

SUPPLEMENTARY MATERIALS

eMethods Details of Statistical Analysis

In the cross-sectional analysis, the baseline serum vitamin D levels or status was used as the outcome after adjusted for covariates. Cross-sectional associations of each of non-essential metals (V, Cr, Ni, Cd, Pb and As) and essential metals (Mn, Fe, Cu, Zn, Co, and Mo) with serum 25 (OH)D levels or VDD were explored via the generalized linear regression models (GLM) or logistics regression analysis. In the longitudinal associations analysis, the incident VDD or longitudinal changes of 25 (OH)D levels were utilized as the outcome with the adjustment for covariates. Logistics regression was conducted to examine the longitudinal link between baseline metal exposure and incident VDD at the two-year follow-up. Longitudinal changes of 25 (OH)D levels were obtained by utilizing the serum 25 (OH)D levels at follow-up minus the serum 25 (OH)D levels at baseline. Meanwhile, the association between each of 12 metals with longitudinal changes of 25 (OH)D levels was performed by utilizing the GLMs after adjusted for baseline 25 (OH)D levels and covariates. Meanwhile, comprehensive GLM models were established by incorporating a concurrent analysis of non-essential metals and essential metals simultaneously.

Then, we used BKMR explore the nonlinear associations and the exposure-response relationship of the non-essential metals and essential metals. Following 20,000 iterations of the Markov chain Monte Carlo procedure, the overall effect of metal mixtures involving all metals was estimated at specified quantiles (25th, 30th, 35th, ..., 75th), using the 50th percentile as the reference. Subsequently, univariate exposure-response curves were generated by treating one metal as a continuous independent variable, while the other 11 metals were held constant at the 50th percentile. The individual effect of each metal was then assessed by varying its concentration from the 25th to the 75th percentile, with the remaining metals fixed at the corresponding percentiles. These plots were utilized to assess the overall association of the metal mixture with vitamin D concentrations or status, and to depict the exposure-response patterns for each metal while maintaining the other exposures at the 50th percentile and holding covariates constant.

Supplementary Table S1. Distribution and the lower limit of detection (LOD) of serum 12 metals

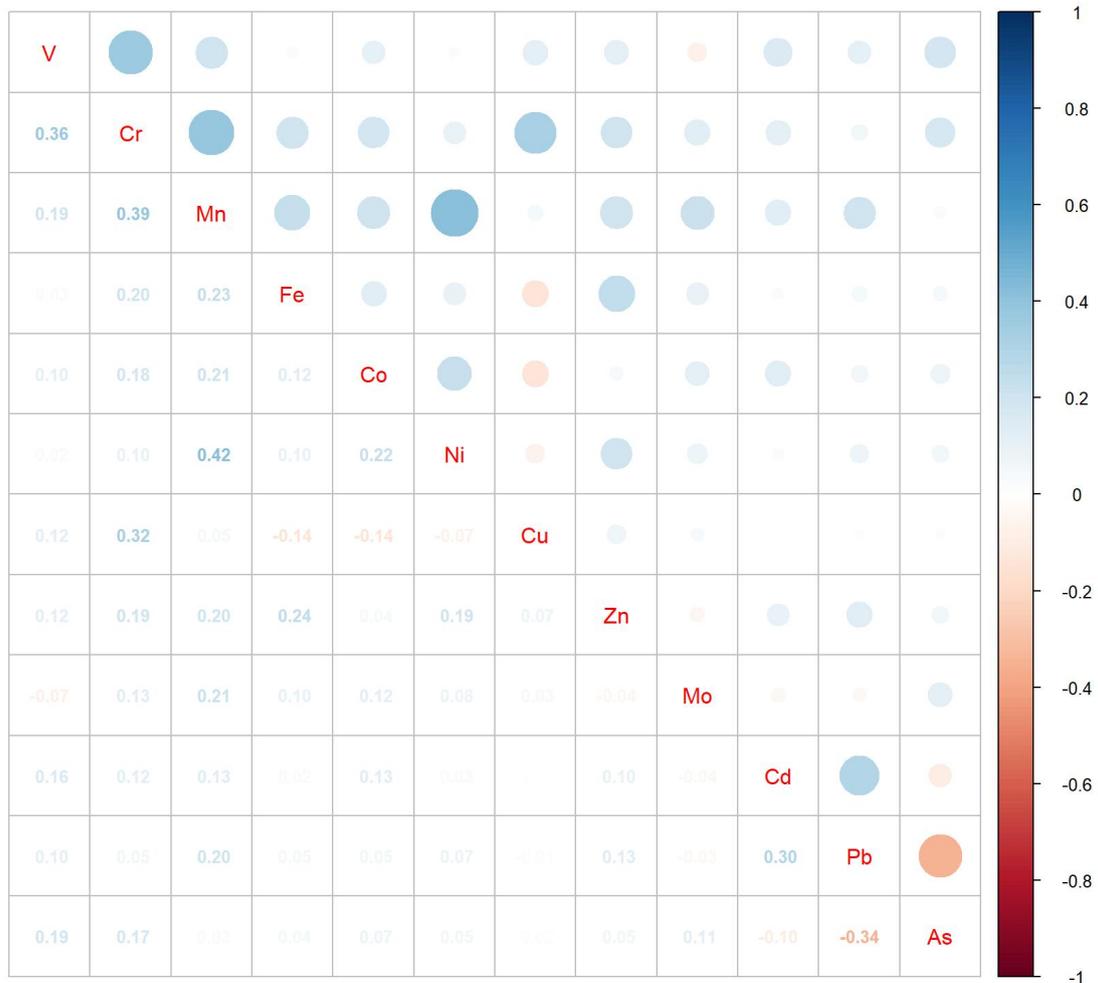
Metals	LOD	Female					Male				
		Min	25 th	50 th	75 th	95 th	Min	25 th	50 th	75 th	95 th
V	0.0008	1.484	2.351	2.541	2.953	3.678	1.630	2.343	2.532	2.939	3.673
Cr	0.0022	3.394	5.980	6.492	7.008	8.264	3.488	5.889	6.433	6.963	8.067
Mn	0.0027	0.420	0.845	1.037	1.280	2.444	0.403	0.852	1.034	1.306	2.402
Fe	0.0340	208.308	727.004	917.451	1113.428	1515.646	212.747	723.568	919.330	1137.206	1527.356
Co	0.0009	0.069	0.169	0.208	0.276	0.441	0.056	0.160	0.199	0.265	0.379
Ni	0.0056	0.067	0.425	0.628	0.956	2.019	0.056	0.414	0.626	0.888	1.770
Cu	0.0048	445.962	664.430	728.447	817.927	982.377	423.132	662.155	753.121	858.909	1035.846
Zn	0.1032	497.062	651.663	701.434	754.398	842.017	463.123	645.226	705.037	764.546	860.710
Mo	0.0003	0.502	1.089	1.274	1.546	1.968	0.506	1.128	1.357	1.626	2.161
Cd	0.0008	0.006	0.042	0.058	0.079	0.129	0.005	0.043	0.058	0.079	0.124
Pb	0.0031	0.668	1.432	1.788	2.278	3.350	0.911	1.716	2.156	2.682	3.929
As	0.0022	0.720	1.525	2.516	4.223	6.442	0.808	1.495	2.883	4.527	6.567

Supplementary Table S2. Cross-section correlates of individual metals with vitamin D deficiency at baseline

Metals	Total		Males		Female	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
V	0.53 (0.11 to 2.60)	0.431	0.53 (0.06 to 4.69)	0.569	0.44 (0.04 to 4.98)	0.508
Cr	3.45 (0.67 to 18.28)	0.142	9.25 (0.94 to 95.06)	0.058	0.89 (0.07 to 10.64)	0.927
Ni	0.79 (0.54 to 1.17)	0.238	0.87 (0.52 to 1.45)	0.587	0.78 (0.42 to 1.41)	0.407
Cd	0.95 (0.57 to 1.59)	0.853	0.96 (0.48 to 1.93)	0.913	0.77 (0.35 to 1.69)	0.523
Pb	0.88 (0.40 to 1.91)	0.742	0.70 (0.24 to 2.02)	0.510	0.93 (0.27 to 3.11)	0.907
As	0.64 (0.41 to 1.01)	0.056	0.79 (0.44 to 1.45)	0.457	0.50 (0.25 to 1.01)	0.054
V	0.31 (0.05 to 1.81)	0.193	0.19 (0.02 to 2.18)	0.183	0.51 (0.04 to 7.41)	0.622
Cr	3.26 (0.60 to 17.82)	0.173	8.61 (0.83 to 89.84)	0.072	1.17 (0.09 to 14.91)	0.902
Ni	0.84 (0.57 to 1.24)	0.379	0.90 (0.54 to 1.52)	0.697	0.80 (0.43 to 1.46)	0.464
Cd	1.21 (0.73 to 2.02)	0.465	1.23 (0.60 to 2.49)	0.573	0.95 (0.44 to 2.08)	0.904
Pb	0.53 (0.22 to 1.28)	0.157	0.53 (0.16 to 1.76)	0.298	0.56 (0.14 to 2.16)	0.396
As	0.57 (0.34 to 0.93)	0.026	0.70 (0.36 to 1.39)	0.308	0.46 (0.22 to 0.99)	0.046
Mn	1.74 (0.90 to 3.34)	0.096	1.76 (0.73 to 4.18)	0.206	1.73 (0.62 to 4.87)	0.297
Fe	1.64 (0.77 to 3.54)	0.204	2.13 (0.75 to 6.12)	0.158	1.16 (0.37 to 3.73)	0.798
Co	1.12 (0.53 to 2.33)	0.767	0.63 (0.22 to 1.69)	0.346	2.29 (0.75 to 6.99)	0.144
Cu	0.30 (0.06 to 1.44)	0.132	0.59 (0.08 to 4.27)	0.598	0.07 (0.01 to 0.944)	0.046
Zn	0.88 (0.09 to 8.28)	0.909	0.79 (0.04 to 15.62)	0.882	1.24 (0.03 to 46.41)	0.907
Mo	0.83 (0.32 to 2.18)	0.701	2.30 (0.66 to 8.18)	0.195	0.16 (0.03 to 0.78)	0.025
Mn	1.89 (0.92 to 3.87)	0.083	1.75 (0.67 to 4.55)	0.255	2.32 (0.73 to 7.30)	0.152
Fe	1.40 (0.63 to 3.12)	0.415	1.80 (0.59 to 5.51)	0.305	1.22 (0.35 to 4.18)	0.755
Co	1.03 (0.48 to 2.21)	0.939	0.52 (0.18 to 1.54)	0.238	2.47 (0.78 to 7.83)	0.126
Cu	0.25 (0.06 to 0.99)	0.049	0.31 (0.05 to 1.85)	0.199	0.13 (0.02 to 1.38)	0.090
Zn	0.57 (0.10 to 3.36)	0.534	0.36 (0.03 to 3.84)	0.396	2.38 (0.14 to 41.32)	0.551
Mo	0.63 (0.23 to 1.76)	0.379	1.98 (0.52 to 7.51)	0.315	0.08 (0.02 to 0.45)	0.004

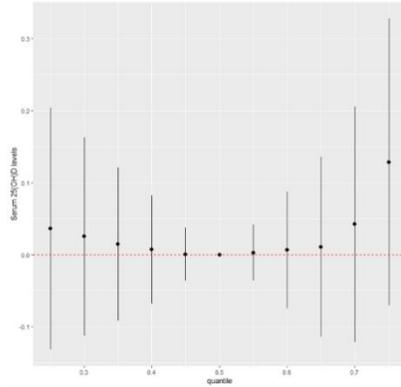
Supplementary Table S3. Relationship between single serum metal concentrations at baseline and changes of 25 (OH)D levels at follow-up

Metals	Total		Males		Female	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
V	-2.35 (-0.81 to -0.07)	0.001	-2.19 (-0.99 to -0.06)	0.028	-0.66 (-0.81 to 0.40)	0.506
Cr	2.79 (-0.84 to 6.42)	0.132	1.37 (-3.49 to 6.24)	0.580	5.04 (-0.31 to 10.39)	0.065
Ni	0.22 (-0.63 to 1.07)	0.615	-0.08 (-1.19 to 1.03)	0.887	0.69 (-0.62 to 2.00)	0.301
Cd	0.81 (-0.33 to 1.94)	0.162	0.76 (-0.75 to 2.28)	0.323	0.89 (-0.81 to 2.60)	0.304
Pb	0.23 (-1.49 to 1.95)	0.796	-0.33 (-2.60 to 1.94)	0.775	1.15 (-1.49 to 3.79)	0.393
As	-0.18 (-1.17 to 0.80)	0.715	-0.58 (-1.87 to 0.71)	0.380	0.43 (-1.09 to 1.95)	0.579
V	1.77 (-2.15 to 5.69)	0.376	2.31 (-2.99 to 7.60)	0.393	0.17 (-5.76 to 6.10)	0.955
Cr	2.07 (-1.96 to 6.10)	0.314	1.05 (-4.43 to 6.52)	0.708	4.13 (-1.84 to 10.10)	0.175
Ni	0.25 (-0.62 to 1.13)	0.573	0.04 (-1.11 to 1.19)	0.948	0.59 (-0.77 to 1.95)	0.394
Cd	0.72 (-0.47 to 1.92)	0.236	0.75 (-0.85 to 2.35)	0.360	0.57 (-1.26 to 2.39)	0.544
Pb	-0.52 (-2.47 to 1.43)	0.599	-1.35 (-3.93 to 1.23)	0.304	0.99 (-2.03 to 4.03)	0.518
As	-0.45 (-1.56 to 0.65)	0.421	-0.98 (-2.45 to 0.48)	0.188	0.44 (-1.26 to 2.15)	0.610
Mn	0.60 (-0.83 to 2.09)	0.398	-0.27 (-2.19 to 1.65)	0.784	2.08 (-0.18 to 4.34)	0.071
Fe	-0.67 (-2.36 to 1.02)	0.437	-0.69 (-2.93 to 1.55)	0.547	-0.79 (-3.34 to 1.77)	0.546
Co	1.49 (-0.16 to 3.13)	0.076	1.63 (-0.57 to 3.84)	0.147	0.76 (-1.70 to 3.22)	0.546
Cu	-0.36 (-3.82 to 3.10)	0.838	-1.48 (-5.81 to 2.85)	0.502	2.41 (-3.39 to 8.21)	0.416
Zn	-1.80 (-6.74 to 3.14)	0.474	-3.65 (-10.04 to 2.73)	0.262	0.72 (-7.16 to 8.61)	0.857
Mo	0.06 (-2.07 to 2.19)	0.959	0.14 (-2.58 to 2.85)	0.920	-0.06 (-3.54 to 3.42)	0.972
Mn	0.76 (-0.88 to 2.39)	0.363	-0.26 (-2.42 to 1.90)	0.812	2.59 (0.015 to 5.17)	0.049
Fe	-0.82 (-2.64 to 1.00)	0.376	-0.79 (3.26 to 1.68)	0.529	-1.33 (-4.10 to 1.44)	0.346
Co	1.43 (-0.28 to 3.13)	0.101	1.75 (-0.58 to 4.09)	0.141	0.33 (-2.26 to 2.92)	0.801
Cu	-0.22 (-3.78 to 3.35)	0.906	-1.10 (-5.65 to 3.44)	0.634	2.20 (-3.78 to 8.17)	0.470
Zn	-1.87 (-7.09 to 3.36)	0.483	-2.95 (-9.73 to 3.83)	0.394	-0.69 (-9.19 to 7.81)	0.873
Mo	-0.40 (-2.67 to 1.87)	0.728	0.09 (-2.82 to 2.99)	0.951	-1.21 (-4.99, 2.58)	0.532

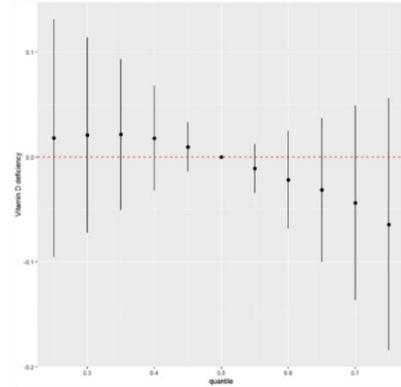


Supplementary Figure S1. Spearman's correlation matrix of In-transformed plasma metals concentrations at baseline. The color circle at the top right and the number at the bottom left show the Spearman correlation coefficient between the two plasma metals. The red color signifies negative correlations and blue signifies positive correlations.

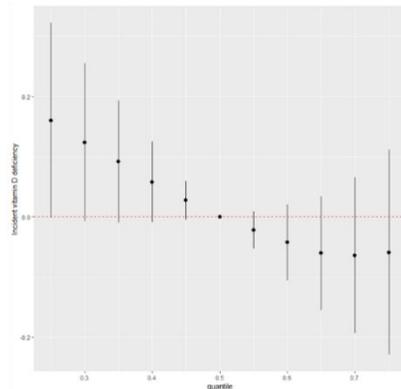
(i) Non-essential metals



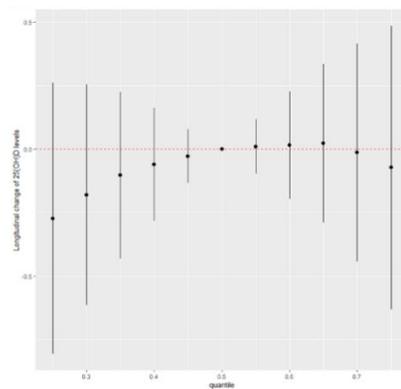
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency

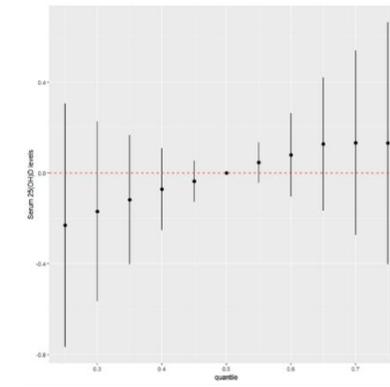


(C) Incident vitamin D deficiency

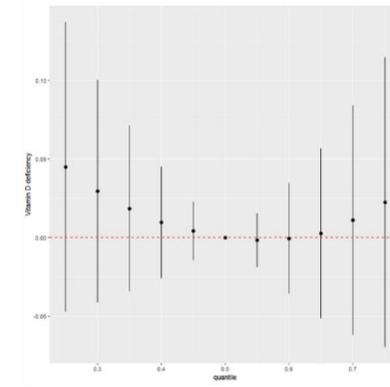


(D) Longitudinal change of 25(OH)D levels

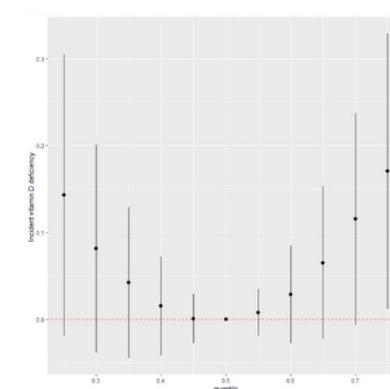
(ii) Essential metals



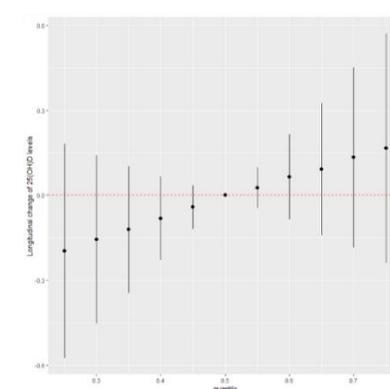
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency



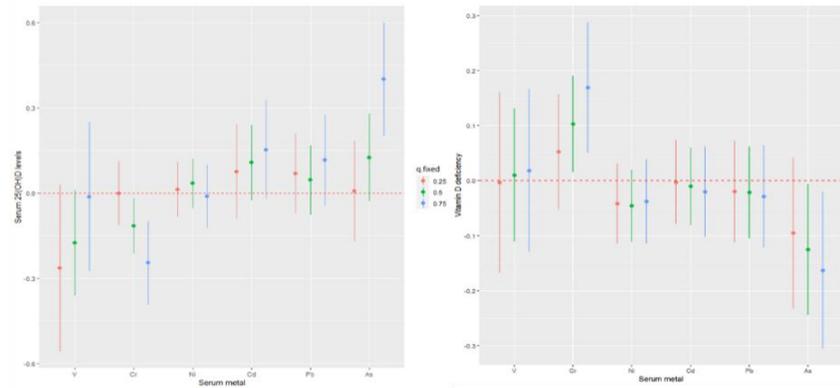
(C) Incident vitamin D deficiency



(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S2. The overall impact of metal mixture on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C) and longitudinal change of 25 (OH)D levels (D) in the overall sample based on BKMR models.

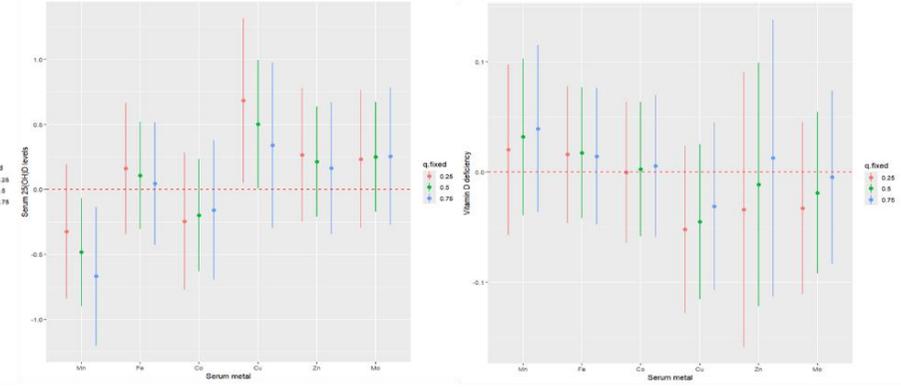
(i) Non-essential metals



(A) Baseline serum 25(OH)D levels

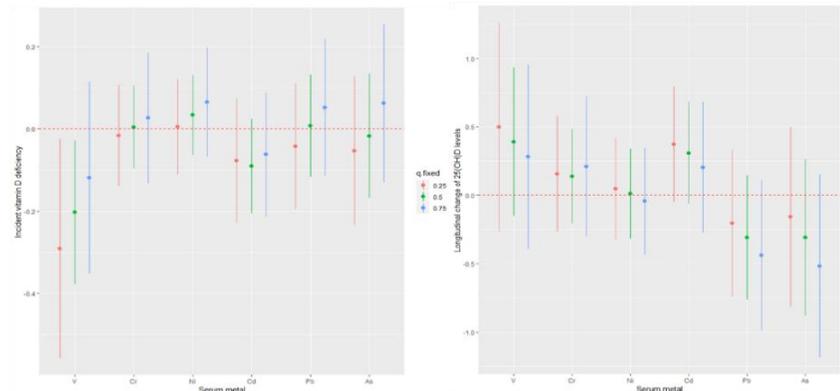
(B) Baseline vitamin D deficiency

(ii) Essential metals



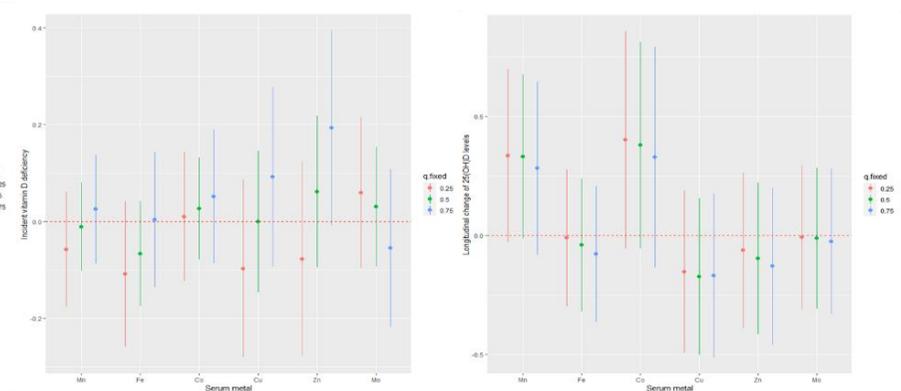
(A) Baseline serum 25(OH)D levels

(B) Baseline vitamin D deficiency



(C) Incident vitamin D deficiency

(D) Longitudinal change of 25(OH)D levels

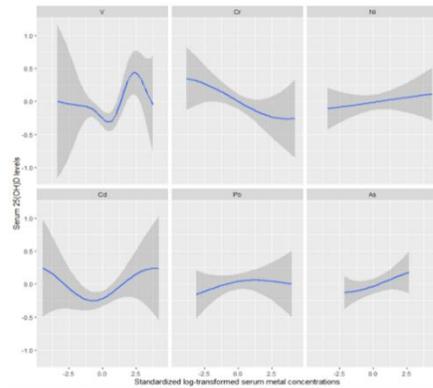


(C) Incident vitamin D deficiency

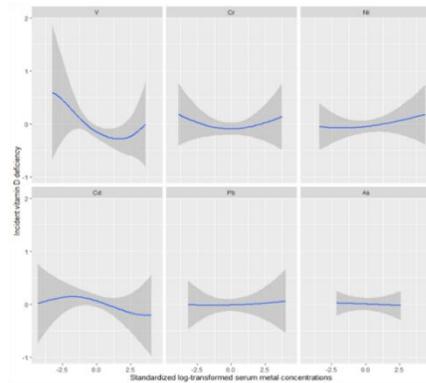
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S3. Single effects (95% CI) of each individual metals on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C) and longitudinal change of 25 (OH)D levels (D) in the overall sample based on BKMR models.

(i) Non-essential metals

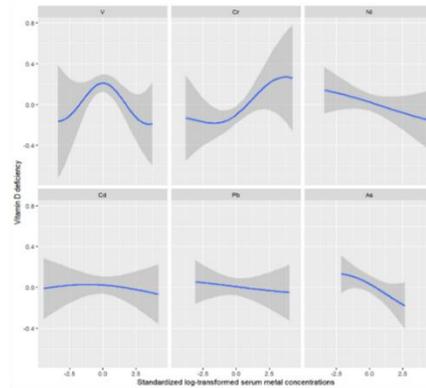


(A) Baseline serum 25(OH)D levels

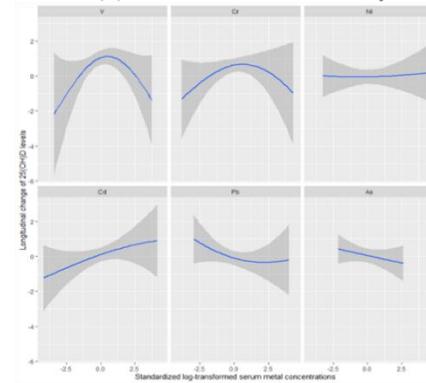


(C) Incident vitamin D deficiency

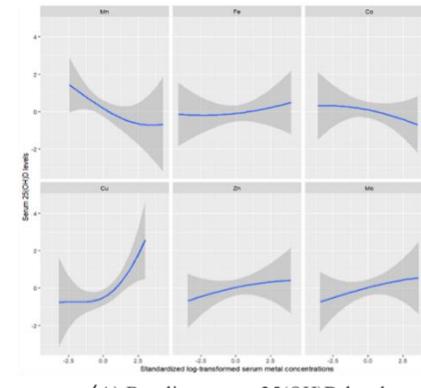
(ii) Essential metals



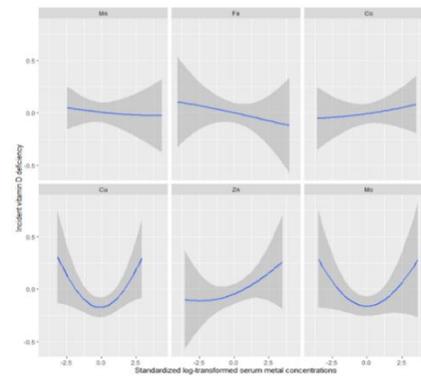
(B) Baseline vitamin D deficiency



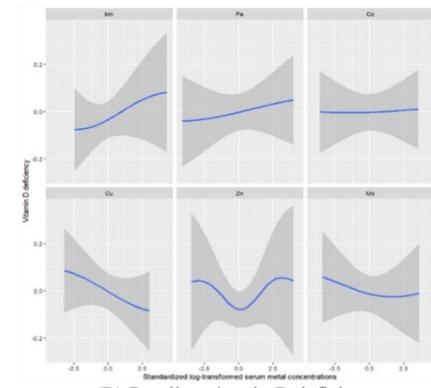
(D) Longitudinal change of 25(OH)D levels



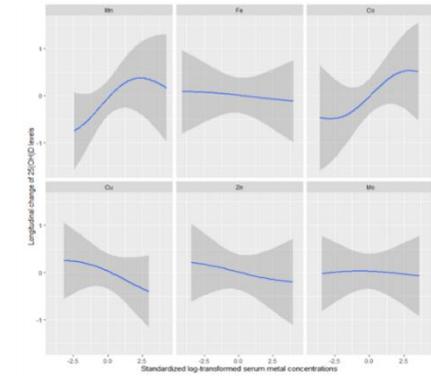
(A) Baseline serum 25(OH)D levels



(C) Incident vitamin D deficiency



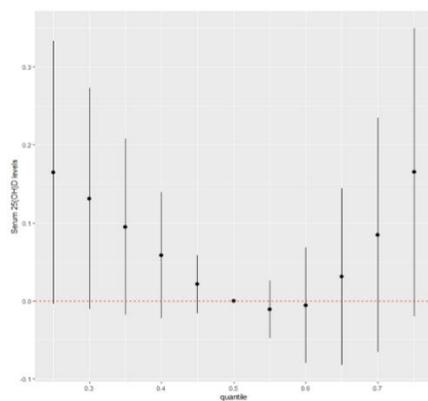
(B) Baseline vitamin D deficiency



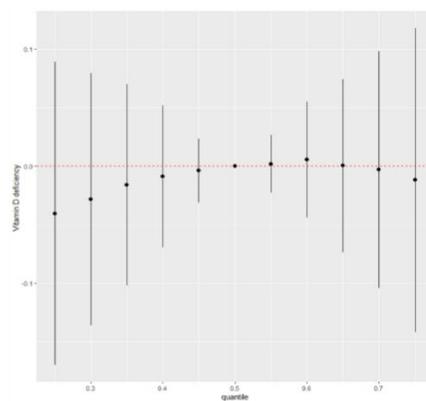
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S4. The univariate exposure-response relationships between individual metals and baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C) and longitudinal change of 25 (OH)D levels (D) in the overall sample based on BKMR models.

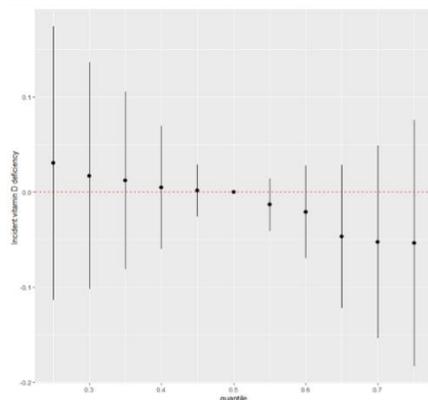
(i) Non-essential metals



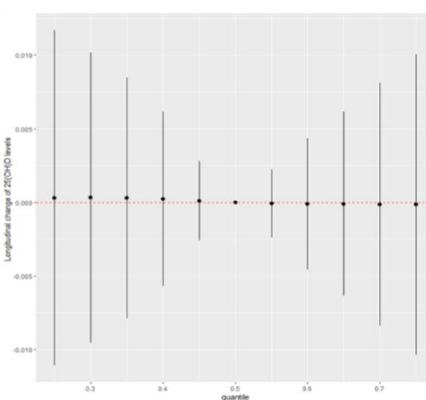
(A) Baseline serum 25(OH)D levels



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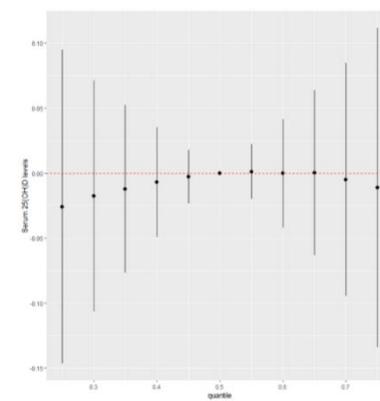


(C) Incident vitamin D deficiency

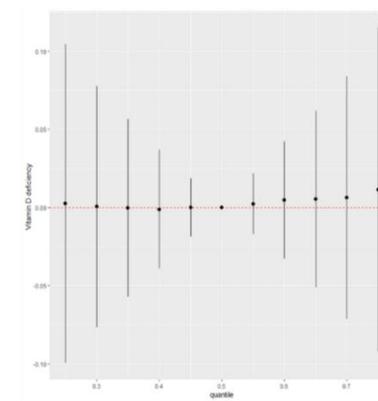


(D) Longitudinal change of 25(OH)D levels

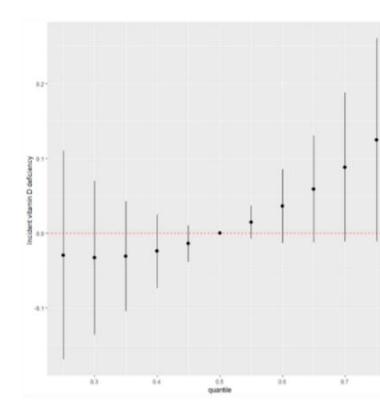
(ii) Essential metals



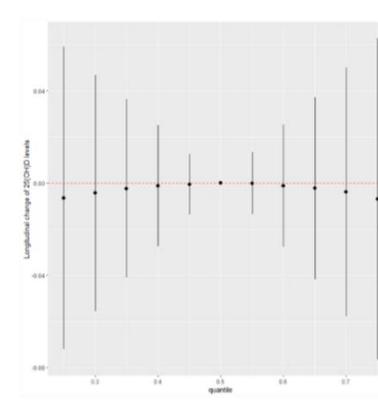
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency



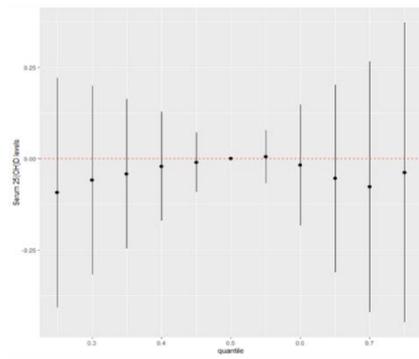
(C) Incident vitamin D deficiency



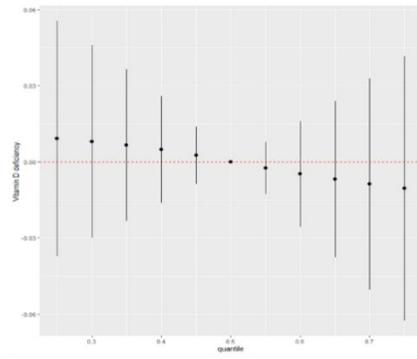
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S5. The overall impact of metal mixture on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D), in males based on BKMR models.

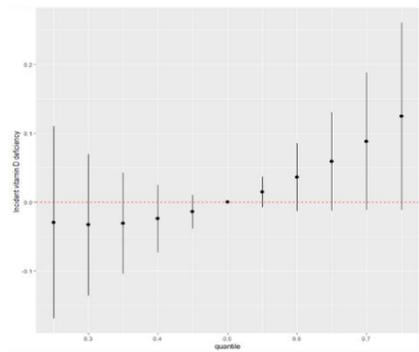
(i) Non-essential metals



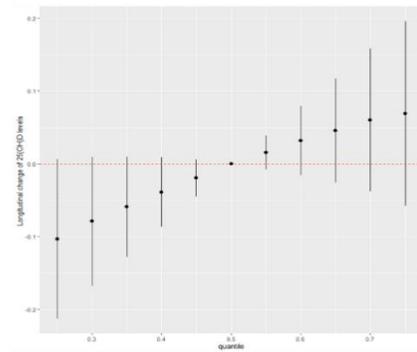
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency

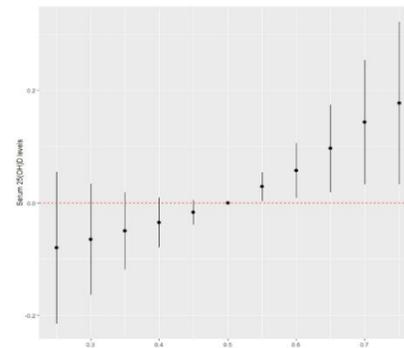


(C) Incident vitamin D deficiency

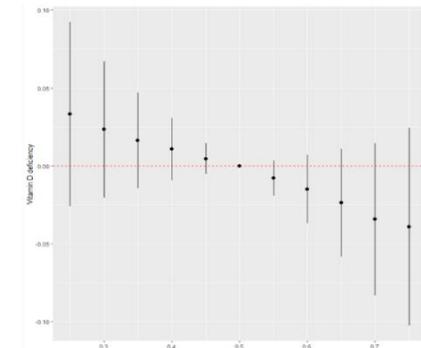


(D) Longitudinal change of 25(OH)D levels

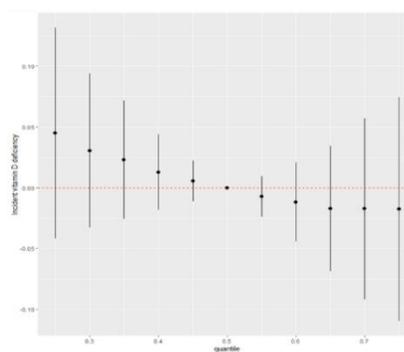
(ii) Essential metals



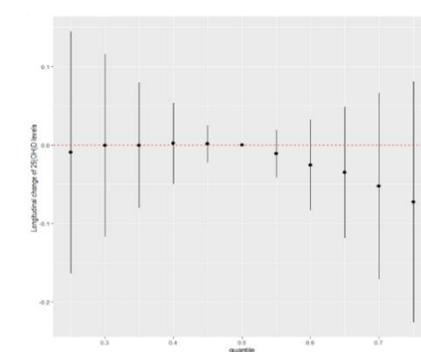
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency



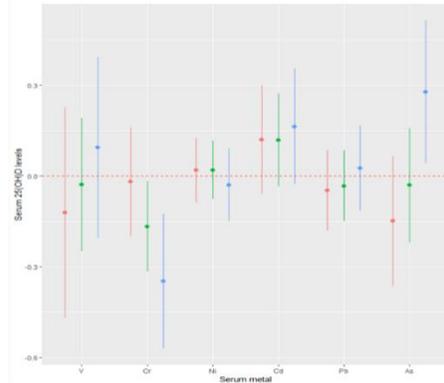
(C) Incident vitamin D deficiency



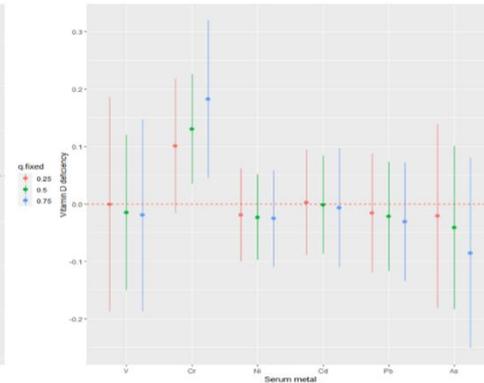
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S6. The overall impact of metal mixture on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D), in females based on BKMR models.

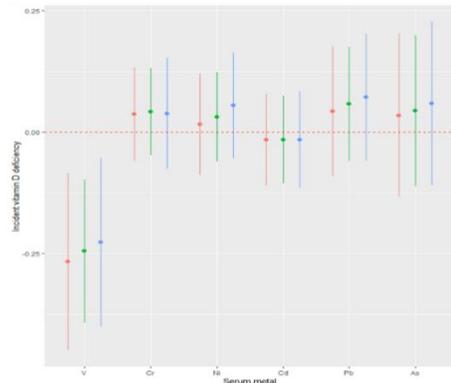
(i) Non-essential metals



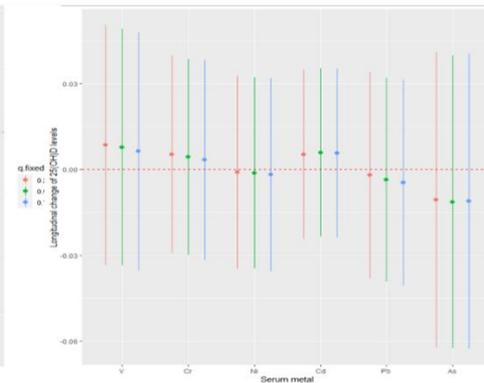
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency

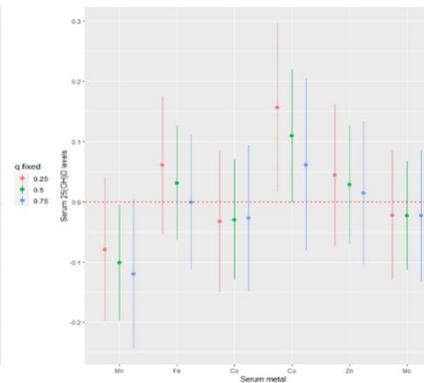


(C) Incident vitamin D deficiency

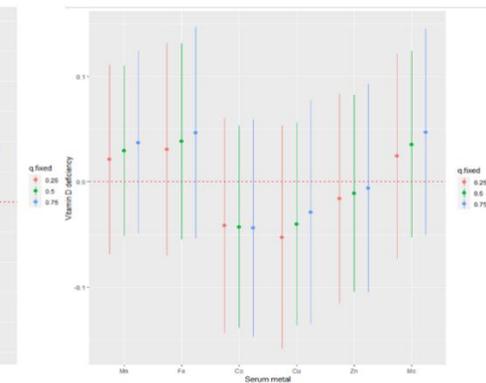


(D) Longitudinal change of 25(OH)D levels

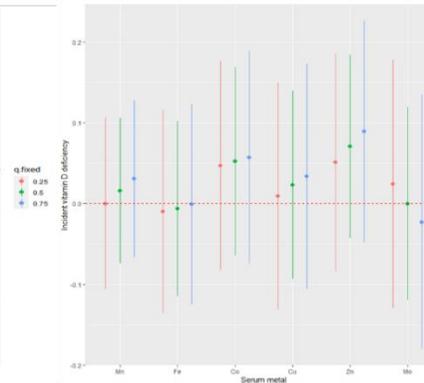
(ii) Essential metals



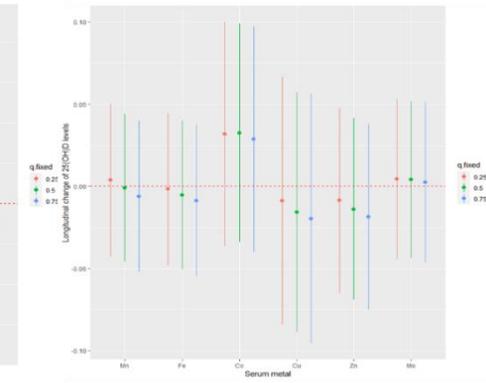
(A) Baseline serum 25(OH)D levels



(B) Baseline vitamin D deficiency



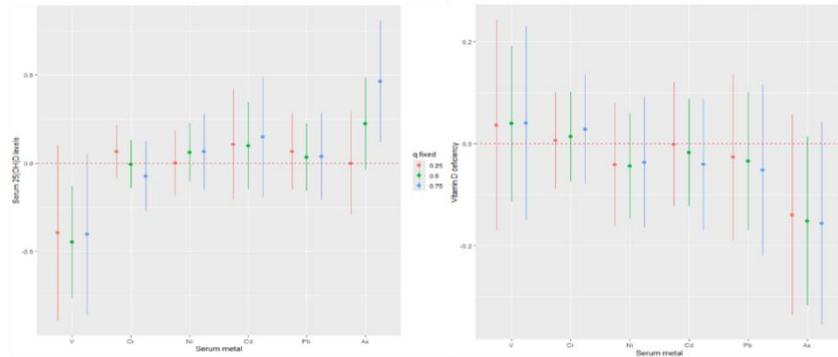
(C) Incident vitamin D deficiency



(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S7. Single effects (95% CI) of each individual metal on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D) in males based on BKMR models.

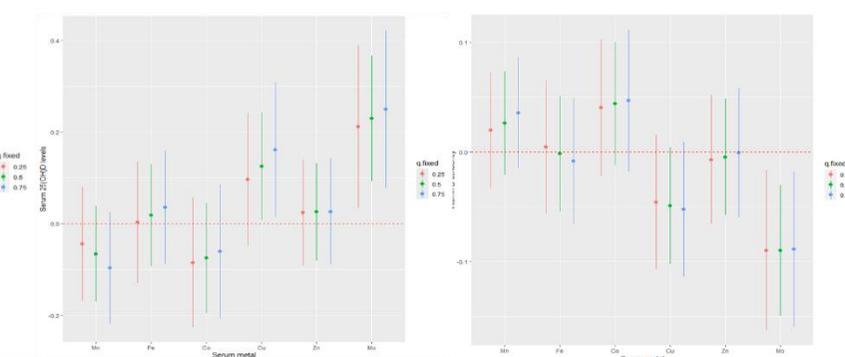
(i) Non-essential metals



(A) Baseline serum 25(OH)D levels

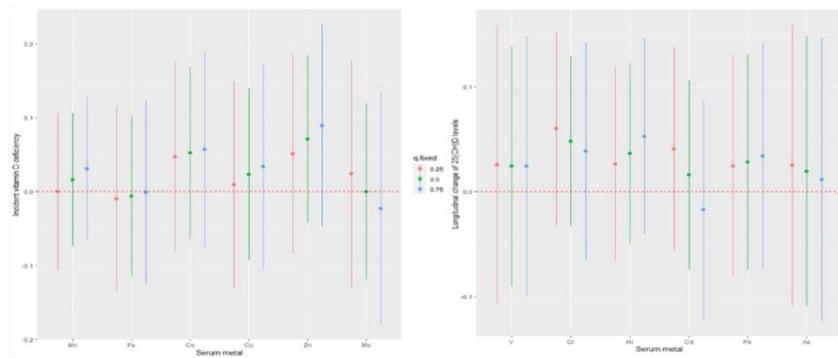
(B) Baseline vitamin D deficiency

(ii) Essential metals



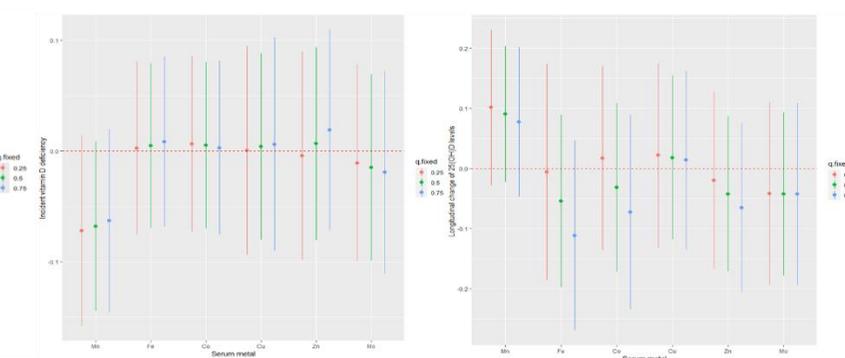
(A) Baseline serum 25(OH)D levels

(B) Baseline vitamin D deficiency



(C) Incident vitamin D deficiency

(D) Longitudinal change of 25(OH)D levels

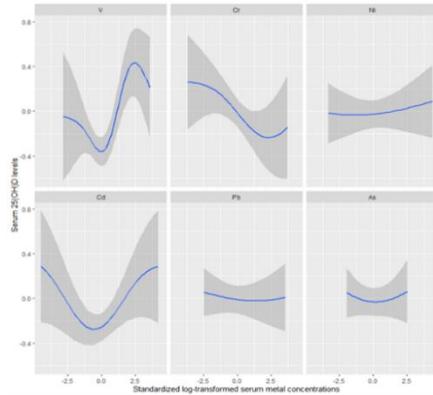


(C) Incident vitamin D deficiency

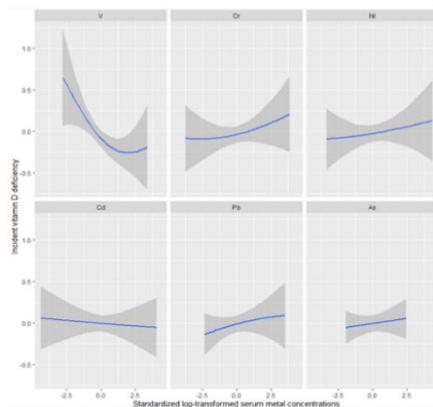
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S8. Single effects (95% CI) of each individual metal on baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D) in females based on BKMR models.

(i) Non-essential metals

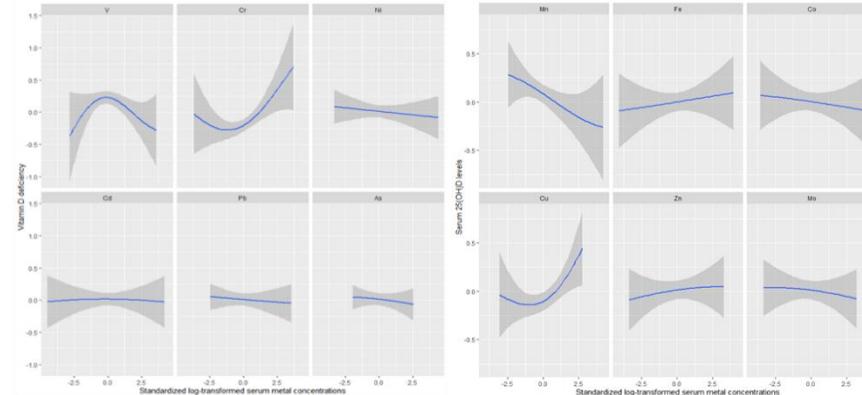


(A) Baseline serum 25(OH)D levels

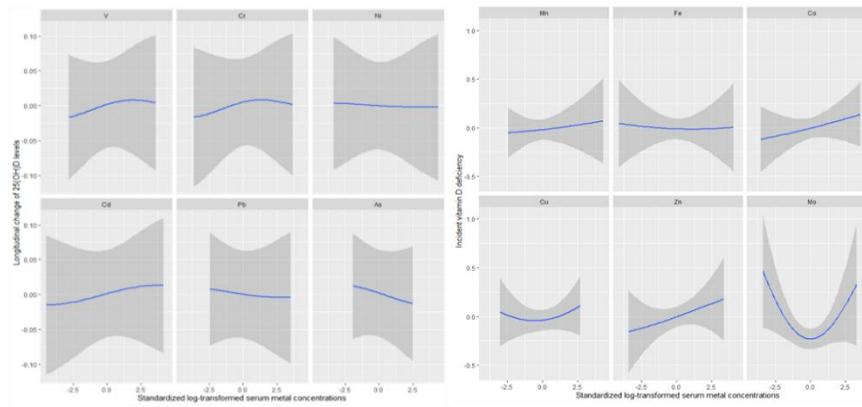


(C) Incident vitamin D deficiency

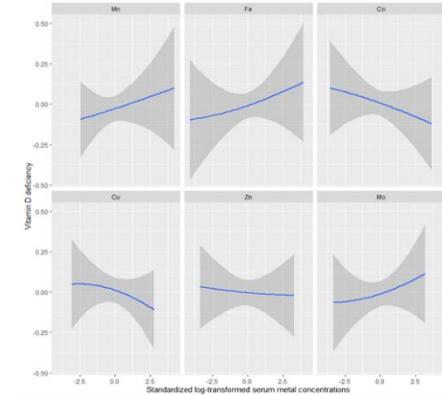
(ii) Essential metals



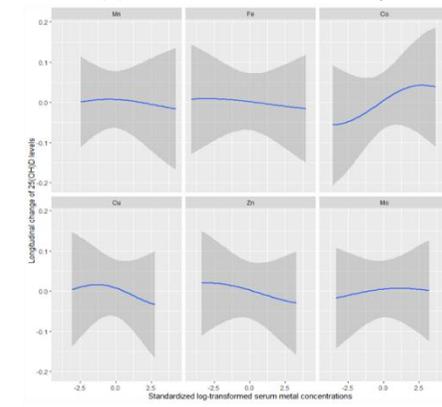
(B) Baseline vitamin D deficiency



(D) Longitudinal change of 25(OH)D levels



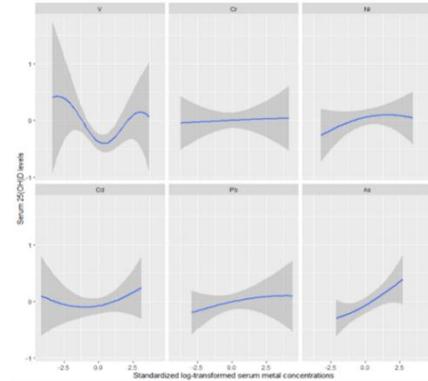
(B) Baseline vitamin D deficiency



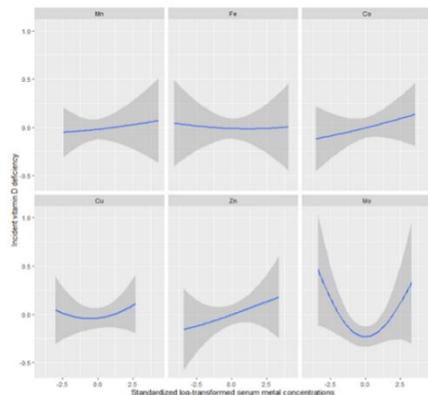
(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S9. The univariate exposure-response relationships between individual metals and baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D), in males based on BKMR models.

(i) Non-essential metals

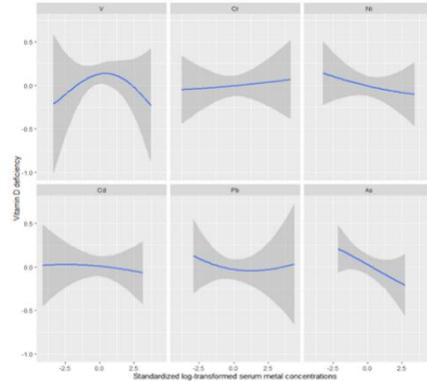


(A) Baseline serum 25(OH)D levels

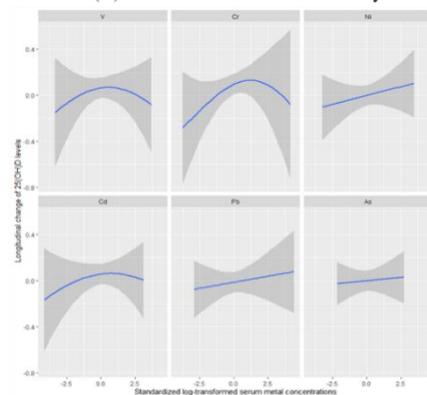


(C) Incident vitamin D deficiency

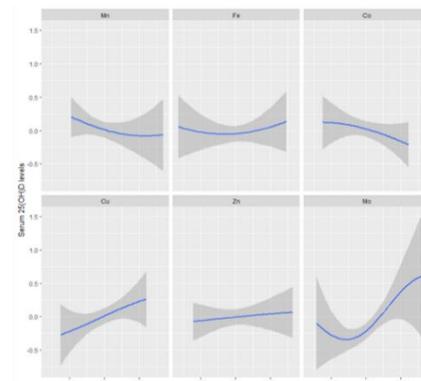
(ii) Essential metals



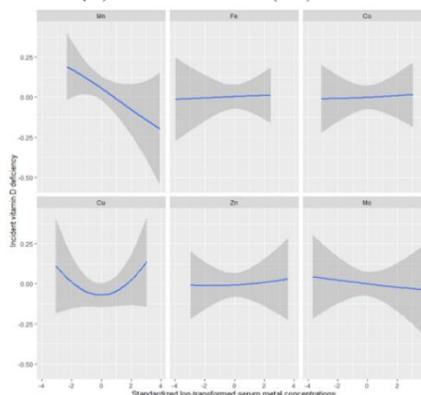
(B) Baseline vitamin D deficiency



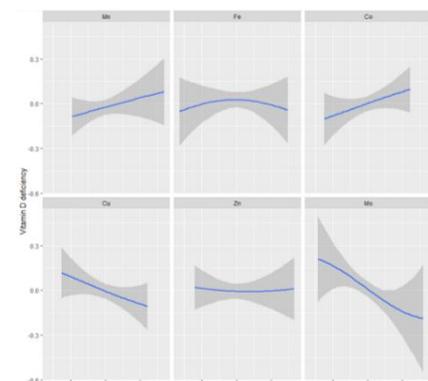
(D) Longitudinal change of 25(OH)D levels



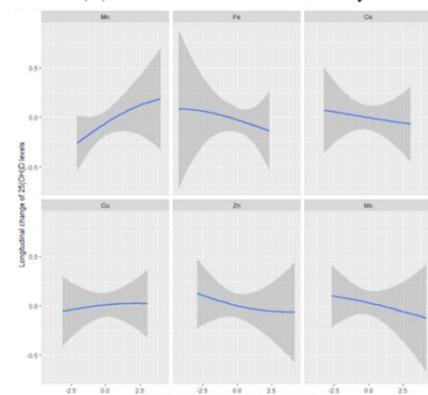
(A) Baseline serum 25(OH)D levels



(C) Incident vitamin D deficiency



(B) Baseline vitamin D deficiency



(D) Longitudinal change of 25(OH)D levels

Supplementary Figure S10. The univariate exposure-response relationships between individual metals and baseline serum 25 (OH)D levels (A), baseline vitamin D deficiency (B), incident vitamin D deficiency (C), and longitudinal change of 25 (OH)D levels (D), in females based on BKMR models.