Supplementary Table S1. Comparisons of basic characteristics of participants (*n* = 1,000)

Characteristics[a]	Total population	Diabetes group, *n* = 500	Control group, *n* = 500	*P* value[b]
Age (years), mean±SD	71.04±5.75	70.97±5.75	71.11±5.76	0.703
Gender				1.000
Male	460 (46.00)	230 (46.00)	230 (46.00)	
Female	540 (54.00)	270 (54.00)	270 (54.00)	
Residence				0.020
Urban area	347 (34.70)	156 (31.20)	191 (38.20)	
Rural area	653 (65.30)	344 (68.80)	309 (61.80)	
Marriage[c]				0.014
With a spouse	803 (80.30)	417 (83.40)	386 (77.20)	
Without a spouse	197 (19.70)	83 (16.60)	114 (22.80)	
Educational level				0.178
Illiteracy	500 (50.00)	263 (52.60)	237 (47.40)	
Elementary school	257 (25.70)	117 (23.40)	140 (28.00)	
Middle school or above	243 (24.30)	120 (24.00)	123 (24.60)	
Family economy[d, e]				< 0.001
Lower	221 (22.37)	106 (21.63)	115 (23.09)	
Intermediate	464 (46.96)	266 (54.29)	198 (39.76)	
Upper	303 (30.67)	118 (24.08)	185 (37.15)	
Occupation[f]				0.050
Agricultural producer	761 (76.10)	397 (79.40)	364 (72.80)	
Technical labor related worker	115 (11.50)	50 (10.00)	65 (13.00)	
Professional staff	124 (12.40)	53 (10.60)	71 (14.20)	
Physical activity[d, g]				0.007
No	232 (23.22)	137 (27.45)	95 (19.00)	
Moderate intensity	366 (36.64)	174 (34.87)	192 (38.40)	
High intensity	401 (40.14)	188 (37.68)	213 (42.60)	
Alcohol consumption[d, h]				0.023
Never	660 (67.00)	340 (70.10)	320 (64.00)	
Often	143 (14.52)	72 (14.85)	71 (14.20)	
Everyday	182 (18.48)	73 (15.05)	109 (21.80)	
Smoking[d, i]				0.665
Never	686 (68.67)	348 (69.74)	338 (67.60)	

Current smoker	137 (13.71)	67 (13.43)	70 (14.00)	
Former smoker	176 (17.62)	84 (16.83)	92 (18.40)	
BMI (kg/m^2) [j]				< 0.001
Underweight (< 18.5)	40 (4.00)	14 (2.80)	26 (5.20)	
Normal weight (18.5-23.9)	418 (41.80)	184 (36.80)	234 (46.80)	
Overweight (24.0-27.9)	365 (36.50)	188 (37.60)	177 (35.40)	
Obesity (≥ 28.0)	177 (17.70)	114 (22.80)	63 (12.60)	
diet habit[k]				0.007
meat-based diet	131 (13.1)	79 (15.8)	52 (10.4)	
balanced diet	403 (40.3)	209 (41.8)	194 (38.8)	
vegetable-based diet	466 (46.6)	212 (42.4)	254 (50.8)	
Hypertension[l]				< 0.001
No	392 (39.20)	148 (29.60)	244 (48.80)	
Yes	608 (60.80)	352 (70.40)	256 (51.20)	
Liver disease[m]				< 0.001
No	720 (72.0)	327 (65.4)	393 (78.6)	
Yes	280 (28.0)	173 (34.6)	107 (21.4)	
Kidney disease[m]				0.071
No	873 (87.3)	427 (85.4)	446 (89.2)	
Yes	127 (12.7)	73 (14.6)	54 (10.8)	
City				< 0.001
Fuyang	434 (43.3)	298 (59.6)	136 (27.2)	
Lu'an	566 (56.6)	202 (40.4)	364 (72.8)	

Note. Abbreviations: SD, standard deviation; BMI, body mass index.

[a] Results presented are *n* (%) if not otherwise specified.

[b] *t*-test and Chi-squared test were applied to assess differences in variables between case and control group.

[c] Marriage was classified into two categories: with a spouse (married) and without a spouse (widowed/divorced/single).

[d] Note that subgroup totals might not equal the complete sample size due to missing values in adjustment variables.

[e] Family economy was presented as lower, intermediate, and upper tertiles. For urban areas, the lower, intermediate, and upper tertiles of annual family income were ¥0–30,000, ¥30,001–50,000, and ¥50,001–800,000, respectively. For rural areas, the lower, intermediate, and upper tertiles of annual family income were ¥0–3,000, ¥3,001–10,000, and ¥10,001–130,000, respectively.

[f] Occupations prior to retirement were categorized into three groups: agricultural producer (e.g., farming, fish-farming, and factory work), technical labor related worker (e.g., drivers), and

professional staff (e.g., clerk, craftsman, and teacher).

[g] Physical activities were grouped into three categories: (1) no physical activity, (2) moderate physical activities, (3) severe physical activities (moderate physical activities were defined as tasks that caused light sweating or a slight to moderate increase in breathing or heart rate. severe physical activities were defined as tasks that caused heavy sweating or large increases in breathing or heart rate).

[h] Alcohol consumption was grouped into never, often (once to six times a week), and everyday (once per day or more).

[i] Smoking was classified into never (< 100 cigarettes), current smoker (≥ 100 cigarettes and smoking currently), and former smoker (≥ 100 cigarettes and no smoking at present).

[j] Body Mass Index (BMI) is calculated and classified into four categories: underweight (< 18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥ 28.0 kg/m^2).

[k] Diet habit: According to participants' self-reported diet habit.

[l] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported history of hypertension, or use of antihypertensive medications.

[m] Kidney and liver diseases are both diagnosed based on ultrasound results.

Supplementary Table S2. Precisions and recoveries of blood heavy metals (HMs)

HMs	Precision (RSD%)		Spiked (μg/L)	Recovery (%)
	Intra-day CV (%)	Inter-day CV (%)		
Ba	4.71	11.44	2	102.41
			5	121.40
			10	117.80
Cd	5.85	11.29	0.5	94.53
			1	97.40
			2	96.63
Co	10.73	8.11	0.5	115.71
			1	119.20
			2	120.35
Sr	1.28	5.02	1	116.54
			2	124.58
			5	117.59
Tl	9.18	6.26	0.5	105.91
			1	108.60
			2	106.63

Note. Abbreviations: RSD, relative standard deviation; CV, coefficients of variation; Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium.

Supplementary Table S3. A coding chart for classifying APOE genotypes from the two SNPs

Base pairing sites		Genotypes
rs429358	rs7412	
TT	TT	ε2/ε2: (rs429358T-rs7412T) / (rs429358T-rs7412T)
TT	CT	ε2/ε3: (rs429358T-rs7412T) / (rs429358T-rs7412C)
TT	CC	ε3/ε3: (rs429358T-rs7412C) / (rs429358T-rs7412C)
TC	CT	ε2/ε4: (rs429358T-rs7412T) / (rs429358C-rs7412C)
TC	CC	ε3/ε4: (rs429358T-rs7412C) / (rs429358C-rs7412C)
CC	CC	ε4/ε4: (rs429358C-rs7412C) / (rs429358C-rs7412C)

Note. APOE, apolipoprotein E; SNPs, single nucleotide polymorphisms.

Supplementary Table S4. Detection rates and concentrations of heavy metals (HMs) in the blood of controls and cases (μg/L)

HMs	LOD (μg/L)	DR (%)	Total	Diabetes group (*n* = 500)[a]	Control group (*n* = 500)[a]	*P* value[b]
Ba	0.0083	100.0	42.21 (33.02, 57.75)	42.65 (33.29, 57.82)	41.79 (32.89, 57.52)	0.430
Cd	0.0060	100.0	1.0 7 (0.67, 1.66)	1.25 (0.72, 1.72)	0.97 (0.66, 1.54)	0.003
Co	0.0052	99.8	0.14 (0.11, 0.19)	0.14 (0.11, 0.19)	0.13 (0.10, 0.19)	0.012
Sr	0.0092	100.0	25.69 (20.69, 32.16)	26.50 (21.62, 33.24)	24.81 (19.42, 31.25)	< 0.001
Tl	0.0053	95.6	0.06 (0.04, 0.10)	0.06 (0.05, 0.10)	0.06 (0.04, 0.10)	0.731

Note. Abbreviations: LOD, limits of detection; DR, detection rate; Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium.

[a] Date were presented as median and quartile interval.

[b] *P* value was obtained from the Mann-Whitney U test.

Supplementary Table S5. Correlations between blood concentrations of heavy metals (HMs) using Spearman's rank correlation coefficients (μg/L)

HMs	Ba	Cd	Co	Sr	Tl
Ba	1.000				
Cd	0.160**	1.000			
Co	0.172**	0.200**	1.000		
Sr	0.287**	0.266**	0.199**	1.000	
Tl	0.224**	-0.078*	0.165**	-0.167**	1.000

Note. Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium.

* $P < 0.05$; ** $P < 0.01$.

Supplementary Table S6. APOE genotypes and genotype frequencies in study population (*n* = 1,000)

Variable	Total population [*n* (%)]	Diabetes group [*n* (%)]	Control group [*n* (%)]
Haplotype frequencies			
ε2/ε2	9 (0.9)	1 (0.2)	8 (1.6)
ε2/ε3	137 (13.7)	71 (14.2)	66 (13.2)
ε3/ε3	679 (67.9)	337 (67.4)	342 (68.4)
ε2/ε4	16 (1.6)	8 (1.6)	8 (1.6)
ε3/ε4	150 (15.0)	80 (16.0)	70 (14.0)
ε4/ε4	9 (0.9)	3 (0.6)	6 (1.2)
APOE ε4 genotype[a]			
APOE-	825 (82.5)	409 (81.8)	416 (83.2)
APOE+	175 (17.5)	91 (18.2)	84 (16.8)
Total	1,000	500	500

Note. Abbreviation: APOE, apolipoprotein E.

[a] APOE genotype was categorized as APOE- (ε4 non-carriers) *vs*. APOE+ (ε4 carriers) depending on ε4 allele.

Supplementary Table S7. The interaction between single HMs and APOE ε4 genotype

HMs	APOE ε4 genotype[a]	*OR* (95% *CI*)	*P*	*P* for interaction
Ba	APOE-	1.23 (0.98, 1.56)	0.076	0.019
	APOE+	1.54 (0.90, 2.64)	0.117	
Cd	APOE-	1.25 (1.03, 1.51)	0.026	0.013
	APOE+	1.40 (0.91, 2.15)	0.132	
Co	APOE-	1.10 (0.93, 1.30)	0.288	0.103
	APOE+	1.32 (0.88, 1.99)	0.182	
Sr	APOE-	1.11 (0.89, 1.39)	0.358	0.516
	APOE+	0.98 (0.59, 1.61)	0.926	
Tl	APOE-	1.14 (0.99, 1.31)	0.076	0.080
	APOE+	1.17 (0.84, 1.64)	0.351	

Note. Abbreviation: APOE, apolipoprotein E.

[a] APOE genotype was categorized as APOE- (ε4 non-carriers) *vs*. APOE+ (ε4 carriers) depending on ε4 allele.

Models were adjusted for residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city.

Supplementary Table S8. Associations between heavy metals (HMs) and diabetes mellitus in populations excluding those with chronic kidney disease or chronic liver disease (*n* = 633)

HMs[a]	Continuous *OR* (95% *CI*)	Q1	Q2 *OR* (95% *CI*)	Q3 *OR* (95% *CI*)	Q4 *OR* (95% *CI*)	*P* for trend[b]
Ba						
Model 1	1.15 (0.93, 1.43)	Ref	1.10 (0.70, 1.71)	1.23 (0.79, 1.92)	1.17 (0.75, 1.82)	0.430
Model 2	1.47 (1.11, 1.95)	Ref	1.01 (0.61, 1.69)	1.38 (0.81, 2.37)	1.47 (0.82, 2.62)	0.061
Model 3	1.41 (1.05, 1.90)	Ref	1.03 (0.62, 1.74)	1.51 (0.88, 2.61)	1.54 (0.85, 2.80)	0.134
Cd						
Model 1	1.11 (0.94, 1.31)	Ref	1.24 (0.79, 1.94)	1.79 (1.14, 2.80)	1.64 (1.05, 2.57)	0.013
Model 2	1.27 (1.03, 1.56)	Ref	1.56 (0.90, 2.70)	1.58 (0.82, 3.04)	1.78 (0.71, 4.49)	0.008
Model 3	1.26 (1.02, 1.56)	Ref	1.74 (1.02, 2.97)	1.97 (1.12, 3.46)	2.42 (1.30, 4.49)	0.013
Co						
Model 1	1.27 (1.06, 1.51)	Ref	1.29 (0.82, 2.03)	1.86 (1.19, 2.92)	1.68 (1.07, 2.64)	0.009
Model 2	1.15 (0.95, 1.40)	Ref	0.81 (0.44, 1.49)	1.04 (0.50, 2.19)	0.96 (0.33, 2.74)	0.202
Model 3	1.08 (0.88, 1.34)	Ref	0.86 (0.51, 1.46)	1.17 (0.69, 2.01)	1.03 (0.60, 1.78)	0.721
Sr						
Model 1	1.38 (1.13, 1.70)	Ref	1.68 (1.07, 2.64)	1.61 (1.02, 2.54)	2.08 (1.32, 3.27)	0.003
Model 2	1.08 (0.84, 1.39)	Ref	1.11 (0.55, 2.22)	0.93 (0.37, 2.34)	1.03 (0.28, 3.85)	0.642
Model 3	0.97 (0.74, 1.28)	Ref	1.15 (0.67, 1.98)	0.87 (0.48, 1.56)	1.05 (0.58, 1.89)	0.979
Tl						
Model 1	1.04 (0.90, 1.19)	Ref	1.07 (0.69, 1.66)	1.20 (0.77, 1.86)	1.00 (0.64, 1.56)	0.972
Model 2	1.11 (0.95, 1.31)	Ref	0.70 (0.39, 1.26)	1.13 (0.58, 2.19)	1.58 (0.64, 3.89)	0.043
Model 3	1.05 (0.88, 1.26)	Ref	0.62 (0.36, 1.06)	0.98 (0.57, 1.66)	1.29 (0.74, 2.25)	0.186

Note. Abbreviations: *OR*, odds ratio; *CI*, confidence interval; Ref, reference; Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; Q, quartile. Bold values indicate statistically significant.

[a] Concentrations of HMs were ln-transformed and standardized for analysis.

[b] *P* for trend was obtained from the median of each quartile (standardized after ln-transformed) as a continuous variable in conditional logistic regression model.

Model 1 was a crude model.

Model 2 was adjusted for age, gender, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, body mass index (BMI), hypertension, diet habit, and city.

Model 3 included covariates in model 2 and other HMs.

Supplementary Table S9. Association between APOE genotype and diabetes mellitus in populations excluding those with chronic kidney disease or chronic liver disease (*n* = 633)

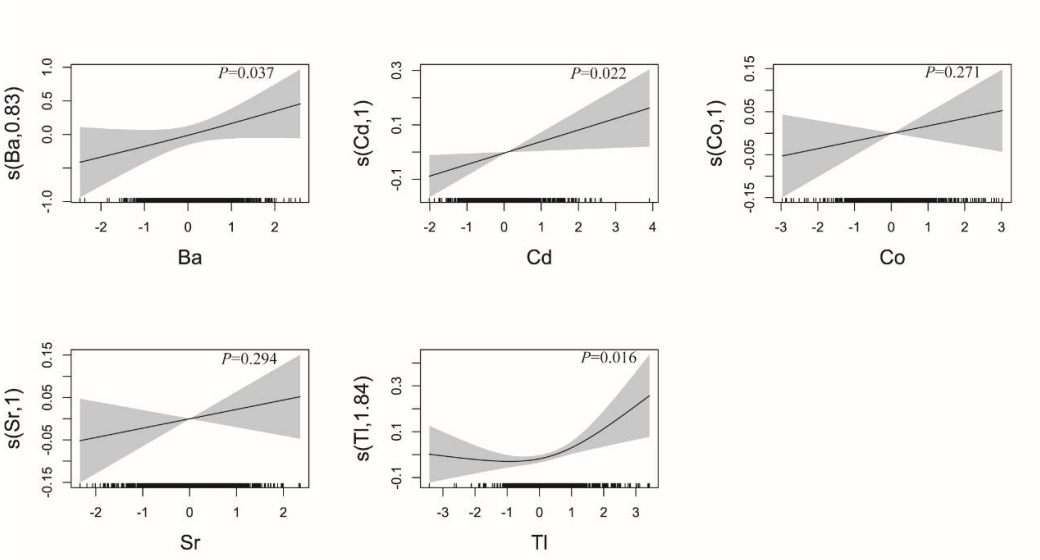
Genotype[a]	Model 1		Model 2	
	OR (95% *CI*)	*P* value	OR (95% *CI*)	*P* value
APOE-	Ref		Ref	
APOE+	1.16 (0.77, 1.73)	0.481	1.24 (0.80, 1.91)	0.343

Note. Abbreviations: APOE, apolipoprotein E; *OR*, odds ratio; *CI*, confidence interval; Ref, reference.

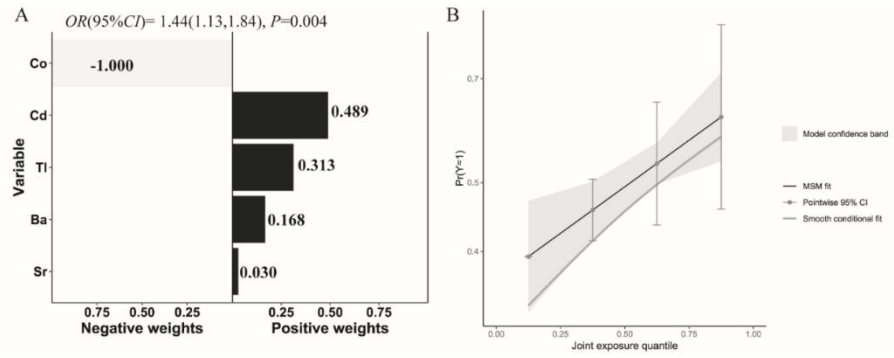
[a] APOE genotype was categorized as APOE- (ε4 non-carriers) *vs*. APOE+ (ε4 carriers) depending on ε4 allele.

Model 1 was a crude model.

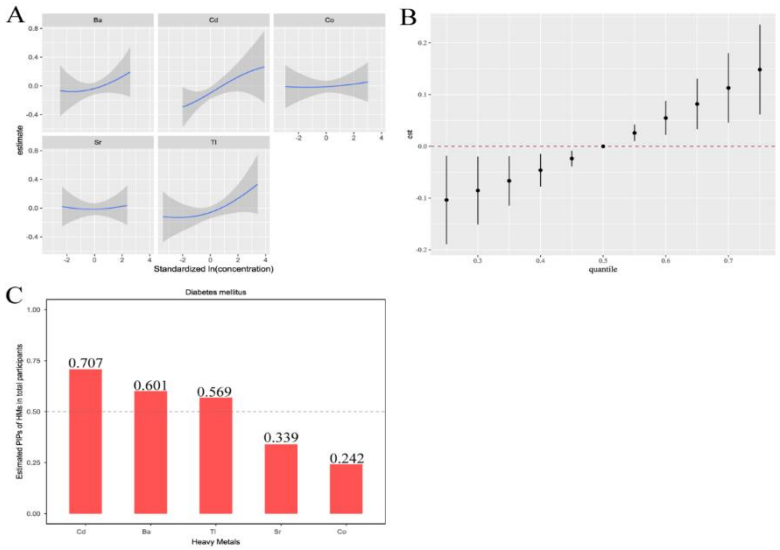
Model 2 was adjusted for age, gender, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, body mass index (BMI), diet habit, hypertension, and city.



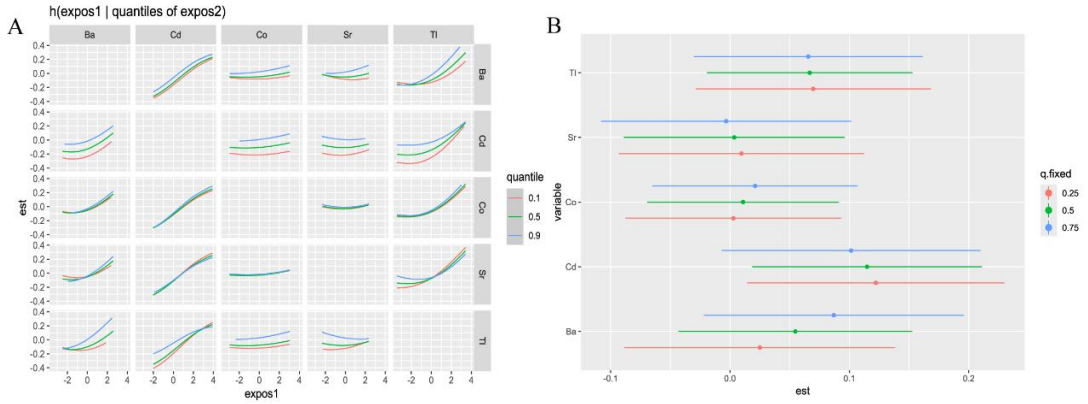
Supplementary Figure S1. The nonlinear associations between HMs (Ba, Cd, Co, Sr, and Tl) and diabetes mellitus (DM) using generalized additive models (GAMs) (A-E). The three knots were located at the 10th, 50th, and 90th percentiles of HM concentrations, respectively. Models were adjusted for residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city. HMs were ln-transformed and standardized. Solid black lines represent the mean difference of DM and grey area indicate 95% *CI*. The estimated degrees of freedom (EDF) were used to quantify nonlinearity, where EDF = 1 indicates a linear association. The results suggested a positive linear relationship for Cd (EDF = 1, *P* = 0.022) and positive nonlinear relationships for Ba (EDF = 0.83, *P* = 0.037) and Tl (EDF = 1.84, *P* = 0.016). Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; HMs, heavy metals; BMI, body mass index; *CI*, confidence interval.



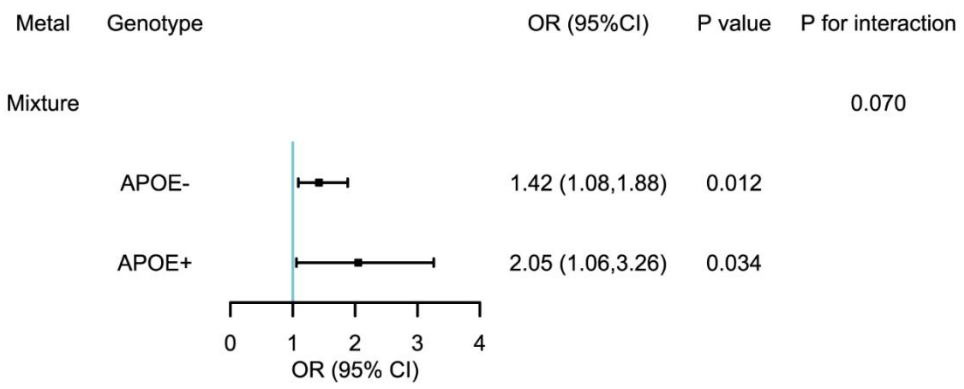
Supplementary Figure S2. Estimation of the effect of HM mixture on DM using the quantile g-computation (QGC) model. (*n* = 1,000) The QGC model was adjusted for age, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city. (A) The weight values for individual HMs were assessed in both positive and negative directions, and the effect value [*OR* (95% *CI*)] of combined exposure was evaluated. (B) Plot of the combined effect [95% *CI*] of HMs on DM. Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; HMs, heavy metals; *OR*, odds ratio; *CI*, confidence interval.



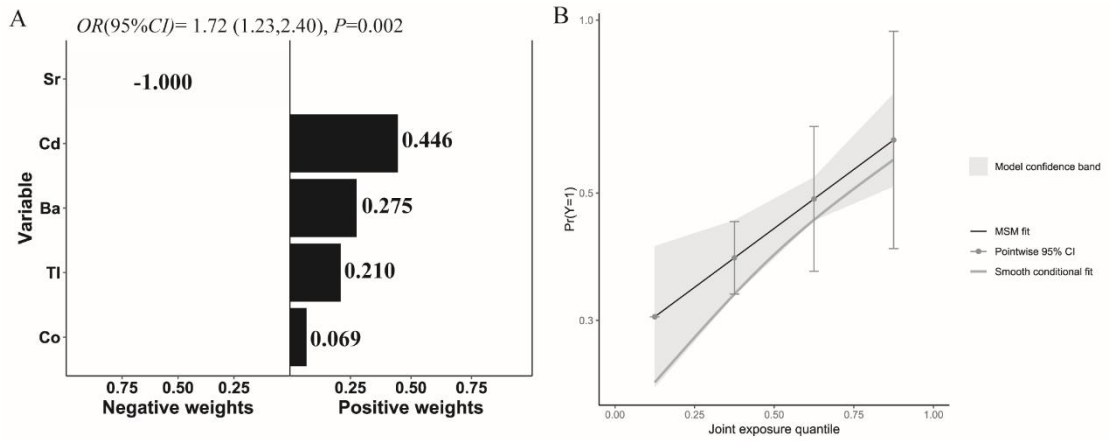
Supplementary Figure S3. Associations between HMs (Ba, Cd, Co, Sr, and Tl) and diabetes mellitus in elderly individuals, using BKMR. (*n* = 1,000) The BKMR model was adjusted for age, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city. (A) Univariate exposure-response functions and 95% *CIs* for each HM, when keeping the remaining metals fixed at the median. (B) Combined effect of the mixture and 95% *CIs*, defined as differences in diabetes mellitus when all HMs were fixed at particular quantiles (25th to 75th percentile), as compared to when all of the HMs were fixed at the 50th percentile values. (C) Posterior inclusion probabilities (PIPs) of each HM for diabetes mellitus from the BKMR model. PIP quantifies the significance of each HM in the mixture with respect to the outcome, with a range from 0 to 1. A higher PIP value indicates greater importance of the HM in the mixture. Generally, variables with PIP > 0.5 are considered to have significant effects. The PIP values of Cd, Tl, and Ba are greater than 0.5, making them the main contributors to the mixture effect. Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; HMs, heavy metals; *CIs*, confidence intervals.



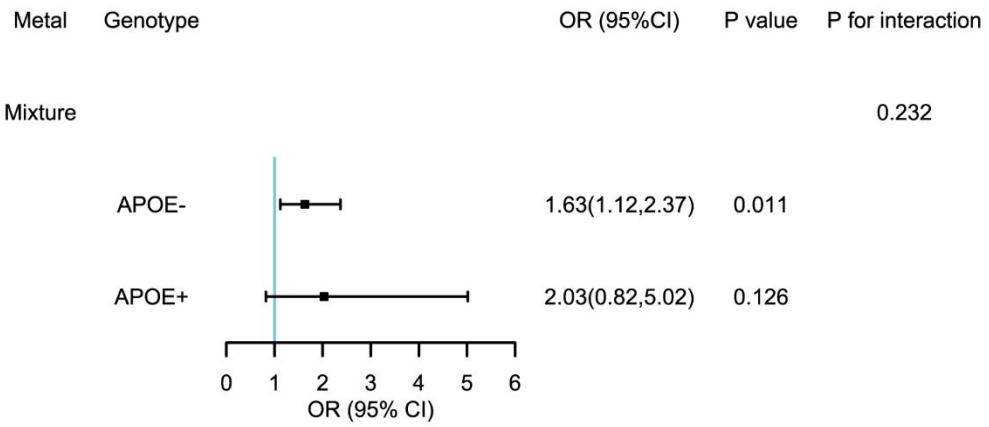
Supplementary Figure S4. Associations between HMs (Ba, Cd, Co, Sr, and Tl) and diabetes mellitus in elderly individuals, using BKMR. (*n* = 1,000) The BKMR model was adjusted for age, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city. (A) Single-exposure effects (95% *CIs*), defined as the heavy metals associated with diabetes mellitus from its 25th to its 75th percentile, where all of the remaining HMs were fixed at a specific quantile (the 25th, 50th, or 75th percentile). (B) Bivariate exposure response functions. Each cell represented the exposure-response curve for the column HM when the row HM was fixed at 25th, 50th, and 75th percentiles and the remaining HMs were fixed at their medians. Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; HMs, heavy metals; *CIs*, confidence intervals.



Supplementary Figure S5. Association between the blood HM mixture and diabetes mellitus stratified by APOE genotype using the quantile g-computation (QGC) model. (*n* = 1,000) Models were adjusted for age, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, liver disease, kidney disease, and city. APOE genotype was categorized as APOE- *vs*. APOE+ depending on ε4 allele. Abbreviations: *OR*, odds ratio; *CI*, confidence interval; APOE, apolipoprotein E; HM, heavy metal.



Supplementary Figure S6. Estimation of the effect of HM mixture on DM using the quantile g-computation (QGC) model in populations excluding those with chronic kidney disease or chronic liver disease. (*n* = 633) The QGC model was adjusted for age, gender, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, and city. (A) The weight values for individual HMs were assessed in both positive and negative directions, and the effect value [*OR* (95% *CI*)] of combined exposure was evaluated. (B) Plot of the combined effect [95% *CI*] of HMs on DM. Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Sr, strontium; Tl, thallium; HMs, heavy metals; *OR*, odds ratio; *CI*, confidence interval.



Supplementary Figure S7. Association between the blood HM mixture and diabetes mellitus stratified by APOE genotype using the quantile g-computation (QGC) model in populations excluding those with chronic kidney disease or chronic liver disease. (*n* = 633) Models were adjusted for age, gender, residence, marriage, educational level, family economy, occupation, physical activity, alcohol consumption, smoking, BMI, diet habit, hypertension, and city. APOE genotype was categorized as APOE- *vs*. APOE+ depending on ε4 allele. Abbreviations: *OR*, odds ratio; *CI*, confidence interval; APOE, apolipoprotein E; HM, heavy metal.