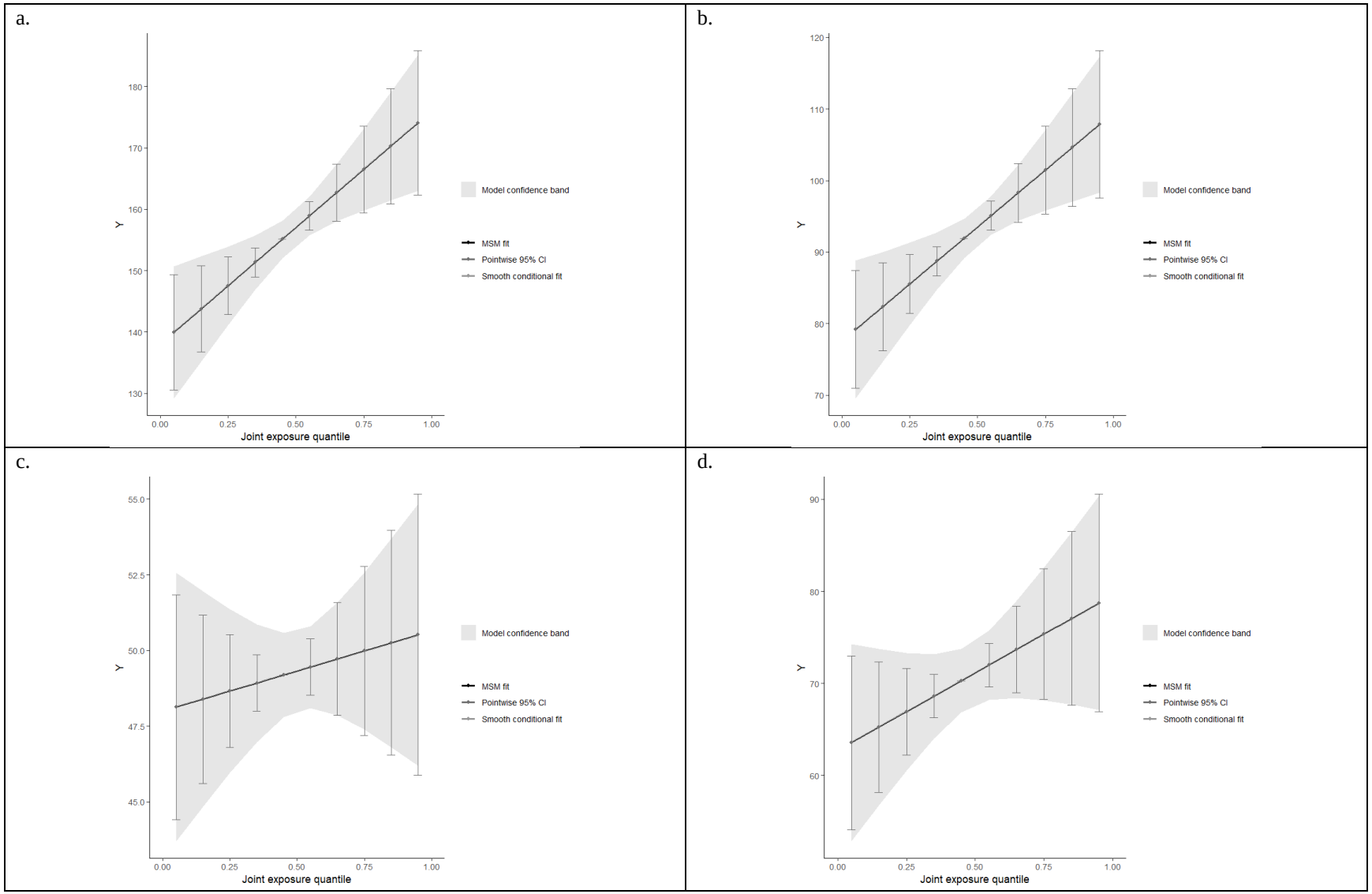
Table S4. Quantile g-computation weights for each metal in the mixture in relation to each lipid measure (n=291)

Exposure	**Total cholesterol** (mg/dL)		**Low-density lipoprotein cholesterol** (mg/dL)		**High-density lipoprotein cholesterol** (mg/dL)		**Triglycerides** (mg/dL)	
	Pos[a]	Neg[a]	Pos[a]	Neg[a]	Pos[a]	Neg[a]	Pos[a]	Neg[a]
Mn	0.15		0.17		0.02			0.37
Co		0.53		0.71	0.27			0.63
Se	0.46		0.38		0.32		0.25	
Mo	0.10		0.23			0.67	0.25	
Cd		0.48		0.29		0.21	0.36	
Hg	0.03		0.05			0.12	0.11	
Pb	0.26		0.17		0.40		0.03	

[a] Sum of positive and negative coefficients were 4.35 and -0.56 for total cholesterol, 2.21 and -0.53 for triglycerides, 1.17 and -0.90 for high-density lipoprotein cholesterol, and 3.95 and -0.76 for low-density lipoprotein cholesterol, respectively.

Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S7. Joint associations of the metals with (A) total cholesterol, (B) low-density lipoprotein (LDL) cholesterol, (C) high-density lipoprotein (HDL) cholesterol, and (D) triglycerides at 4 years of age, estimated by quantile g-computation (n=291)



All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Table S5. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations and holding all other metals in the mixture at their median values, estimated by BKMR additionally adjusting for red meat consumption (n=291)

Lipid measure	**75th vs. 25th percentiles**
Total cholesterol (mg/dL)	8.44 (0.04, 16.84)
Low-density lipoprotein cholesterol (mg/dL)	7.30 (0.82, 13.78)
High-density lipoprotein cholesterol (mg/dL)	1.07 (-1.68, 3.82)
Triglycerides (mg/dL)	0.70 (-3.44, 4.85)

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Table S6. Posterior inclusion probabilities (PIP) and effect estimates for each metal, holding all other metals in the mixture constant at their median values, in association with lipid measures at 4 years of age, estimated by BKMR additionally adjusting for red meat consumption (n=291)

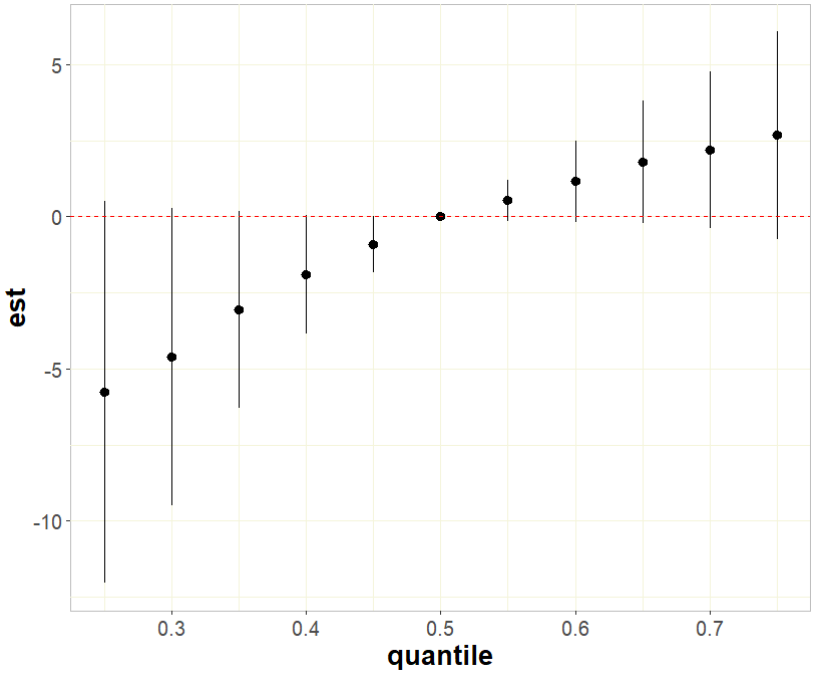
Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]
Mn	<0.01	0.01 (-0.42, 0.44)	0.03	0.05 (-0.92, 1.03)	0.01	<-0.01 (-0.18, 0.18)	0.03	-0.02 (-1.14, 1.10)
Co	<0.01	0 (0, 0)	0.03	-0.01 (-0.77, 0.76)	0.06	-0.02 (-0.63, 0.59)	0.04	0.02 (-1.05, 1.09)
Se	0.92	8.48 (0.66, 16.30)	0.96	8.43 (2.33, 14.53)	0.03	0.04 (-0.51, 0.59)	0.05	0.03 (-1.27, 1.33)
Mo	0.04	0.11 (-1.39, 1.60)	0.21	0.80 (-2.82, 4.43)	0.10	-0.20 (-1.57, 1.18)	0.08	0.19 (-1.67, 2.04)
Cd	0.30	0.94 (-3.06, 4.93)	0.76	1.89 (-2.52, 6.30)	0.01	-0.01 (-0.26, 0.24)	0.12	0.42 (-2.61, 3.46)
Hg	0.01	0.01 (-0.49, 0.51)	<0.01	<-0.01 (-0.25, 0.25)	0.01	-0.01 (-0.24, 0.23)	0.16	0.44 (-2.64, 3.52)
Pb	0.19	1.14 (-4.09, 6.37)	0.04	0.14 (-1.48, 1.75)	0.53	1.00 (-1.55, 3.55)	0.02	<0.01 (-0.80, 0.80)

[a] The difference in the lipid measure when setting each metal component to its 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

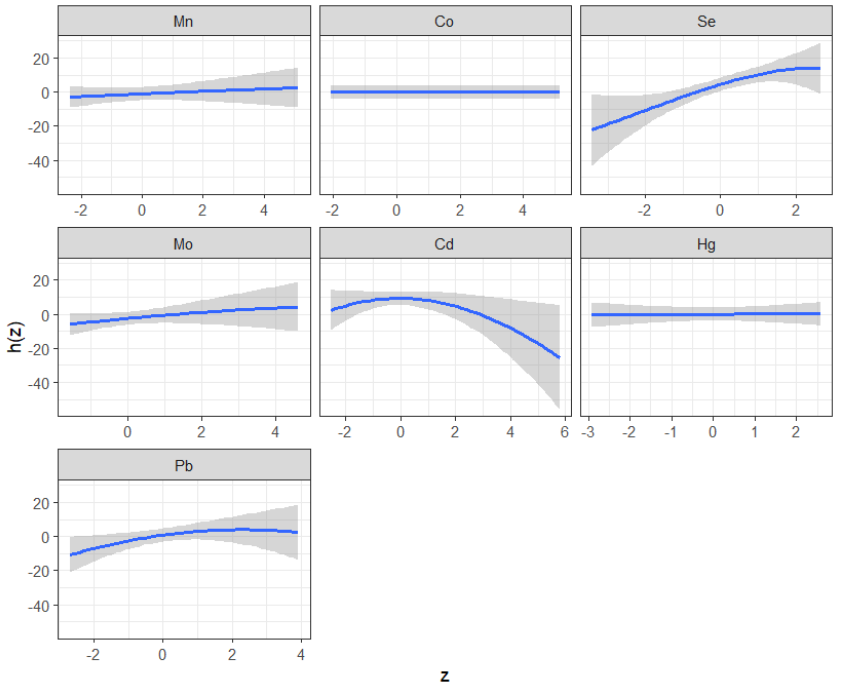
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Figure S8. Joint associations of the metals with total cholesterol at 4 years of age estimated by BKMR additionally adjusting for red meat consumption (n=291)

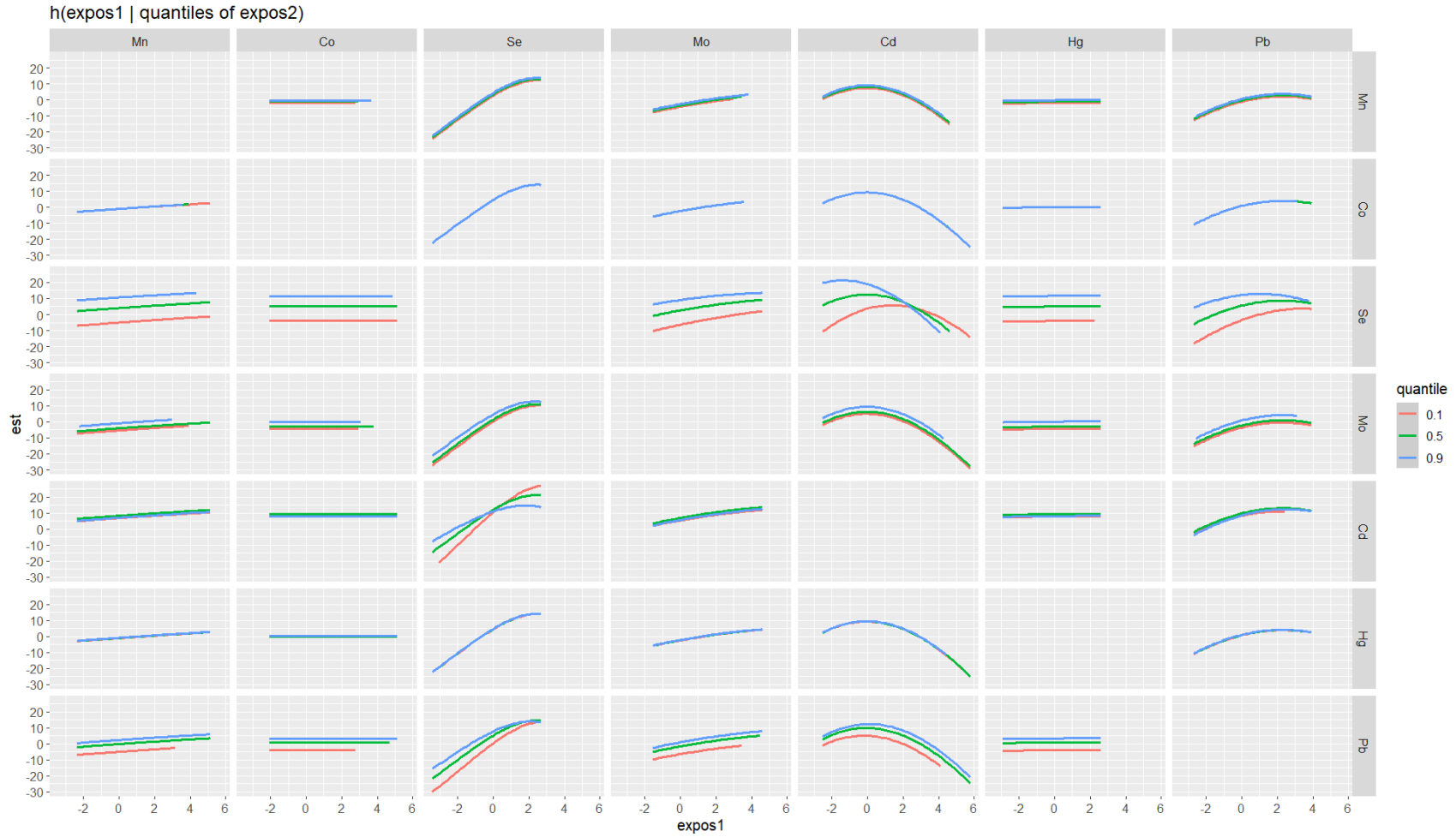
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



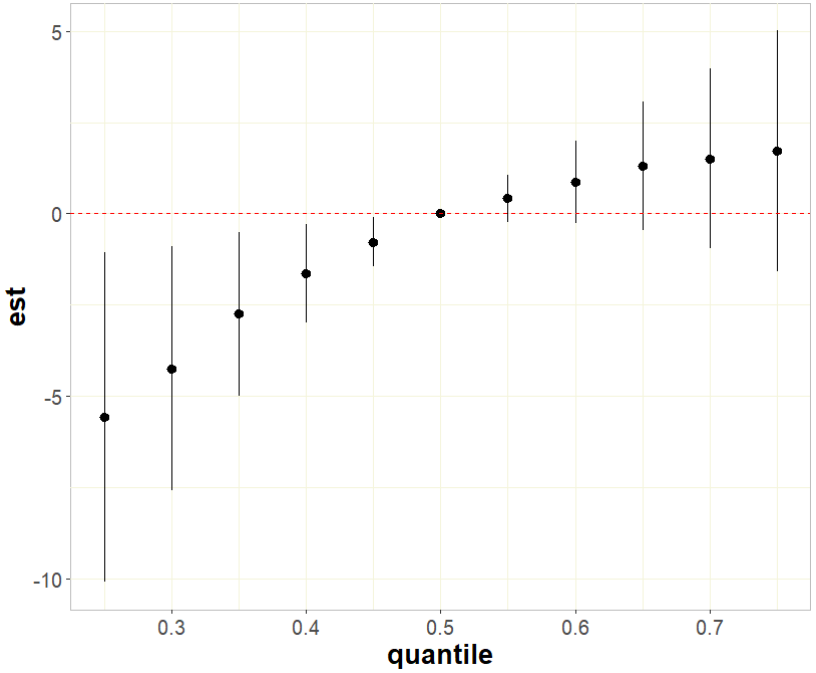
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



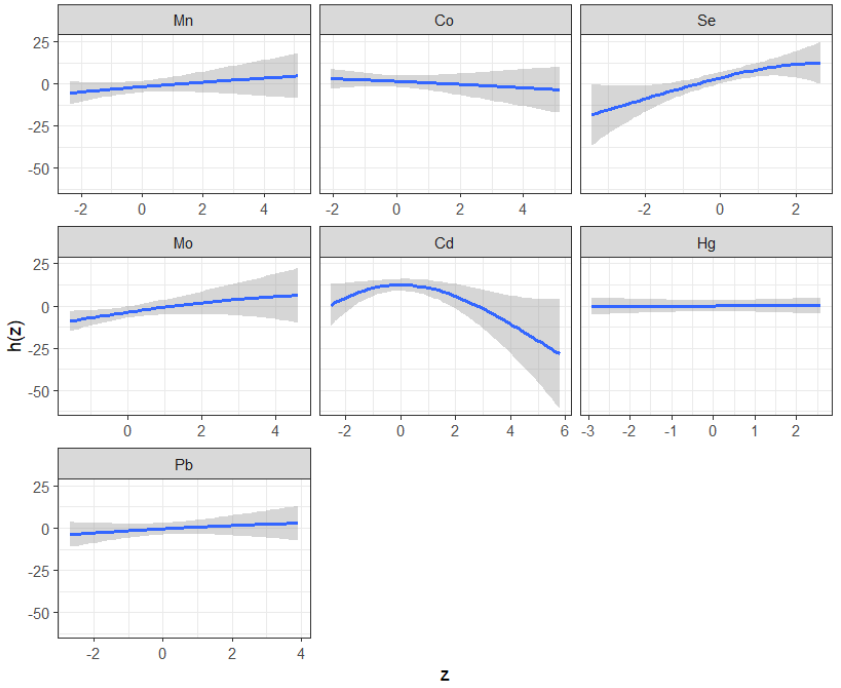
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Figure S9. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for red meat consumption (n=291)

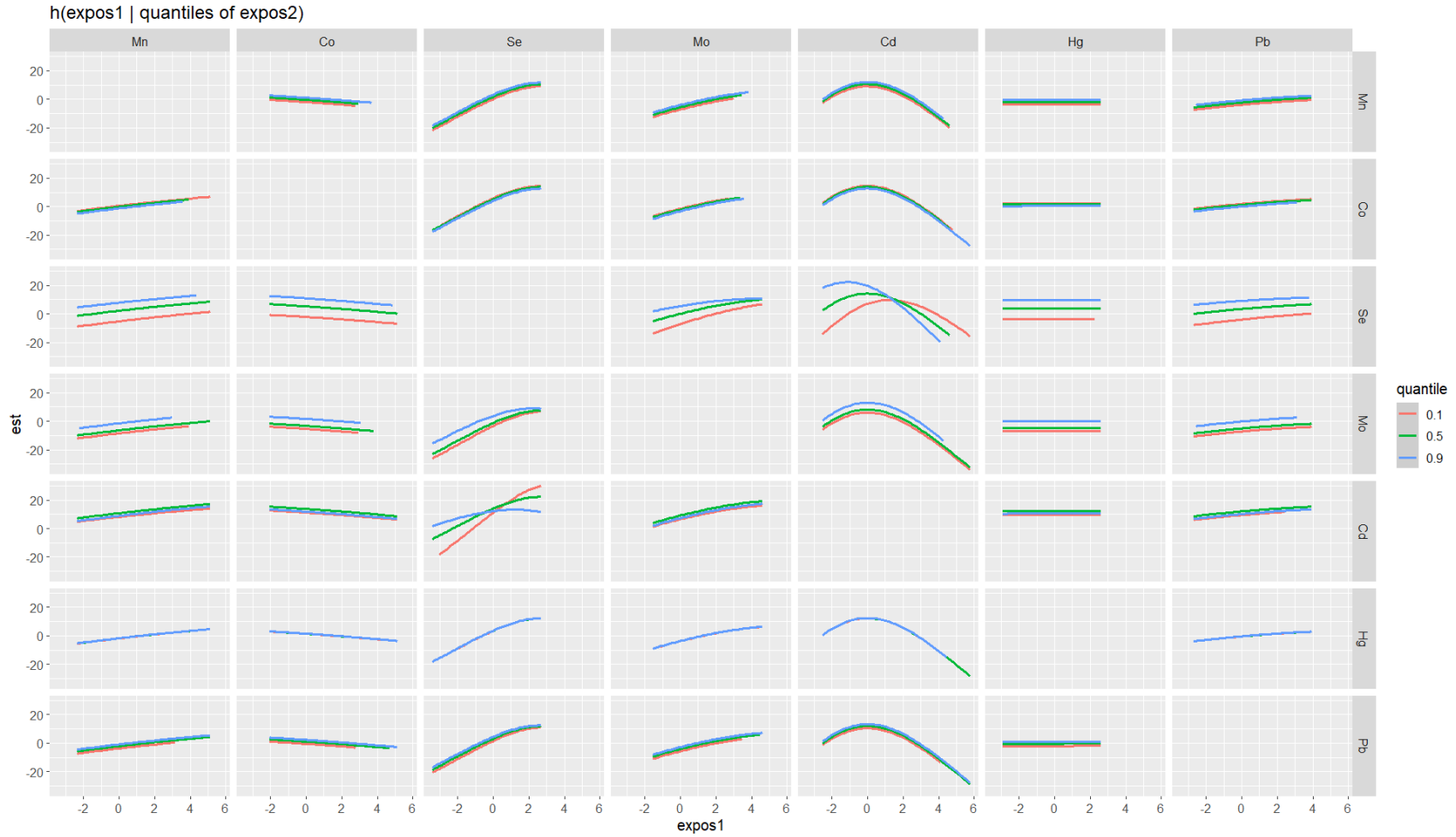
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



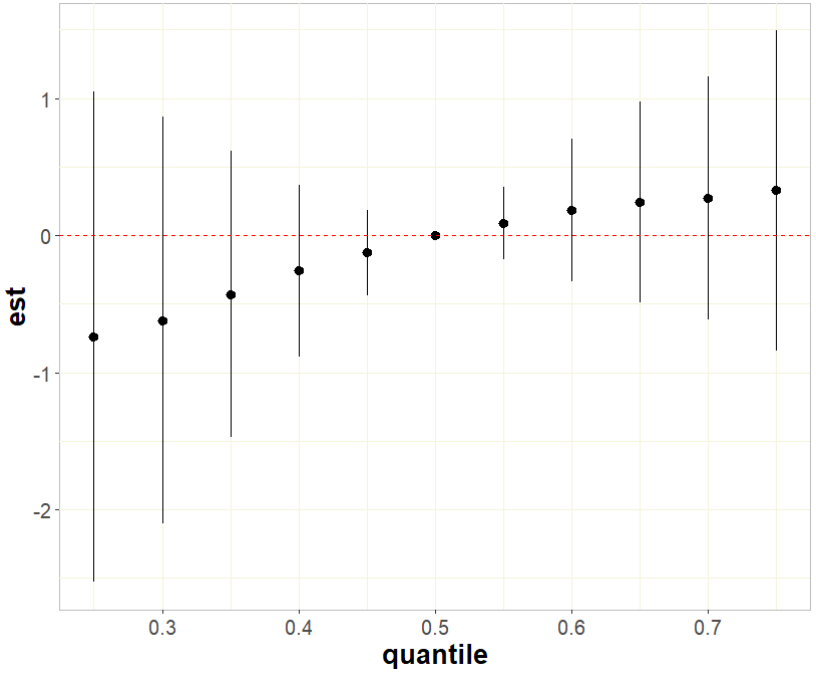
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



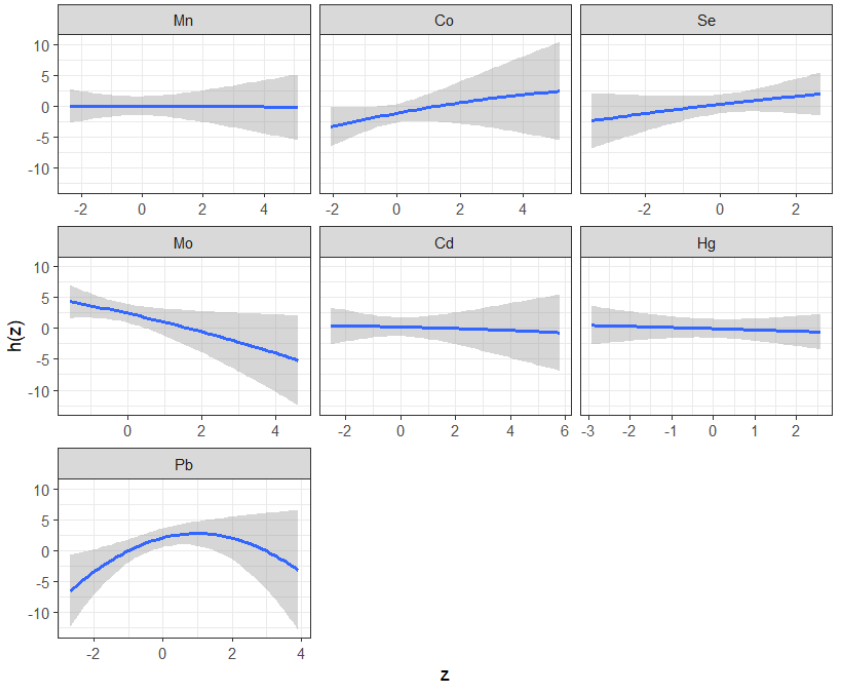
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Figure S10. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for red meat consumption (n=291)

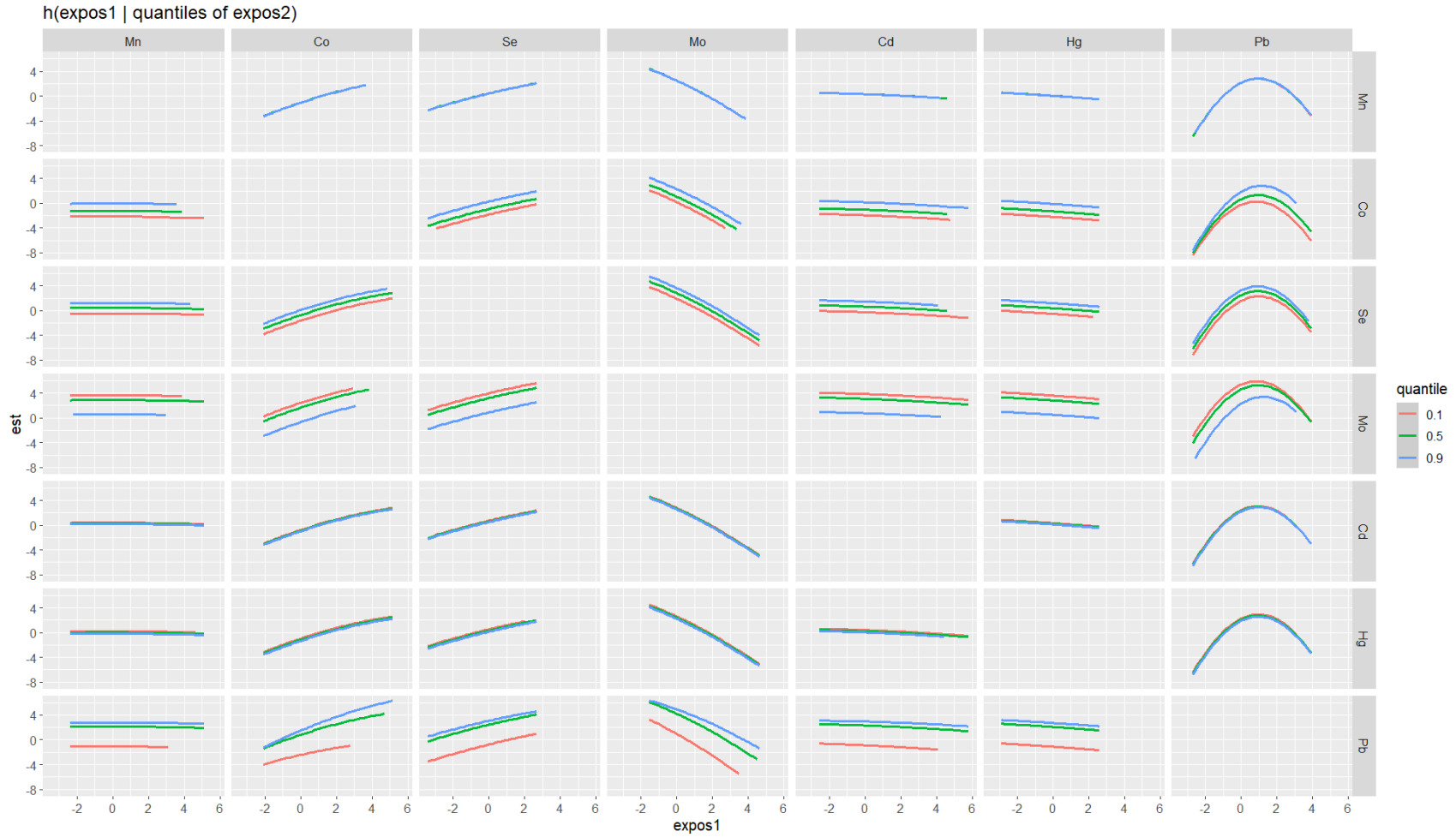
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



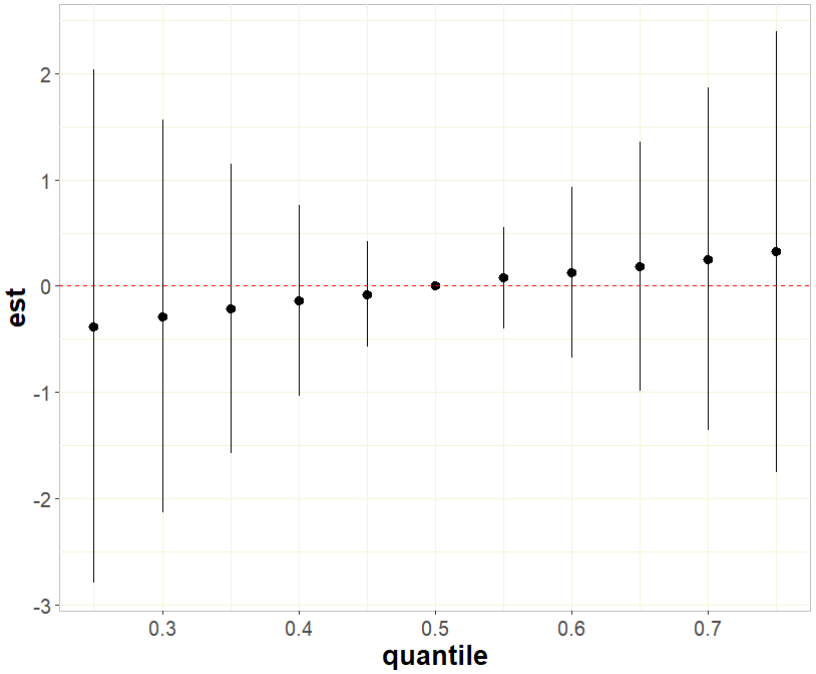
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



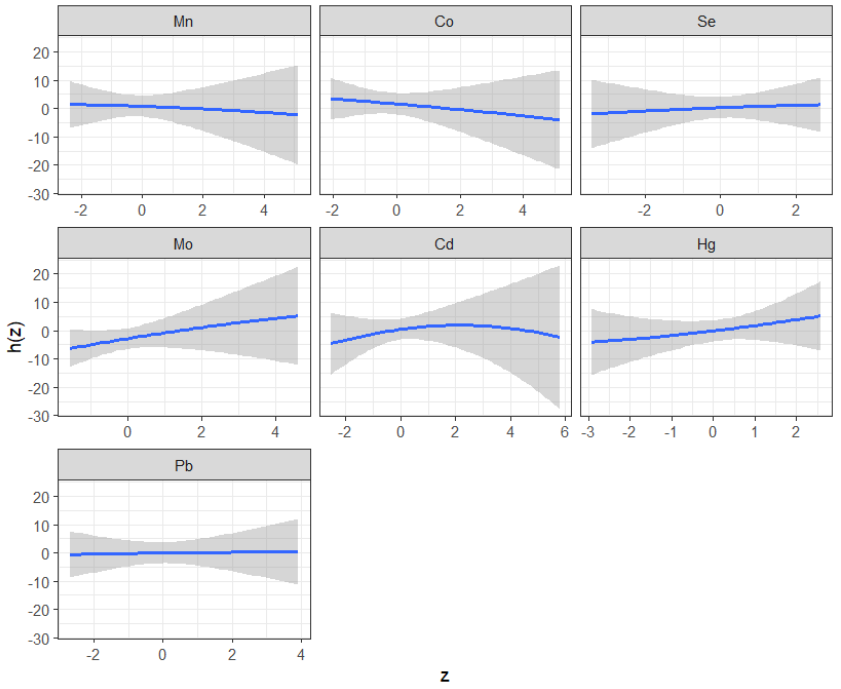
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Figure S11. Joint associations of the metals with triglycerides at 4 years of age estimated by BKMR additionally adjusting for red meat consumption (n=291)

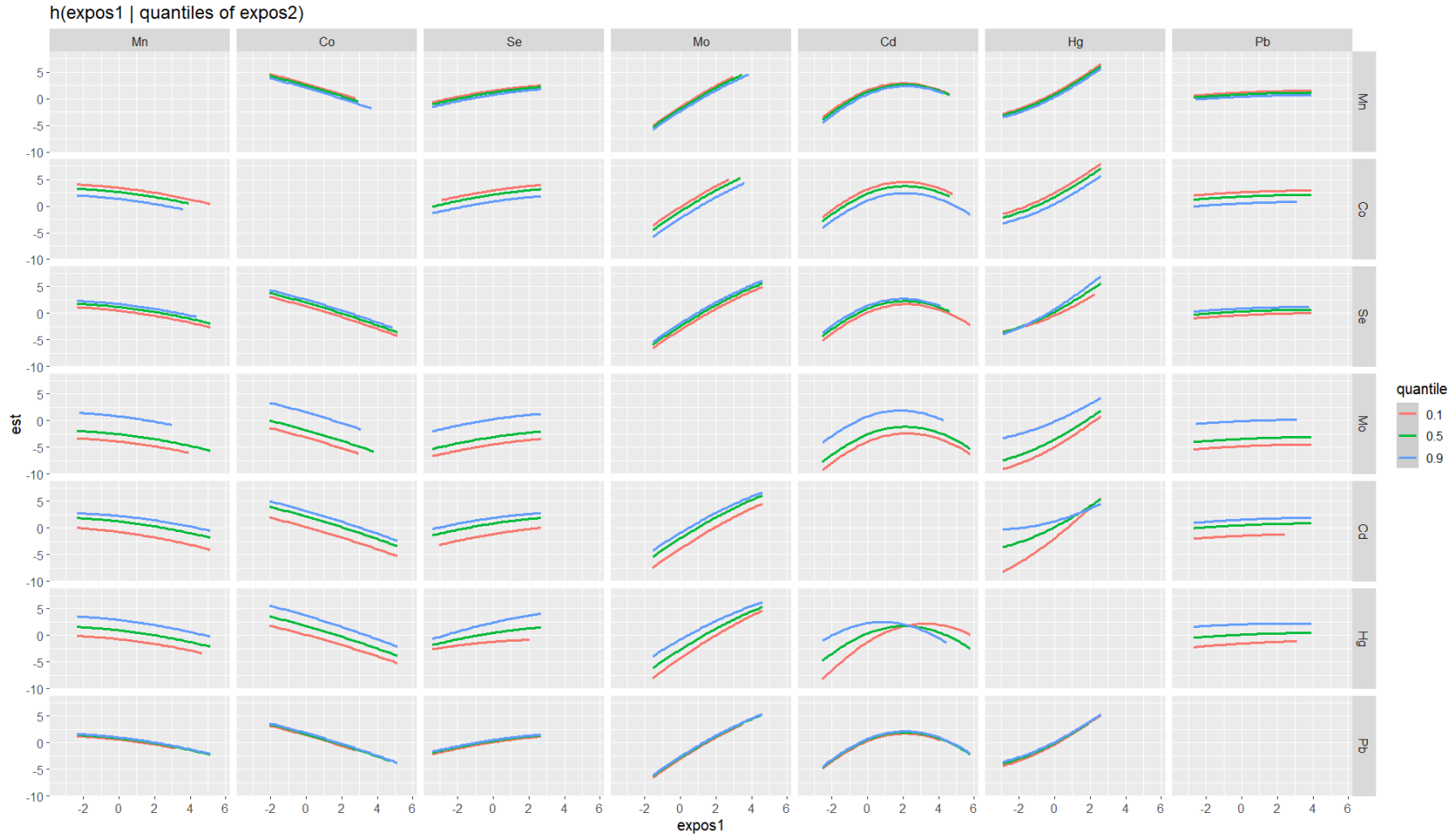
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and red meat consumption at 4 years of age.

Table S7. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations and holding all other metals in the mixture at their median values, estimated by BKMR additionally adjusting for egg intake (n=291)

Lipid measure	**75th vs. 25th percentiles**
Total cholesterol (mg/dL)	9.18 (1.23, 17.13)
Low-density lipoprotein cholesterol (mg/dL)	7.45 (1.29, 13.62)
High-density lipoprotein cholesterol (mg/dL)	1.01 (-1.78, 3.80)
Triglycerides (mg/dL)	0.52 (-2.94, 3.97)

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Table S8. Posterior inclusion probabilities (PIP) and effect estimates for each metal, holding all other metals in the mixture constant at their median values, in association with lipid measures at 4 years of age, estimated by BKMR additionally adjusting for egg intake (n=291)

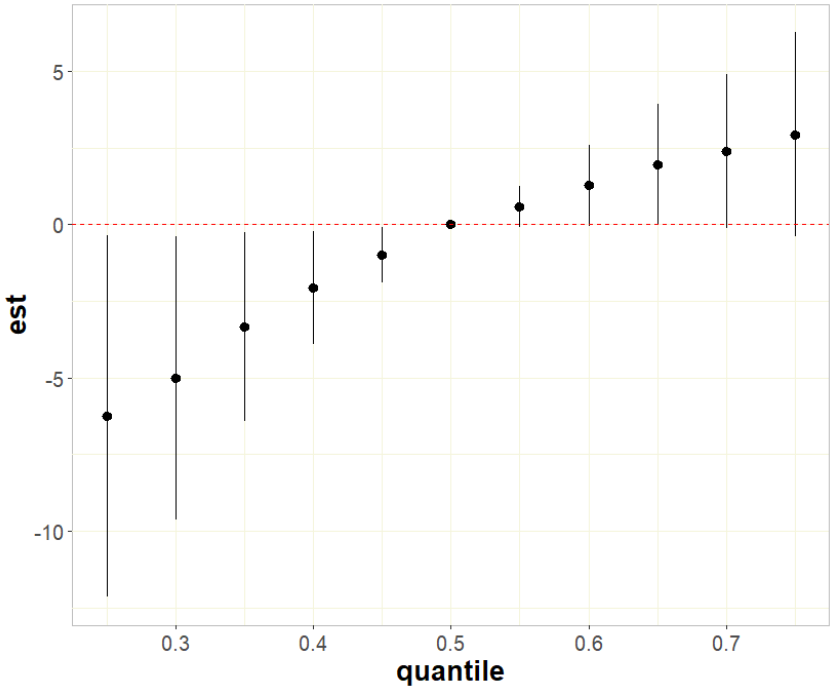
Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]
Mn	0.01	0.03 (-0.76, 0.82)	0.02	0.04 (-0.87, 0.95)	0.02	<-0.01 (-0.29, 0.29)	0.02	<-0.01 (-0.74, 0.73)
Co	0.02	0.02 (-0.68, 0.72)	0.01	-0.01 (-0.55, 0.53)	0.04	-0.02 (-0.55, 0.51)	0.06	-0.02 (-1.14, 1.11)
Se	0.96	8.94 (2.02, 15.86)	0.98	8.75 (2.99, 14.51)	0.06	0.07 (-0.68, 0.83)	0.04	0.07 (-1.14, 1.28)
Mo	0.03	0.08 (-1.19, 1.34)	0.18	0.69 (-2.68, 4.06)	0.10	-0.18 (-1.46, 1.10)	0.07	0.15 (-1.58, 1.89)
Cd	0.31	0.80 (-2.96, 4.57)	0.73	1.84 (-2.55, 6.23)	0.01	<-0.01 (-0.16, 0.16)	0.09	0.25 (-1.88, 2.39)
Hg	<0.01	0 (0, 0)	0.01	<-0.01 (-0.43, 0.43)	0.01	<-0.01 (-0.21, 0.21)	0.07	0.22 (-1.99, 2.44)
Pb	0.25	1.55 (-4.35, 7.45)	0.03	0.06 (-1.07, 1.20)	0.49	0.97 (-1.54, 3.48)	0.03	0.01 (-0.99, 1.01)

[a] The difference in the lipid measure when setting each metal component to its 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

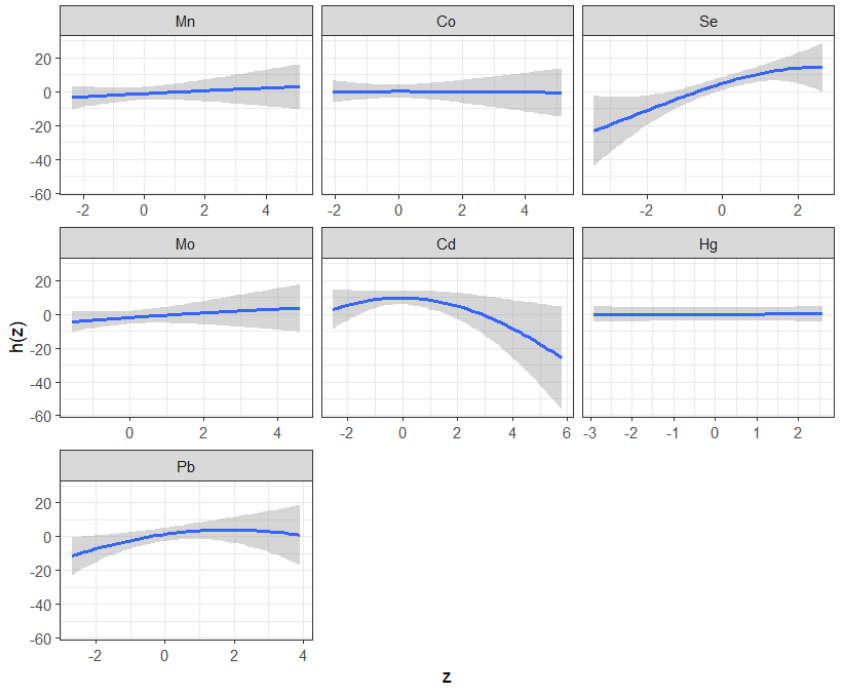
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Figure S12. Joint associations of the metals with total cholesterol at 4 years of age estimated by BKMR additionally adjusting for egg intake (n=291)

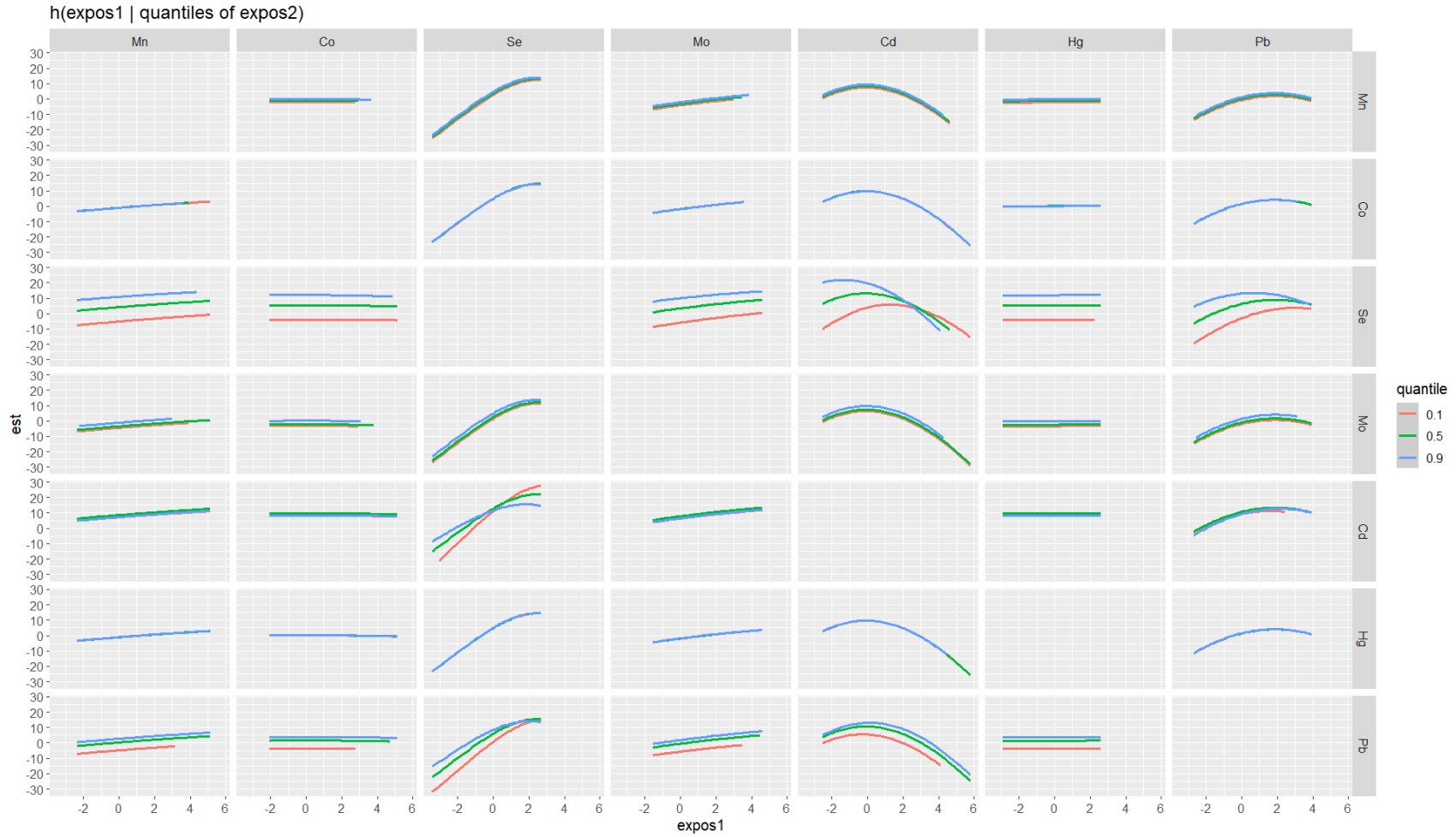
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



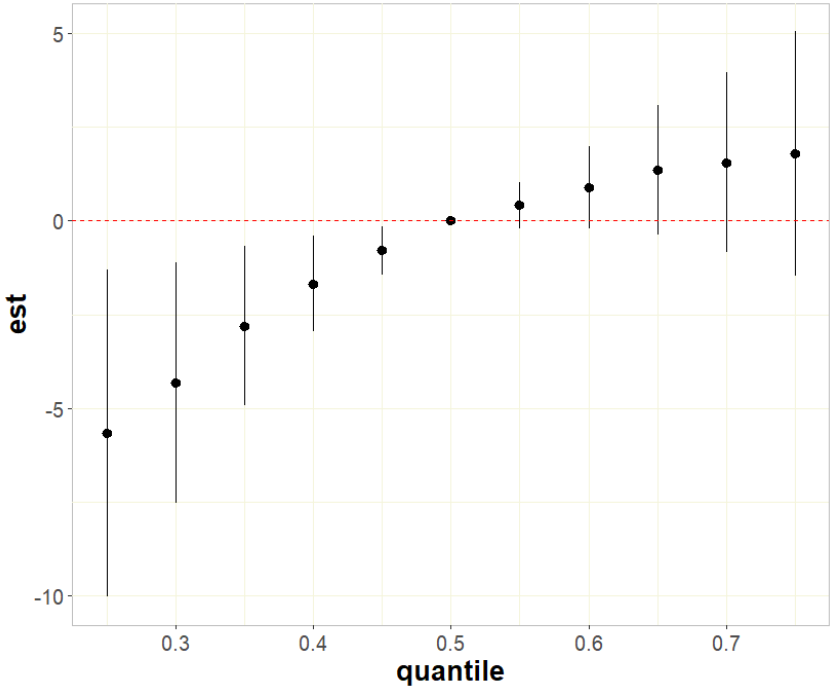
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



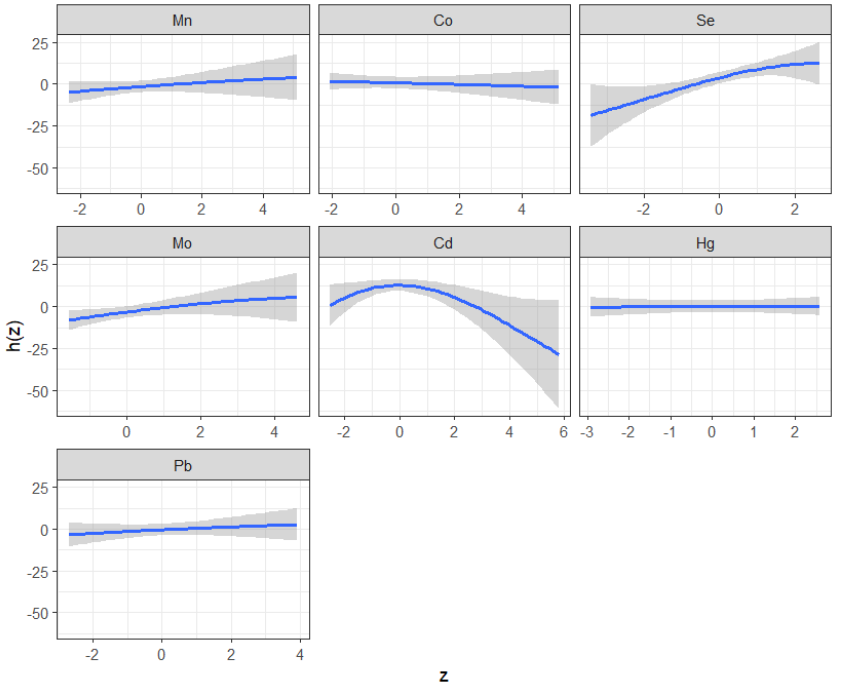
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Figure S13. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for egg intake (n=291)

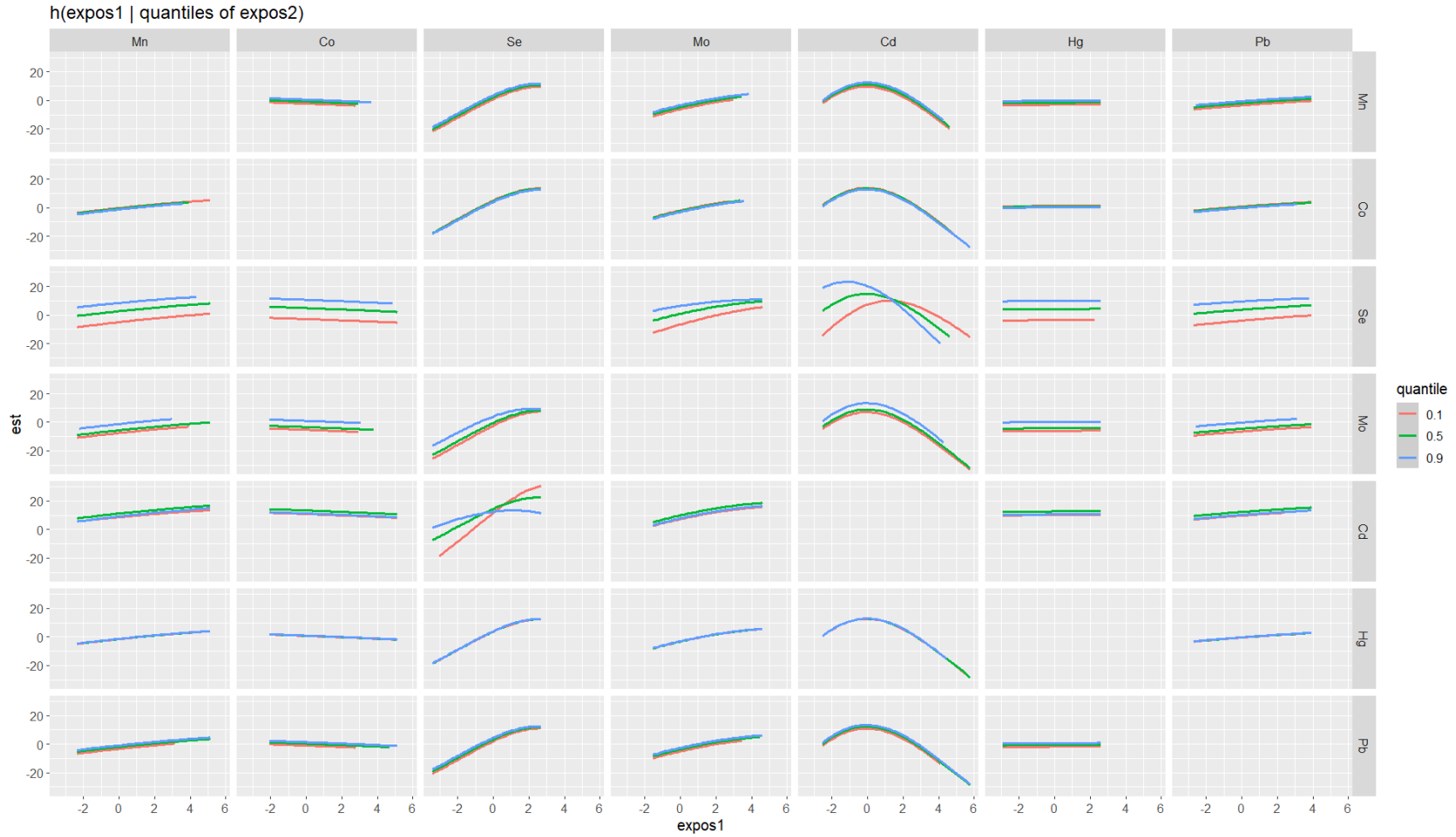
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



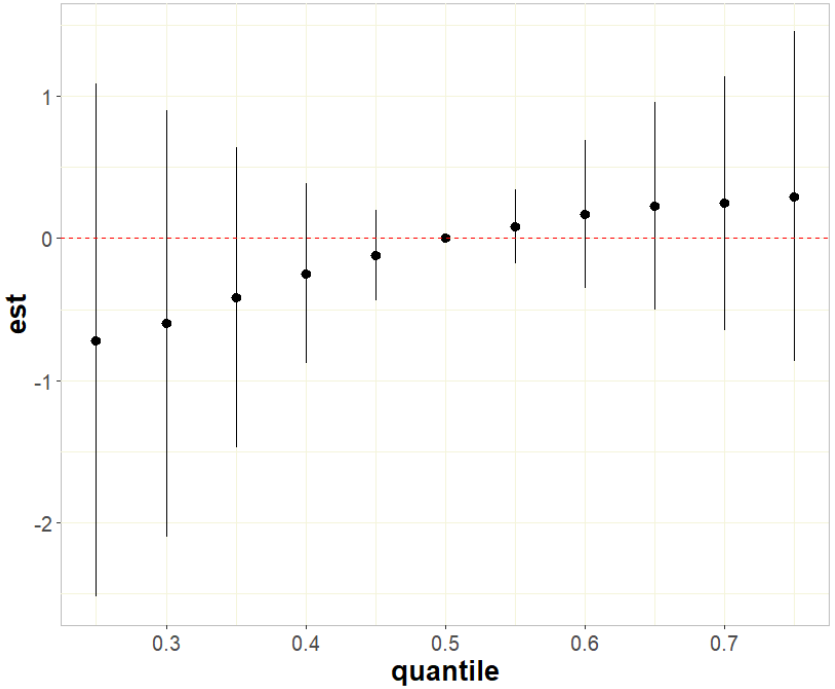
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



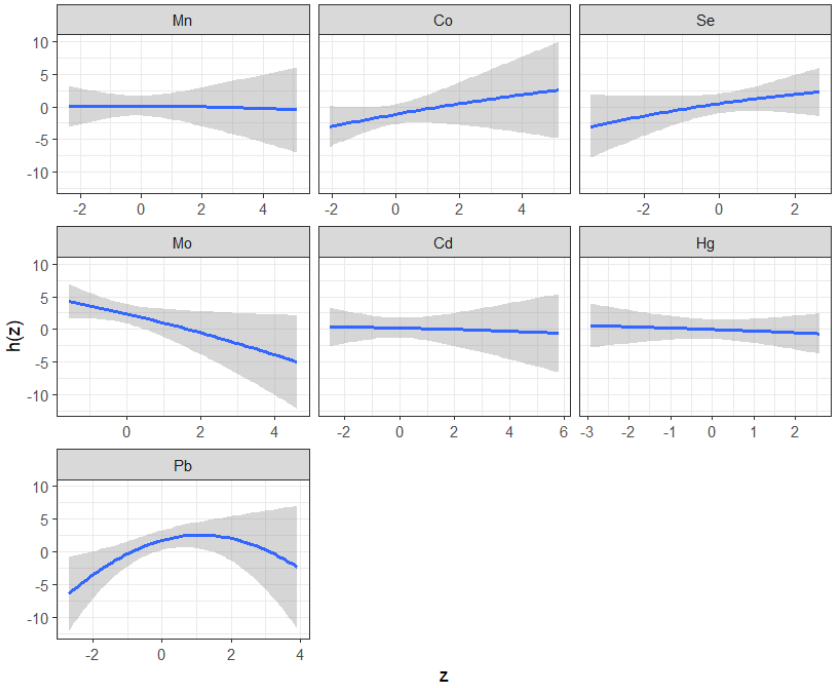
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Figure S14. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for egg intake (n=291)

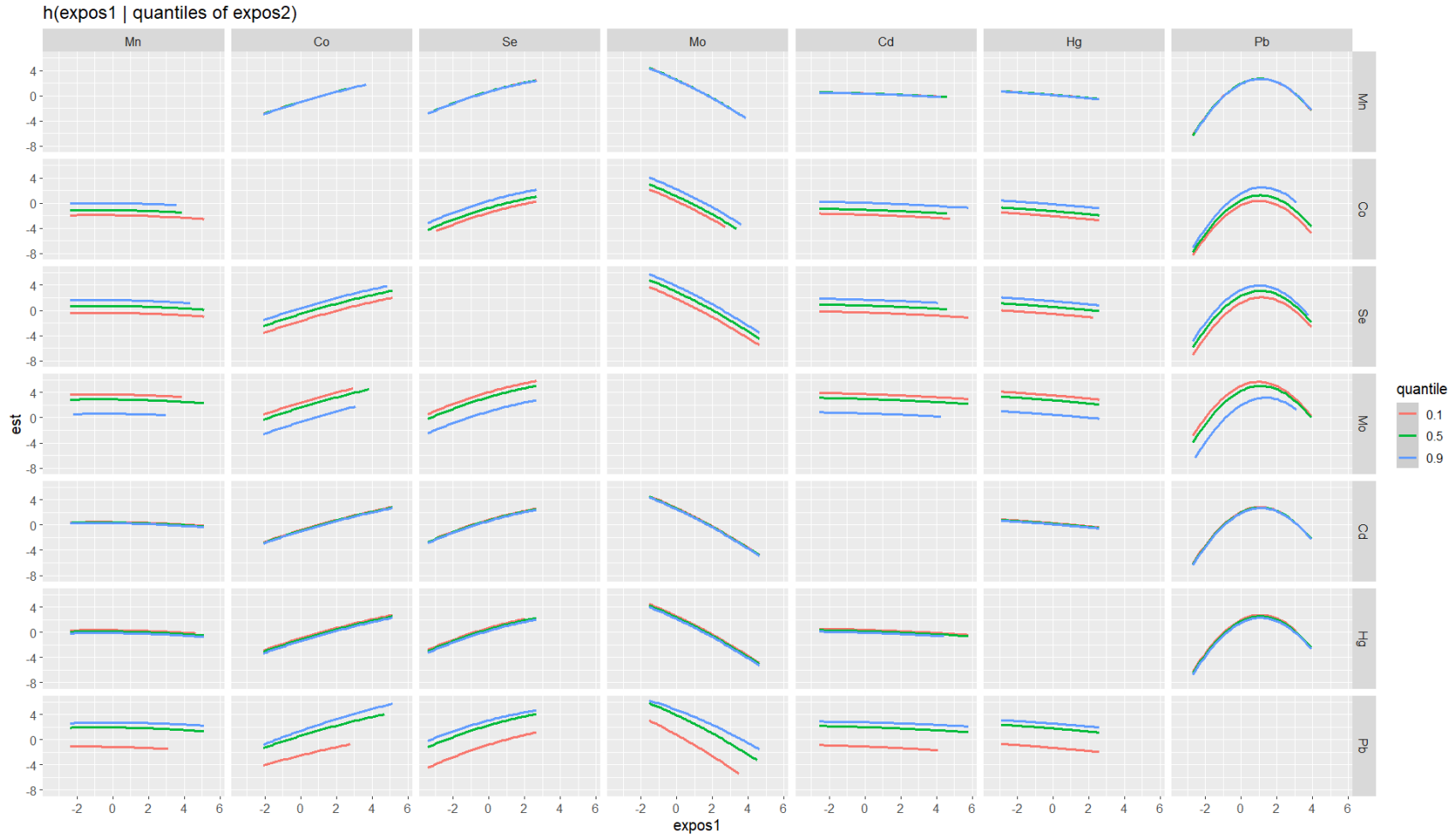
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



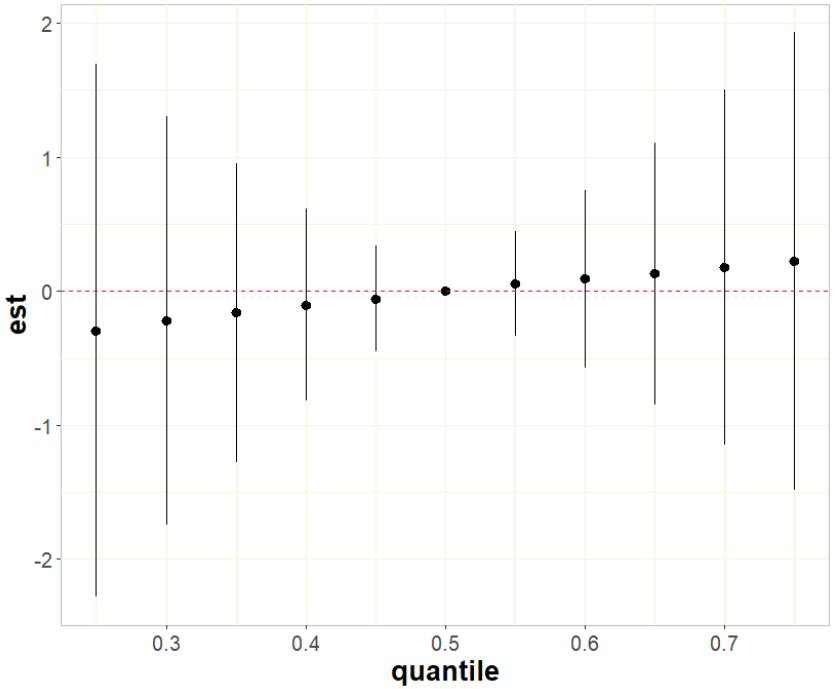
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



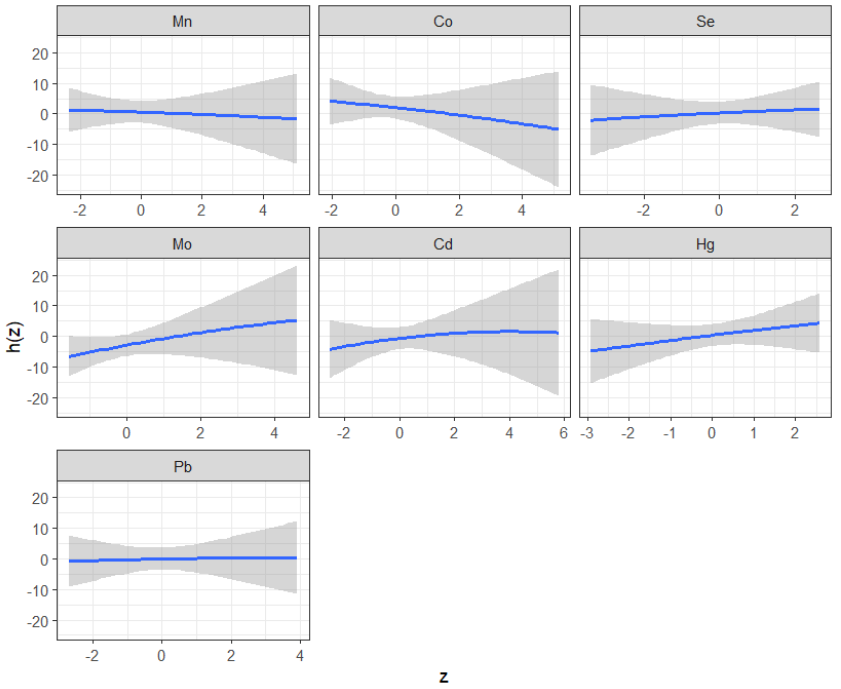
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Figure S15. Joint associations of the metals with triglycerides at 4 years of age estimated by BKMR additionally adjusting for egg intake (n=291)

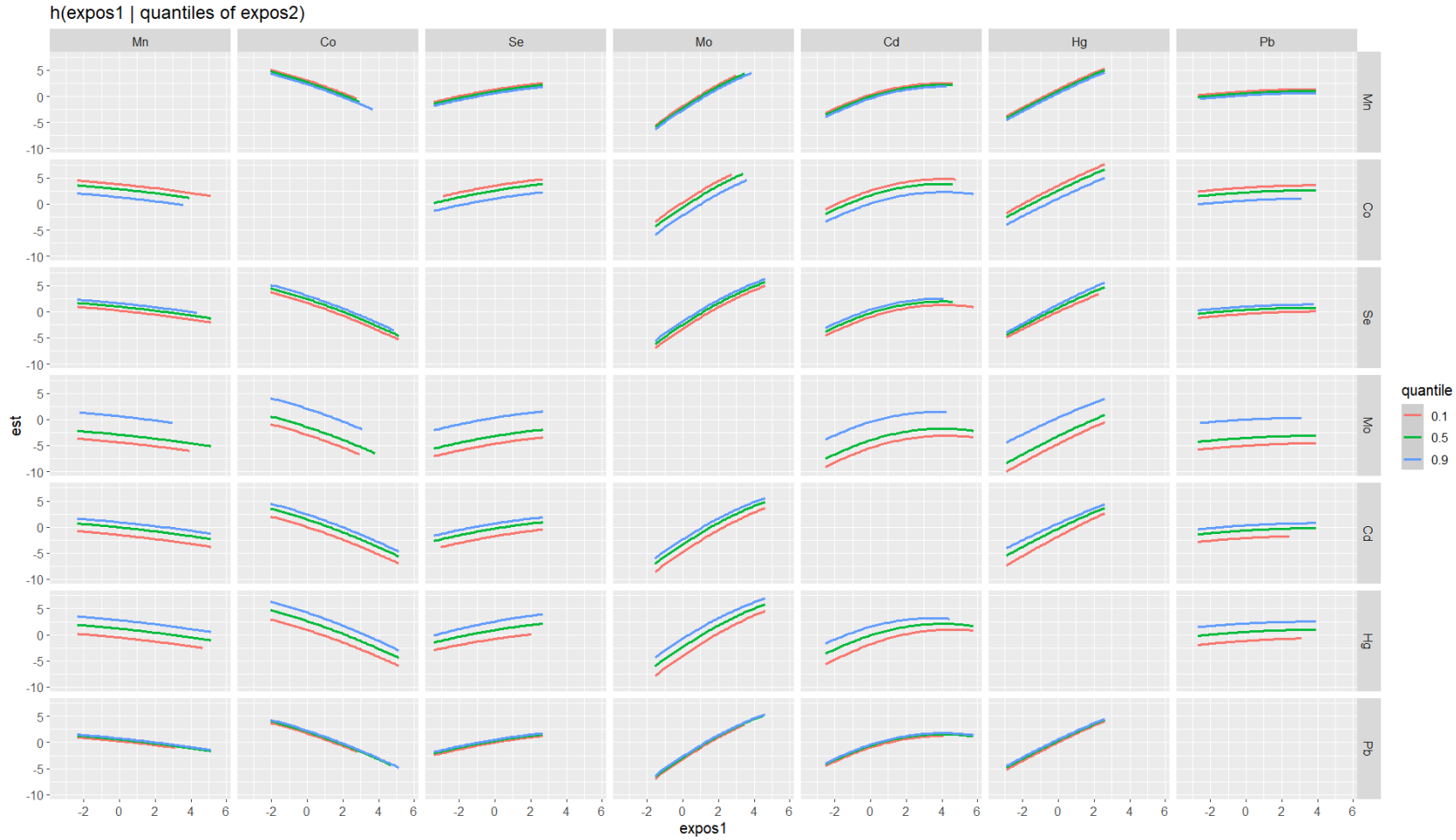
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and egg intake at 4 years of age.

Table S9. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations and holding all other metals in the mixture at their median values, estimated by BKMR additionally adjusting for dairy intake (n=291)

Lipid measure	**75th vs. 25th percentiles**
Total cholesterol (mg/dL)	9.60 (0.50, 18.70)
Low-density lipoprotein cholesterol (mg/dL)	8.44 (1.60, 15.29)
High-density lipoprotein cholesterol (mg/dL)	1.21 (-1.60, 4.02)
Triglycerides (mg/dL)	0.59 (-3.39, 4.57)

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Table S10. Posterior inclusion probabilities (PIP) and effect estimates for each metal, holding all other metals in the mixture constant at their median values, in association with lipid measures at 4 years of age, estimated by BKMR additionally adjusting for dairy intake (n=291)

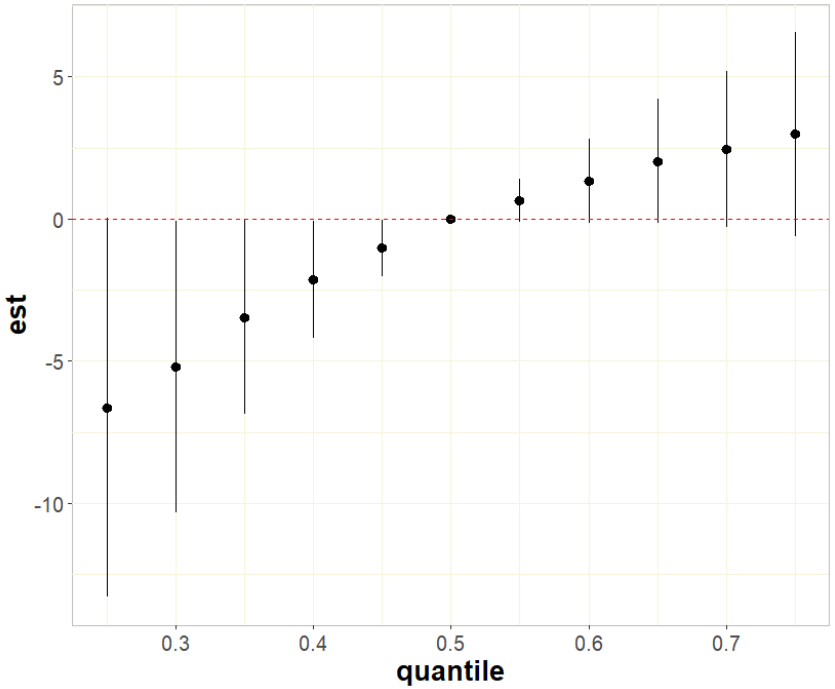
Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]
Mn	0.02	0.04 (-0.89, 0.97)	0.06	0.08 (-1.20, 1.35)	<0.01	<-0.01 (-0.13, 0.13)	0.05	0.02 (-1.00, 1.03)
Co	0.02	0.03 (-0.84, 0.89)	0.01	<-0.01 (-0.46, 0.45)	0.07	-0.01 (-0.64, 0.62)	0.05	0.02 (-1.27, 1.31)
Se	0.94	9.18 (1.58, 16.78)	0.98	9.07 (3.21, 14.93)	0.04	0.04 (-0.46, 0.54)	0.04	0.06 (-1.35, 1.47)
Mo	0.04	0.10 (-1.34, 1.55)	0.26	1.03 (-3.11, 5.17)	0.09	-0.19 (-1.55, 1.18)	0.07	0.21 (-1.79, 2.21)
Cd	0.52	1.96 (-3.39, 7.31)	0.85	2.99 (-1.95, 7.93)	<0.01	<-0.01 (-0.12, 0.12)	0.08	0.28 (-2.15, 2.71)
Hg	0.01	0.01 (-0.53, 0.54)	0.01	<0.01 (-0.49, 0.50)	0.01	<-0.01 (-0.18, 0.18)	0.13	0.33 (-2.35, 3.02)
Pb	0.23	1.17 (-3.91, 6.25)	0.03	0.08 (-1.19, 1.35)	0.54	1.09 (-1.50, 3.68)	0.04	<0.01 (-1.13, 1.13)

[a] The difference in the lipid measure when setting each metal component to its 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

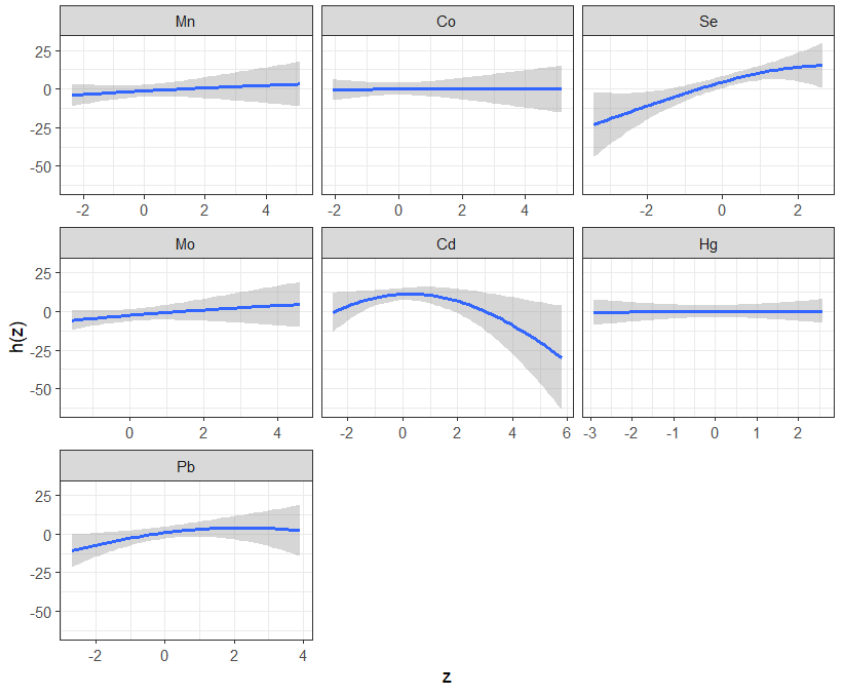
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Figure S16. Joint associations of the metals with total cholesterol at 4 years of age estimated by BKMR additionally adjusting for dairy intake (n=291)

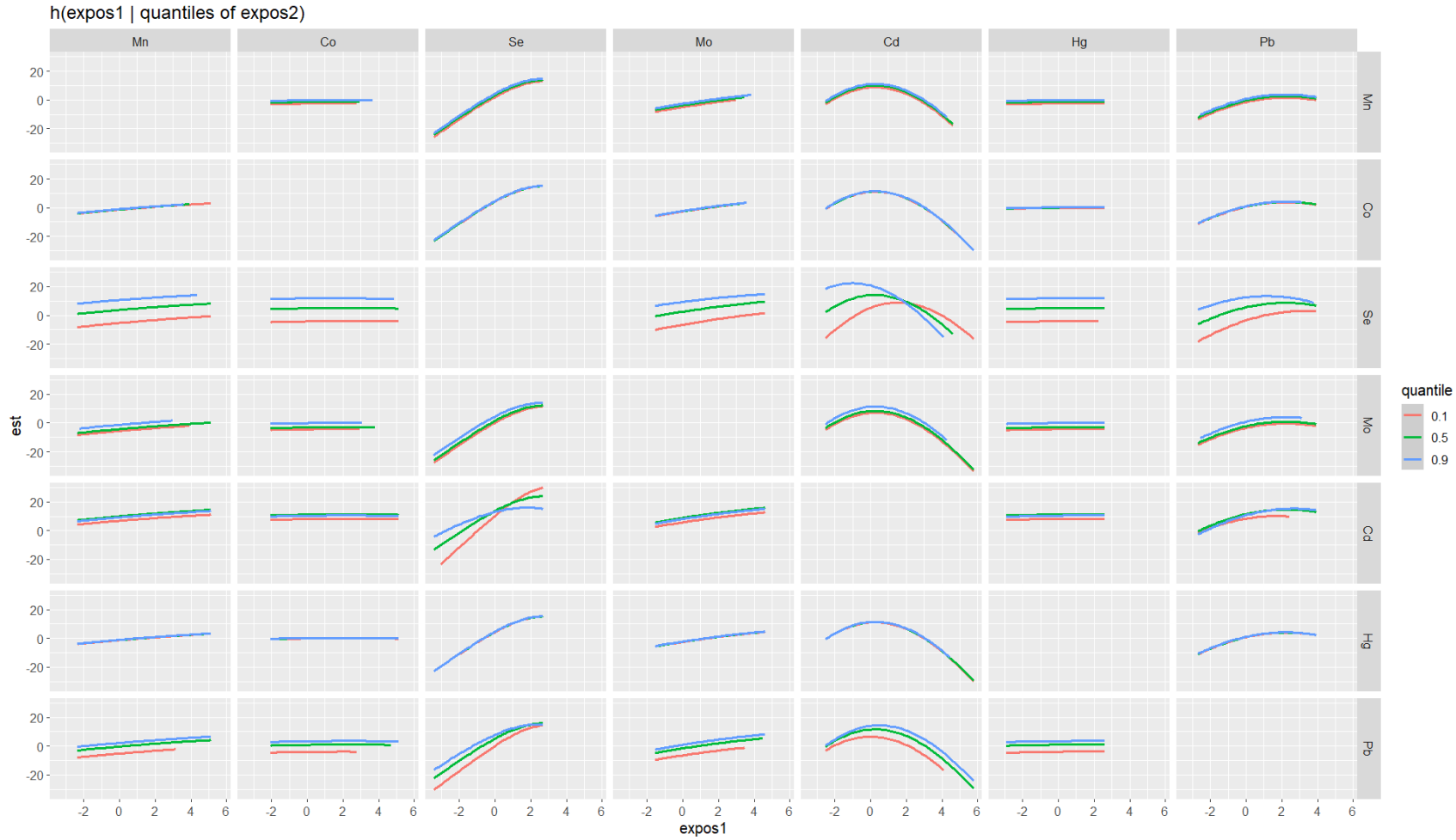
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



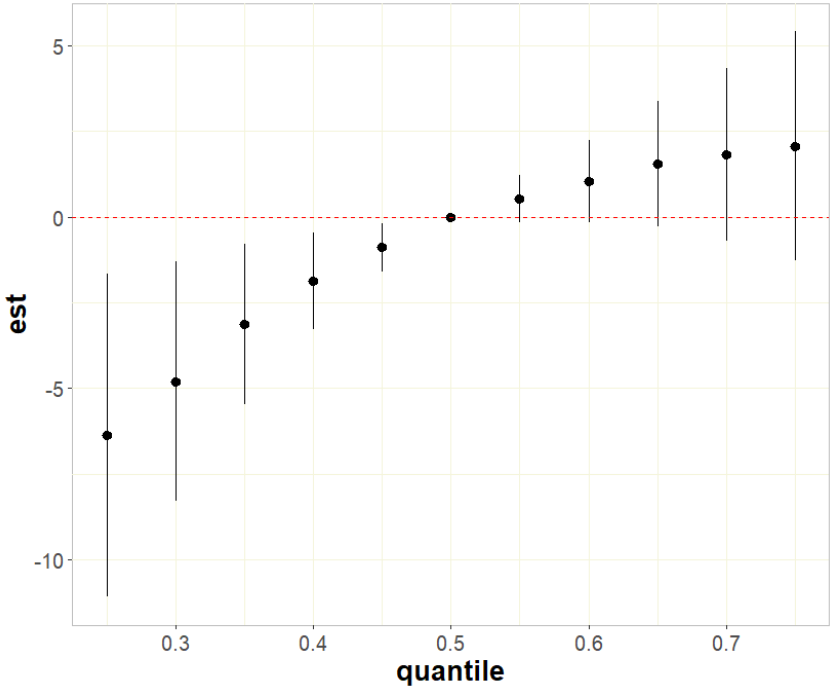
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



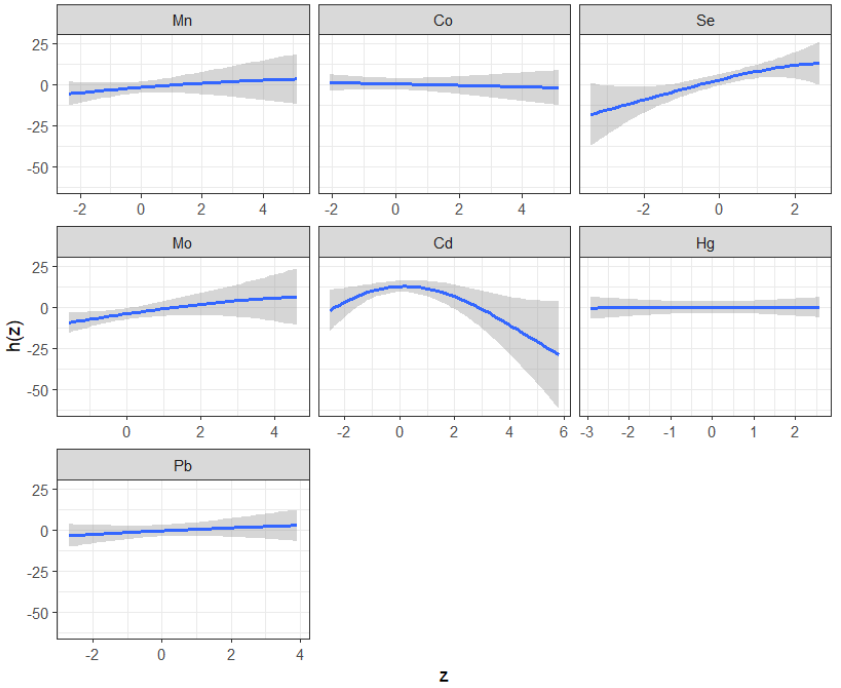
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Figure S17. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for dairy intake (n=291)

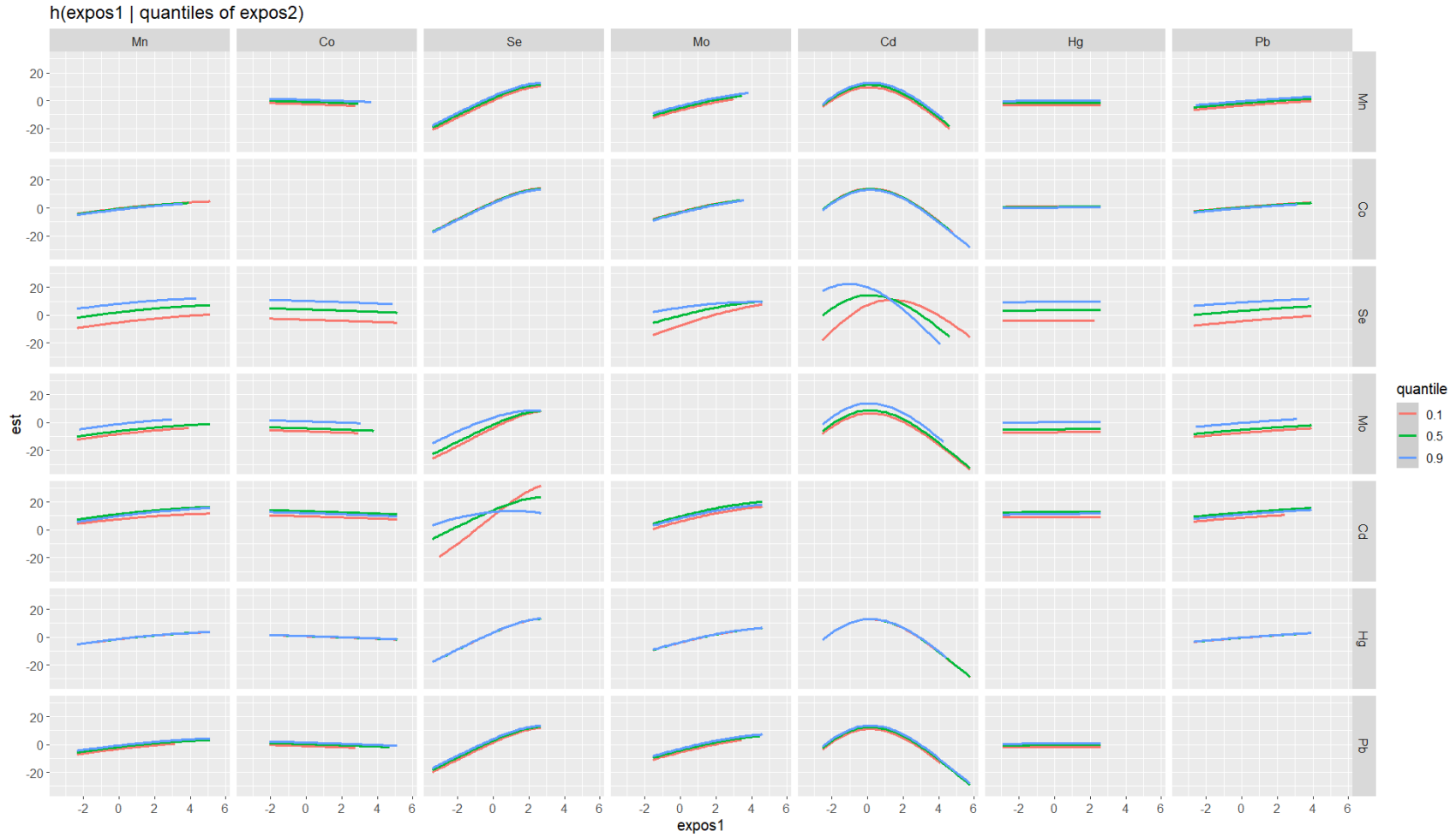
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



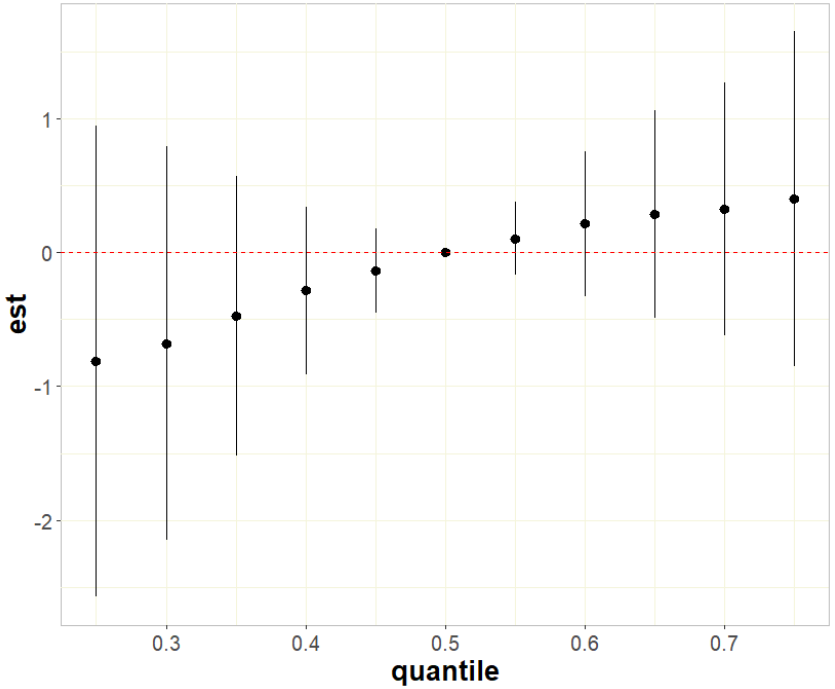
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



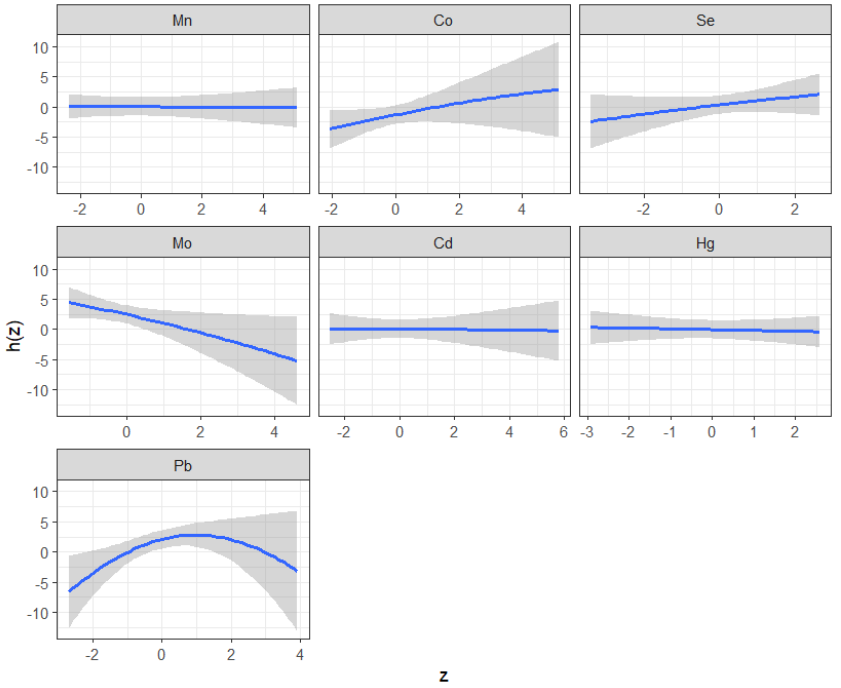
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Figure S18. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for dairy intake (n=291)

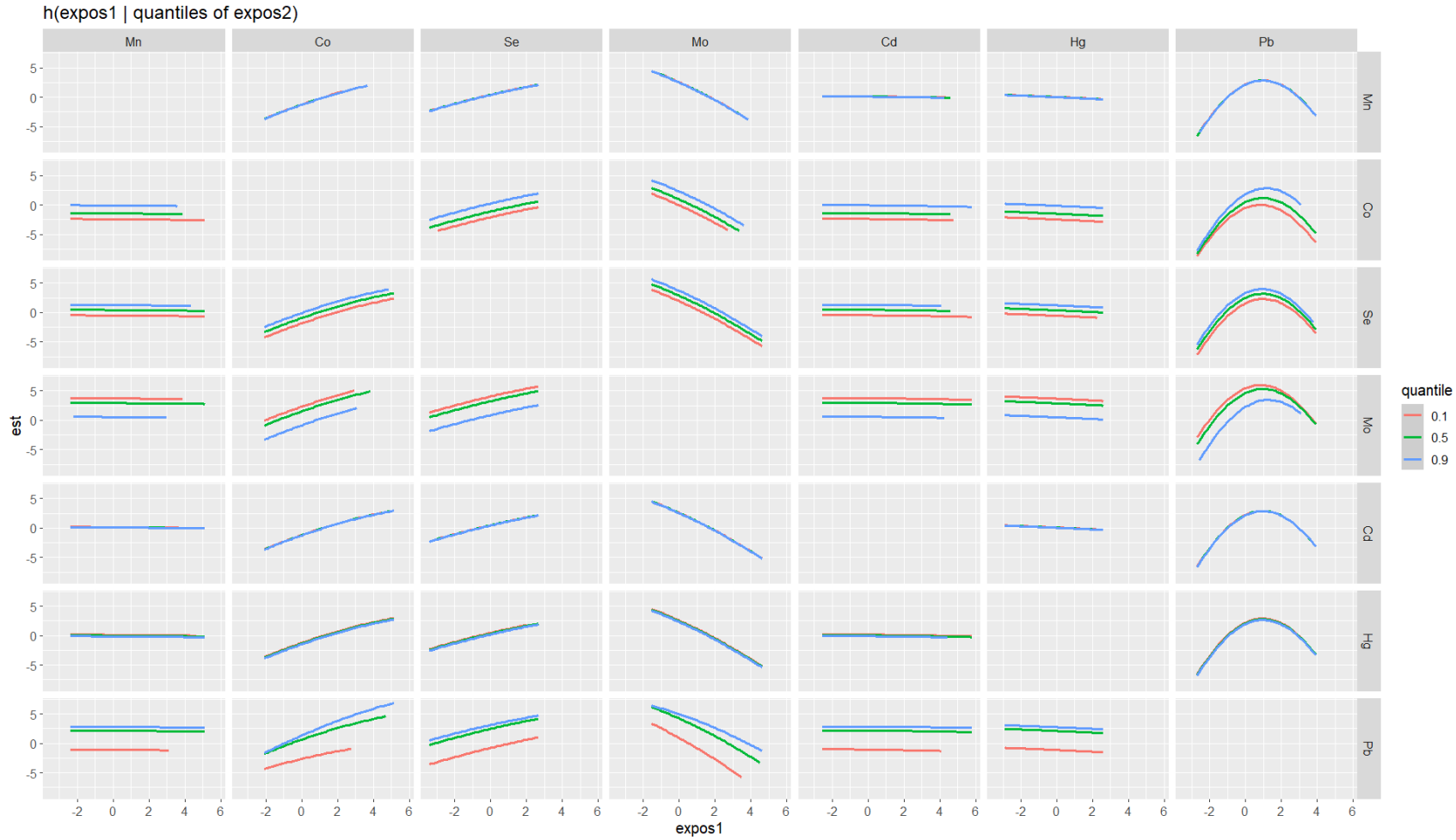
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



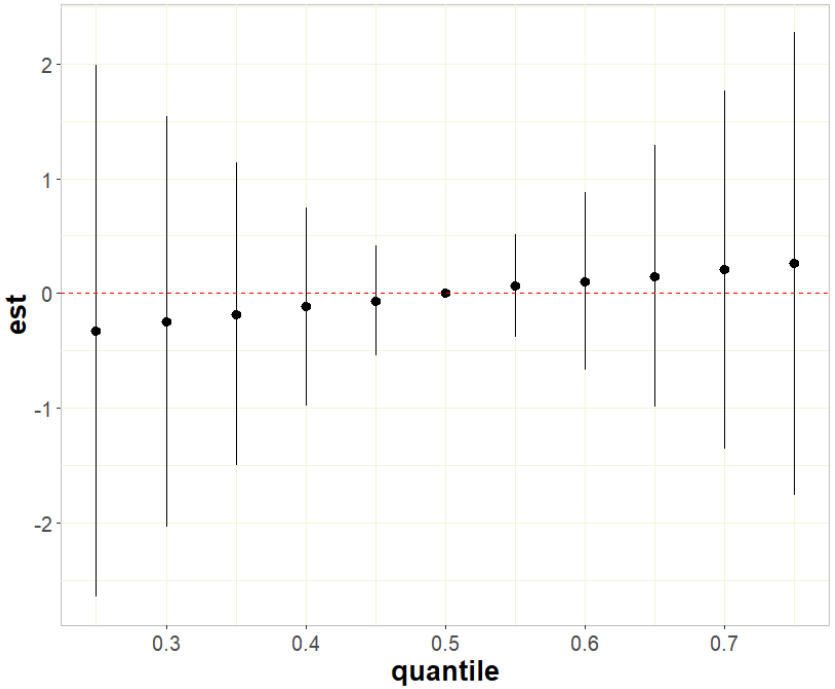
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



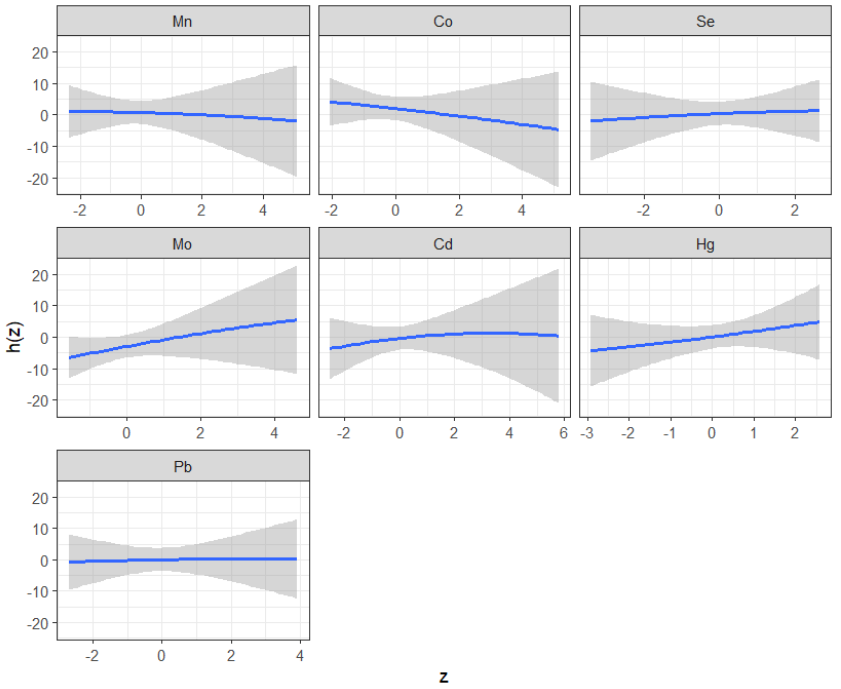
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Figure S19. Joint associations of the metals with triglycerides at 4 years of age estimated by BKMR additionally adjusting for dairy intake (n=291)

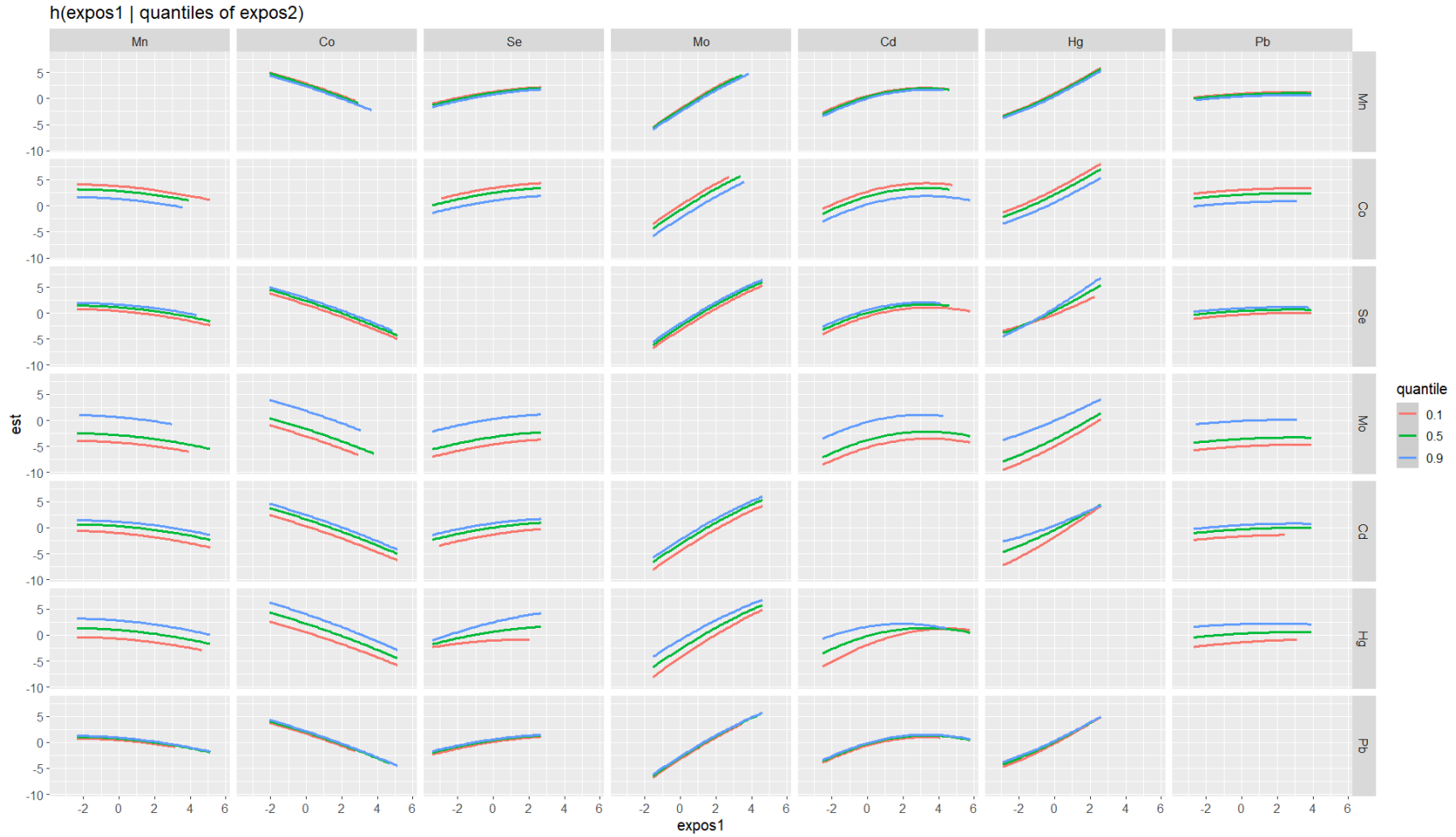
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and dairy intake at 4 years of age.

Table S11. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations and holding all other metals in the mixture at their median values, estimated by BKMR additionally adjusting for supplement use (n=291)

Lipid measure	**75th vs. 25th percentiles**
Total cholesterol (mg/dL)	8.24 (-0.03, 16.51)
Low-density lipoprotein cholesterol (mg/dL)	7.14 (0.27, 14.01)
High-density lipoprotein cholesterol (mg/dL)	1.22 (-1.51, 3.95)
Triglycerides (mg/dL)	0.58 (-3.79, 4.95)

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Table S12. Posterior inclusion probabilities (PIP) and effect estimates for each metal, holding all other metals in the mixture constant at their median values, in association with lipid measures at 4 years of age, estimated by BKMR additionally adjusting for supplement use (n=291)

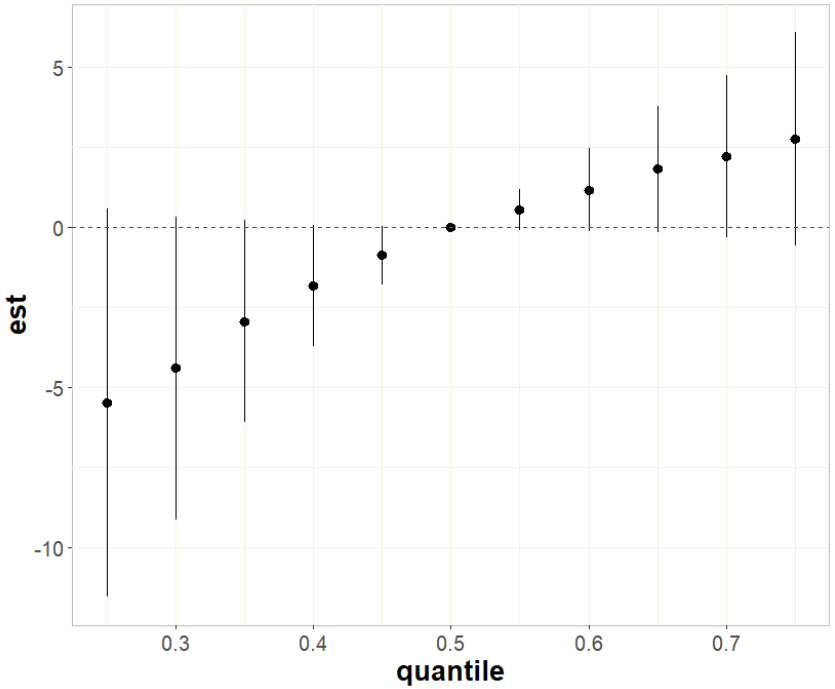
Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]	PIP	75th vs. 25th percentiles[a]
Mn	0.01	0.02 (-0.62, 0.65)	0.05	0.09 (-1.20, 1.38)	0.01	<0.01 (-0.16, 0.16)	0.06	-0.06 (-1.84, 1.71)
Co	<0.01	<-0.01 (-0.29, 0.29)	0.03	-0.02 (-0.83, 0.80)	0.04	-0.02 (-0.55, 0.51)	0.04	-0.01 (-1.10, 1.07)
Se	0.91	8.21 (0.55, 15.87)	0.93	8.25 (1.63, 14.87)	0.03	0.03 (-0.46, 0.52)	0.04	0.02 (-1.08, 1.13)
Mo	0.04	0.11 (-1.38, 1.60)	0.16	0.67 (-2.76, 4.10)	0.07	-0.15 (-1.36, 1.07)	0.06	0.20 (-1.80, 2.20)
Cd	0.28	0.80 (-2.92, 4.53)	0.73	1.83 (-2.54, 6.20)	0.02	<-0.01 (-0.27, 0.26)	0.15	0.50 (-2.81, 3.81)
Hg	<0.01	0 (0, 0)	<0.01	<0.01 (-0.24, 0.25)	0.03	-0.01 (-0.33, 0.31)	0.17	0.52 (-3.07, 4.10)
Pb	0.17	1.01 (-4.07, 6.09)	0.04	0.13 (-1.48, 1.75)	0.57	1.18 (-1.43, 3.79)	0.06	0.02 (-1.42, 1.46)

[a] The difference in the lipid measure when setting each metal component to its 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

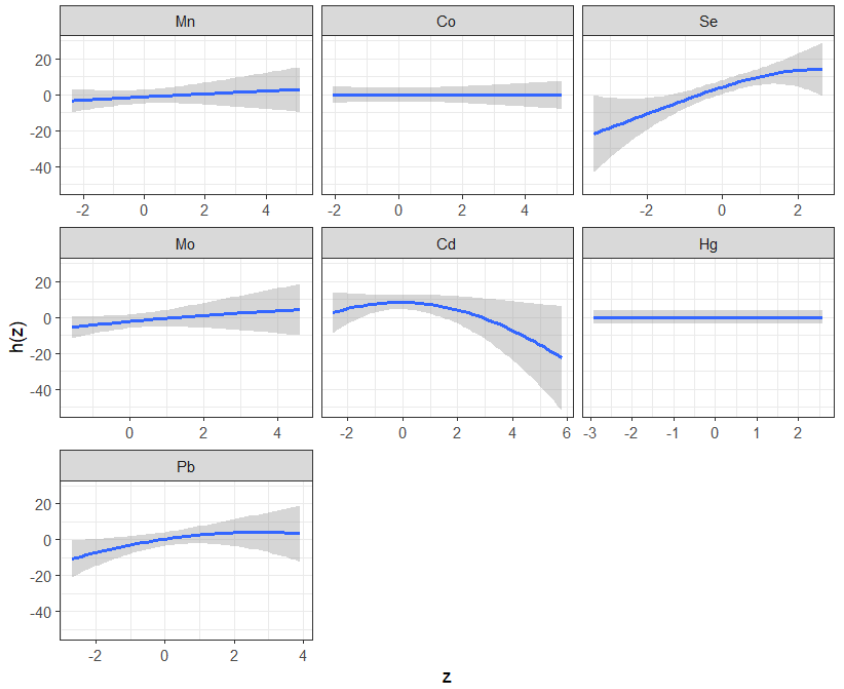
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Figure S20. Joint associations of the metals with total cholesterol at 4 years of age estimated by BKMR additionally adjusting for supplement use (n=291)

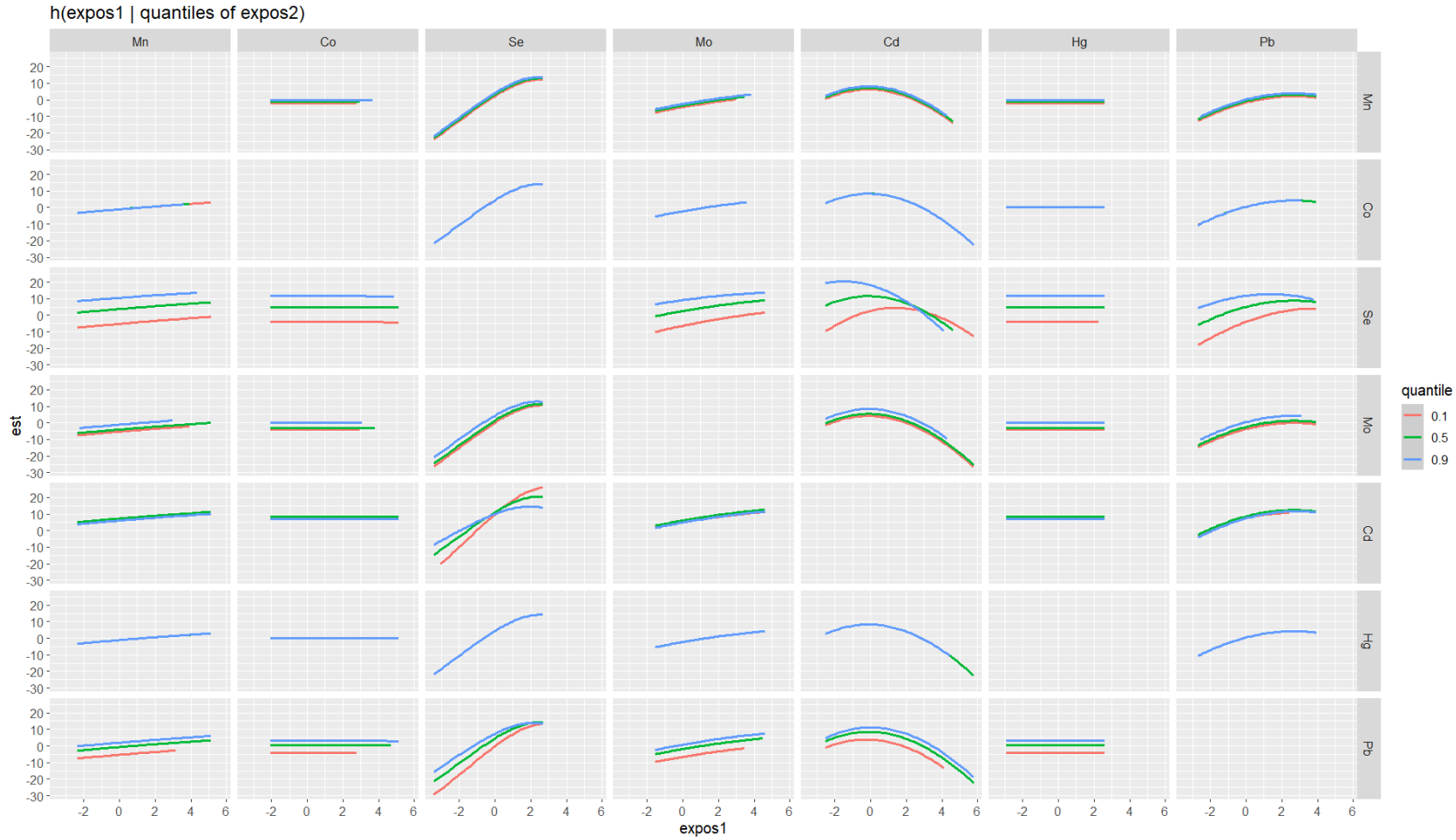
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



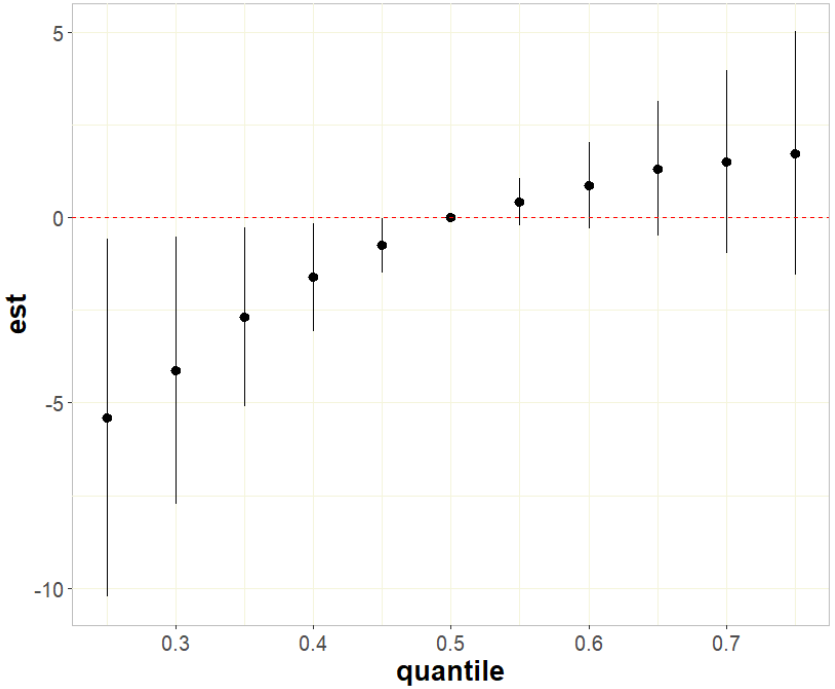
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



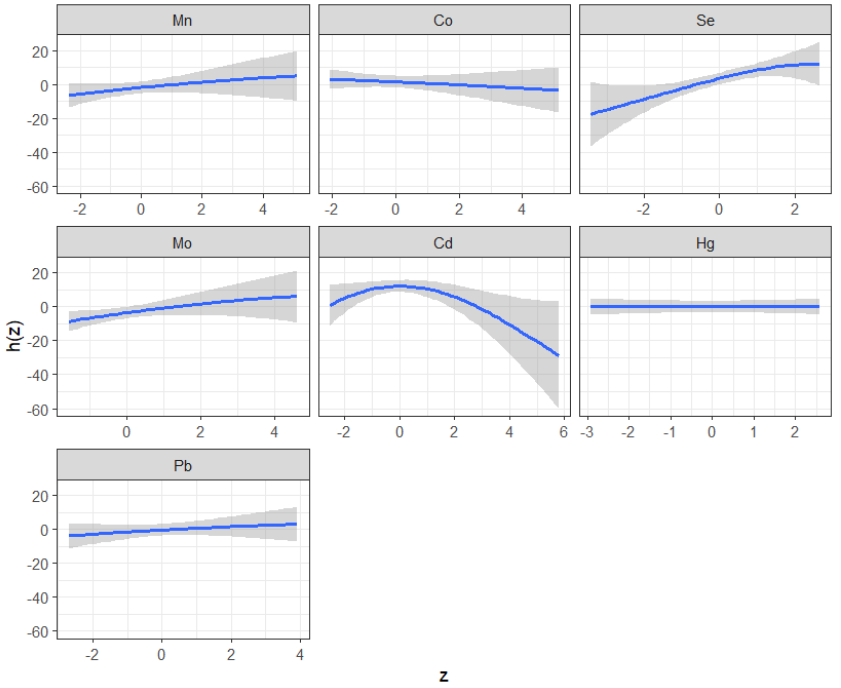
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Figure S21. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for supplement use (n=291)

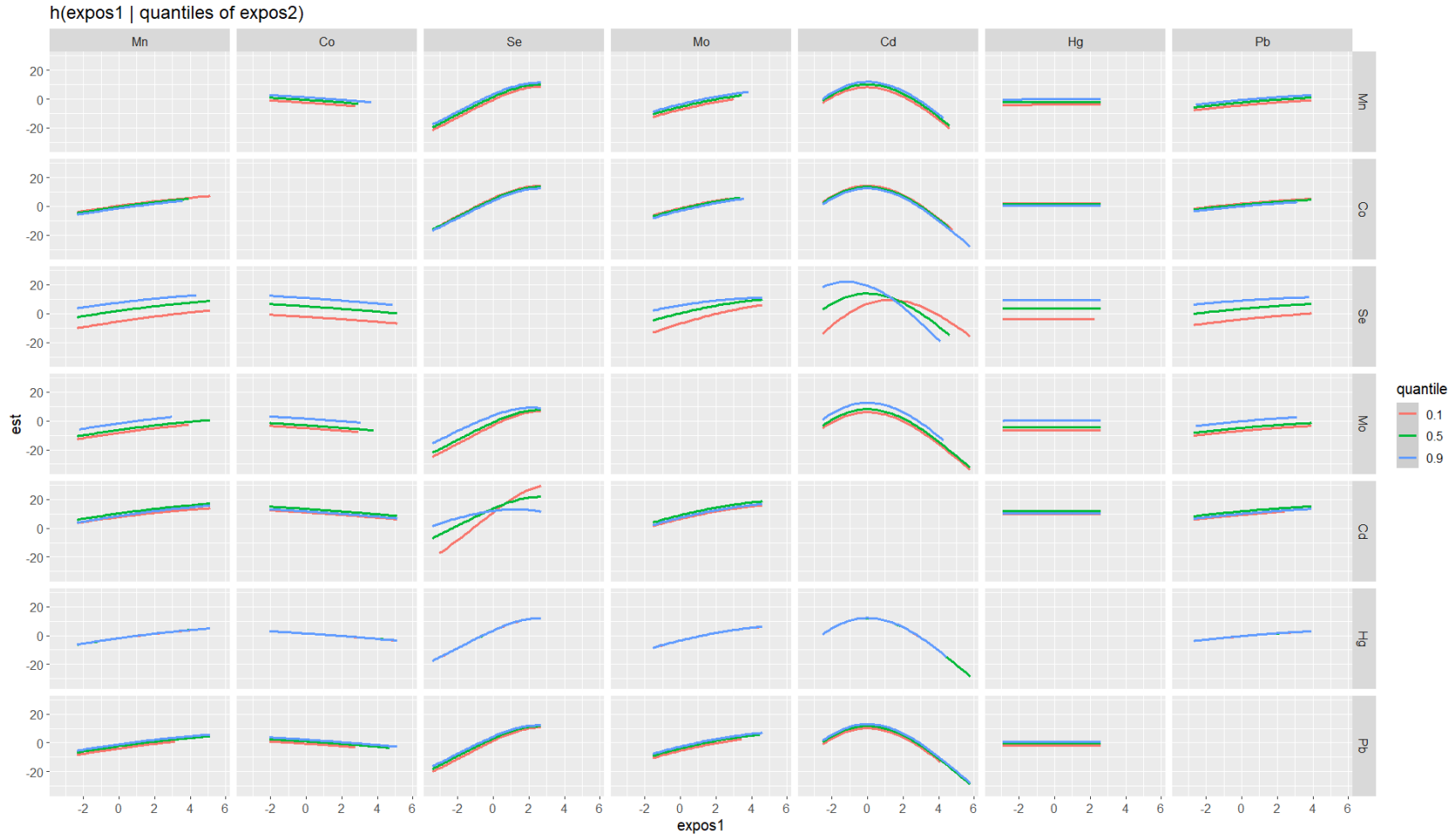
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



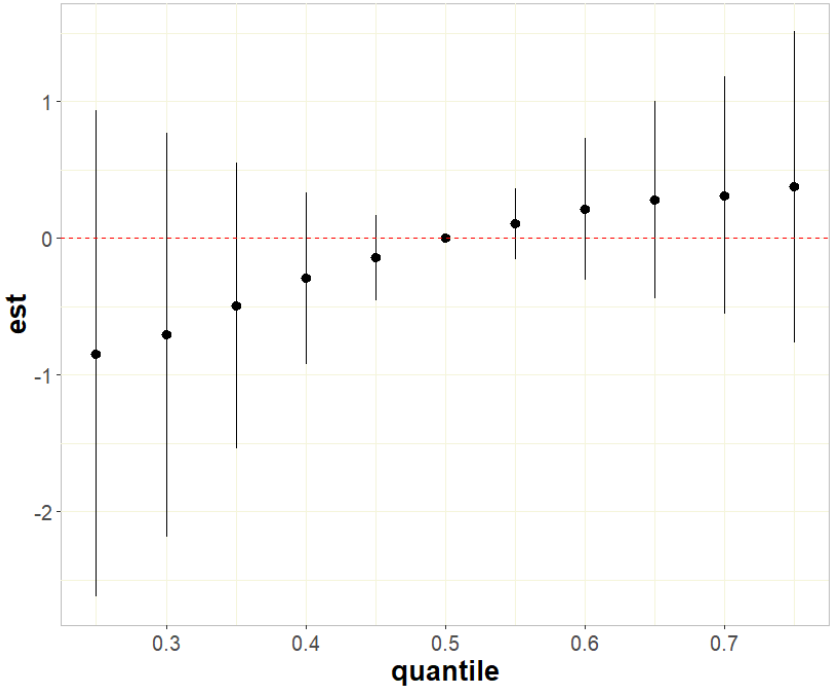
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



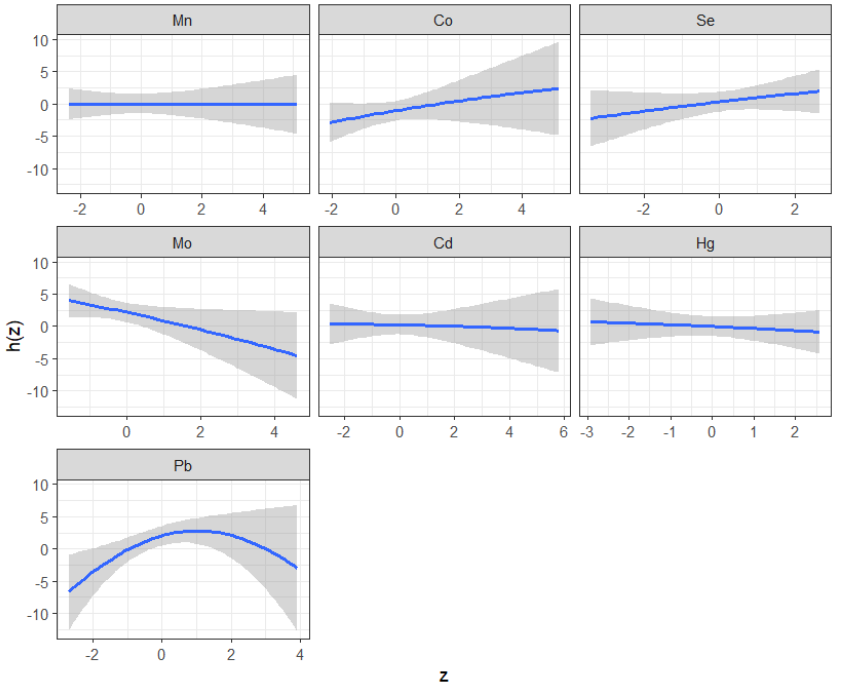
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Figure S22. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age estimated by BKMR additionally adjusting for supplement use (n=291)

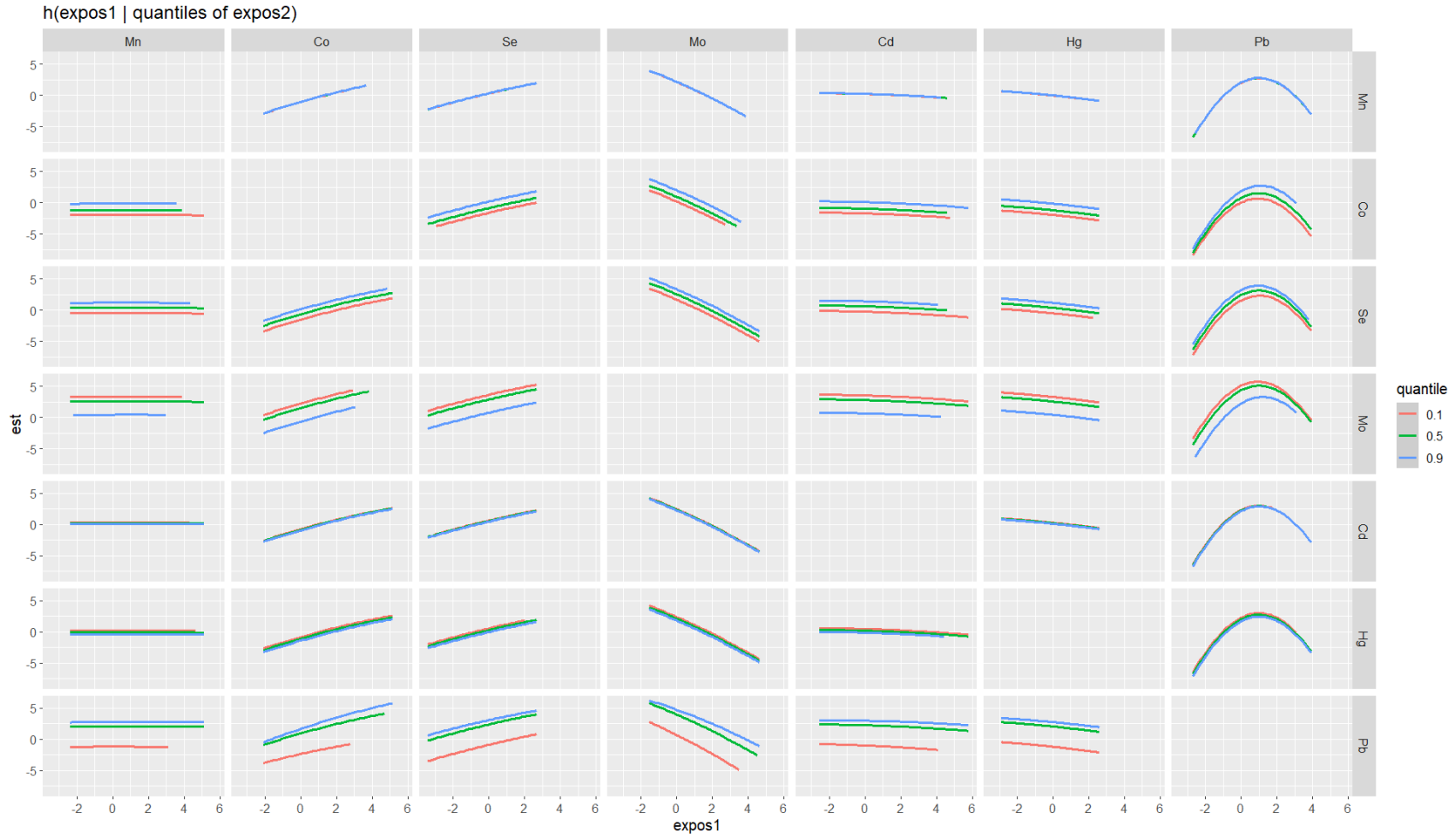
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



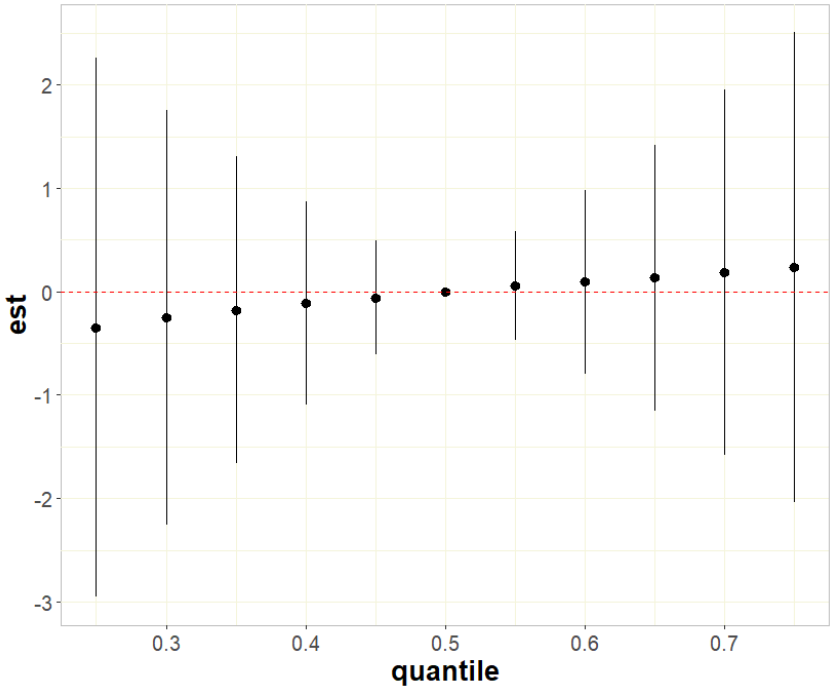
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



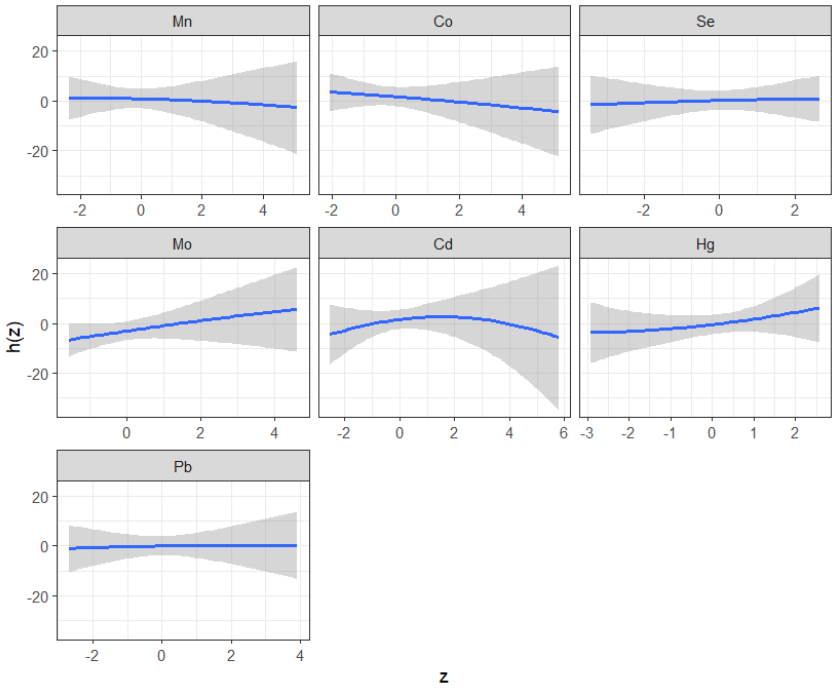
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Figure S23. Joint associations of the metals with triglycerides at 4 years of age estimated by BKMR additionally adjusting for supplement use (n=291)

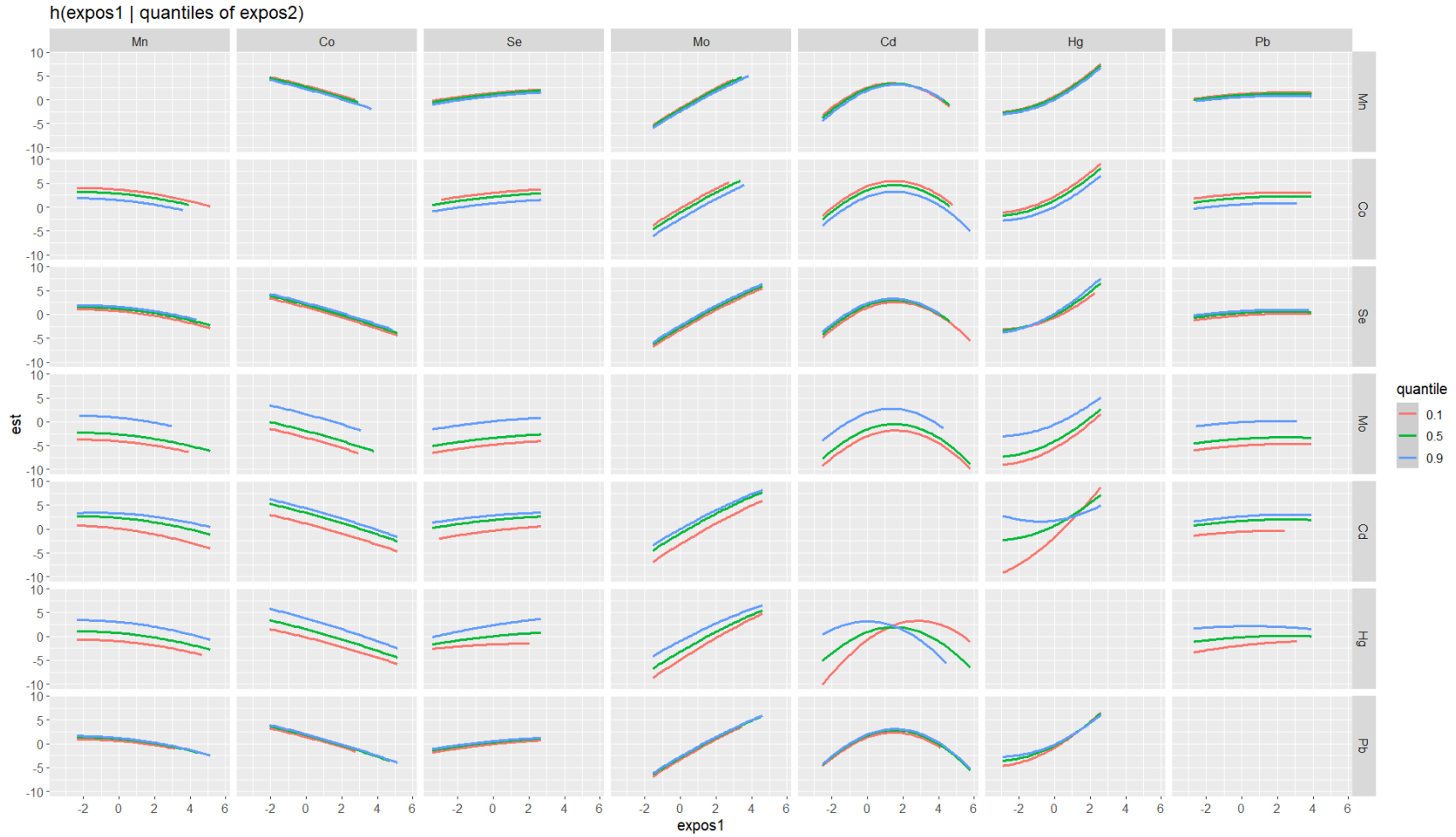
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, child fish/seafood intake, and supplement use at 4 years of age.

Table S13. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations stratified by sex, estimated by BKMR

Lipid measure	**75th vs. 25th percentiles**	
	Boys (n=160)	**Girls (n=131)**
Total cholesterol (mg/dL)	11.31 (-2.38, 25.00)	4.54 (-5.90, 14.97)
Low-density lipoprotein cholesterol (mg/dL)	8.15 (-2.44, 18.75)	4.04 (-5.52, 13.61)
High-density lipoprotein cholesterol (mg/dL)	0.51 (-4.35, 5.37)	1.73 (-2.44, 5.91)
Triglycerides (mg/dL)	2.32 (-6.39, 11.03)	-4.03 (-21.70, 13.64)

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Table S14. Posterior inclusion probabilities and effect estimates for each metal within the mixture in association with lipid measures stratified by sex, estimated by BKMR

Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]
Among boys (n=160)								
Mn	0.49	1.10 (-3.76, 5.96)	0.34	0.28 (-3.44, 4.01)	0.32	0.29 (-1.49, 2.08)	0.25	0.35 (-4.12, 4.82)
Co	0.40	-0.32 (-4.53, 3.90)	0.26	-0.54 (-4.50, 3.42)	0.37	0.25 (-1.91, 2.41)	0.22	-0.13 (-3.25, 2.99)
Se	0.91	9.03 (-1.04, 19.10)	0.90	7.88 (-0.65, 16.41)	0.49	0.92 (-1.92, 3.76)	0.26	-0.19 (-3.42, 3.04)
Mo	0.48	0.76 (-3.12, 4.64)	0.59	1.97 (-2.71, 6.65)	0.48	-1.00 (-3.74, 1.75)	0.37	0.38 (-3.14, 3.91)
Cd	0.49	-0.94 (-6.29, 4.41)	0.55	-0.53 (-5.55, 4.49)	0.42	-0.76 (-3.90, 2.38)	0.24	0.60 (-2.92, 4.13)
Hg	0.31	0.21 (-2.98, 3.40)	0.21	0.17 (-2.21, 2.54)	0.41	-0.32 (-2.17, 1.52)	0.42	1.51 (-3.78, 6.80)
Pb	0.59	3.43 (-5.00, 11.86)	0.32	1.30 (-4.07, 6.67)	0.39	0.41 (-2.04, 2.86)	0.14	0.26 (-2.63, 3.14)
Among girls (n=131)								
Mn	0.20	0.14 (-2.84, 3.12)	0.12	0.23 (-1.96, 2.43)	0.24	-0.18 (-1.62, 1.27)	0.33	-2.26 (-10.96, 6.44)
Co	0.19	0.07 (-1.84, 1.97)	0.06	0.01 (-1.16, 1.17)	0.21	0.09 (-0.78, 0.96)	0.15	0.18 (-3.21, 3.57)
Se	0.52	3.08 (-5.35, 11.51)	0.47	3.23 (-5.14, 11.60)	0.19	-0.02 (-1.05, 1.01)	0.26	1.82 (-7.29, 10.93)
Mo	0.24	0.17 (-2.73, 3.07)	0.11	0.22 (-2.06, 2.49)	0.20	-0.21 (-1.64, 1.22)	0.15	0.65 (-4.10, 5.39)
Cd	0.28	0.42 (-2.89, 3.74)	0.15	0.24 (-1.97, 2.46)	0.22	0.10 (-0.99, 1.20)	0.93	1.99 (-8.97, 12.95)
Hg	0.30	0.50 (-2.60, 3.60)	0.15	0.25 (-2.06, 2.56)	0.22	0.02 (-0.98, 1.02)	0.95	5.77 (-6.97, 18.51)
Pb	0.25	0.37 (-2.71, 3.45)	0.08	0.04 (-1.69, 1.78)	0.71	1.66 (-1.77, 5.09)	0.54	-0.24 (-8.50, 8.01)

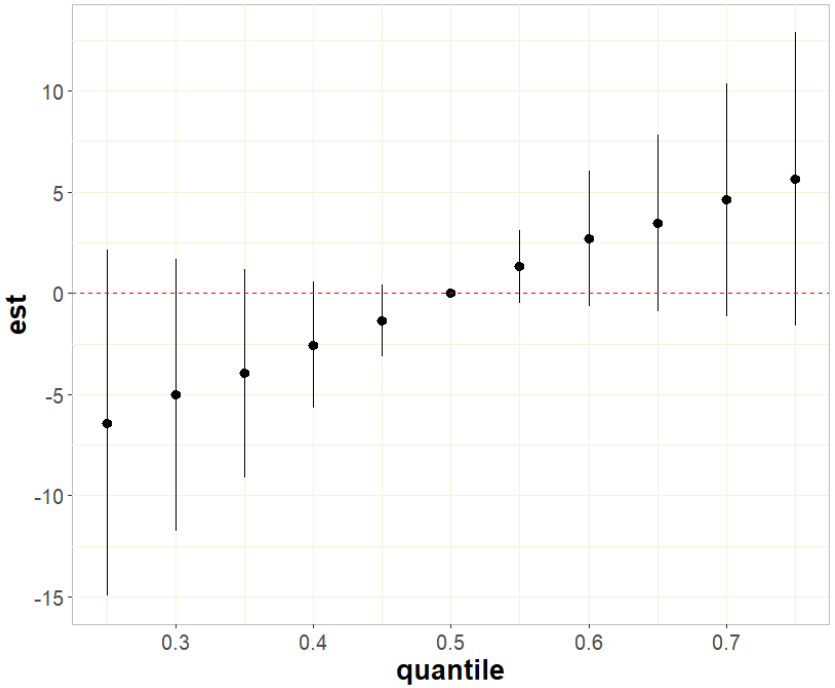
[a] The difference in the lipid measure, comparing each metal component within the mixture at 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

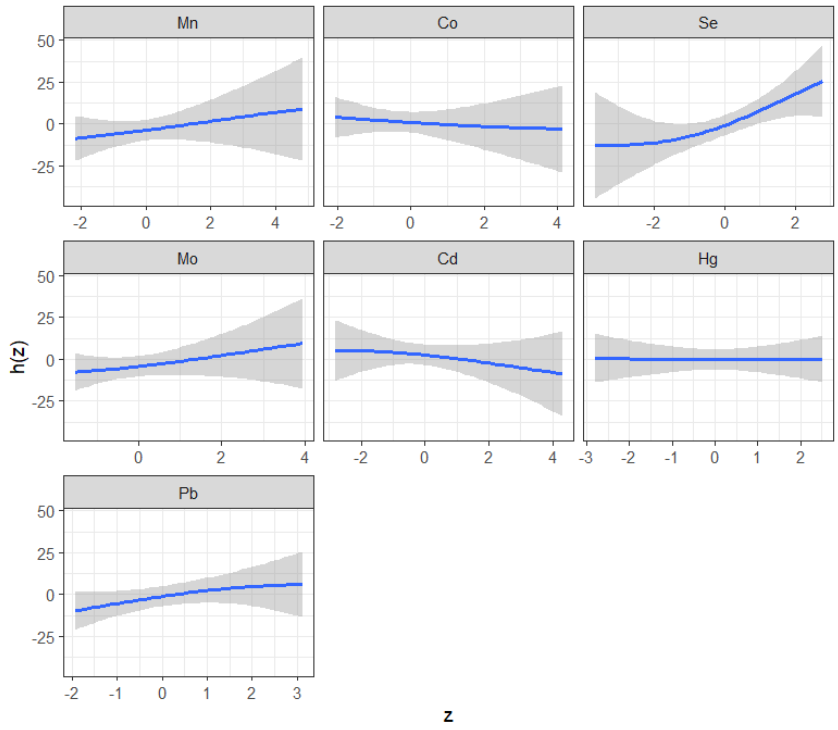
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead.

Figure S24. Joint associations of the metals with total cholesterol at 4 years of age among boys, estimated by BKMR (n=160)

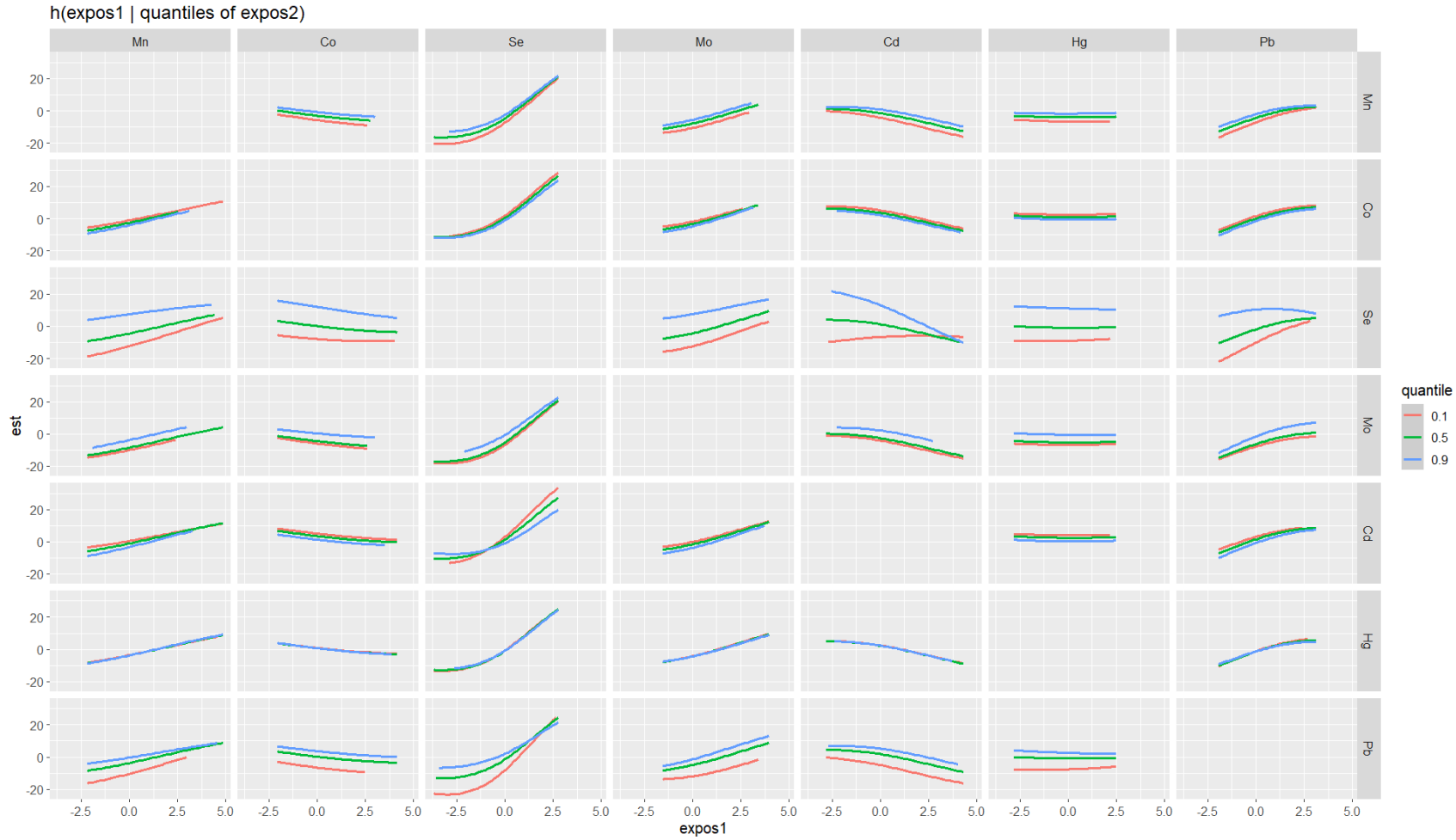
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



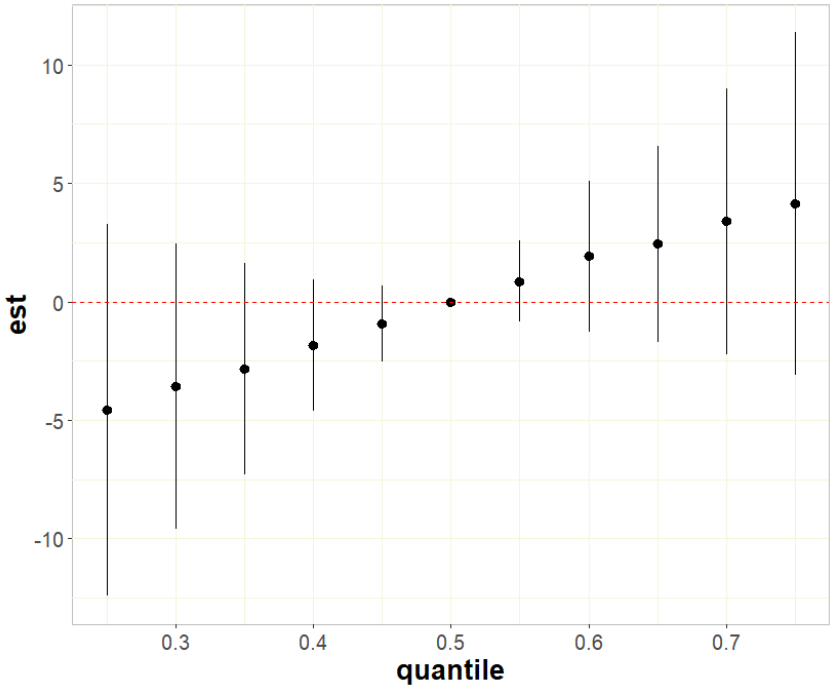
c. Exposure-response function for each metal setting a second metal at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



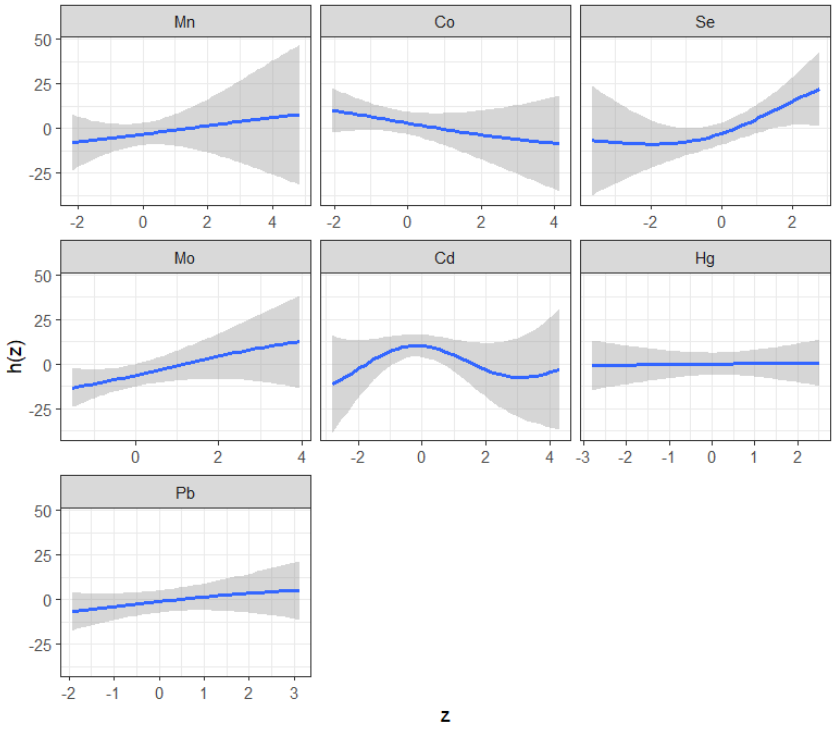
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S25. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age among boys, estimated by BKMR (n=160)

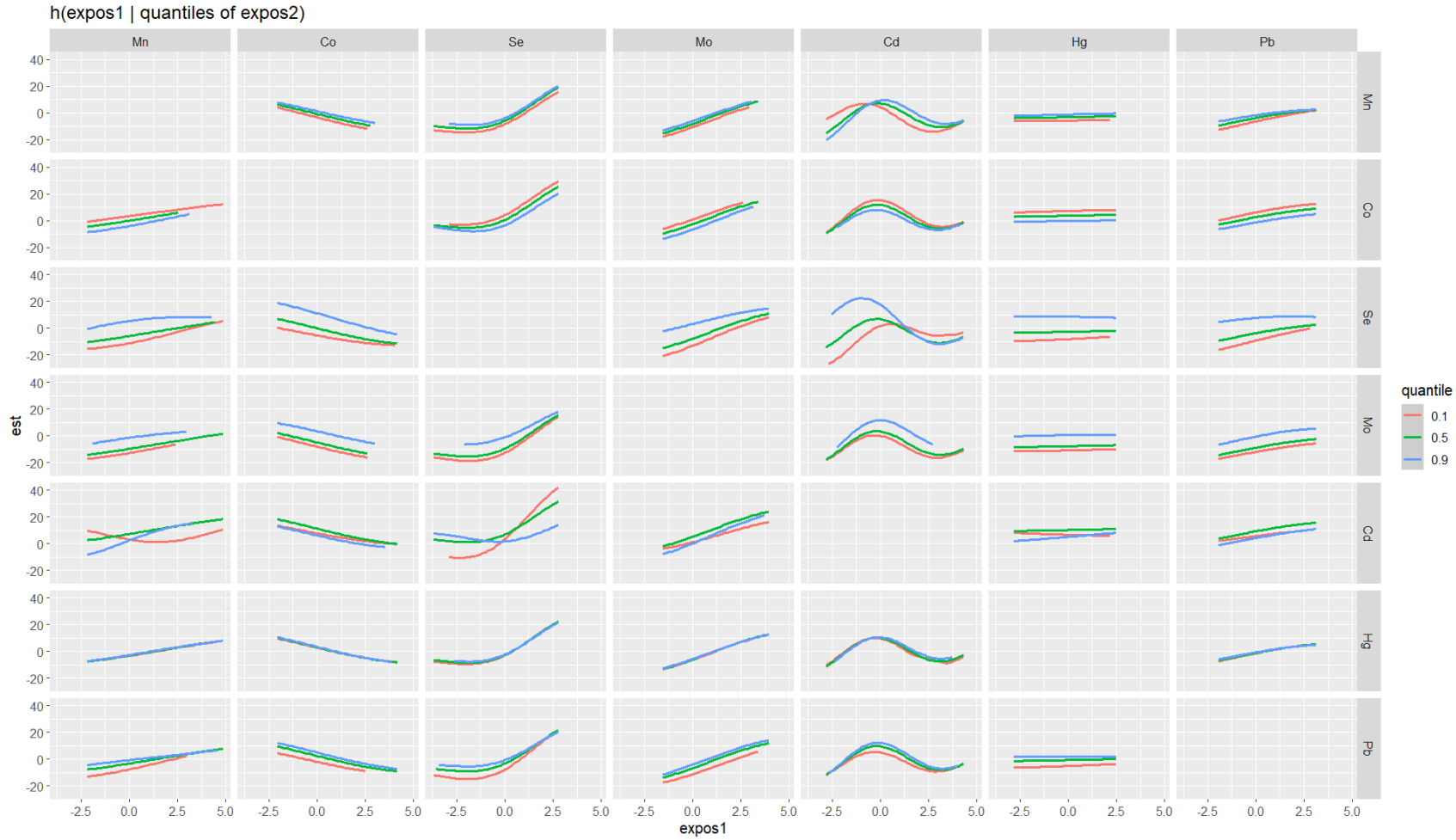
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions for each metal and corresponding 95% credible intervals for while holding the other exposures at their 50th percentiles



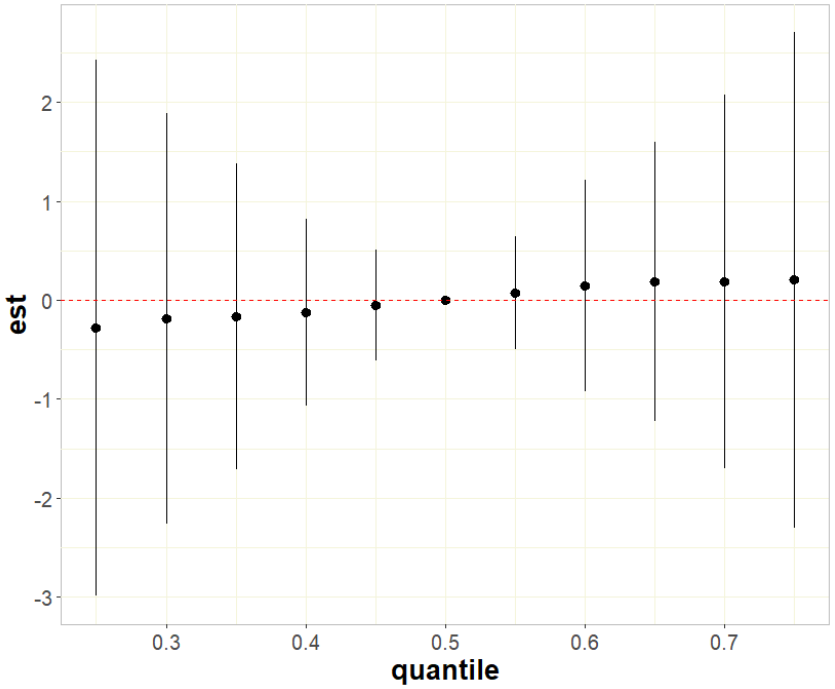
c. Exposure-response functions for each metal exposure (column) setting a second exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



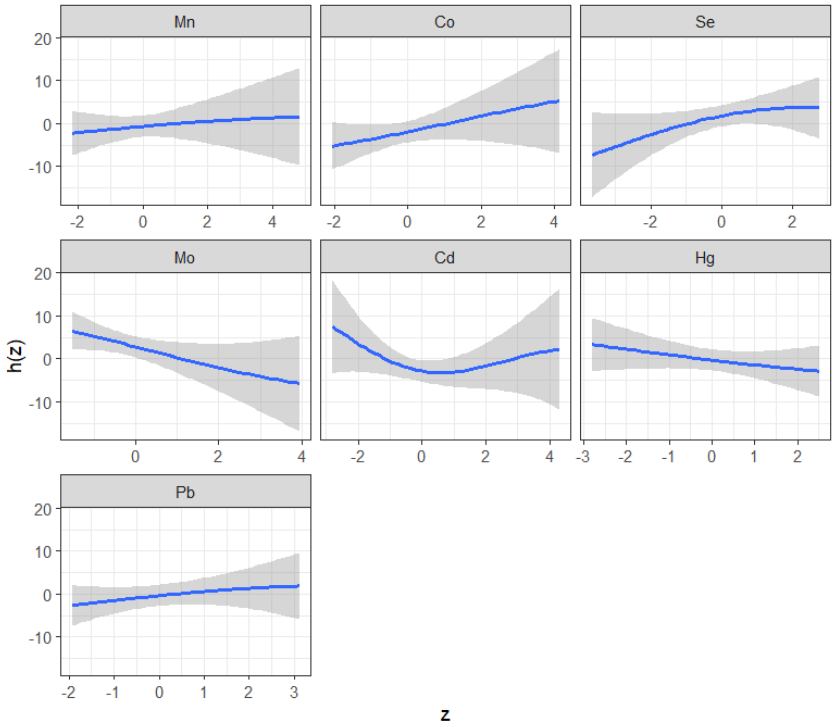
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S26. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age among boys, estimated by BKMR (n=160)

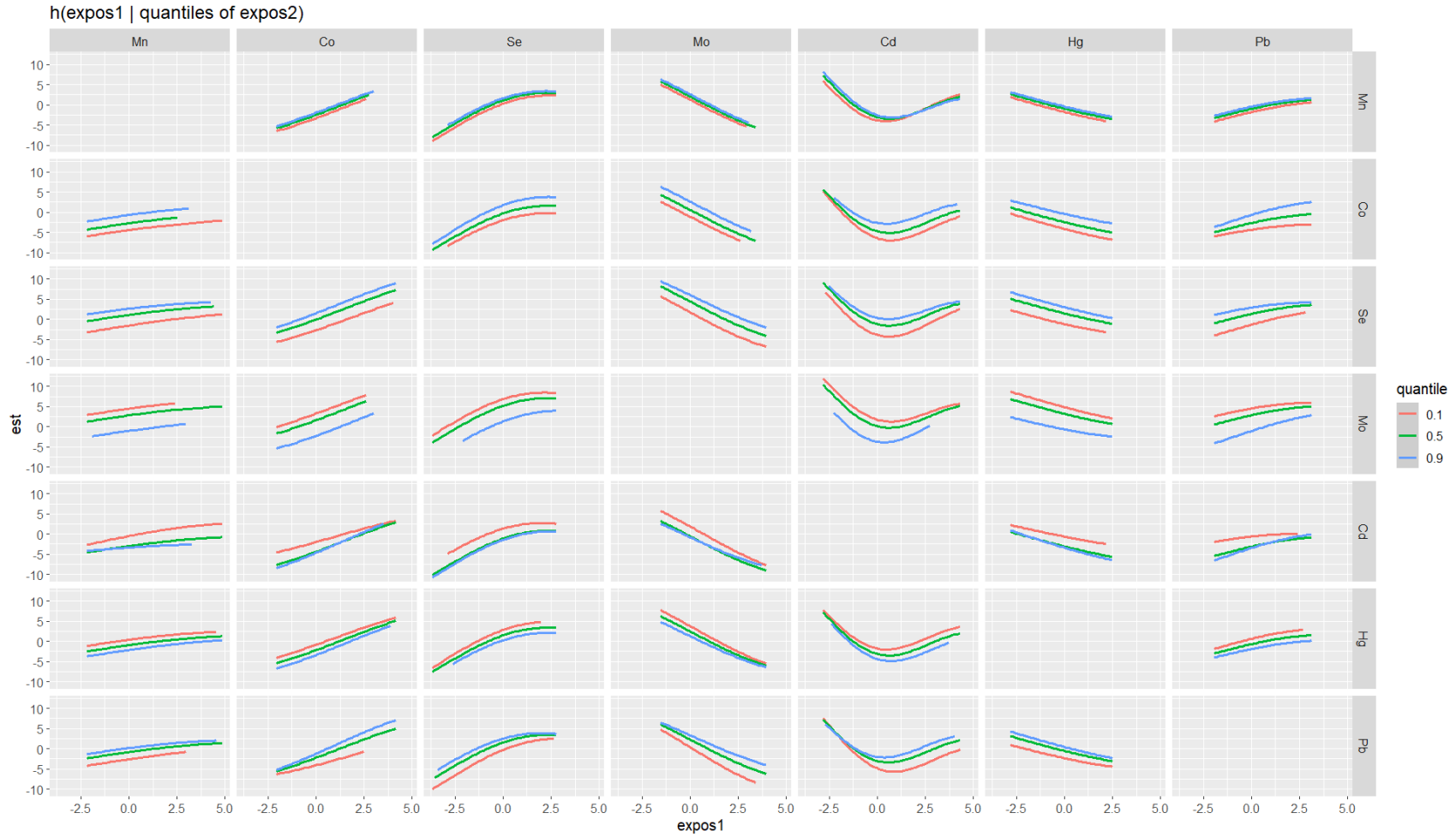
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions for each metal and corresponding 95% credible intervals while holding the other exposures at their 50th percentiles



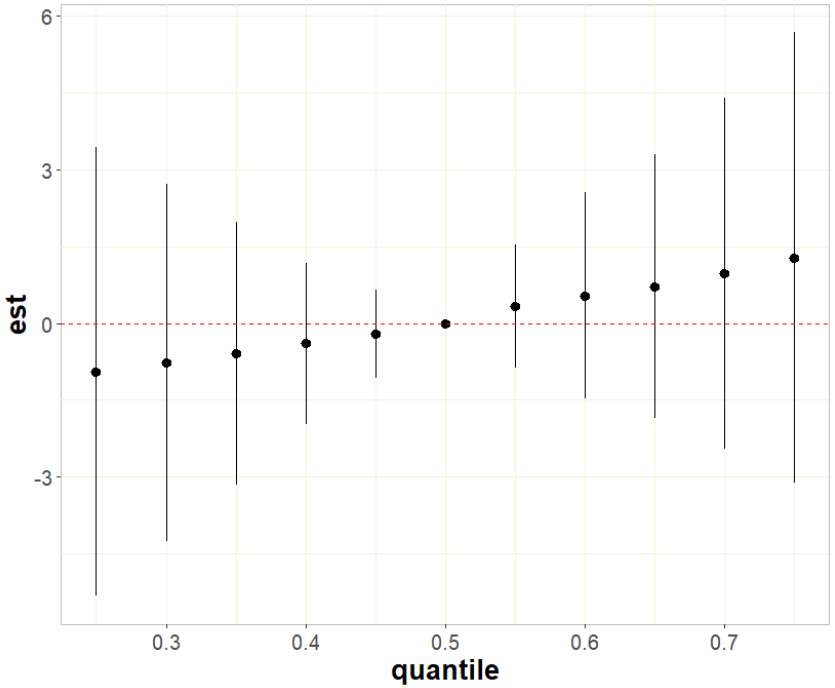
c. Exposure-response function for each metal exposure (column) setting a second exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



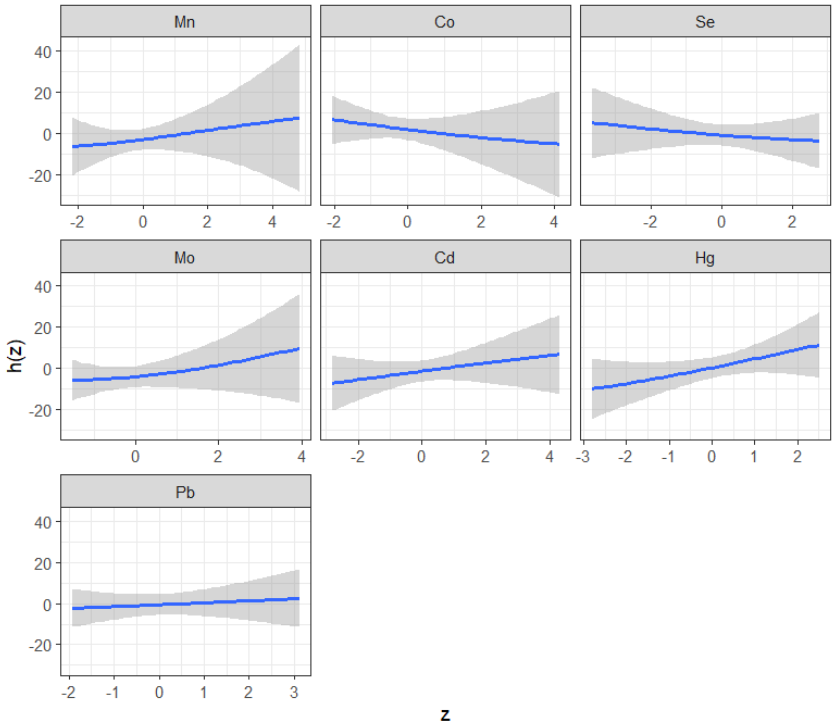
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S27. Joint associations of the metals with triglycerides at 4 years of age among boys, estimated by BKMR (n=160)

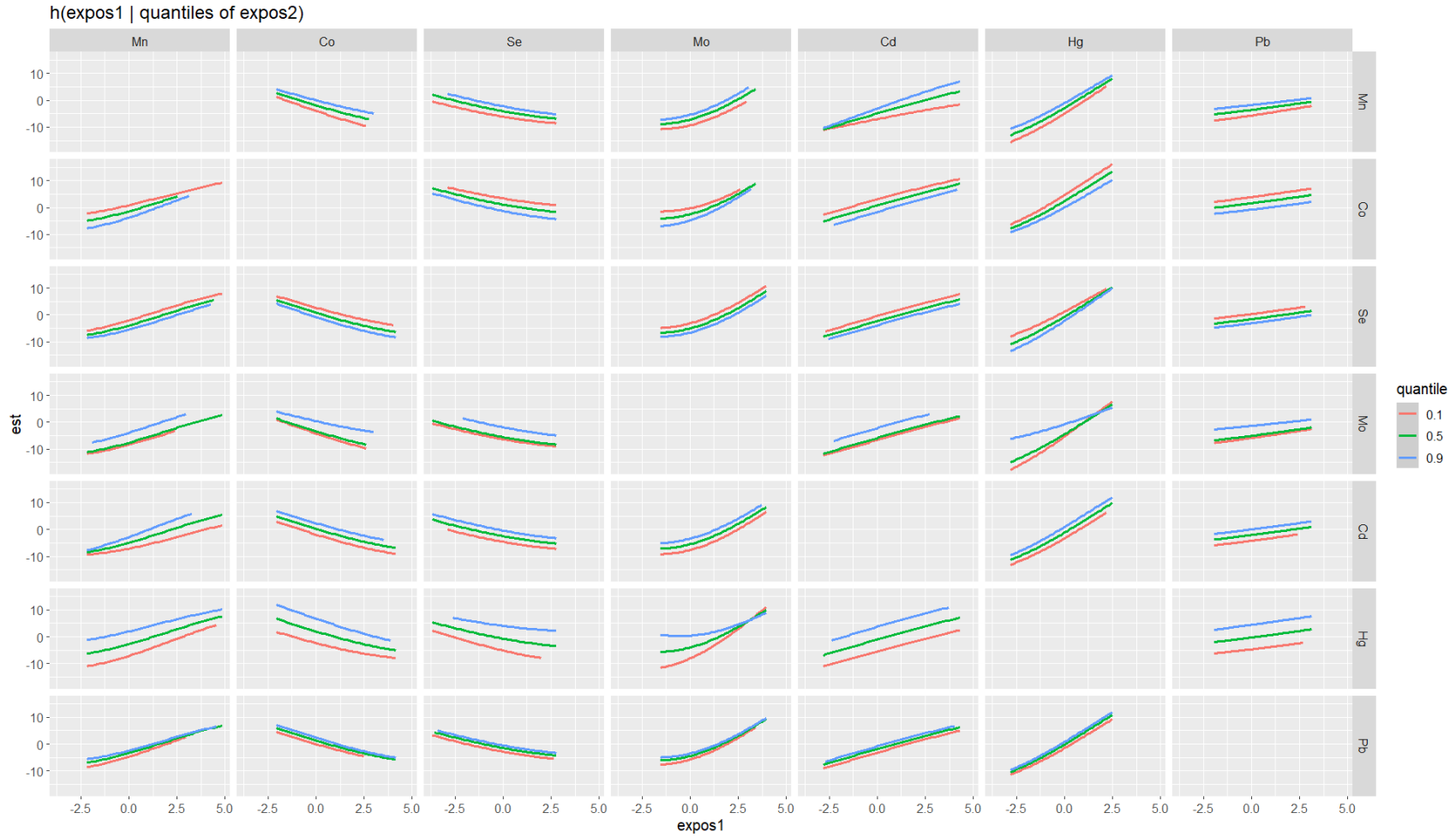
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



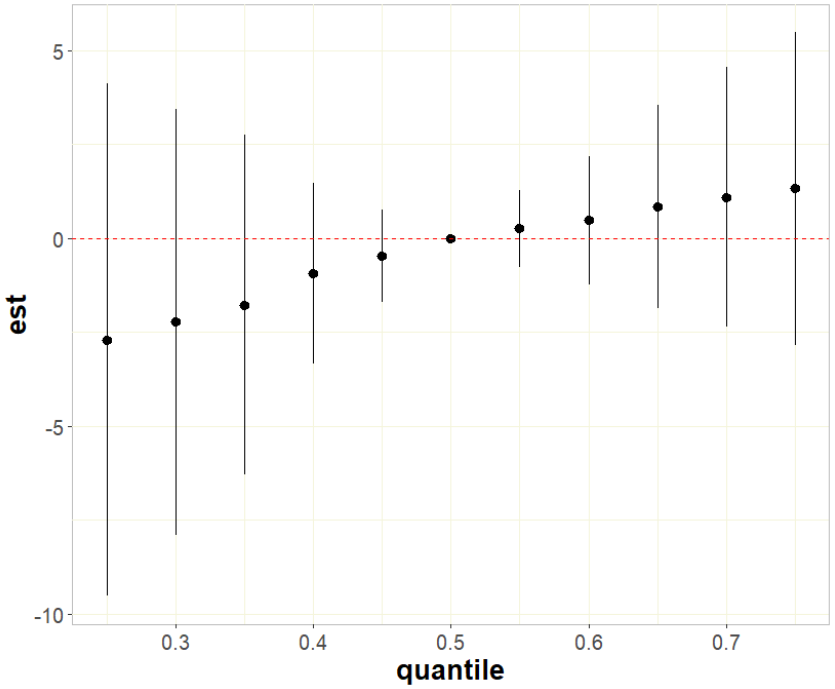
c. Exposure-response function for each metal exposure (column) setting the second metal exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



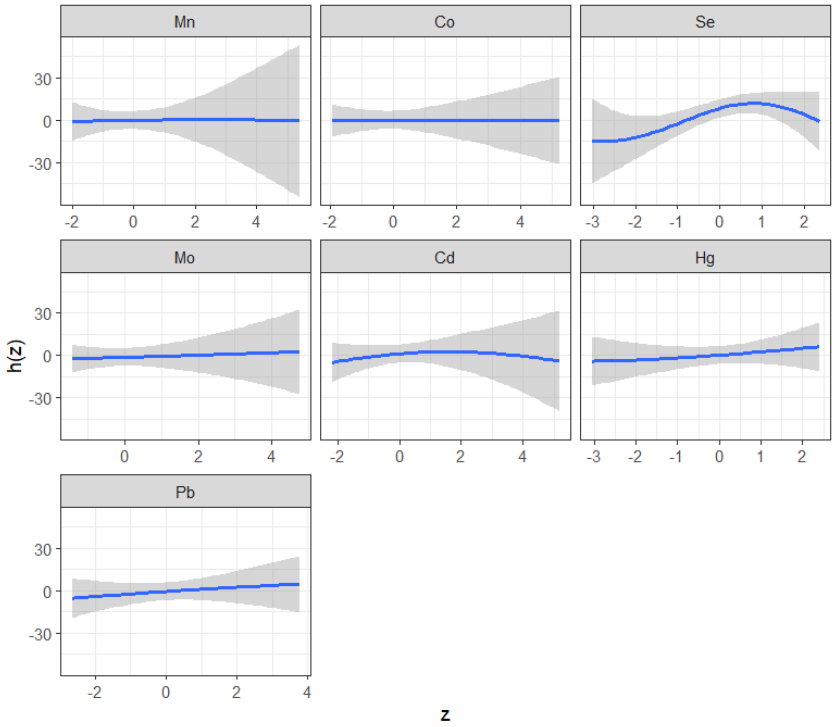
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S28. Joint associations of the metals with total cholesterol at 4 years of age among girls, estimated by BKMR (n=131)

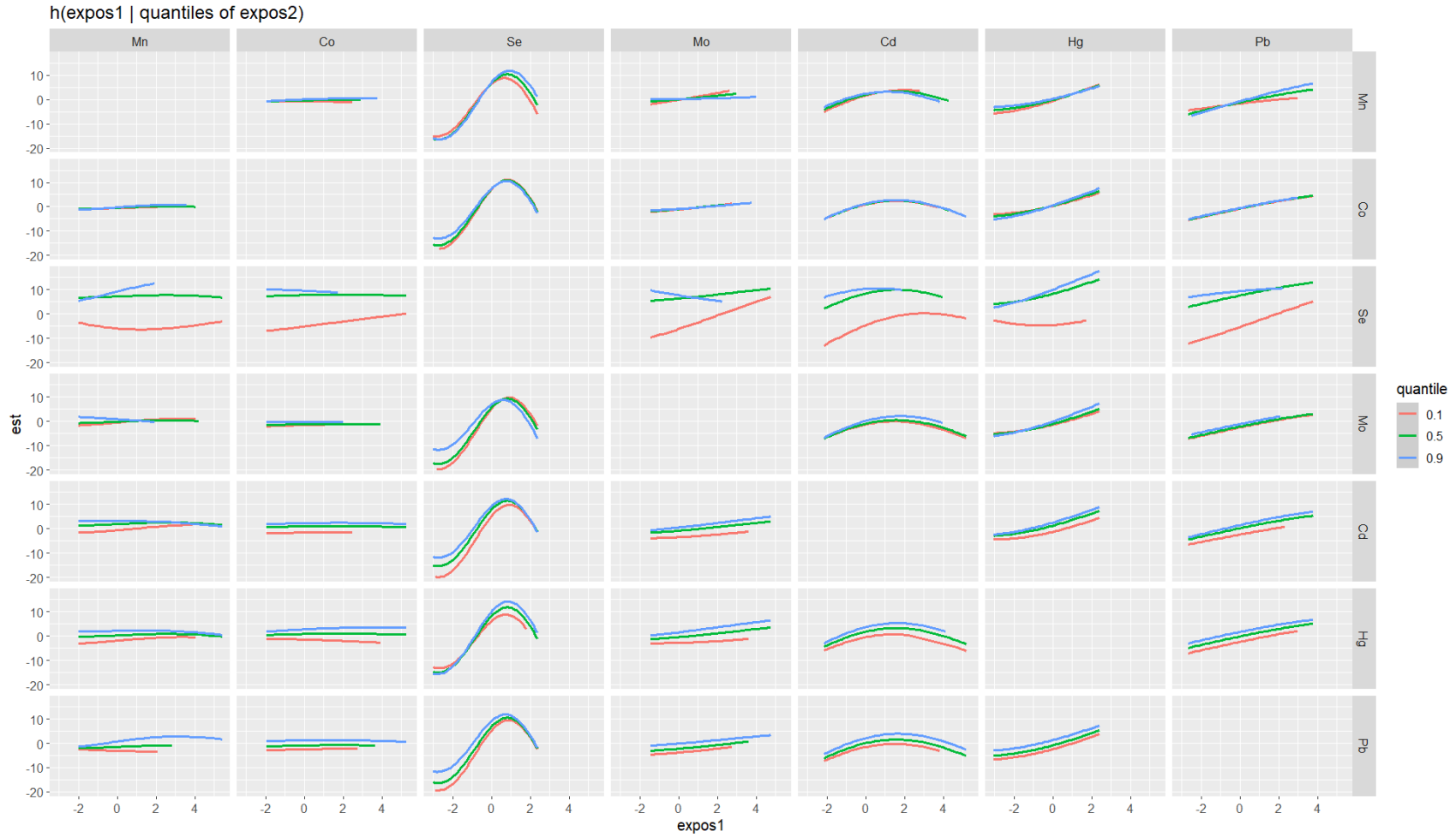
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



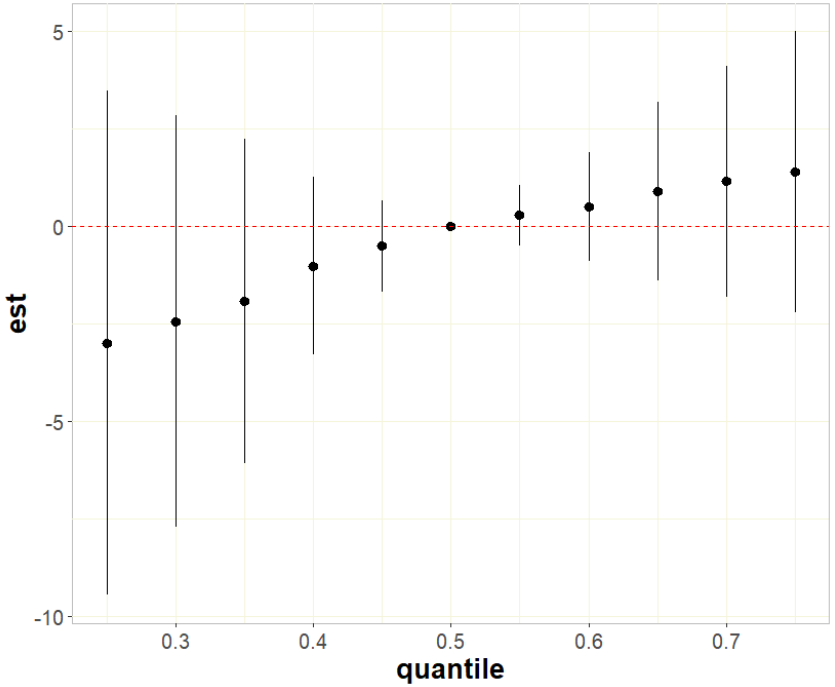
c. Exposure-response function for each metal exposure (column) setting the second exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



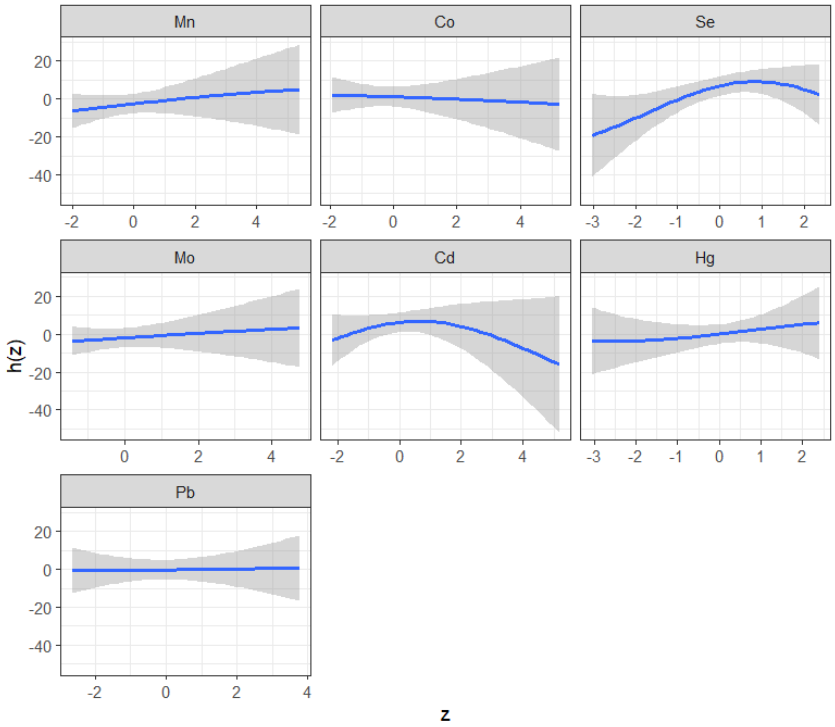
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S29. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age among girls, estimated by BKMR (n=131)

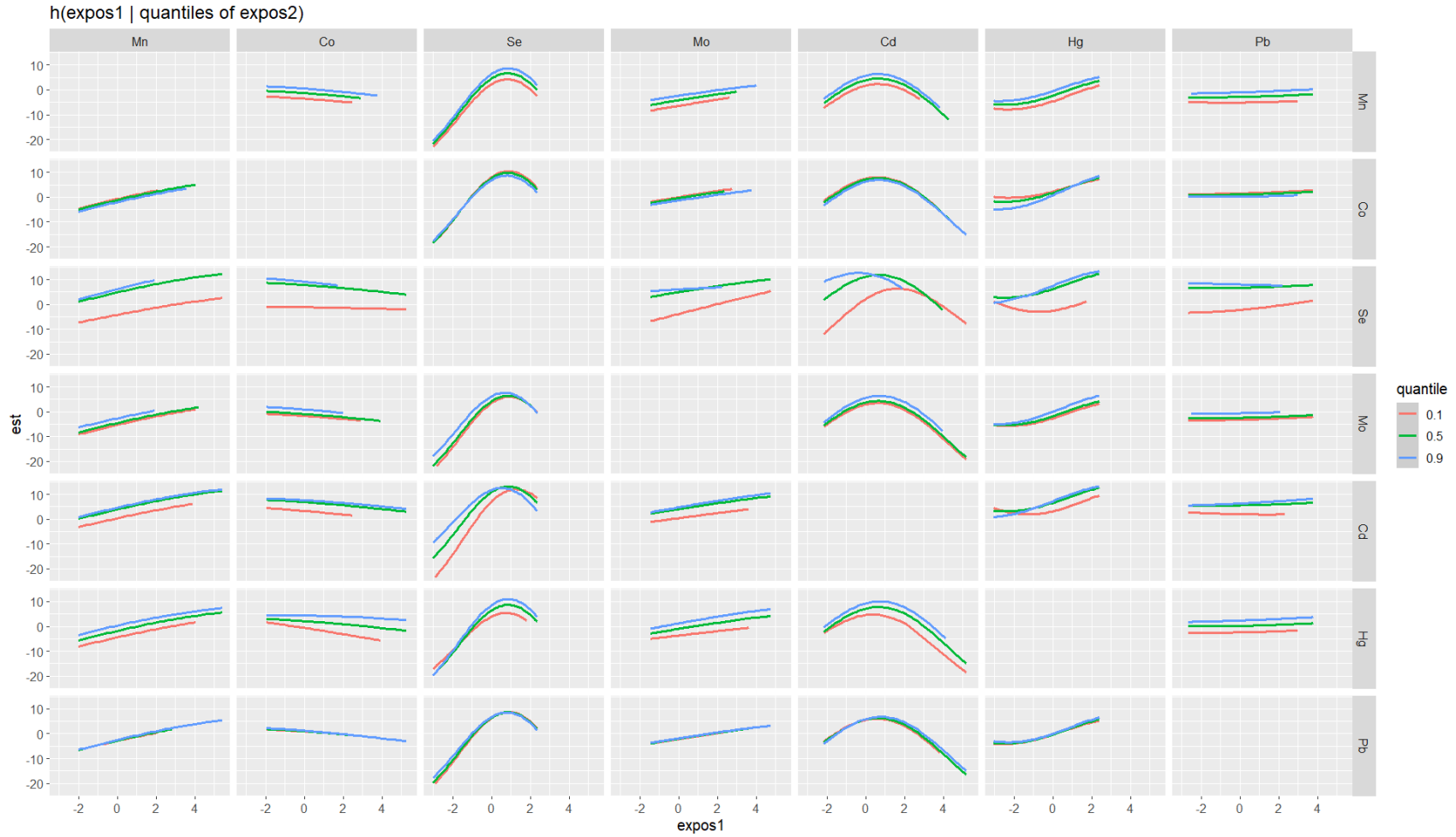
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



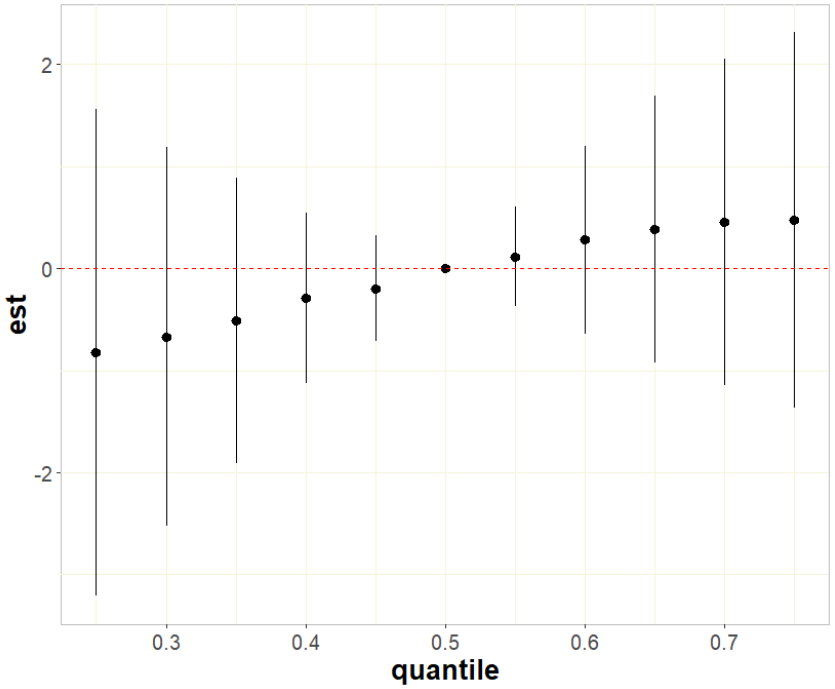
c. Exposure-response function of each metal exposure (column) setting the second exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



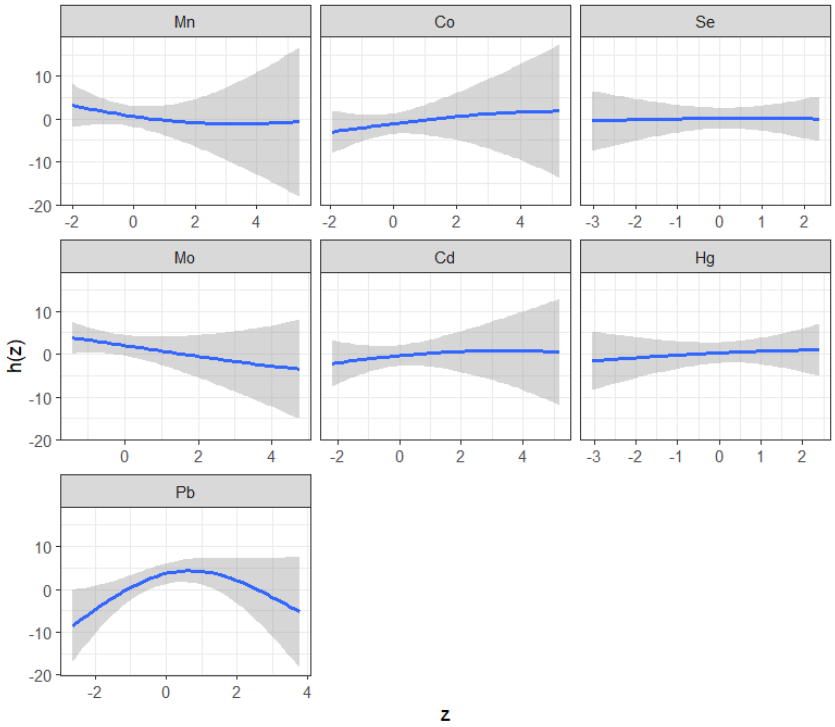
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S30. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age among girls, estimated by BKMR (n=131)

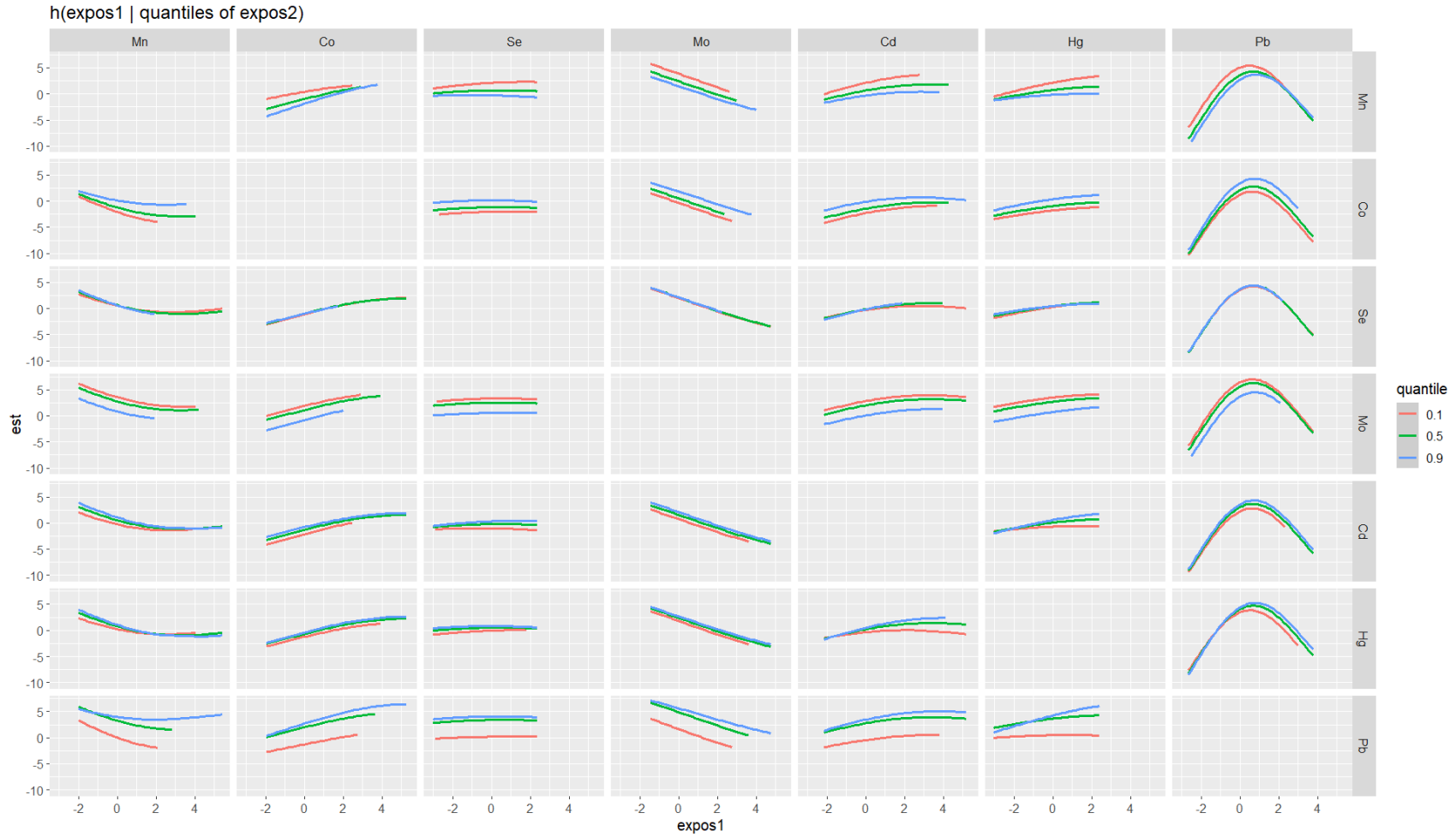
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



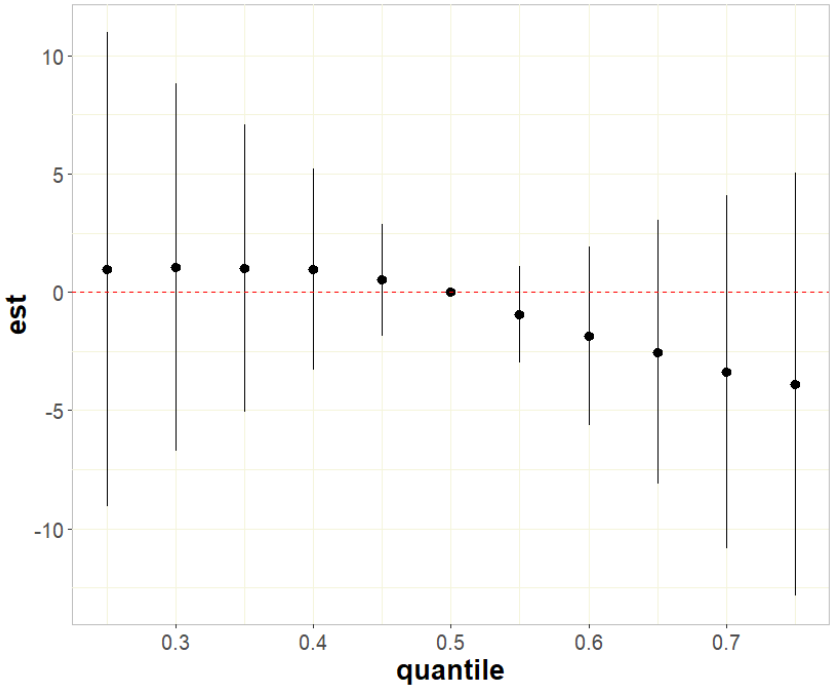
c. Exposure-response function for each metal exposure (column) setting a second exposure (row) to its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



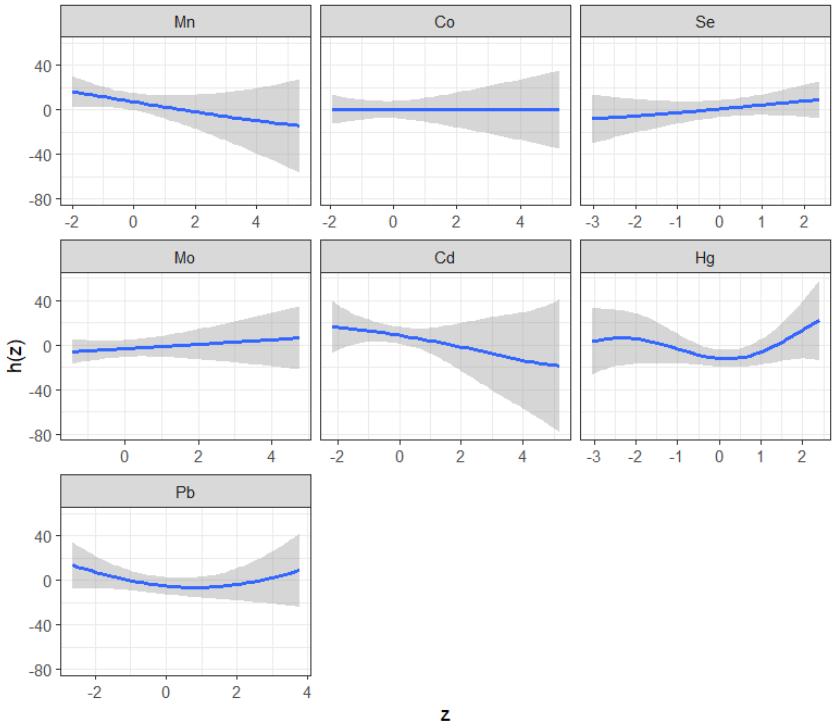
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Figure S31. Joint associations of the metals with triglycerides at 4 years of age among girls, estimated by BKMR (n=131)

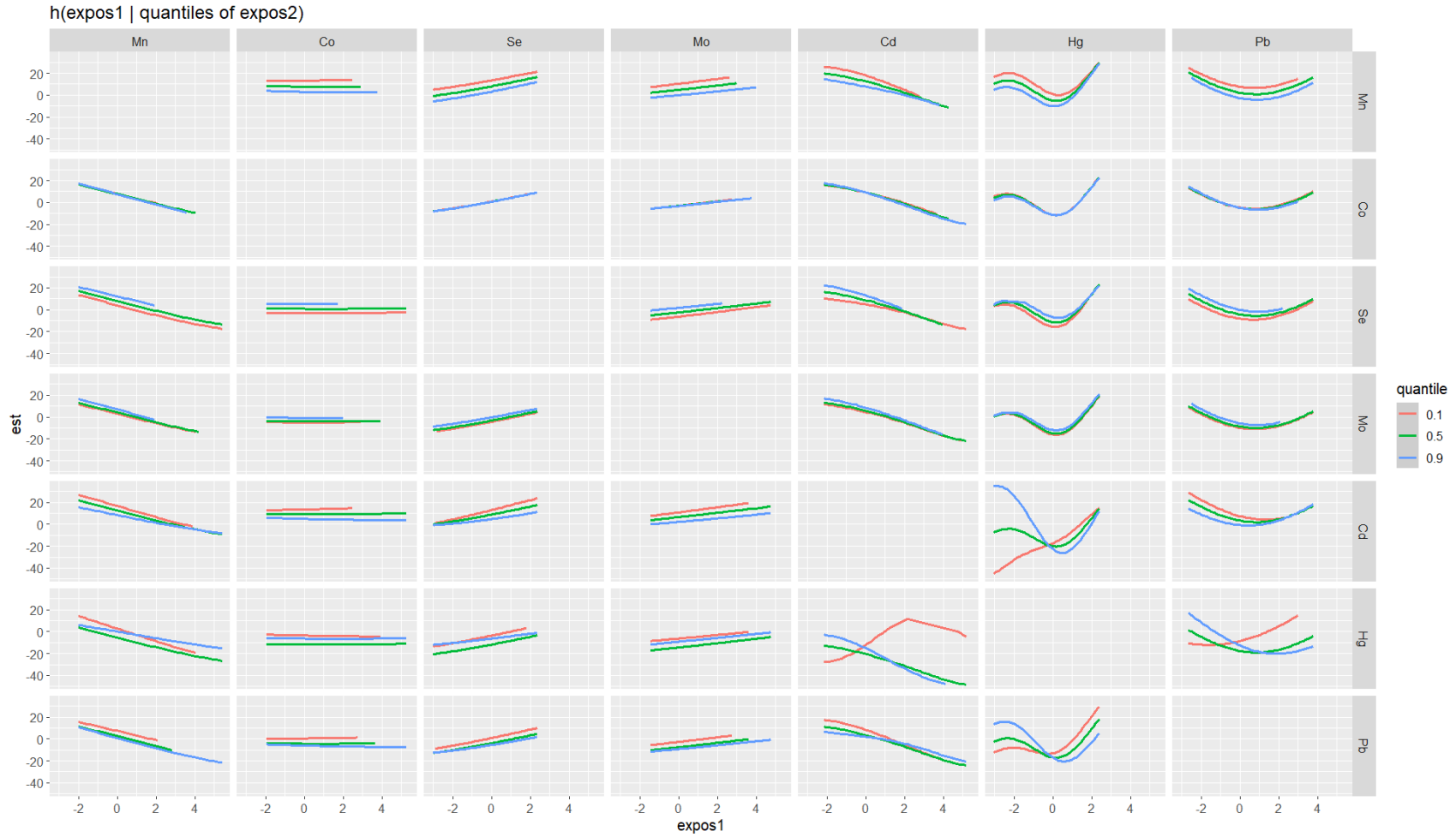
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, child secondhand smoke exposure at 4 years of age, and child fish/seafood intake at 4 years of age.

Table S15. Difference in lipid measure levels setting all metals (Co, Mn, Mo, Se, Cd, Hg, and Pb) to their 75th compared with 25th percentile concentrations and holding all other metals in the mixture at their median values stratified by environmental tobacco smoke (ETS) exposure, estimated by BKMR

Lipid measure	**75th vs. 25th percentiles**	
	Exposed to ETS (n=138)	**Not exposed to ETS (n=153)**
Total cholesterol (mg/dL)	10.96 (1.09, 20.82)	2.36 (-5.42, 10.14)
Low-density lipoprotein cholesterol (mg/dL)	7.71 (-1.79, 17.22)	1.10 (-4.66, 6.87)
High-density lipoprotein cholesterol (mg/dL)	0.74 (-2.15, 3.62)	2.66 (-1.31, 6.62)
Triglycerides (mg/dL)	5.03 (-5.35, 15.40)	0.52 (-4.80, 5.83)

All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Table S16. Posterior inclusion probabilities (PIP) and effect estimates for each metal, holding all other metals in the mixture constant at their median values, in association with lipid measures at 4 years of age, stratified by environmental tobacco smoke (ETS) exposure, estimated by BKMR

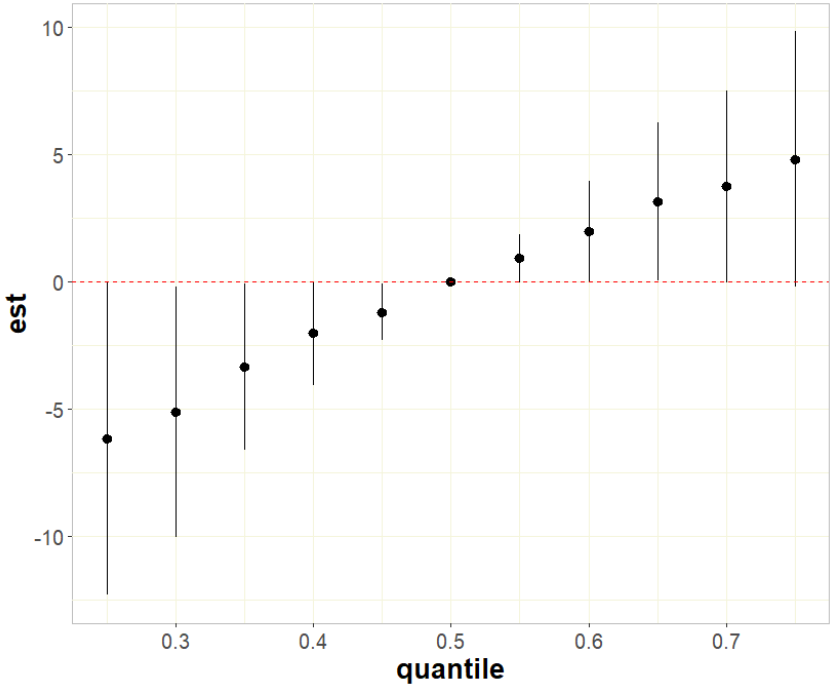
Exposure	Total cholesterol		Low-density lipoprotein cholesterol		High-density lipoprotein cholesterol		Triglycerides	
	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]	PIP	75th vs. 25th percentile[a]
Exposed to ETS (n=138)								
Mn	0.13	1.02 (-4.59, 6.63)	0.18	1.01 (-3.89, 5.91)	0.03	0.05 (-0.70, 0.81)	0.11	0 (-2.84, 2.85)
Co	0.02	0.07 (-1.32, 1.47)	0.05	0.06 (-1.37, 1.49)	0.05	0.06 (-0.76, 0.89)	0.09	-0.11 (-2.56, 2.34)
Se	0.91	9.73 (0.93, 18.53)	0.78	6.32 (-2.11, 14.75)	0.24	0.61 (-1.90, 3.12)	0.05	0.11 (-1.87, 2.09)
Mo	0.01	0.05 (-1.09, 1.18)	0.09	0.33 (-2.31, 2.98)	0.01	-0.01 (-0.32, 0.31)	0.06	0.15 (-2.08, 2.38)
Cd	0.05	0.14 (-1.90, 2.18)	0.19	0.44 (-2.92, 3.79)	0.02	-0.04 (-0.71, 0.63)	0.59	4.64 (-4.98, 14.26)
Hg	<0.01	0.00 (0.00, 0.00)	0.04	0.00 (-1.20, 1.19)	0.01	0.00 (-0.18, 0.18)	0.07	0.12 (-1.98, 2.21)
Pb	0.07	0.42 (-3.38, 4.22)	0.05	0.13 (-1.85, 2.11)	0.05	0.06 (-0.82, 0.94)	0.07	0.09 (-2.30, 2.48)
Not exposed to ETS (n=153)								
Mn	0.02	-0.05 (-1.12, 1.01)	0.01	0 (-0.37, 0.36)	0.04	-0.04 (-0.63, 0.56)	0.04	-0.04 (-1.20, 1.12)
Co	<0.01	0 (-0.35, 0.34)	0.04	-0.04 (-1.08, 0.99)	0.03	0.01 (-0.49, 0.51)	0.07	0.04 (-1.69, 1.77)
Se	0.12	0.69 (-3.76, 5.14)	0.15	0.87 (-3.93, 5.67)	0.04	-0.02 (-0.65, 0.61)	0.12	0.31 (-2.46, 3.07)
Mo	0.02	0.02 (-0.72, 0.77)	0.04	0.15 (-1.56, 1.86)	0.34	-0.81 (-3.52, 1.89)	0.07	0.16 (-1.82, 2.14)
Cd	0.11	0.07 (-1.83, 1.97)	0.18	-0.04 (-2.25, 2.18)	0.09	0.10 (-0.87, 1.06)	0.13	-0.22 (-2.36, 1.91)
Hg	0.02	0.04 (-1.00, 1.08)	0.06	0.11 (-1.31, 1.52)	0.03	-0.02 (-0.46, 0.42)	0.12	0.34 (-2.52, 3.20)
Pb	0.26	1.76 (-4.81, 8.33)	0.08	0.30 (-2.21, 2.80)	0.88	2.72 (-0.73, 6.17)	0.04	0.00 (-1.40, 1.39)

[a] The difference in the lipid measure when setting each metal component to its 75th percentile versus 25th percentile, while holding all other metals constant at their median values.

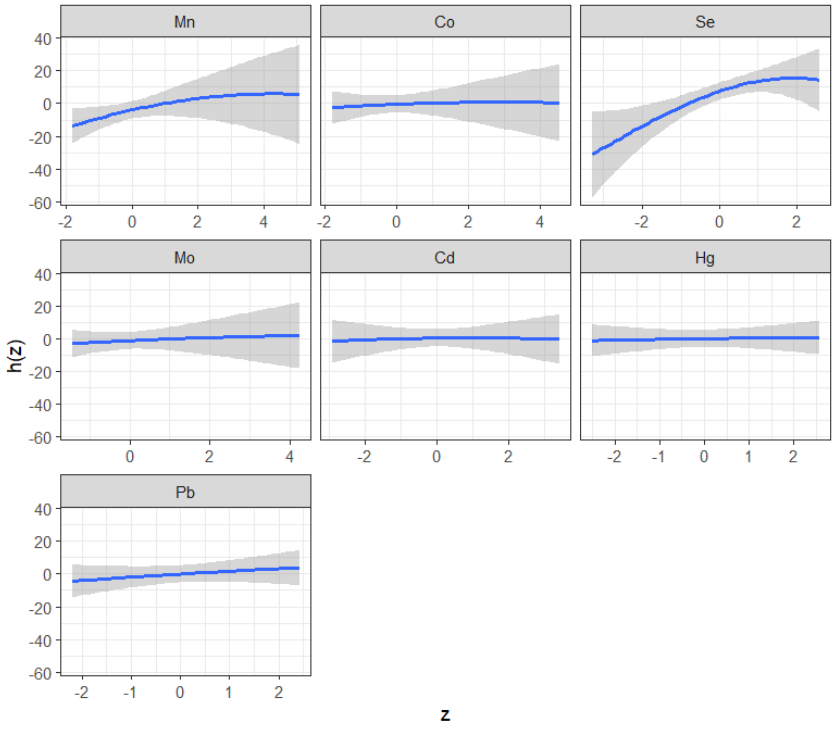
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S32. Joint associations of the metals with total cholesterol at 4 years of age among children exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=138)

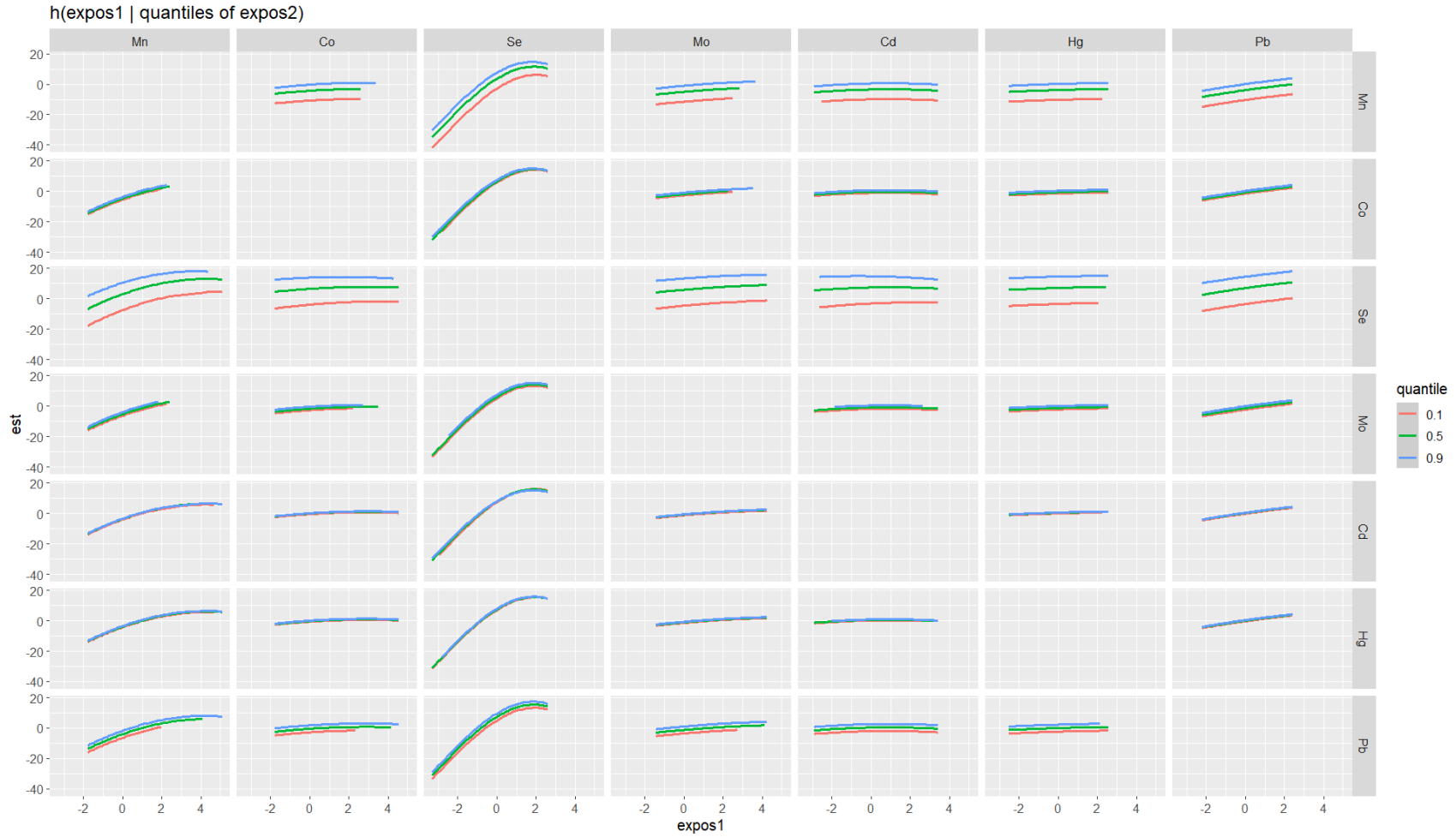
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



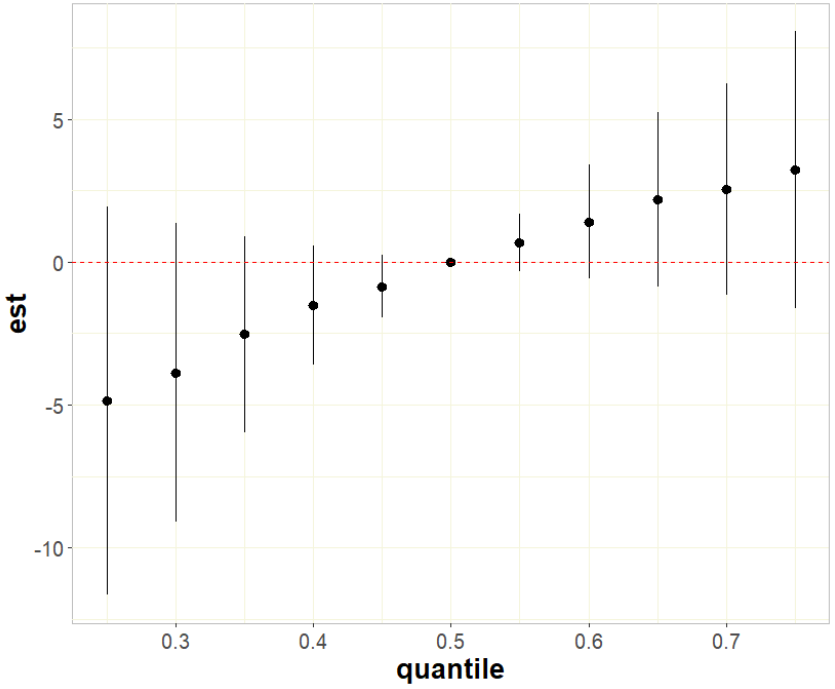
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



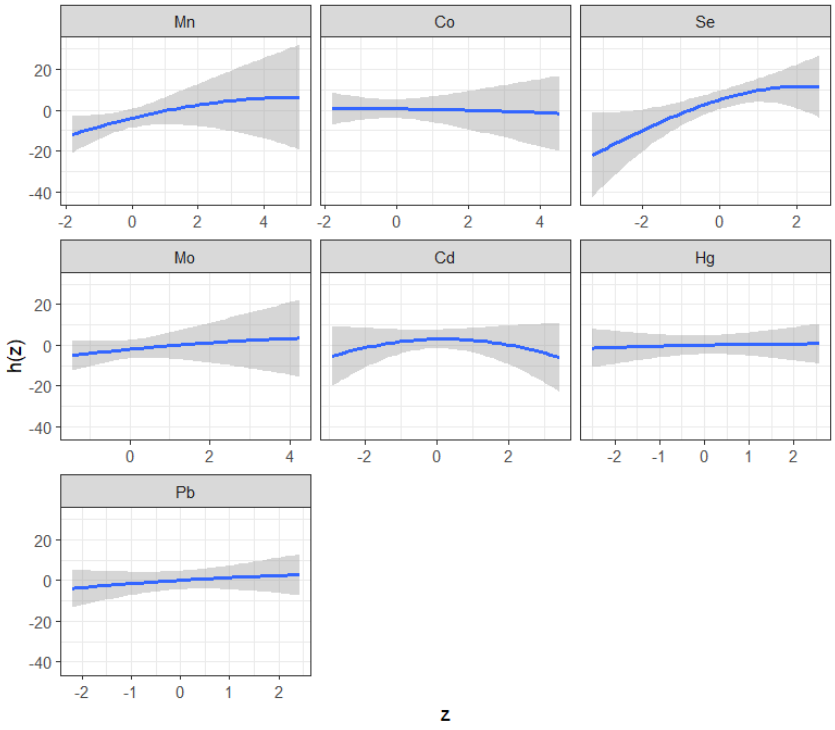
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S33. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age among children exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=138)

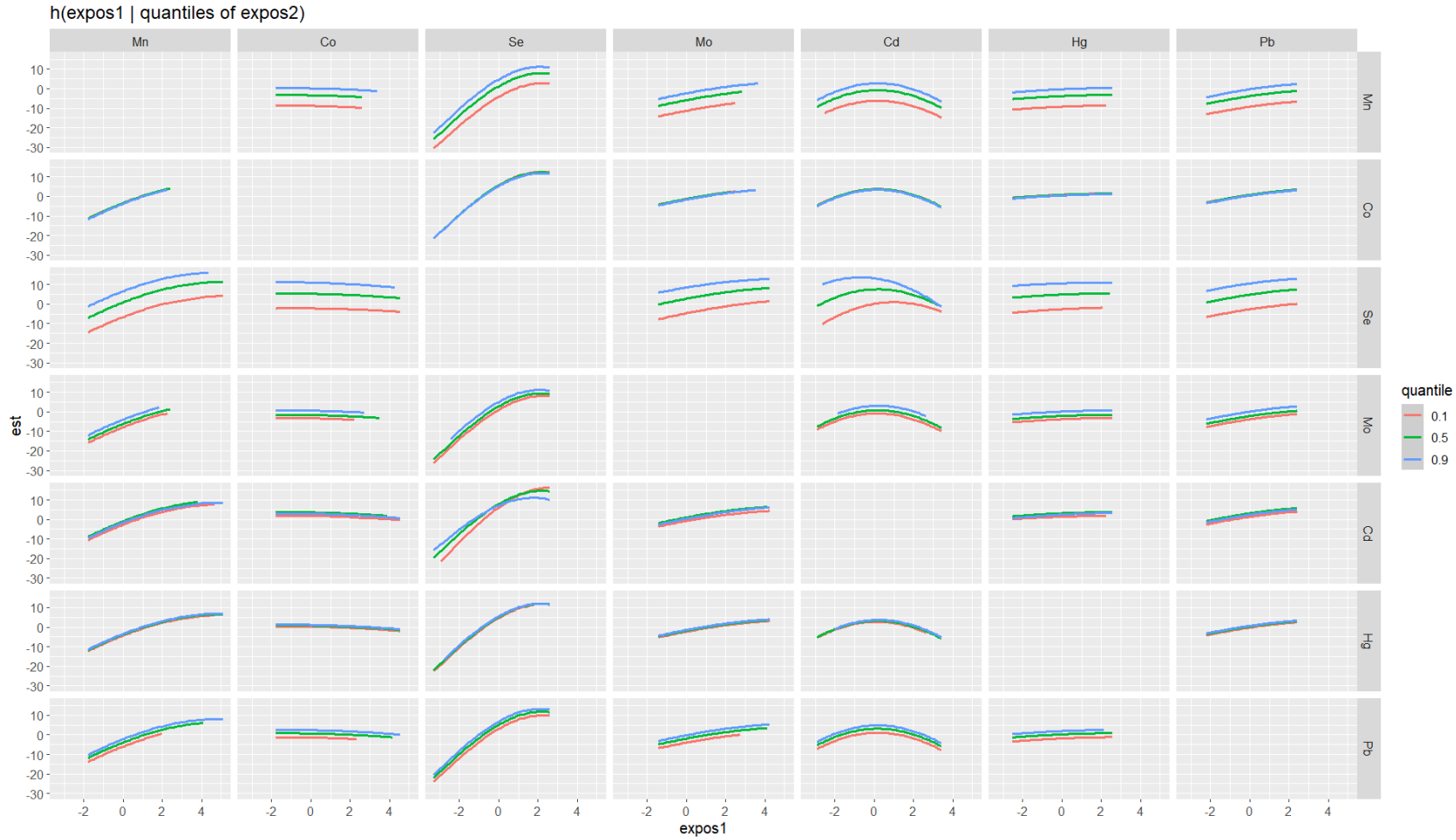
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



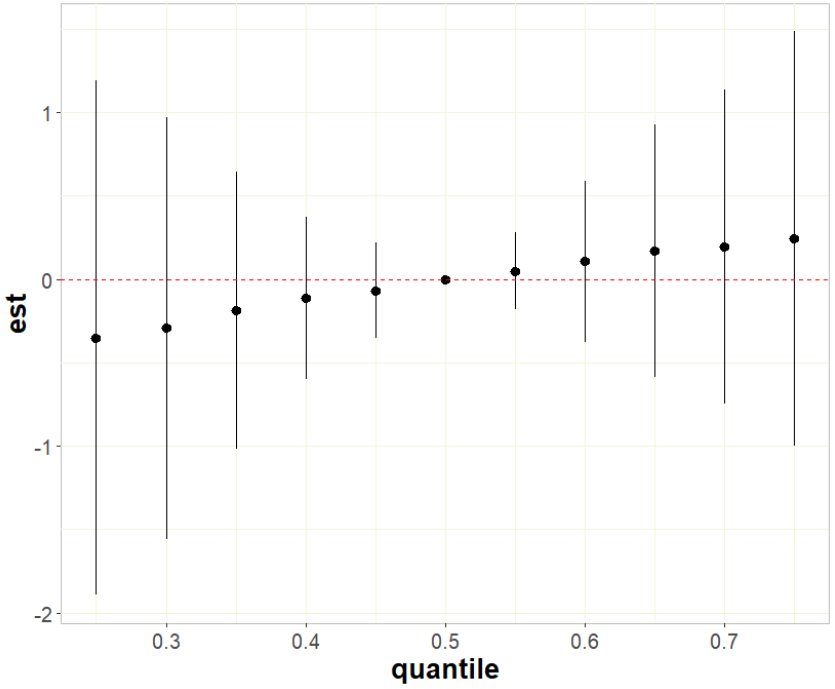
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



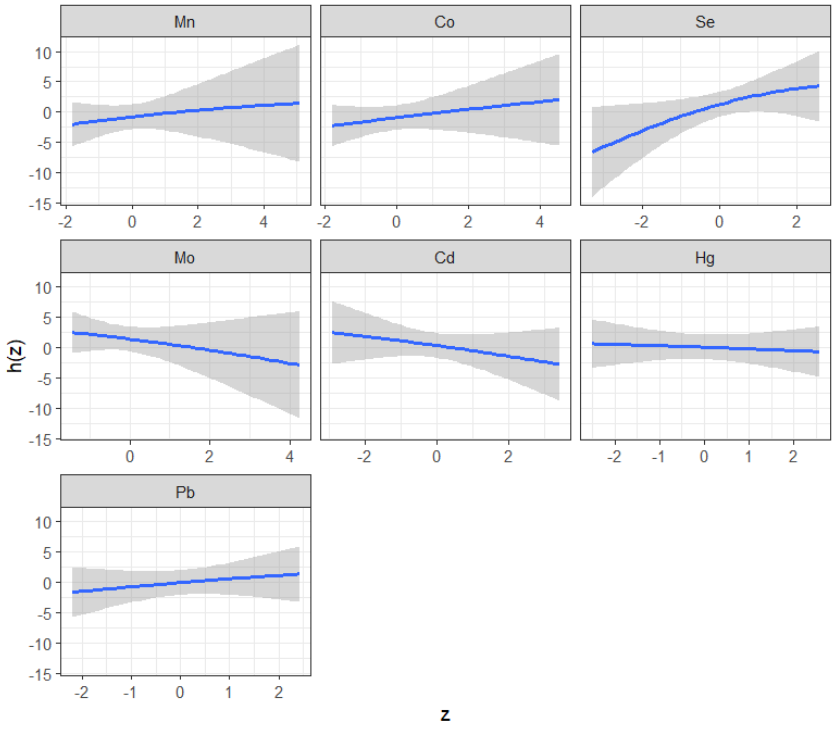
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S34. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age among children exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=138)

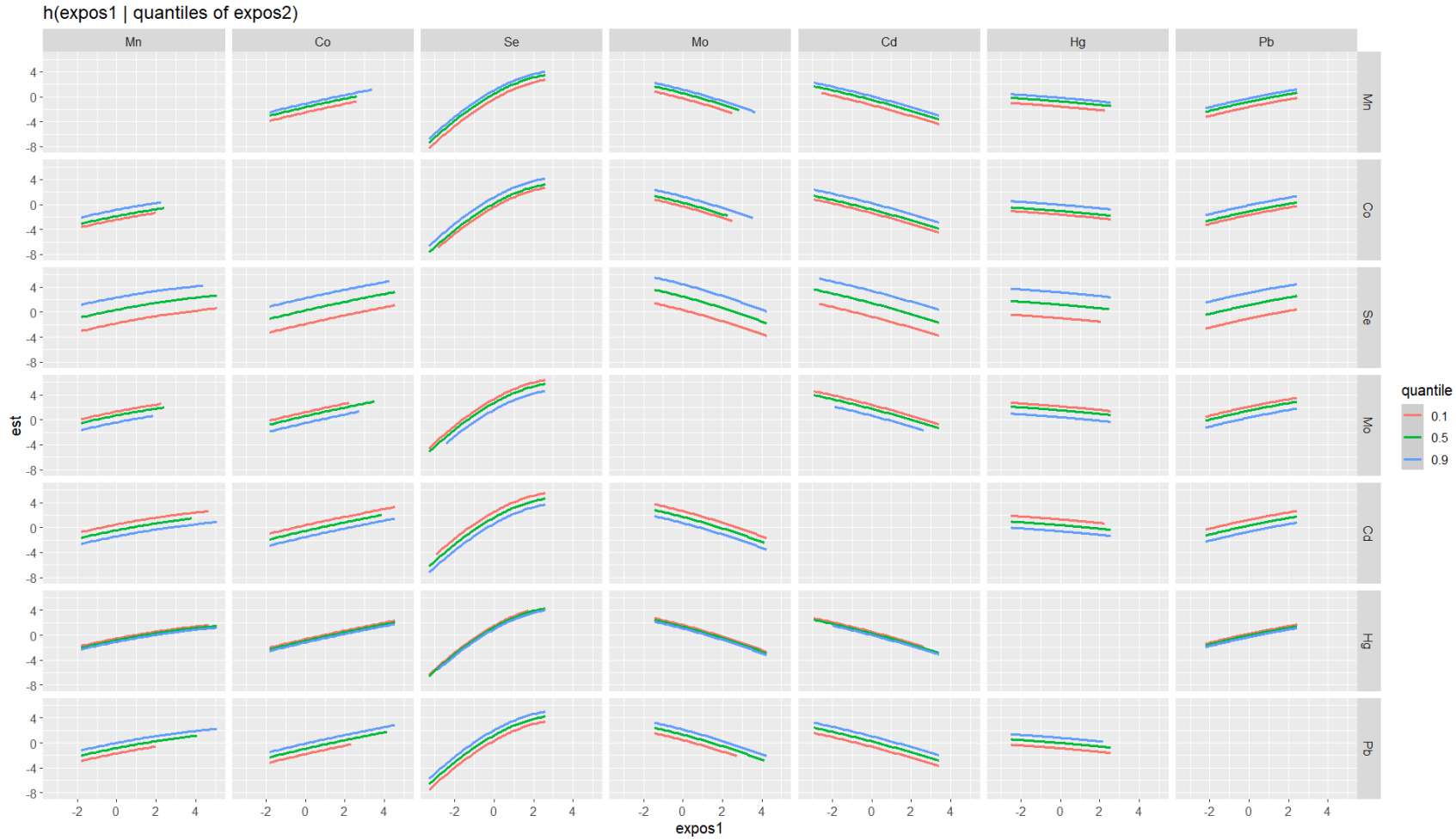
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



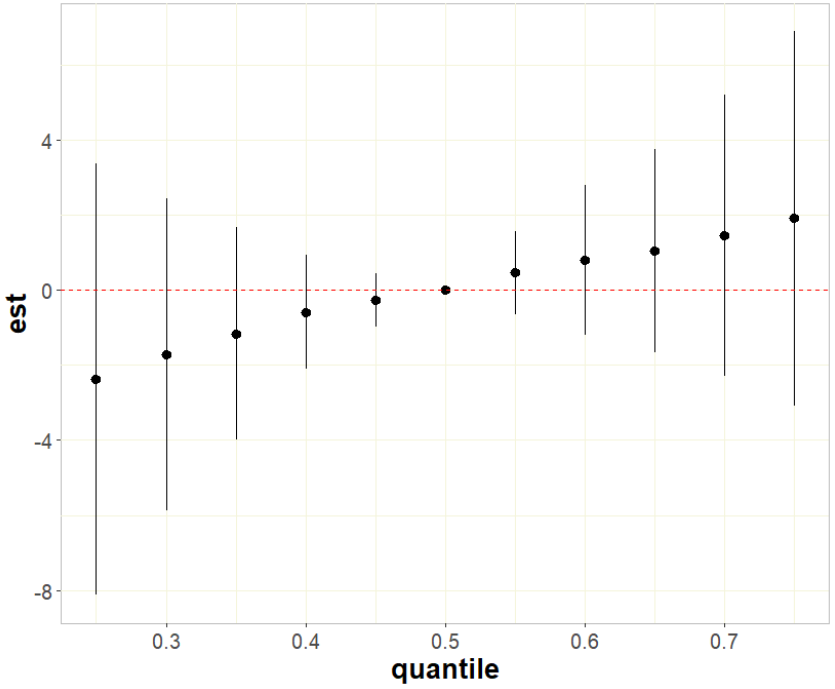
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



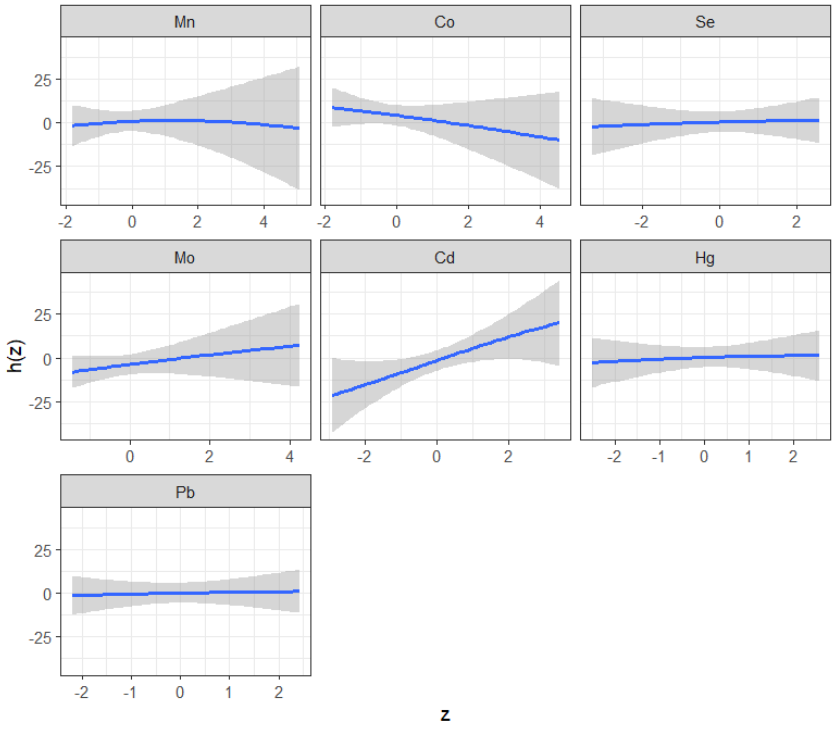
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S35. Joint associations of the metals with triglycerides at 4 years of age among children exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=138)

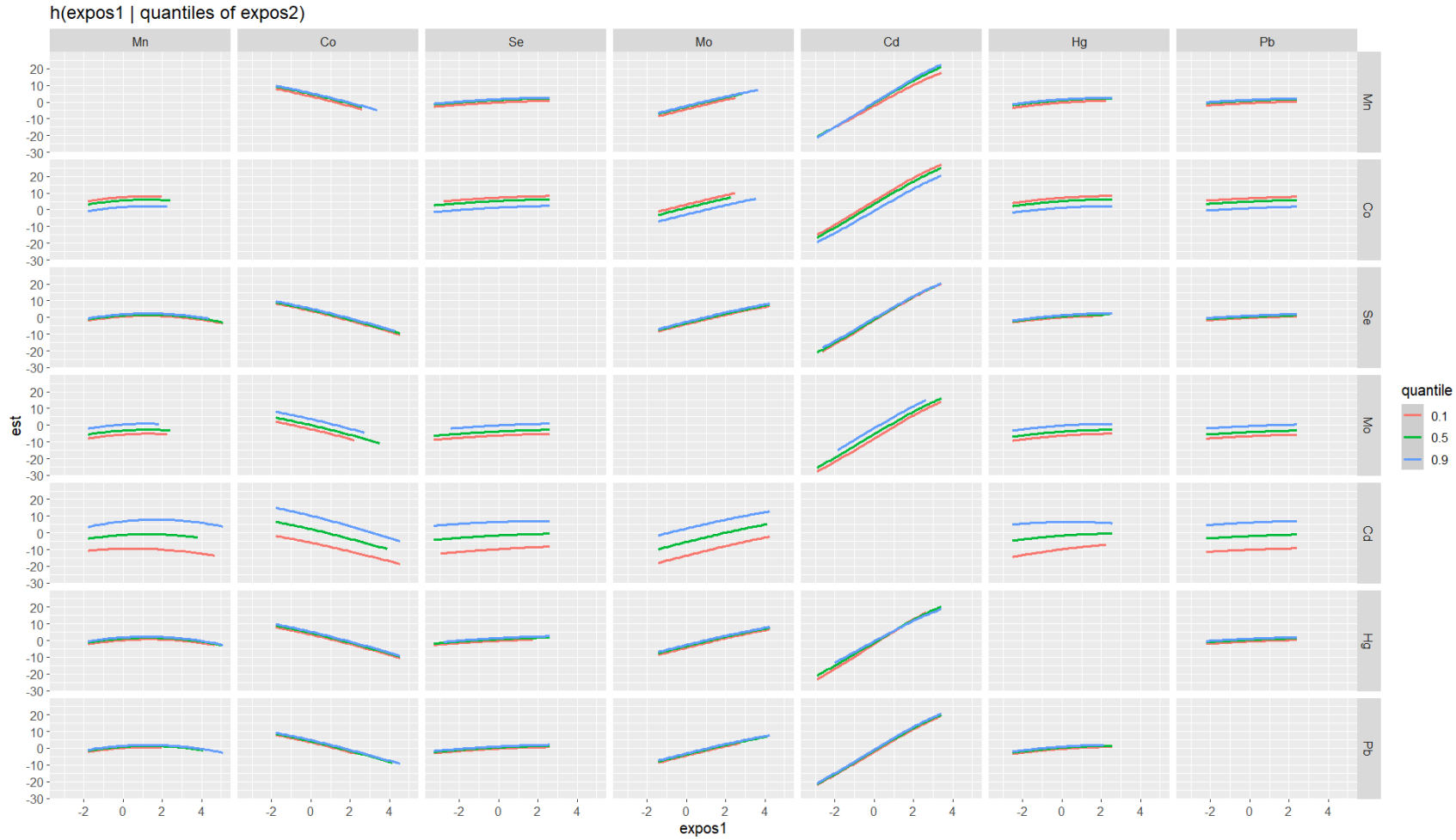
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



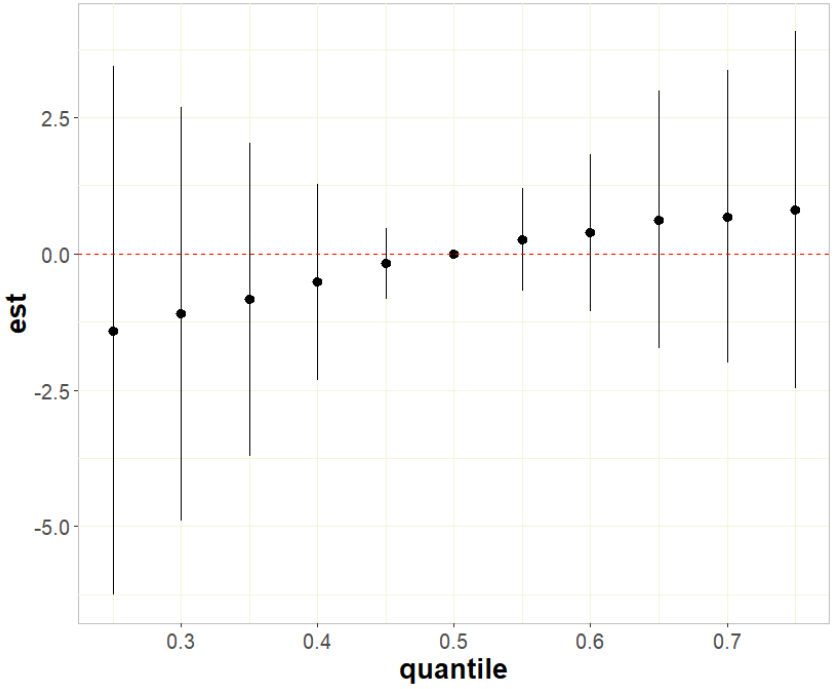
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



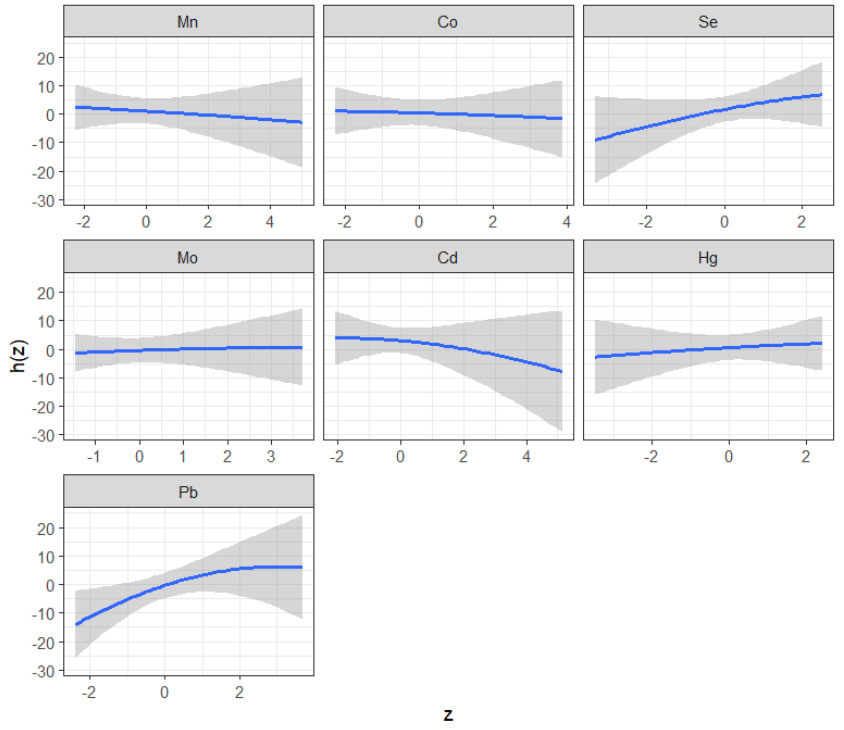
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S36. Joint associations of the metals with total cholesterol at 4 years of age among children not exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=153)

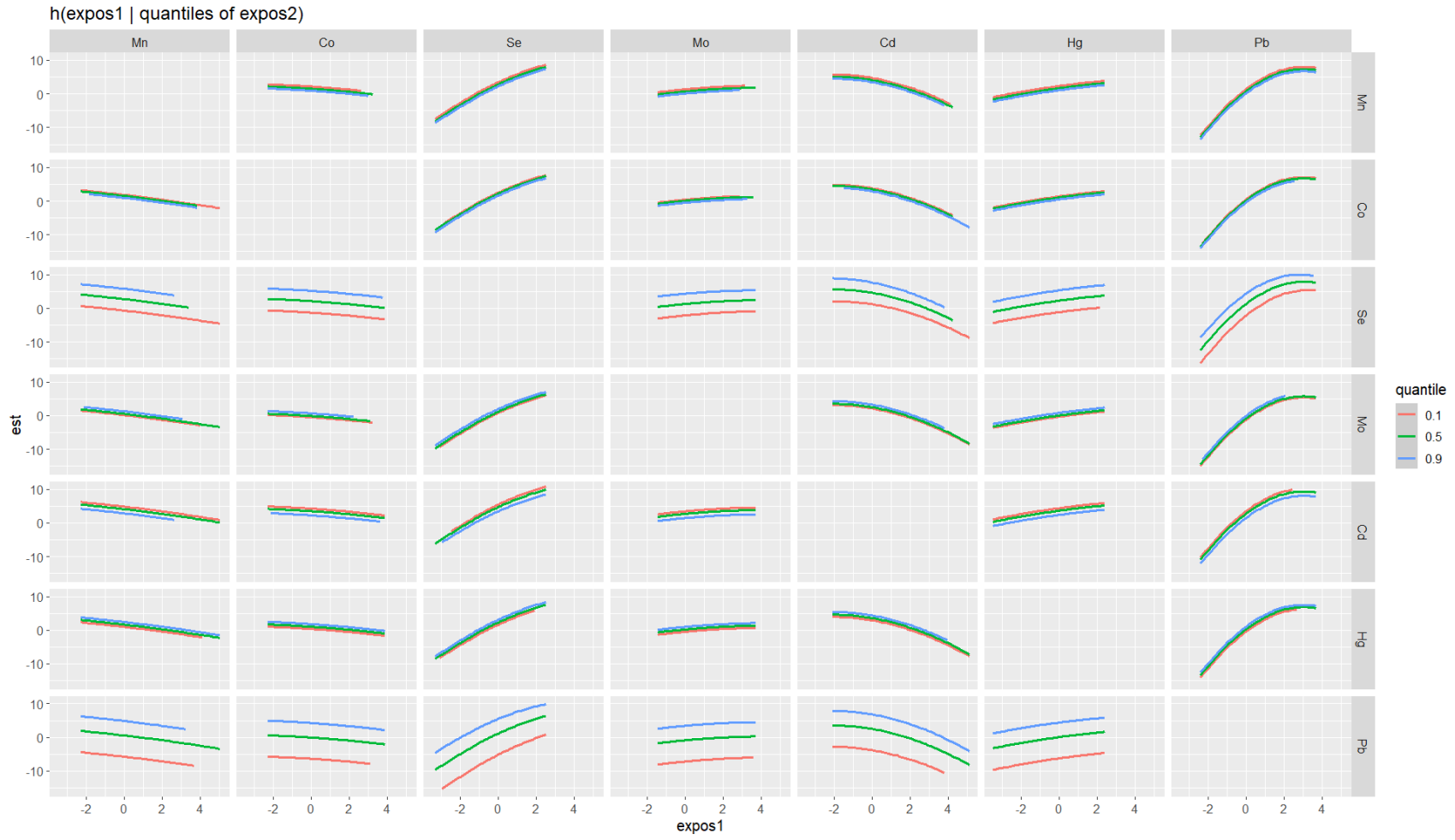
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



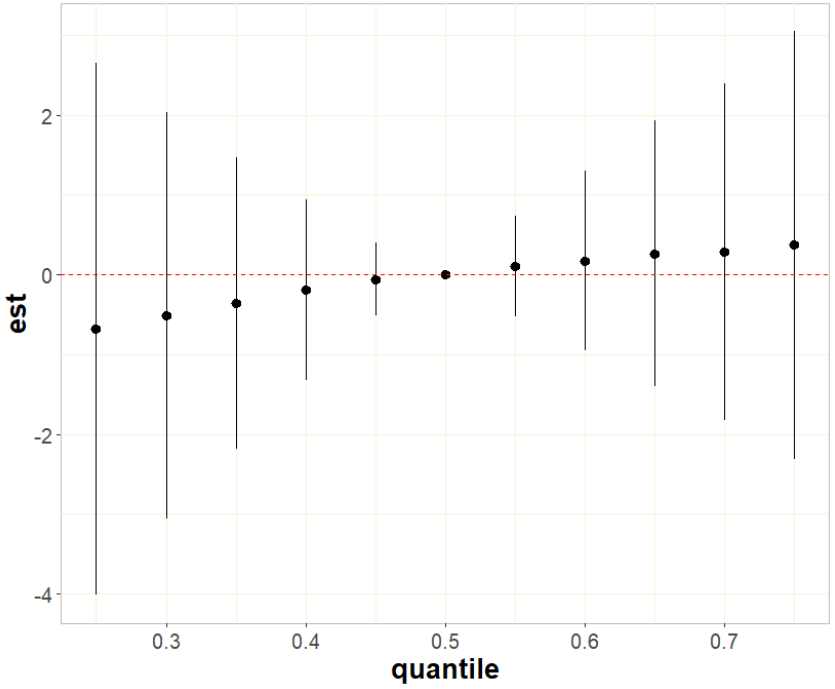
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



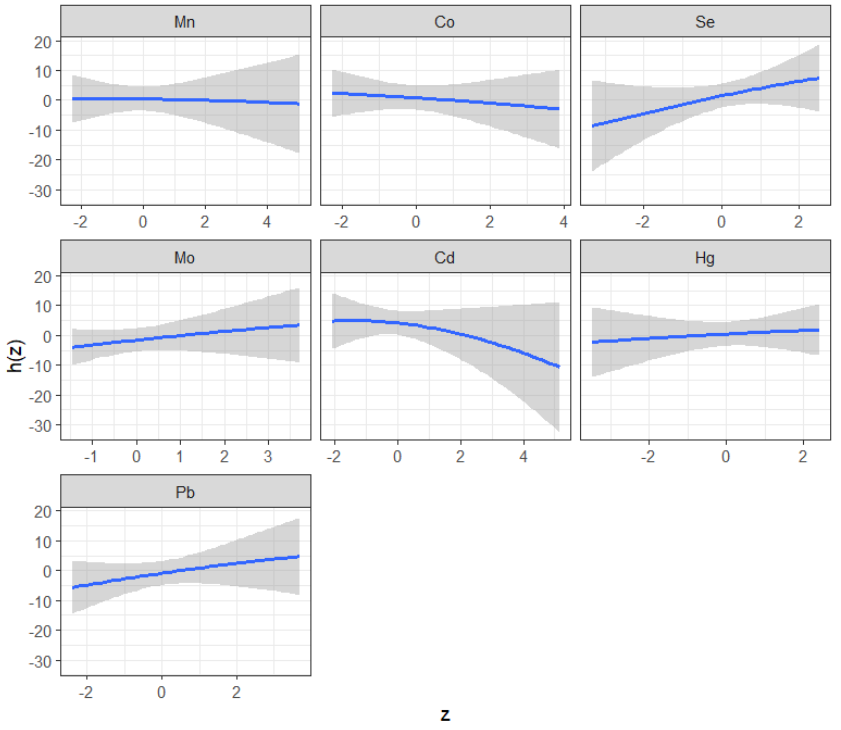
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S37. Joint associations of the metals with low-density lipoprotein cholesterol at 4 years of age among children not exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=153)

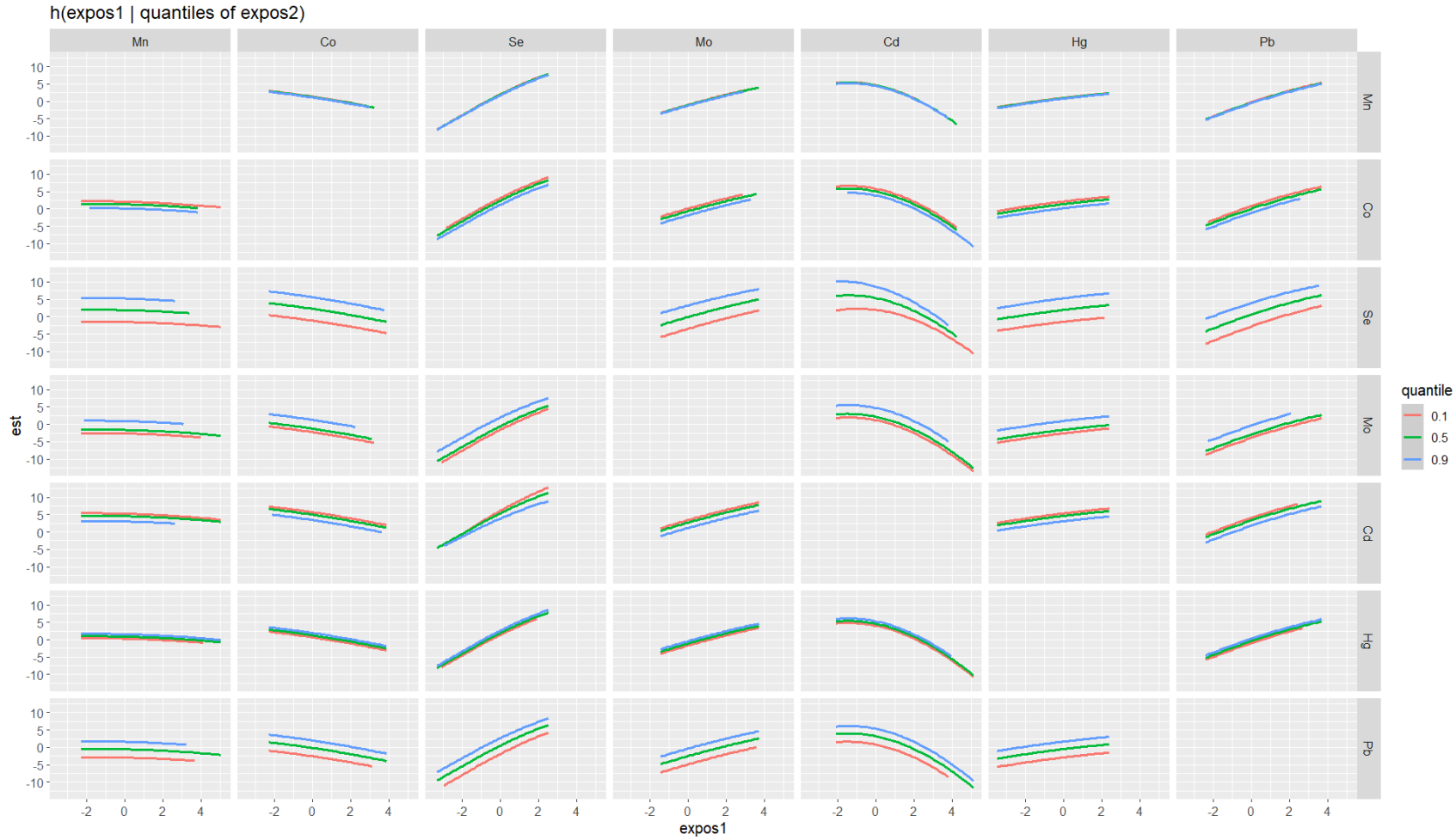
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



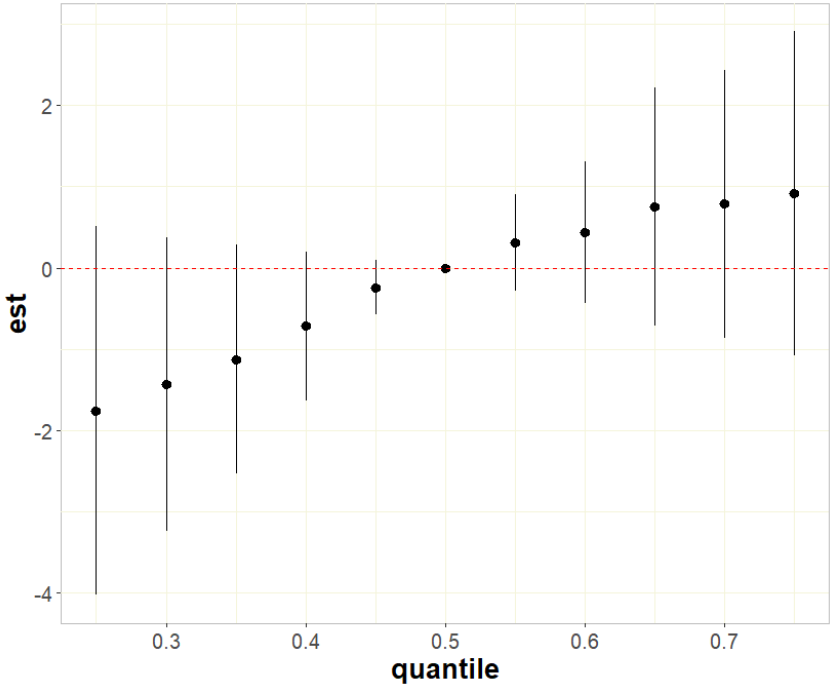
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



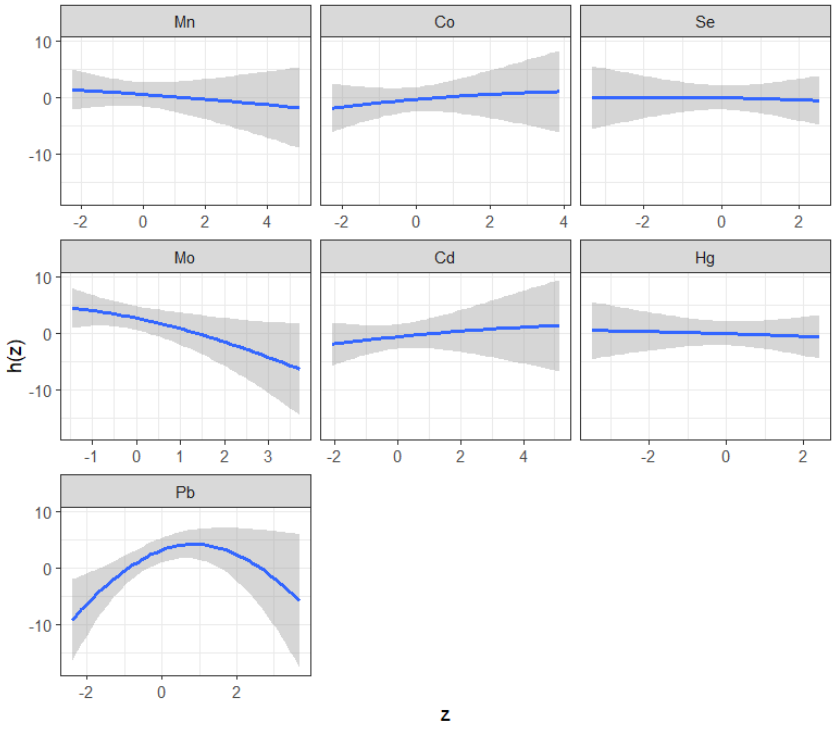
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S38. Joint associations of the metals with high-density lipoprotein cholesterol at 4 years of age among children not exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=153)

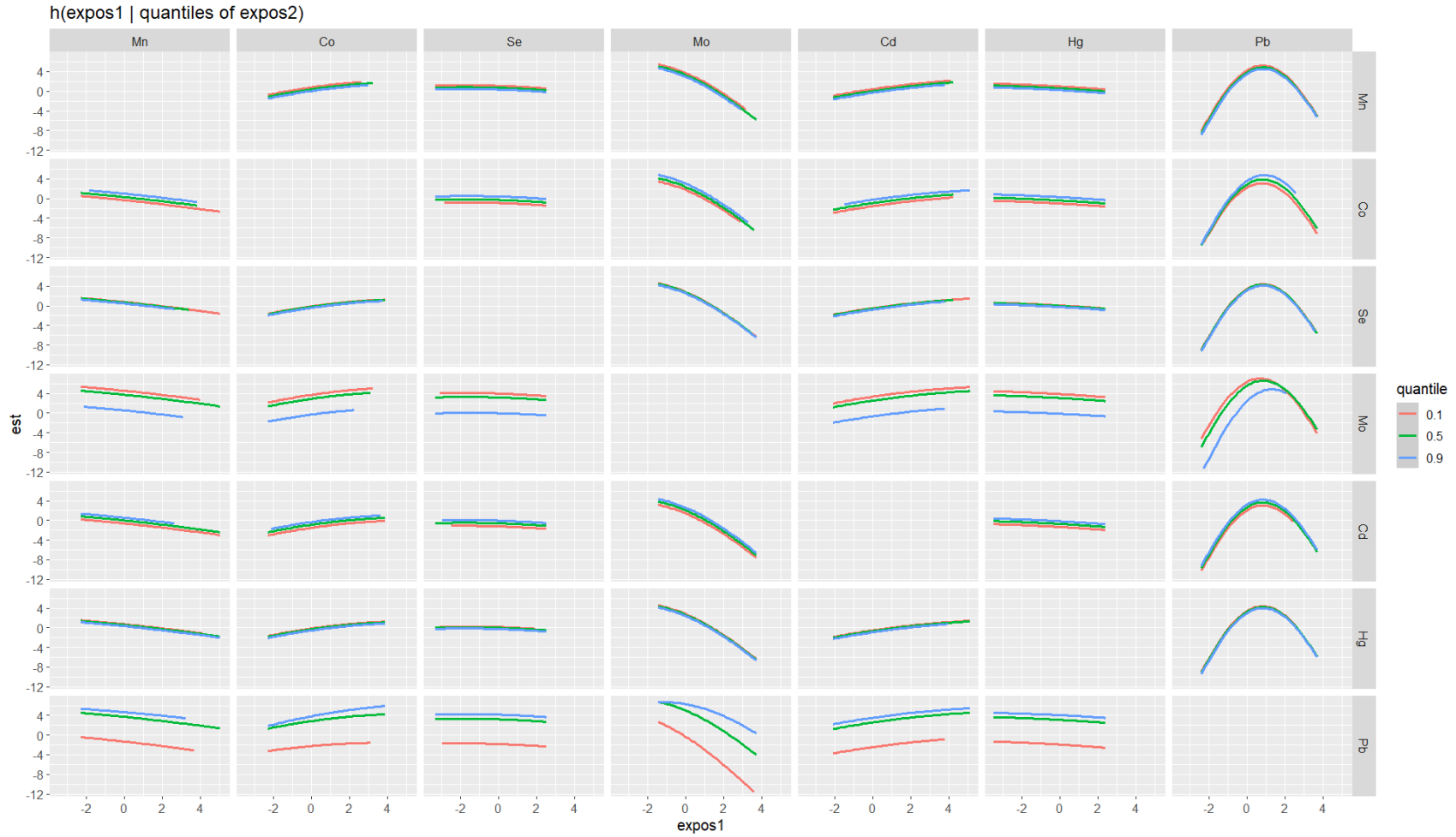
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



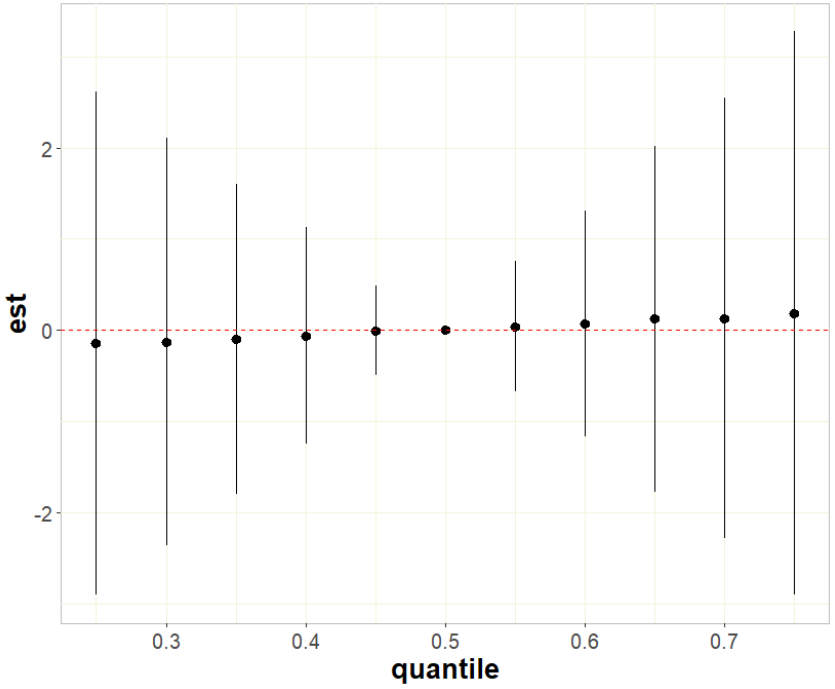
c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



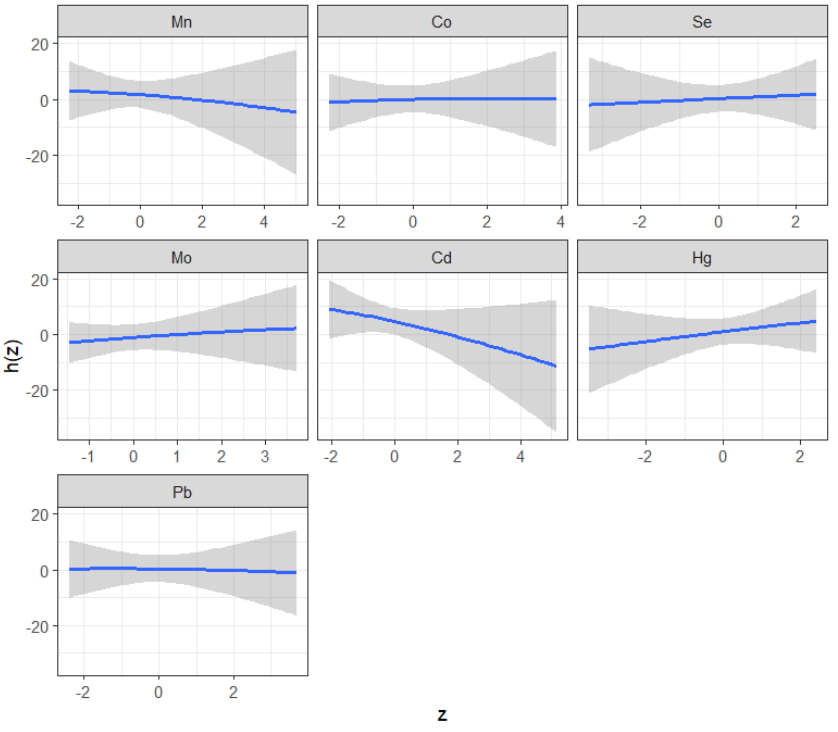
Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.

Figure S39. Joint associations of the metals with triglycerides at 4 years of age among children not exposed to secondhand smoke at 4 years of age, estimated by BKMR (n=153)

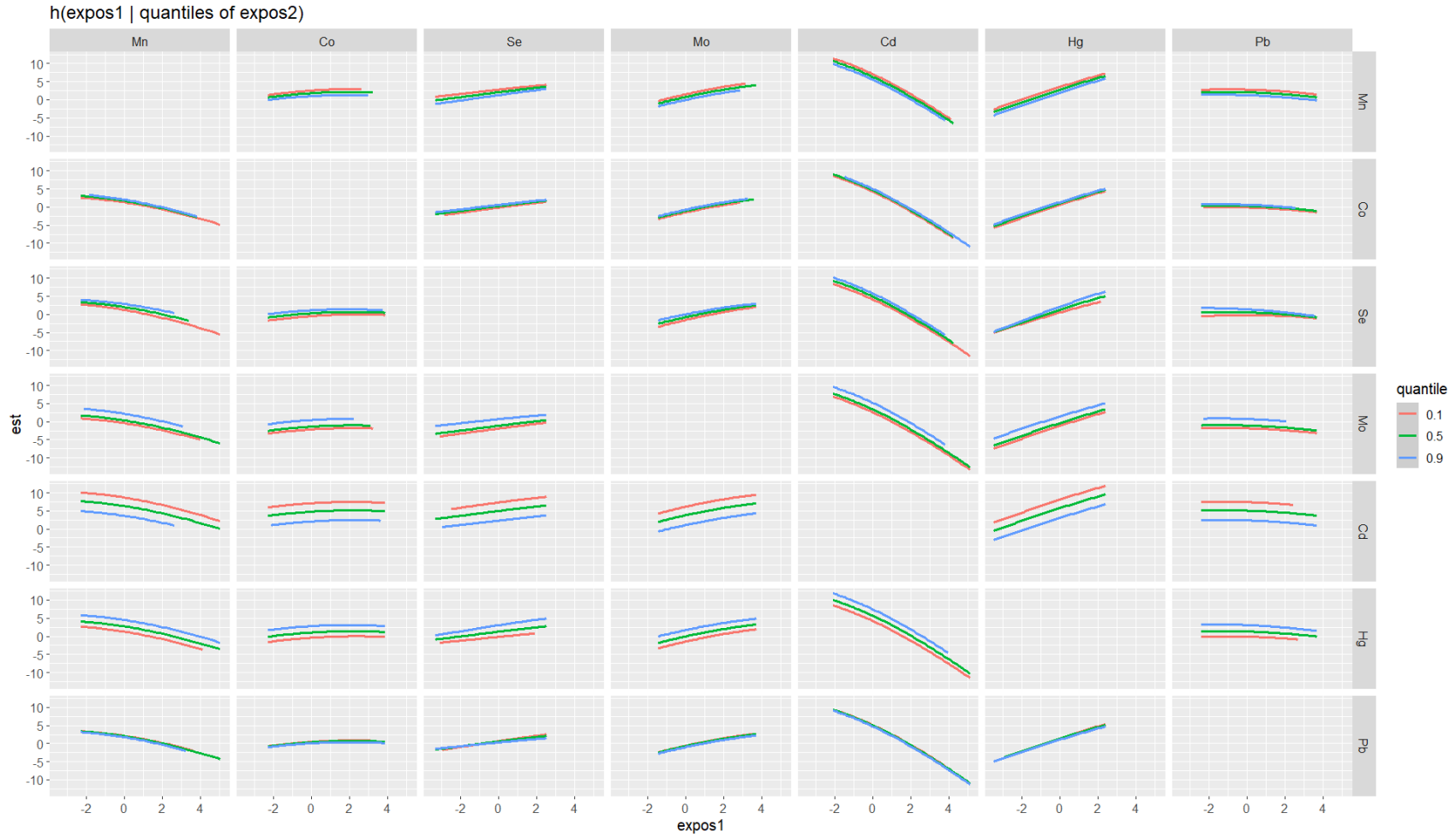
a. Difference in the outcome when setting all metals in the mixture to higher percentiles compared with the reference (25th percentile) with corresponding 95% credible intervals



b. Exposure-response functions and corresponding 95% credible intervals for each metal while holding the other exposures at their 50th percentiles



c. Exposure-response function for each metal exposure (column) with the second exposure (row) fixed at its 10th, 50th, and 90th percentiles, while holding the other exposures at their 50th percentiles



Abbreviations: Mn, manganese; Co, cobalt; Se, selenium; Mo, molybdenum; Cd, cadmium; Hg, mercury; Pb, lead. All models were adjusted for maternal education, child sex, and child fish/seafood intake at 4 years of age.