Electronic Supplementary Material (ESI) for Food & Function.

Joint Associations Among Non-essential Heavy Metals Mixtures and Nutritional Factors on Glucose Metabolism Indexes in the US Adults: Evidence from NHANES 2011–2016

Xiaolang Chen [1,2‡], Peipei Li [1,2‡], Yuanhao Huang [1,2‡], Yingnan Lv [3], Xia Xu [1,2], Huiyun Nong [1,2], Lulu Zhang [3], Huabei Wu [4], Chao Yu [1,2], Lina Chen [1,2], Di Liu [1,2], Lancheng Wei [1,2], Haiying Zhang[1,2,3*]

CONTENTS

Supplementary Method 4
Supplementary Tables 5
Table S1. Descriptive table of urinary metal concentrations. 5
Table S2. Distribution of glucose metabolism indexes. 6
Table S3. The posterior inclusion probabilities of metals under the Bayesian kernel machine regression model in glucose metabolism indexes. 6
Table S4. Descriptive table of nutrients grouped by quantile of energy-adjusted DII. (Median [IQR]). 7
Table S5. Coefficients and 95% confidence intervals for the interquartile change of natural log-transformed urinary metals (ln μg/g creatinine) on glucose metabolism indexes and the interaction term between metal and energy-adjusted diet inflammatory index estimated using multivariate linear regression models. The diet inflammatory index was estimated by 28 nutrients which represent the total consumption from food intake. 8
Supplementary Figures 9
Figure S1. Flowchart of the overall design, NHANES from 2011-2016. NHANES, National Health and Nutrition Examination Survey; E-DII, energy-adjusted diet inflammatory index. 9
Figure S2. Directed acyclic graph of select covariates. 10
Figure S3. Correlations between urinary metal concentrations (ln ug/g creatinine). 11
Figure S4. Association of single heavy metal (ln ug/g creatinine) and fasting plasma glucose (ln-mg/dL) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted fasting plasma glucose (ln-mg/dL) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval. 11
Figure S5. Association of single heavy metal (ln ug/g creatinine) and hemoglobin A1c (%) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted hemoglobin A1c (%) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond

to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval. 12

Figure S6. Association of single heavy metal (ln ug/g creatinine) and homeostatic model assessment for insulin resistance (ln) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted homeostatic model assessment for insulin resistance (ln) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval. 13

Figure S7. The Cd-hemoglobin A1c (%) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index. 14

Figure S8. The W-hemoglobin A1c (%) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index...........15

Figure S9. The Ba- homeostatic model assessment for insulin resistance (HOMA-IR) (ln) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index. 16

Figure S10. The Tl- homeostatic model assessment for insulin resistance (ln) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index. 17

Figure S11. Impact of E-DII and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). DII-ad, adjusted energy diet inflammatory index. 18

Figure S12. Impact of macro-nutritions and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). 19

Figure S13. Impact of minerals and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). 20

Figure S14. Impact of A vitamins and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). 21

Supplementary Method

We defined diabetes according to the following criteria: ① fasting blood glucose (FPG) ≥ 126 mg/dL; ② or postprandial 2h plasma glucose ≥ 200 mg/dL, ③ or glycated hemoglobin A1c (HbA1c) ≥ 6.5%, ④ or self-reported doctor diagnosis of diabetes, ⑤ or use of insulin, ⑥ or oral hypoglycemic medication [1]. According to this definition, our study included 395 individuals with diabetes and 1,343 individuals without diabetes.

We use the Bayesian kernel machine regression (BKMR) model to visualization the interaction between nutritional factors and metals on the outcome of diabetes. When the remaining other variables were fixed at the median, the dose-response curve between expos1 concentration and outcome changed in slope as the expos2 concentration from 10th to 90th, indicating a possible interaction.

Supplementary Tables

Table S1. Descriptive table of urinary metal concentrations.

Metal	LOD (ug/L) (2011-2012)	LOD (ug/L) (2013-2016)	Urinary concentration (ug/L)					Creatinine-adjusted urinary concentration (ug/g creatinine)					Ln-ug/g (creatinine)
			5th	25th	50th	75th	95th	5th	25th	50th	75th	95th	Mean (SD)
Barium	0.1000	0.060	0.200	0.510	1.000	1.950	4.482	22.881	58.333	102.964	184.386	425.762	4.625 (0.908)
Cadmium	0.056	0.036	0.041	0.131	0.255	0.496	1.241	6.065	13.771	26.165	46.034	111.141	3.242 (0.887)
Lead	0.080	0.030	0.080	0.200	0.35	0.62	1.380	11.292	21.564	35.279	57.913	117.919	3.575 (0.741)
Antimony	0.041	0.022	0.016	0.029	0.044	0.074	0.176	1.870	3.183	4.531	6.905	16.111	1.579 (0.659)
Thallium	0.02	0.018	0.047	0.098	0.159	0.251	0.430	6.203	10.98	15.74	22.385	40.866	2.756 (0.579)
Tungsten	0.026	0.018	0.013	0.026	0.053	0.107	0.280	1.545	3.25	5.429	9.214	23.705	1.732 (0.840)
Uranium	0.003	0.002	0.001	0.003	0.005	0.010	0.029	0.166	0.319	0.523	0.938	3.025	-0.542 (0.901)
Arsenic	1.25	0.260	1.510	3.592	6.840	14.45	56.982	199.033	377.597	644.827	1369.921	6616.069	6.677 (1.056)

Table S2. Distribution of glucose metabolism indexes.

Variables	Original distribution					Ln-transformation
	5th	25th	50th	75th	95th	Mean (SD)
FPG (mg/dL)	82.61	93.00	100.00	110.00	165.71	4.65 (0.23)
HbA1c (%)	4.80	5.30	5.60	5.900	7.70	—
HOMA-IR	0.70	1.42	2.34	4.00	10.43	0.90 (0.85)

Table S3. The posterior inclusion probabilities of metals under the Bayesian kernel machine regression model in glucose metabolism indexes.

Variables	Barium	Cadmium	Lead	Antimony	Thallium	Tungsten	Uranium	Arsenic
FPG	0.004	8E-05	0	0	0.016	0.002	0.002	0
HbA1c	0.005	1	1	0.013	0.021	0.897	0.003	0.004
HOMA-IR	1	0.232	0.269	0.379	0.874	0.207	0.544	0.114

Table S4. Descriptive table of nutrients grouped by quantile of energy-adjusted DII. (Median [IQR]).

Nutrients	Overall (n = 1738)	E-DII Q1 (n = 434)	E-DII Q2 (n = 435)	E-DII Q3 (n = 435)	E-DII Q4 (n = 434)
Protein (mg)	78.50 [65.30, 92.11]	87.39 [75.08, 102.91]	82.20 [70.39, 95.13]	77.33 [64.00, 90.11]	68.01 [57.64, 79.37]
Fat (mg)	76.86 [65.70, 87.85]	77.41 [65.30, 88.42]	74.73 [63.23, 86.26]	76.43 [65.99, 85.98]	78.61 [68.32, 89.59]
Carbohydrate (mg)	242.27 [212.97, 273.05]	237.04 [203.34, 267.65]	237.88 [203.79, 269.58]	240.93 [214.36, 268.22]	256.22 [226.56, 289.65]
Fiber (mg)	16.29 [11.89, 20.91]	20.43 [15.79, 25.89]	17.85 [12.94, 21.81]	15.15 [11.47, 19.24]	12.93 [9.87, 16.64]
VitB1 (mg)	1.50 [1.25, 1.79]	1.60 [1.34, 1.91]	1.51 [1.27, 1.83]	1.48 [1.25, 1.79]	1.38 [1.12, 1.65]
VitB2 (mg)	1.89 [1.52, 2.34]	2.15 [1.73, 2.65]	1.97 [1.61, 2.39]	1.85 [1.49, 2.24]	1.63 [1.30, 2.00]
Niacin (mg)	23.69 [19.29, 28.72]	27.24 [22.61, 33.70]	25.61 [20.79, 29.96]	23.15 [19.20, 27.00]	19.76 [16.78, 23.66]
VitB6 (mg)	1.88 [1.49, 2.33]	2.37 [1.96, 2.97]	2.04 [1.71, 2.45]	1.78 [1.49, 2.10]	1.39 [1.09, 1.67]
Folate (μg)	465.21 [366.53, 601.39]	549.43 [406.76, 689.70]	479.66 [387.00, 610.31]	456.08 [362.43, 554.81]	416.47 [313.31, 527.58]
VitB12 (μg)	4.02 [2.78, 5.52]	5.00 [3.26, 7.45]	4.33 [2.95, 5.90]	3.76 [2.57, 5.03]	3.45 [2.43, 4.59]
Calcium (mg)	861.36 [662.48, 1108.72]	953.08 [734.70, 1178.01]	879.26 [684.19, 1107.15]	850.15 [616.57, 1093.05]	801.21 [597.42, 1037.07]
Phosphorus (mg)	1309.74 [1127.10, 1490.40]	1418.60 [1247.29, 1609.61]	1339.05 [1192.37, 1502.98]	1273.99 [1103.69, 1438.05]	1197.24 [1002.27, 1341.12]
Sodium (mg)	3302.07 [2821.10, 3836.44]	3436.56 [2909.12, 3955.52]	3393.01 [2898.41, 3902.03]	3227.25 [2789.78, 3795.48]	3215.48 [2719.35, 3676.03]
Potassium (mg)	2531.89 [2124.93, 2988.90]	3070.07 [2640.53, 3469.88]	2637.30 [2274.20, 3032.93]	2413.73 [2075.62, 2760.26]	2081.79 [1751.14, 2438.53]
Iron (mg)	13.07 [10.98, 16.08]	14.54 [11.93, 17.96]	13.13 [11.18, 16.27]	12.89 [10.99, 15.69]	12.09 [10.10, 14.27]
Zinc (mg)	10.05 [8.40, 12.26]	11.09 [9.09, 14.04]	10.22 [8.76, 12.16]	9.84 [8.23, 12.04]	9.27 [7.84, 11.02]
Selenium (μg)	109.92 [91.12, 130.42]	118.70 [96.59, 138.00]	115.32 [95.84, 134.28]	108.30 [92.13, 129.68]	98.08 [83.13, 114.24]
Magnesium (mg)	283.17 [231.24, 346.04]	357.81 [302.51, 403.29]	299.10 [263.77, 355.19]	269.47 [224.25, 306.30]	223.23 [185.26, 262.45]
Copper (mg)	1.13 [0.92, 1.40]	1.41 [1.19, 1.71]	1.20 [1.00, 1.46]	1.06 [0.90, 1.26]	0.92 [0.74, 1.09]
Cholin (mg)	310.22 [247.48, 383.69]	352.68 [294.12, 425.07]	325.39 [270.66, 394.23]	309.45 [252.67, 368.66]	250.57 [202.60, 313.15]
VitC (mg)	65.07 [32.96, 112.42]	102.71 [62.62, 153.56]	69.63 [37.53, 118.88]	56.85 [29.28, 99.70]	39.74 [15.58, 72.44]
A vitamins (μg)	1271.86 [858.96, 1981.37]	2214.76 [1486.14, 3433.06]	1435.05 [987.99, 1997.38]	1113.42 [778.57, 1572.27]	889.13 [598.51, 1213.81]
Omega 3 (mg)	1.87 [1.46, 2.40]	2.30 [1.77, 2.94]	1.99 [1.56, 2.51]	1.84 [1.45, 2.22]	1.56 [1.25, 1.94]
Omega 6 (mg)	15.56 [12.16, 19.34]	16.85 [13.63, 21.64]	15.84 [12.50, 20.69]	14.91 [11.92, 18.67]	13.91 [11.25, 17.13]

Notes: E-DII, energy-adjusted diet inflammatory index.

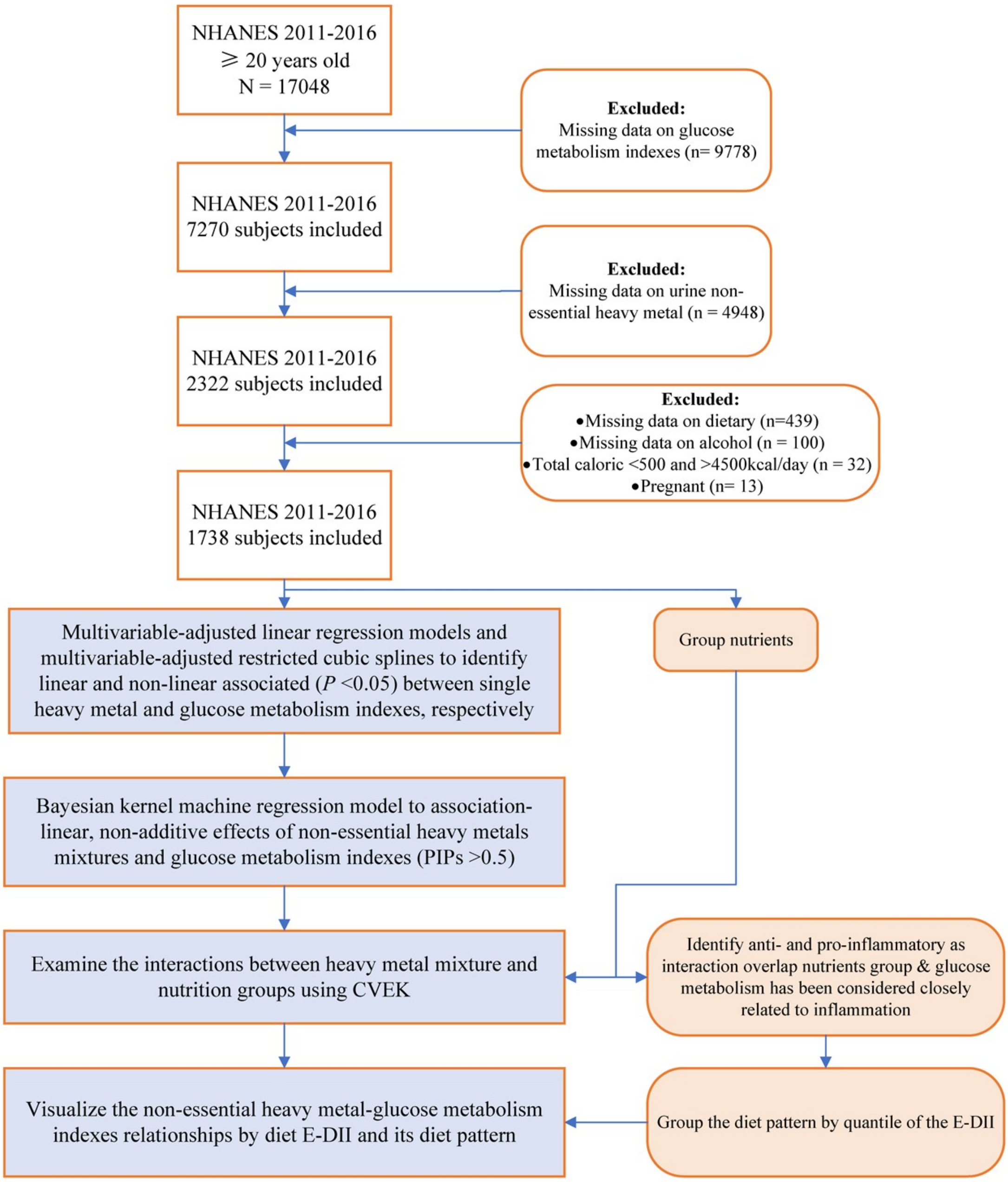
Table S5. Coefficients and 95% confidence intervals for the interquartile change of natural log-transformed urinary metals (ln μg/g creatinine) on glucose metabolism indexes and the interaction term between metal and energy-adjusted diet inflammatory index estimated using multivariate linear regression models. The diet inflammatory index was estimated by 28 nutrients which represent the total consumption from food intake.

	Barium		Cadmium		Tungsten	
	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
Metal	-0.070	< 0.001	-0.142	0.030	-0.126	0.001
E-DII	-0.187	0.018	-0.127	0.177	-0.097	0.236
Metal x E-DII	0.050	0.046	-0.166	0.091	-0.063	0.099
Metal	0.167	< 0.001	-0.144	0.030	-0.135	0.001
Dietary range1	0.002	0.134	-0.099	0.143	-0.186	0.168
Metal × Dietary range1	-0.001	0.388	-0.002	0.190	-0.001	0.030
Metal	0.127	0.000	-0.150	0.030	-0.130	0.001
Dietary range2	0.002	0.558	-0.087	0.004	0.139	0.500
Metal × Dietary range2	-0.001	0.620	0.000	0.184	0.002	0.736
Metal	0.183	< 0.001	-0.141	0.030	-0.137	0.001
Dietary range3	2.818e-04	0.669	0.024	0.599	-0.172	0.003
Metal × Dietary range3	-6.611e-05	0.256	0.001	0.608	-0.001	0.045
Metal	0.1710	< 0.001	-0.144	0.030	-0.129	0.001
Dietary range4	0.001	0.000	0.031	0.006	-0.006	0.398
Metal × Dietary range4	-0.001	0.212	0.002	0.478	-0.001	0.263

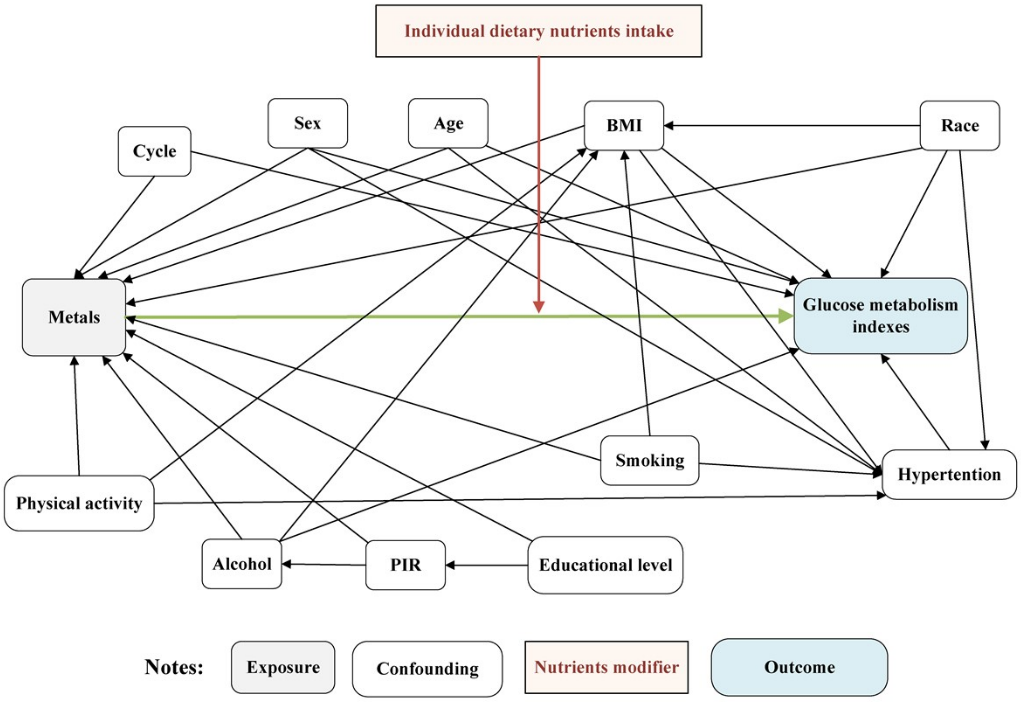
Notes: Barium corresponds to homeostatic model assessment for insulin resistance as the outcome; Cadmium and Tungsten correspond to hemoglobinA1c as the outcome. The dietary range 1 to 4 for Barium-homeostatic model assessment for insulin resistance were carbohydrate, protein, phosphorus, and magnesium; the dietary range 1 to 4 for Cadmium-hemoglobin A1c were carbohydrate, phosphorus, potassium, and iron; the dietary range 1 to 4 for Tungsten-hemoglobin A1c were carbohydrate, protein, phosphorus, and selenium. All linear regression models were adjusted with one metal, one interaction term of metal and nutrient, and the same set of covariates. All linear regression models have included the following covariates: survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, BMI (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no).

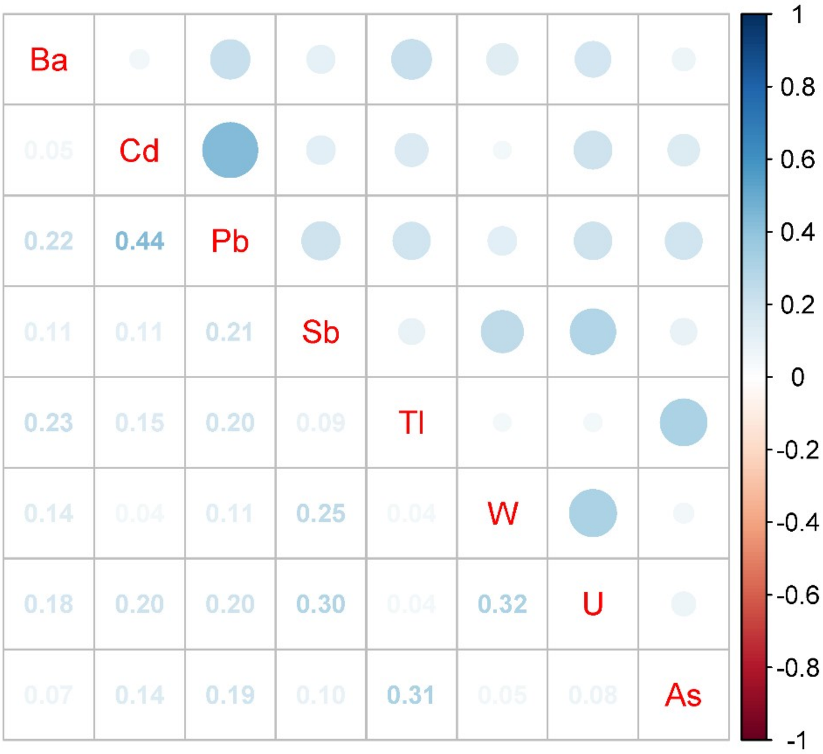
Supplementary Figures

Figure S1. Flowchart of the overall design, NHANES from 2011-2016. NHANES, National Health and Nutrition Examination Survey; E-DII, energy-adjusted diet inflammatory index.



143 Figure S2. Directed acyclic graph of select covariates.





144 Figure S3. Correlations between urinary metal concentrations (ln ug/g creatinine).

Figure S4. Association of single heavy metal (ln ug/g creatinine) and fasting plasma glucose (ln-mg/dL) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted fasting plasma glucose (ln-mg/dL) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval.

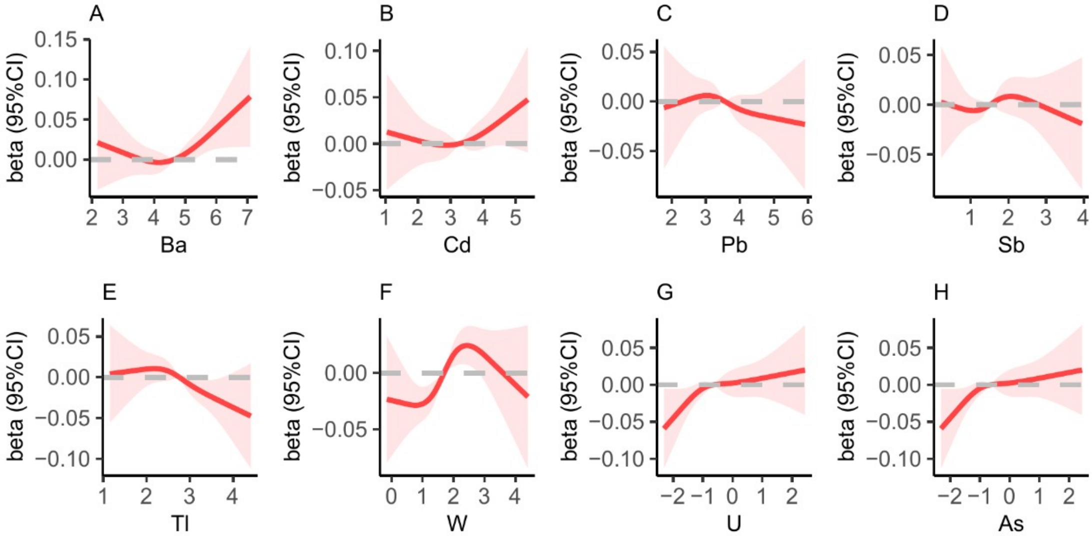


Figure S5. Association of single heavy metal (ln ug/g creatinine) and hemoglobin A1c (%) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted hemoglobin A1c (%) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval.

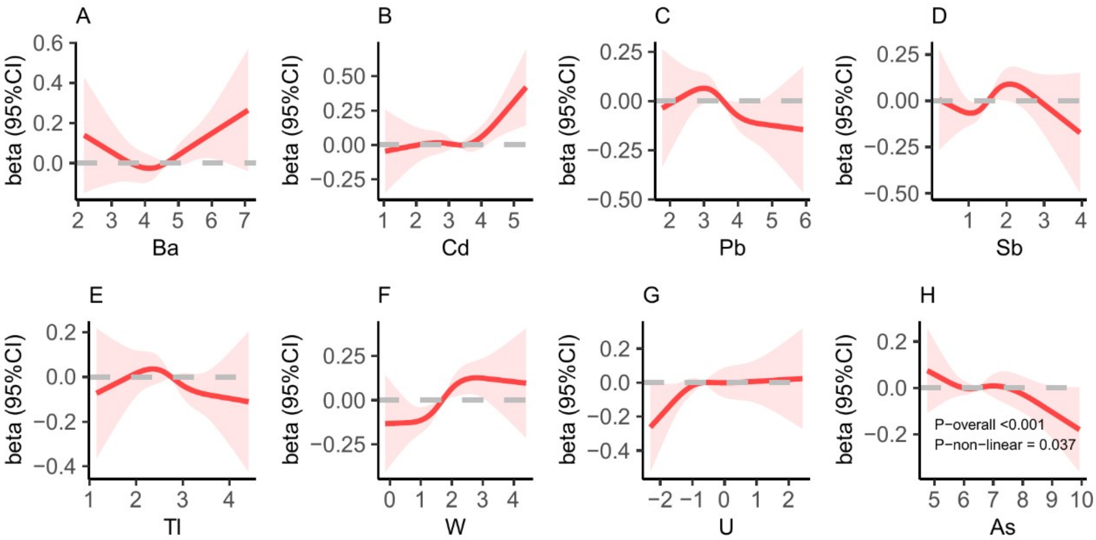


Figure S6. Association of single heavy metal (ln ug/g creatinine) and homeostatic model assessment for insulin resistance (ln) in multivariable-adjusted restricted cubic splines. Beta indicates change in predicted homeostatic model assessment for insulin resistance (ln) for a unit change in metal. Beta =0 means no association between exposures and the outcome; beta >0 means a positive association between exposures and outcomes; beta <0 means a negative association between exposures and outcomes. The solid red lines correspond to the central estimates, and the red-shaded regions indicate the 95% confidence intervals. The model was adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). NHANES, National Health and Nutrition Examination Survey; CI, confidence interval.

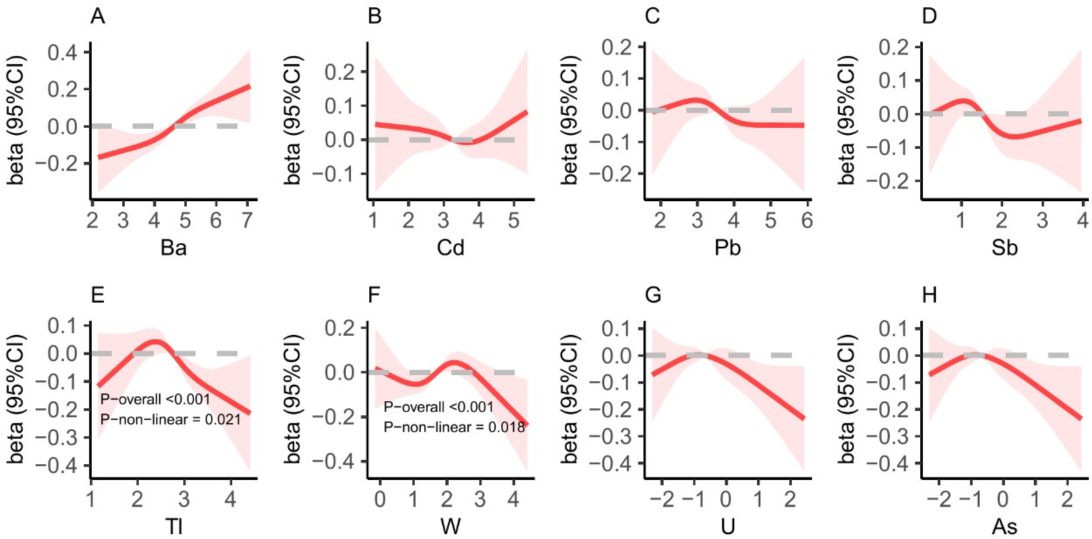
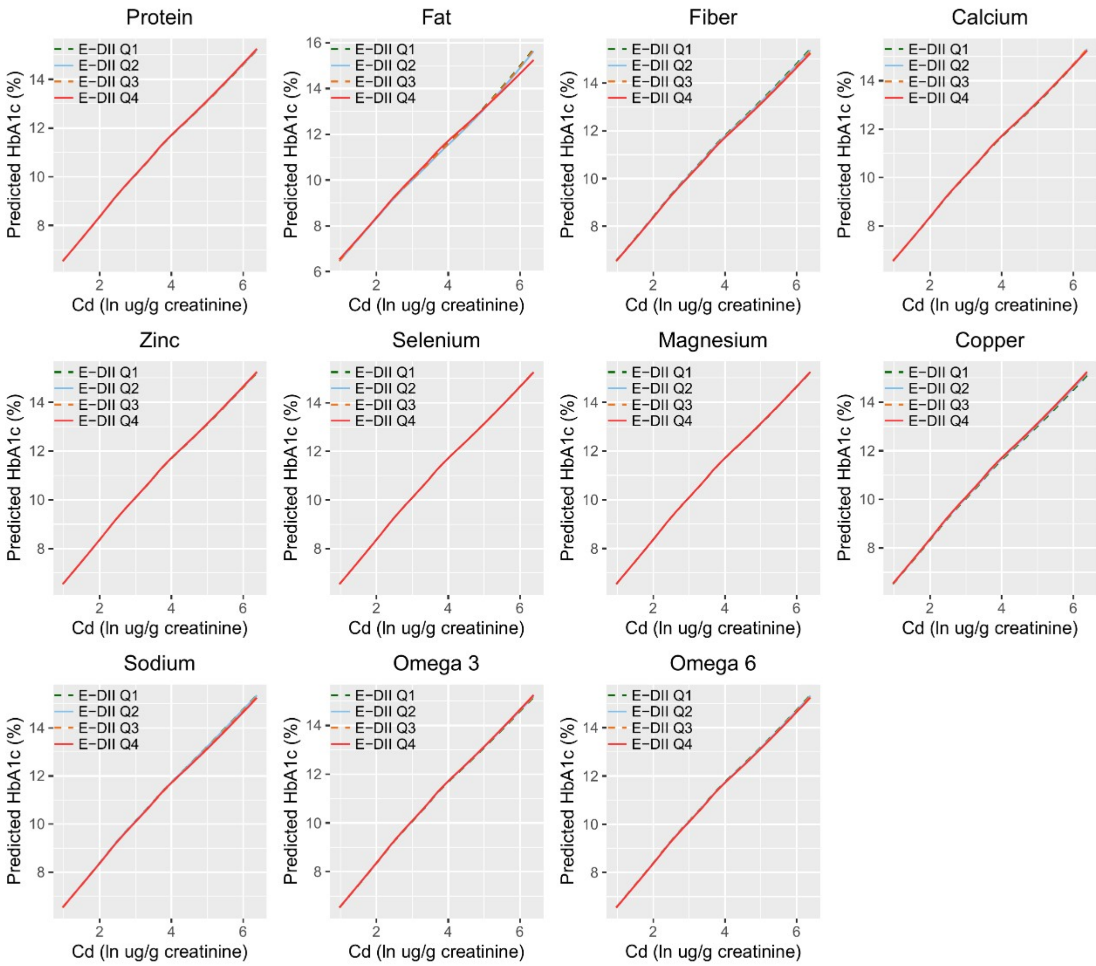


Figure S7. The Cd-hemoglobin A1c (%) relationships in the "E-DII Q4" group and in the hypothetically "E-DII Q1-3" group. E-DII, energy-adjusted diet inflammatory index.



178 Figure S8. The W-hemoglobin A1c (%) relationships in the "E-DII Q4" group and in the hypothetically "E-DII Q1-3" group. E-DII, energy-adjusted diet inflammatory index.

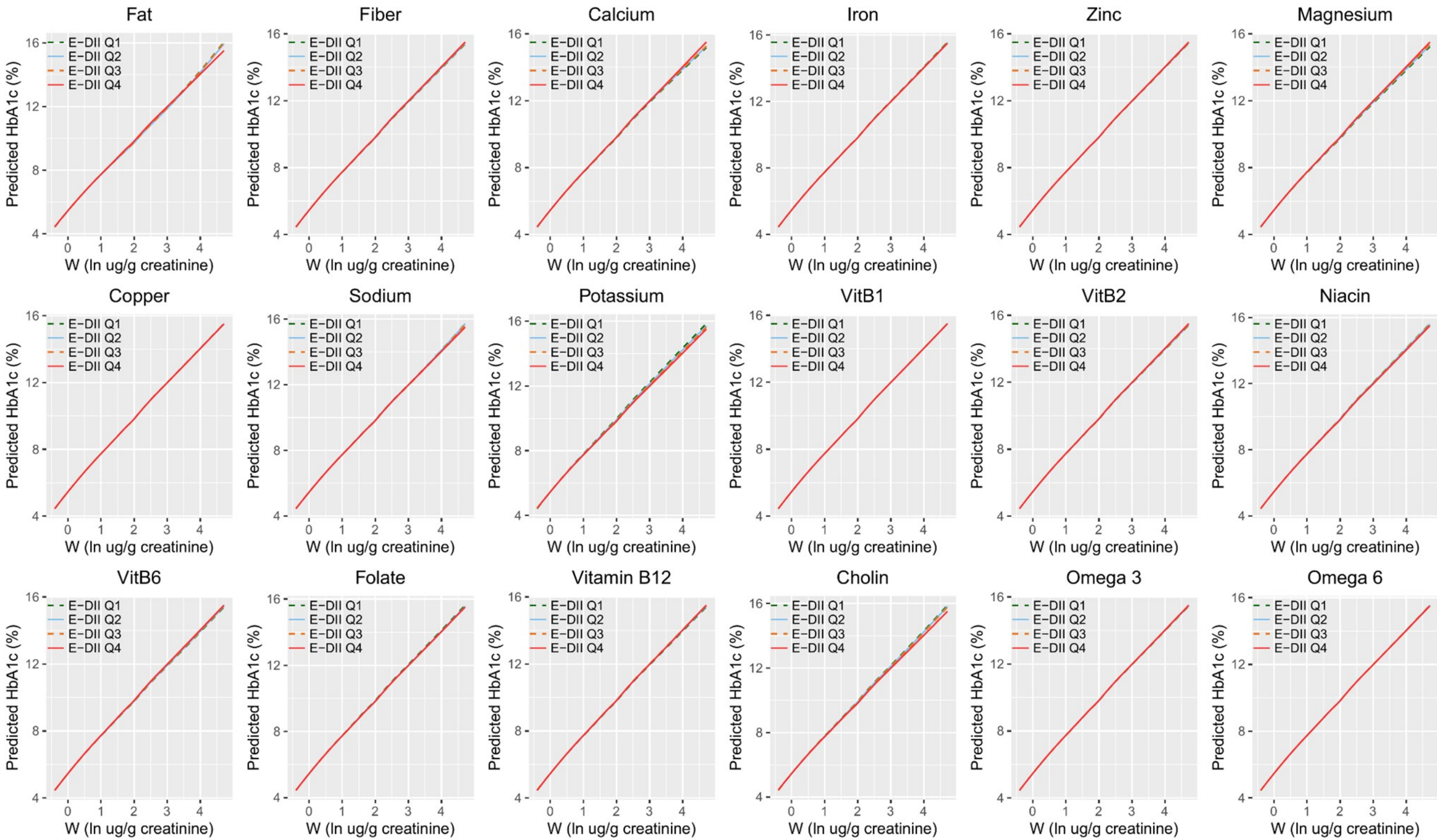


Figure S9. The Ba- homeostatic model assessment for insulin resistance (HOMA-IR) (ln) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index.

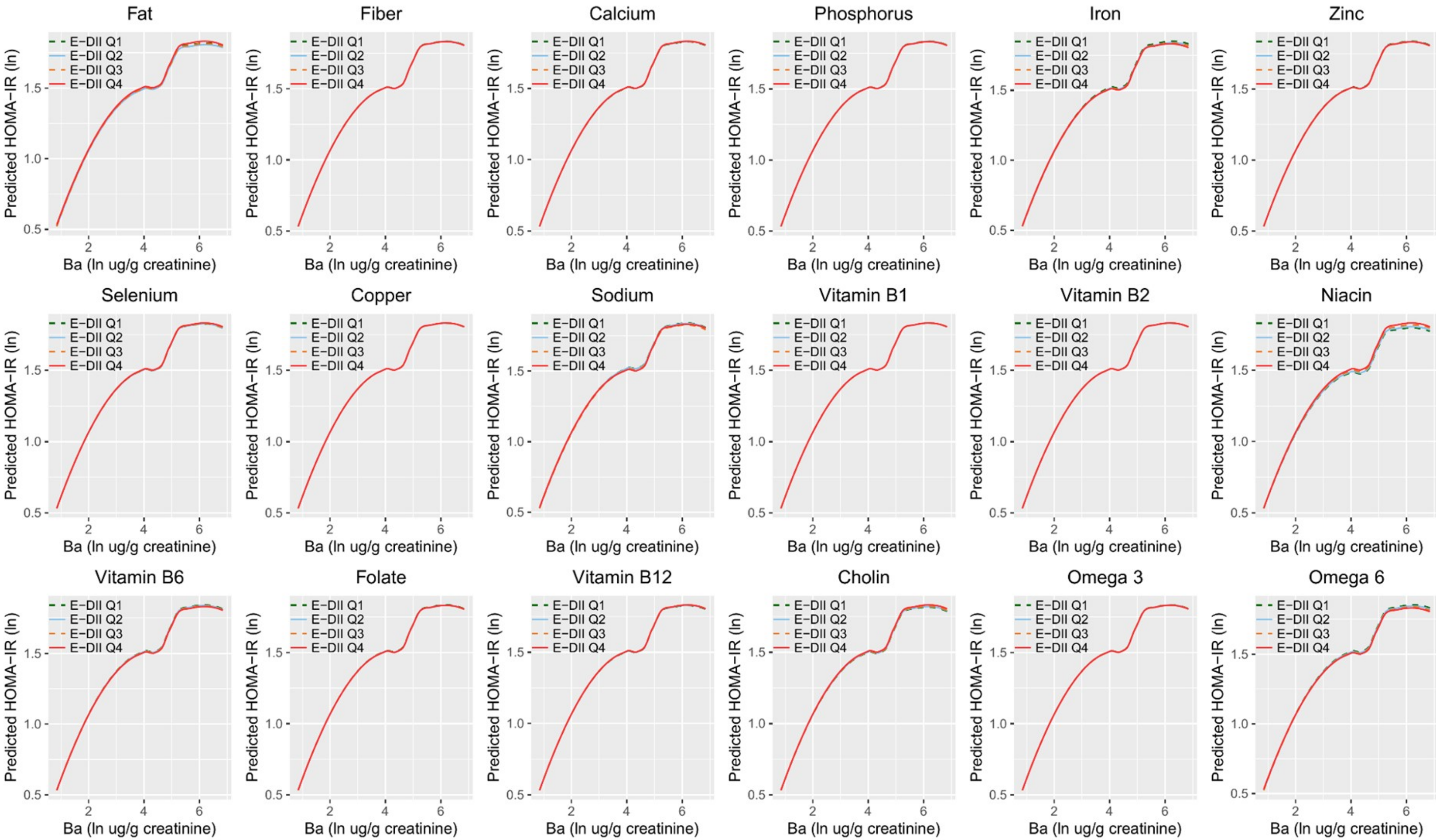


Figure S10. The Tl- homeostatic model assessment for insulin resistance (ln) relationships in the “E-DII Q4” group and in the hypothetically “E-DII Q1-3” group. E-DII, energy-adjusted diet inflammatory index.

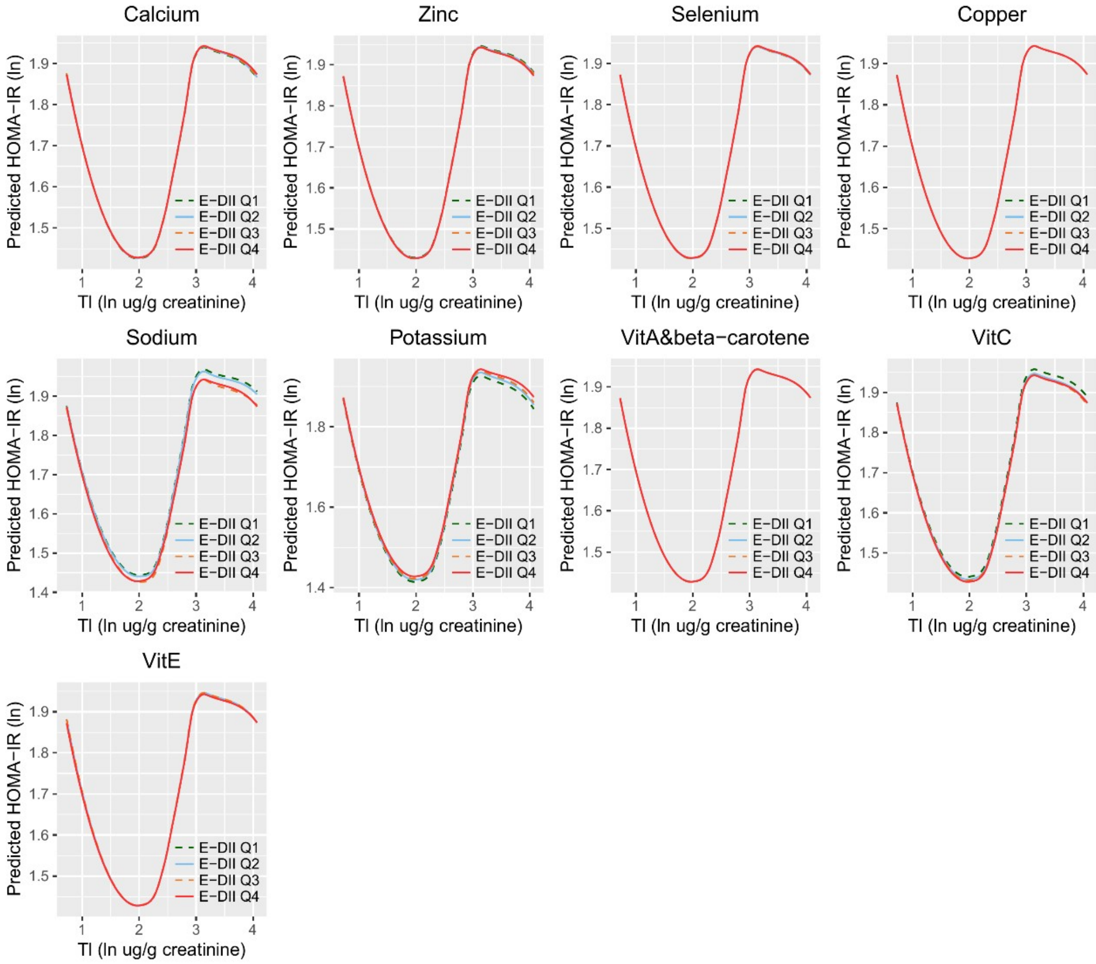


Figure S11. Impact of E-DII and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no). DII-ad, adjusted energy diet inflammatory index.

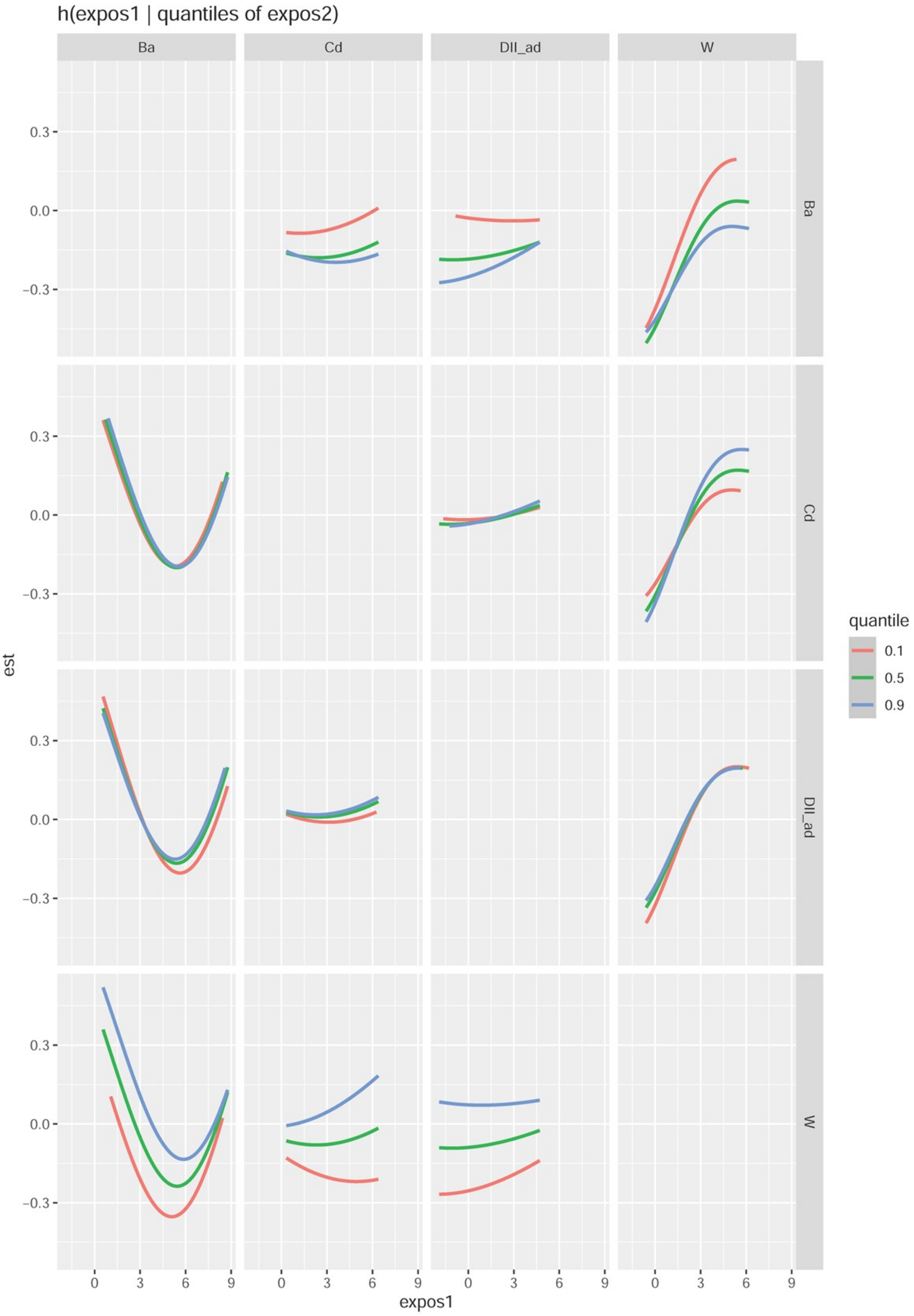


Figure S12. Impact of macro-nutritions and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no).

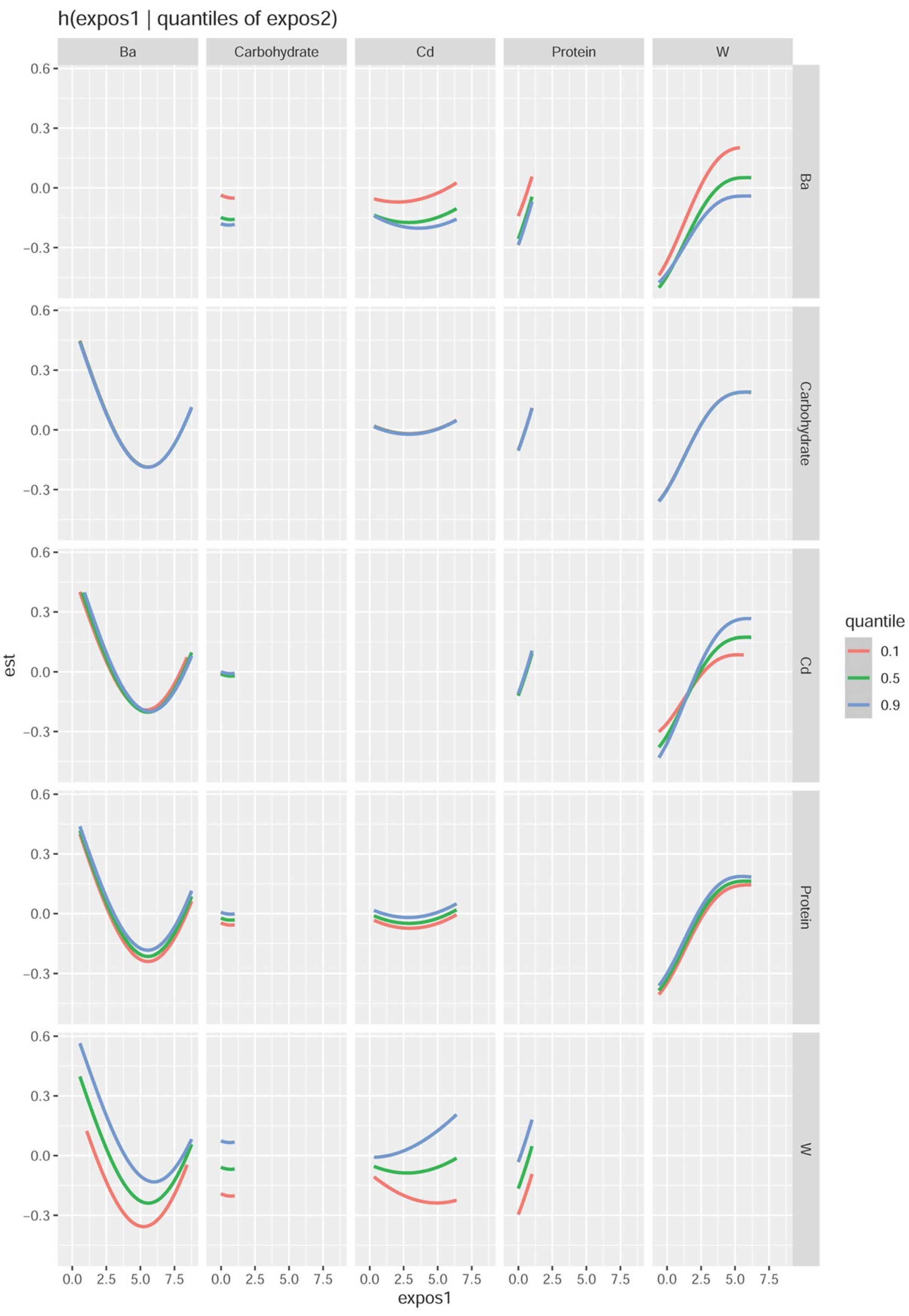


Figure S13. Impact of minerals and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no).

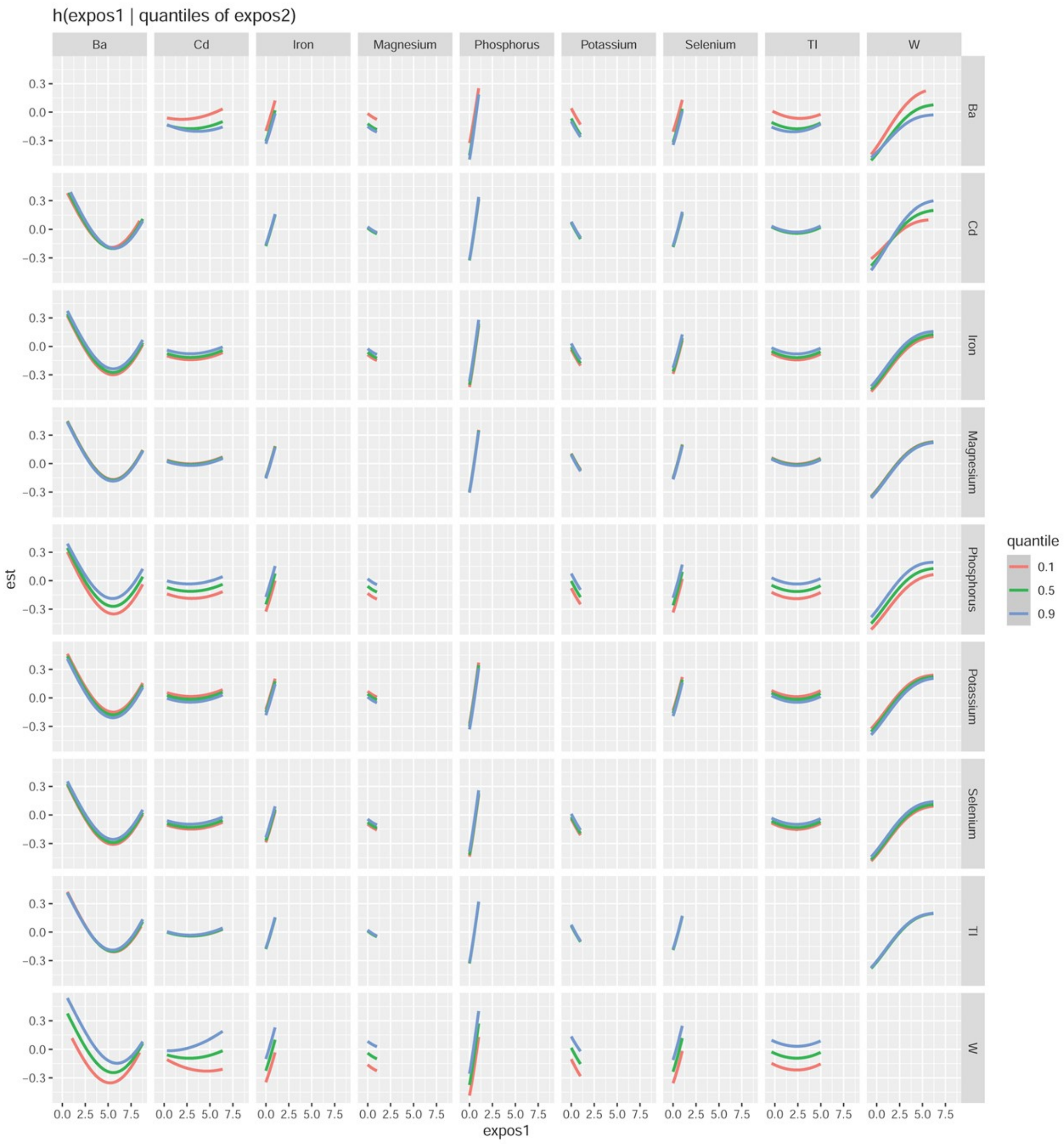
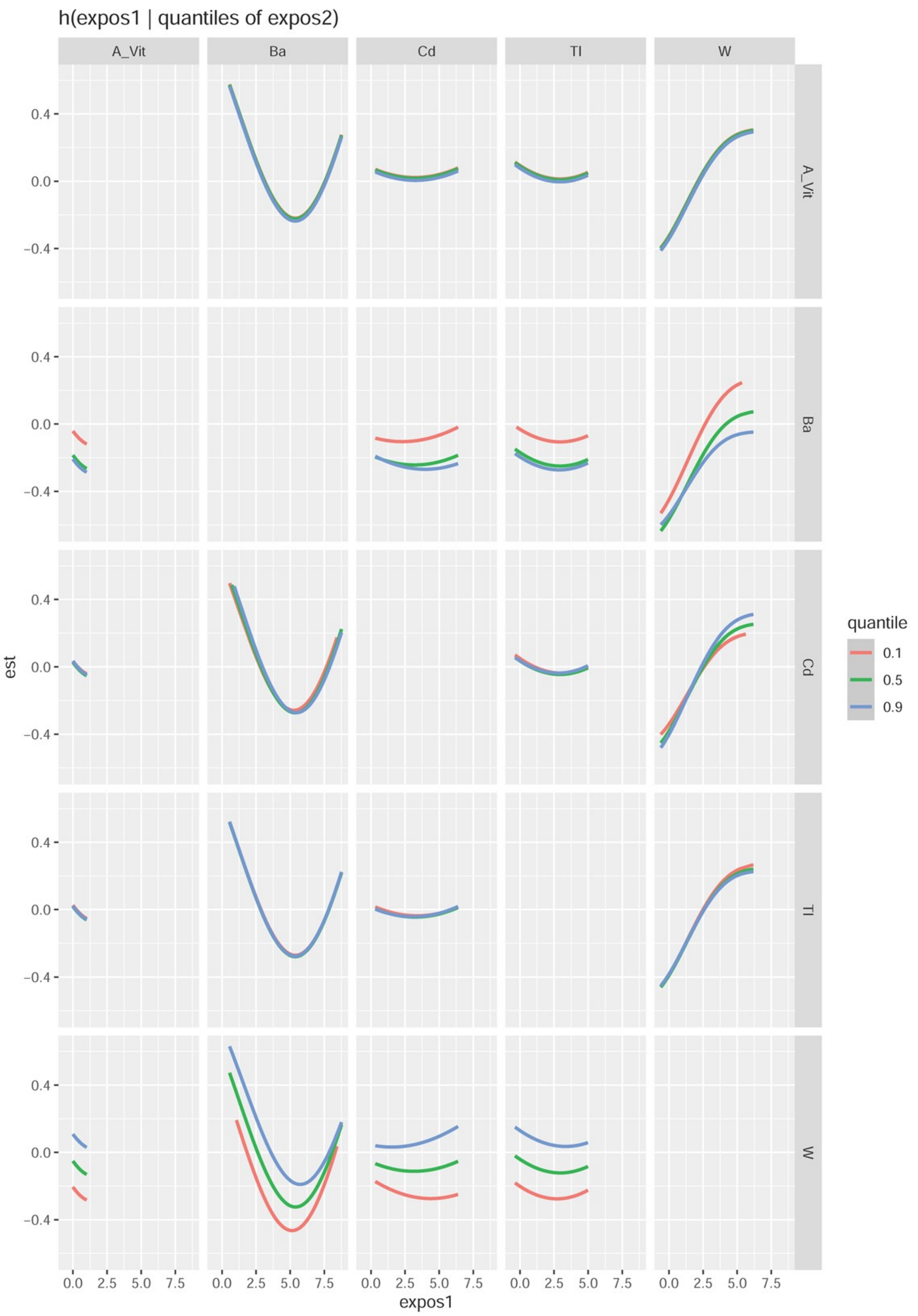


Figure S14. Impact of A vitamins and metal interactions on diabetes. Bivariate exposure–response functions for each of the exposure presented on the upper coordinate axis when the other variables presented on the right longitudinal axis holding at different quantiles (10th, 50th, and 90th percentiles) and the other variables were held at the median. Model adjusted for survey cycle of NHANES (2011-2012, 2013-2014, and 2015-2016), age (continuous), sex, body mass index (continuous), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), alcohol consumption (≥ 12 drinks/year and < 12 drinks/year), and hypertension (yes or no).



Reference

1. Qiu Z, Chen X, Geng T, et al. Associations of serum carotenoids with risk of cardiovascular mortality among individuals with type 2 diabetes: results from NHANES. *Diabetes care*, 2022, **45**: 1453-1461.