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RESEARCH ARTICLE

Association between mixed urinary metal exposure and liver function: analysis of NHANES data

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Abstract
Metals have been reported to affect liver functions; however, the association between mixed metal exposure in the urine and liver functions remains unclear. The present study analyzed data from the National Health and Nutrition Examination Survey (NHANES) program collected in 2005–2018. Weighted multiple linear regression and Bayesian kernel machine regression (BKMR) were used to explore the relationship between mixed urinary metal contents and liver function tests (LFTs). A total of 8158 participants were analyzed in this study. Multiple methods suggested that cadmium (Cd) was significantly positively related to LFTs, while cobalt (Co) was negatively related to LFTs. Meanwhile, some other metals showed a significant relationship with some indicators of LFTs. Urine metal is related to LFTs, with Cd and Co content changes being closely related to LFTs. The metal in urine may represent a marker for predicting liver dysfunction. Further studies are needed to verify this hypothesis.

Keywords Urinary metal · LFT · NHANES · BKMR

Introduction

As a vital organ in the human body, the liver has several functions of synthesis and secretion (Hu et al. 2019). Due to environmental, infective, genetic, and other factors, liver diseases are associated with a heavy burden (Peery et al. 2019; Yang et al. 2019). According to Globocan, the incidence of liver cancer ranks sixth in newly diagnosed cancer cases, while the mortality of liver cancer ranks third in new death cases (Sung et al. 2021). The incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) are rising rapidly worldwide. And it is estimated that 25% of individuals worldwide suffer from NAFLD to date (Huang et al. 2021).

There are generally no signs or symptoms in the early stage of liver disease. As cheap diagnostic methods, liver function tests (LFTs) can rule out liver abnormalities to some extent (Newsome et al. 2018). LFT indicators mainly include alanine aminotransferase (AST), aspartate aminotransferase (ALT), γ-glutamyl transferase (GGT), total bilirubin (TBIL), and alkaline phosphatase (ALP). The increase in AST and ALT levels is the most common indicator of abnormal liver function, among which ALT is considered more specific in liver tissue (Tian et al. 2023). Although these two enzymes also exist in other tissues, abnormalities in their levels can prompt attention to the liver. The increase in ALT can indicate biliary obstruction, and the content of GGT can help judge the abnormal position (Lin et al. 2022; Zhang et al. 2022). As a by-product of heme metabolism, the increase in bilirubin may be an indicator of metabolic abnormalities, hemolysis, or liver disease (Liu et al. 2018).

Contact with metals or metalloids can have lifelong disease consequences (Tracy et al. 2020). A meta-analysis based on 21 original studies showed that the serum contents of chromium, nickel, and mercury in leukemia patients increased significantly, while the serum manganese concentration decreased significantly (Shen et al. 2023). Another study found that

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As, Cd, and Cu were at greater risk of cancer by studying 77 research papers (Hou et al. 2023). Several studies have suggested that metals are involved in several diseases, including cardiovascular, diabetes, kidney, nervous system, and cancer diseases, resulting in a severe burden (Al-Aly and Bowe 2020; Shen et al. 2018; Shi et al. 2021; Wang et al. 2020).

The liver is an important organ for the metabolism of heavy metals. At the same time, liver cells are exposed to chemicals, which may lead to liver damage and dysfunction (Park et al. 2021). A previous study demonstrated that heavy metals can cause various liver diseases, including nonfatty acid liver disease (Chung et al. 2020). A study from Northeast China found that mixed metal exposure was related to several liver function indexes through testing 1171 individuals (Zhao et al. 2022). A study from South Korea also suggested that exposure to lead (Pb), cadmium (Cd), and mercury (Hg) may be closely related to liver function damage (Kim et al. 2021). A study from Zambia found that metal exposure significantly impacted the hepatogenic system in 504 patients (Nakata et al. 2021). However, most current research only focuses on a few metals, such as Pb, and the number of research samples is not large enough.

Therefore, the present study used the American National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2018 to investigate the associations between metal mixture in urine and LFTs using weighted multiple linear regression and Bayesian kernel machine regression (BKMR).

Methods

Study population

We conducted a secondary analysis of the data from NHANES. NHANES was implemented by the National Center for Health Statistics (NCHS) and is a program of studies designed to assess people's health and nutritional status in the USA since 1960. Details of the study design, method, or data are available online at https://www.cdc.gov/nchs/nhanes/index.htm.

A total of seven cycles of NHANES data from 2005 to 2018, including 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018, were used in the present analysis.

Among the total 70,190 participants, 51,522 were excluded because of missing urinary metal data, while 4183 were excluded due to liver function data being absent. Moreover, a total of 222 participants who were pregnant were excluded. In addition, a further 205 participants with hepatitis B and C virus or liver cancer were excluded. And 5900 participants with missing data on covariate were excluded. Finally, 8158 participants from NHANES were included in the current analysis.

All the participants in these NHANES studies provided consent, and NCHS Research Ethics Review Board approved the study protocols.

Urinary metal measurements

Between 2005 and 2018, ten metal elements were part of the NHANES urine routine examination and measured in each cycle, including barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), lead (Pb), antimony (Sb), thallium (Tl), tungsten (Tu), and uranium (Ur). Because many data in the detection of Ur were below the lower monitoring limit, this metal was discarded in the present analysis. Samples were processed, stored, and transported for analysis and were directly measured using mass spectrometry. Details of these dates can be seen on the website (https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/UHM_D.htm).

Liver function tests (LFTs)

In the 2005–2018 NHANES cycles, LFTs in serum were measured using different methods with a Beckman Coulter UniCel DxC800 Synchron Clinical System. The present study selected ALT, AST, TBIL, GGT, ALP, ASL/ALT ratio, and hepatic steatosis index (HSI) as liver function indicators. ALT and AST are enzymes released after liver cell membrane injury and will rise rapidly during acute liver injury and are measured using kinetic rate methods. The increase in ALP level is seen in cholestasis. The method to measure ALP utilizes a simple reaction wherein ALP acts upon a substrate in the presence of magnesium and zinc activators to form a colored product whose optical density is measured at 450 nm. GGT is used to identify the causes of cholestasis in the clinical setting (Lee et al. 2022). The concentration of TBIL in serum depends on bilirubin production and hepatocyte clearance so that TBIL can reveal the balance between them (Xiao et al. 2021). TBIL serum level was measured using a timed-endpoint Diazo method. HSI is an effective marker for predicting liver fat content (Meffert et al. 2014). The formula is $HSI = 8 \times (ALT/AST) + BMI + 2$ (for female) + 2 (for diabetes).

Covariates

Previous studies collected covariates linked to liver functions or urinary metals from questionnaires and laboratory examinations. In the present study, data including age, sex, education levels, race, economic, smoking, and drinking status, as well as the history of diagnosis of diabetes mellitus or hypertension from questionnaires, were collected. Data including BMI, total cholesterol (TCHO), and high-density lipoprotein cholesterol (HDL-C), were collected from laboratory examination records.

Educational levels were classified as < 9th grade, 9th–11th grade, high school, college, and graduate or above. Ethnicity was classified as follows: Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other ethnic groups. If participants had smoked at least 100 cigarettes in their lifetime or had at least 12 alcoholic drinks in 1 year, they would be considered smokers or drinkers, respectively. The history of diabetes mellitus or hypertension was determined according to the self-reported history of physician-diagnosed diabetes mellitus or hypertension. Laboratory results were measured using different standardized methods. Details of them were described on the NHANES website.

Statistical analysis

NHANES used complex methods like survey design and non-response and post-stratification adjustment to form accurate estimates. In the present study, continuous variables like age were expressed as median ± standard deviation. Categorical variables like sex were represented as numerical and frequency distribution. Because the urinary metals did not belong to the normal distribution, these were transformed logarithmically to normalize their distributions.

Linear regression

A survey-weighted multiple linear regression model was used to assess the associations between urinary metals (Ba, Cd, Co, Cs, Mo, Pb, Sb, Tl, and Tu) and LFTs (ALP, ALT, AST, GGT, TBIL, AST/ALT, and HSI). In the model, data were adjusted for age, sex, education level, race, poverty, smoking, alcohol user, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes, and hypertension. Subsequently, the urinary metal content was divided into four quartiles. The first quartile was regarded as a reference value. We used a multiple linear regression model to explore the potential dose–response relationship. In the models, we judge whether there is collinearity between metals by variance inflation factor (VIF). The fitting of statistical model is measured by Akaike information criterion (AIC) (Fu et al. 2021; Kailembo et al. 2018). We calculated the false discovery rate (FDR) by the Benjamini-Hochberg (BH) procedure. The analysis was implemented in R via the package "survey."

Bayesian kernel machine regression (BKMR)

BKMR is a new method to estimate the health effects of multivariate exposure (Bobb et al. 2018). This method can estimate the ability of a multi-pollutant mixture to affect health and estimate the total exposure, the impact of a single exposure, and the interaction between chemicals. The current study compared nine types of urine metal contents with different percentiles fixed simultaneously and with those fixed at the median to estimate the overall impact on LFTs.

To estimate the single effect of metal content in urine, the difference associated with LFTs was set when a certain metal content was at the 75th and 25th percentiles and the other eight metal contents were fixed at the 25th, 50th, and 75th percentiles, respectively. Through the BKMR model, we calculate the posterior inclusion probability (PIP). PIP is a variable importance measurement method from 0 to 1, which can determine the relative importance of different urine metals to liver function (Laine et al. 2020; Yu et al. 2022). PIP threshold of 0.5 is usually used to judge whether this effect is significant or not. The Spearman correlation coefficient between metals was calculated to judge the correlation between metals. The analysis was implemented in R via the package "bkmr."

R software (v4.2.2; https://www.r-project.org/) was used to perform the aforementioned analyses. $P < 0.05$ (two-tailed) was considered to indicate a statistically significant difference.

Results

Baseline characteristics of participants

A total of 8158 participants met the conditions for analysis. Details are shown in Fig. 1.

Among the 8158 participants, the average age was 49.398 years, 51.0% were men, and 46.0% were non-Hispanic white. In terms of education level, college education accounted for 29.4%. About 45.7% and 71.8% of participants were considered smokers and drinkers, respectively. In addition, 35.0% and 12.3% of participants had a history of hypertension and diabetes, respectively. The average levels of HDL-C and TCHO were 1.364 mg/L and 5.016 mmol/L, respectively. The details of the baseline characteristics of participants are shown in Table 1.

Weighted multiple linear regression

Urine metal content level data were subject to weighted multiple linear regression after logarithmic transformation. Results showed that AST was positively correlated with Cd but negatively correlated with Cs, Pb, and Tl. ALT was negatively related to Cs but positively correlated with Cd. And Cd was positively correlated with GGT, while Cs and Mo were negatively correlated with GGT. TBIL was positively correlated Ba and Cd, while it was negatively correlated to Co and Cs. In addition, Cd and Pb were positively correlated with ALP, while Cs was negatively correlated with ALP.

For AST/ALT, Ba and Tl were negatively correlated with it, while Co and Sb were positively correlated with

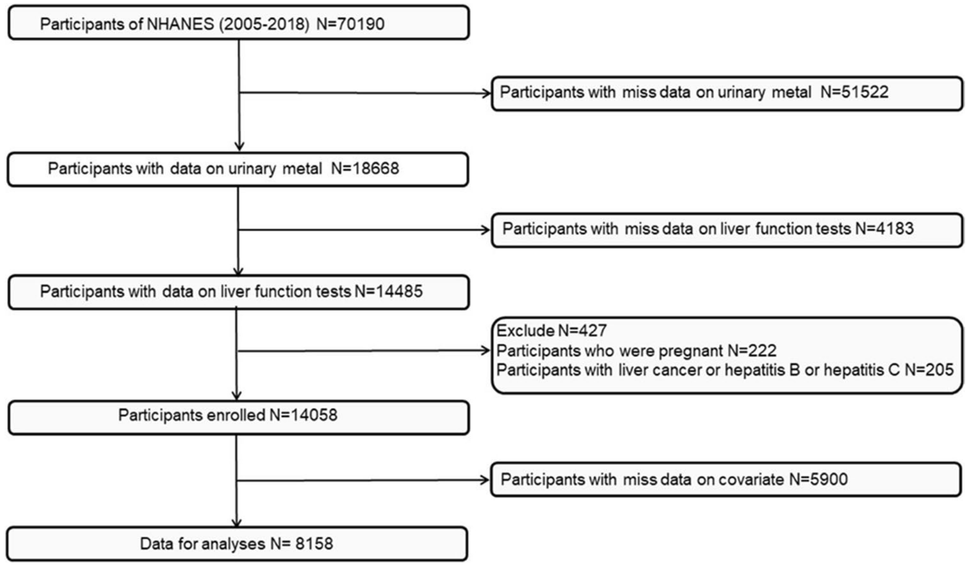

Fig. 1 Flow chart of the study population. NHANES, National Health and Nutrition Examination Survey

it. Moreover, Ba and Tl were positively correlated with HSI, and Co was negatively correlated with it. The details of the analysis results are shown in Table 2 and Supplement Table 1.

After testing, the VIF values in all models were less than 10, suggesting that there was no obvious collinearity problem. Details are shown in supplementary Table 2. In addition, the AIC values of each model can also be seen in supplementary Table 3.

Weighted multiple linear regression after quartile grouping

To further explore the relationship between urinary metal and liver function, urinary metal quartiles were grouped and then subjected to weighted multiple linear regression.

Compared with the reference quartile, Ba was positively correlated with ALT and HSI, but negatively with AST/ALT. Cd had a significant positive correlation with ALP, ALT, AST, GGT, and TBIL. Co was negatively related to ALT, TBIL, and HSI, but positively correlated with AST/ALT. Moreover, Sb was positively correlated with AST/ALT. And Tl was negatively related to AST/ALT, but positively correlated with HSI.

Meanwhile, Cs, Mo, and Tu did not show a significant correlation with LFTs. Details are shown in Table 3 and Supplement Table 4. The VIF values in each model were less than 10, indicating that there was no obvious collinearity problem. Details are shown in supplementary Table 5. The AIC values of each model are shown in supplementary Table 6.

Bayesian kernel machine regression

The BKMR analysis showed no statistically significant overall effect in the AST, ALT, GGT, and AST/ALT models.

TBIL increased significantly when all urinary metal content was in the 25th and 55th percentiles, while no significant effect was above the 55th percentile. As for ALP, analyses showed a significantly positive overall effect of ALP levels in the 25th and 75th percentiles. And analyses showed a significantly negative overall effect of HSI levels in the 25th and 75th percentiles, while no significant effect was above the 45th percentile.

In multivariable-adjusted models, the contents of eight urine metals were fixed at the 25th, 50th, and 75th percentiles. It was found that Cd had a significant positive correlation with AST. By contrast, Cs had a negative correlation with AST. In the ALT model, Ba and Cd were positively correlated with it, but Co and Cs were negatively correlated. And Cd was significantly positively correlated to GGT, while Cs was significantly negatively correlated to GGT.

The results of the TBIL model were more complex. Although only Pb had a significant positive relationship when the content of other metals was fixed at the 25th percentile, Cd, Pb, Sb, and Tl had a significant positive correlation when fixed at the 50th and 75th percentiles. And when the content of other metals was fixed at the 25th percentile, only Co had a significant negative correlation with TBIL. When fixed at the 50th and 75th percentiles, Co and Mo had a significant negative correlation with TBIL.

In addition, Co and Pb had a positive correlation with ALP, while Cs had a negative correlation. Results are shown in Figs. 1 and 2. Ba, Co, Sb, and Tl were positively

Table 1 Baseline characteristics of the study participants

Variable	Cycle 2005–2018 ($N=8158$)
Age (years)	49.398 (17.746)
Male (%)	4157 (51.0%)
Race/ethnicity (%)	
Mexican American	1280 (15.7%)
Other Hispanic	775 (9.5%)
Non-Hispanic white	3754 (46.0%)
Non-Hispanic black	1610 (19.7%)
Other races	739 (9.1%)
Education level (%)	
< 9th grade	860 (10.5%)
9–11th grade	1143 (14.0%)
High school	1827 (22.4%)
College	2398 (29.4%)
Graduate or above	1928 (23.6%)
Poverty	2.553 (1.618)
Smoker (%)	3727 (45.7%)
Drinker (%)	5829 (71.8%)
Hypertension (%)	2856 (35.0%)
Diabetes mellitus (%)	1000 (12.3%)
BMI (kg/m^2)	29.094 (6.827)
HDL-C (mg/L)	1.364 (0.413)
TCHO (mmol/L)	5.016(1.082)
AST (U/L)	25.711 (15.681)
ALT (U/L)	25.277 (17.457)
GGT (IU/L)	28.657 (41.729)
TBIL (mg/dL)	0.697 (0.334)
ALP (IU/L)	68.593 (23.721)

Data are presented as median or *n* (%)

BMI body mass index, *TCHO* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *TBIL* total bilirubin, *ALP* alkaline phosphatase

correlated with AST/ALT, while Cd and Cs were negatively correlated with it. For HSI, only Co had a significant negative correlation with it, while Ba and Tl were positively correlated with it. Results are shown in Fig. 3, Supplement Figs. 3 and Supplement Figs. 4.

PIP values under different models can be seen in supplementary Table 7, and the PIP values of Ca in many models were relatively high, indicating that it had a great influence on LFTs.

We analyzed the correlation of nine metals and found that they were all positively correlated, but none of them reached a significant correlation. Among them, Cs and Tl have the closest relationship ($P=0.77$). The data can be seen in supplementary Fig. 5.

Table 2 Weighted multiple linear regression of urinary metal with AST, ALT, TBIL, GGT, and ALP

Metal	AST			ALT			TBIL			GGT			ALP		
	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}
Ba	0.311	0.360	0.757	1.233	0.387	0.435	0.004	0.005	0.006	0.571	1.042	0.651	0.153	0.372	0.757
Cd	2.002	0.359	< 0.001	1.889	0.365	< 0.001	0.026	0.007	< 0.001	6.236	1.256	< 0.001	2.685	0.439	< 0.001
Co	−0.510	0.345	> 0.900	−2.069	0.361	0.289	−0.047	0.007	< 0.001	−1.523	1.199	0.418	−0.450	0.535	0.504
Cs	−1.966	0.495	0.002	−2.450	0.637	0.001	−0.025	0.009	0.001	−6.385	2.023	0.013	−2.899	0.792	0.002
Mo	−0.474	0.270	0.251	0.123	0.329	0.283	−0.016	0.007	0.888	−2.282	0.839	0.029	−0.750	0.449	0.201
Pb	−0.524	0.397	< 0.001	−0.545	0.365	0.320	0.026	0.008	0.234	1.140	1.179	0.482	1.791	0.441	0.001
Sb	0.420	0.346	0.493	0.017	0.387	0.327	0.015	0.008	> 0.900	0.866	0.758	0.430	0.402	0.381	0.423
Tl	−0.105	0.381	0.037	0.953	0.524	0.981	0.030	0.009	0.148	−0.764	1.302	0.699	−1.577	0.691	0.065
Tu	0.403	0.241	0.173	0.248	0.293	0.248	0.006	0.007	0.574	0.944	0.528	0.197	0.153	0.372	0.230

The model was adjusted as age, sex, education level, race, poverty, smoker, alcohol user, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes, and hypertension. In the analysis, we fully consider the influence of weight

FDR false discovery rate, *CI* confidence interval, *AST* aspartate transaminase, *ALT* alanine transaminase, *TBIL* serum total bilirubin, *GGT* gamma-glutamyl transferase, *ALP* alkaline phosphatase, *Ba* barium, *Cd* cadmium, *Co* cobalt, *Cs* cesium, *Mo* molybdenum, *Pb* lead, *Sb* antimony, *Tl* thallium, *Tu* tungsten

Table 3 Weighted multiple linear regression after quartile grouping of urinary metal with AST, ALT, TBIL, GGT, and ALP

Metal	AST			ALT			TBIL			GGT			ALP		
	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}
Ba															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	−0.436	0.586	0.691	0.685	0.531	0.502	0.012	0.011	0.441	−1.673	1.831	0.550	−1.250	0.878	0.366
Q3	0.055	0.596	> 0.900	1.296	0.630	0.178	0.015	0.012	0.388	1.158	2.135	0.664	0.525	0.987	> 0.900
Q4	0.129	0.678	> 0.900	2.306	0.735	0.029	0.014	0.013	0.418	1.744	2.156	0.572	0.336	1.016	> 0.900
Cd															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	1.302	0.639	0.325	0.884	0.643	0.476	0.05	0.016	0.015	5.627	3.249	0.273	2.029	0.924	0.102
Q3	1.811	0.587	0.050	2.254	0.750	0.031	0.058	0.017	0.009	8.265	2.358	0.015	3.78	1.086	0.016
Q4	4.075	0.877	0.001	3.597	0.940	0.006	0.058	0.018	0.017	13.327	3.795	0.030	5.564	1.147	0.001
Co															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	0.406	0.694	0.799	−0.89	0.767	0.568	−0.039	0.013	0.031	−3.302	1.480	0.211	−1.169	1.024	0.469
Q3	0.227	0.774	> 0.900	−1.887	0.711	0.061	−0.073	0.016	< 0.001	−3.309	1.520	0.191	−1.356	0.999	0.351
Q4	−0.084	0.936	> 0.900	−3.283	0.843	0.010	−0.096	0.016	< 0.001	−1.654	2.350	0.570	−1.781	1.275	0.354
Cs															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	−0.132	1.001	> 0.900	−0.512	0.884	0.727	−0.003	0.017	0.854	−2.194	1.917	0.500	0.255	0.984	> 0.900
Q3	−1.533	0.873	0.293	−1.731	0.942	0.248	−0.011	0.020	0.662	−5.038	2.906	0.306	−2.886	1.192	0.090
Q4	−1.564	0.983	0.293	−2.768	1.061	0.057	−0.010	0.020	0.657	−5.966	3.436	0.348	3.277	1.419	0.088
Mo															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	−0.336	0.734	0.876	0.704	0.792	0.640	−0.011	0.014	0.571	−1.789	1.711	0.543	−0.258	0.782	> 0.900
Q3	−0.964	0.730	0.404	−0.148	0.806	0.888	−0.016	0.015	0.442	−2.559	1.902	0.419	−0.079	0.903	> 0.900
Q4	−0.644	0.844	0.714	0.149	1.001	0.882	−0.042	0.017	0.080	−3.628	1.594	0.254	−0.100	1.080	> 0.900
Pb															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	−0.808	0.589	0.401	−0.341	0.757	0.804	0.021	0.014	0.331	−1.516	1.789	0.571	0.077	0.858	> 0.900
Q3	−1.683	0.657	0.129	−1.116	0.690	0.340	0.021	0.014	0.329	−1.603	2.044	0.562	2.386	1.001	0.085
Q4	−1.306	0.811	0.311	−0.796	0.862	0.650	0.036	0.016	0.097	−3.129	1.960	0.319	3.355	1.177	0.046
Sb															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	1.041	0.810	0.398	0.806	0.720	0.559	0.008	0.013	0.641	2.900	2.992	0.537	0.409	1.050	> 0.900
Q3	0.696	0.767	0.665	0.457	0.768	0.750	0.024	0.017	0.352	3.548	2.694	0.406	0.172	1.174	> 0.900
Q4	1.392	0.838	0.314	0.601	0.838	0.759	0.036	0.018	0.125	5.281	2.701	0.259	2.205	1.052	> 0.900

Table 3 (continued)

Metal	AST			ALT			TBIL			GGT			ALP		
	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}	β	95% CI	P_{FDR}
Tl															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	−1.435	0.731	0.306	−0.736	0.695	0.571	0.016	0.014	0.422	−1.086	2.073	0.651	−1.657	0.948	0.216
Q3	−1.332	0.745	0.314	−0.275	0.816	0.830	0.019	0.018	0.435	−2.61	2.641	0.555	−2.861	1.15	0.093
Q4	−1.430	0.754	0.293	0.428	0.976	0.779	0.047	0.020	0.079	−3.542	2.523	0.412	−3.550	1.215	0.051
Tu															
Q1	Ref			Ref			Ref			Ref			Ref		
Q2	0.032	0.874	> 0.900	0.219	0.913	0.876	0.010	0.014	0.599	−0.948	1.817	0.628	0.281	0.842	> 0.900
Q3	0.197	0.726	> 0.900	0.518	0.825	0.758	0.020	0.014	0.335	−0.719	1.834	0.697	−0.422	0.961	> 0.900
Q4	0.677	0.798	0.677	0.584	0.854	0.746	0.006	0.017	0.735	1.659	2.203	0.559	0.204	0.907	> 0.900

The model was adjusted as age, sex, education level, race, poverty, smoker, alcohol user, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes, and hypertension. In the analysis, we fully consider the influence of weight

FDR false discovery rate, *CI* confidence interval, *AST* aspartate transaminase, *ALT* alanine transaminase, *TBIL* serum total bilirubin, *GGT* gamma-glutamyl transferase, *ALP* alkaline phosphatase, *Ba* barium, *Cd* cadmium, Co cobalt, *Cs* cesium, *Mo* molybdenum, *Pb* lead, *Sb* antimony, *Tl* thallium, *Tu* tungsten

Discussion

The results of analyses found that Cd had a significant positive correlation with liver function, while Co had a significant negative correlation. Ba, Cs, Mo, Sb, Pb, and Tl significantly correlated with some LFTs.

The liver is the main target organ affected by Cd poisoning (Han et al. 2022), which acts mainly on mitochondria (Lee and Thévenod 2020). The existing evidence suggests that Cd can promote the rupture of the outer and inner membranes of mitochondria, leading to mitochondrial damage (Genchi et al. 2020). A recent study showed that Cd could induce toxicity by upregulating mitochondrial calcium single transporter (Liu et al. 2023a). Some studies are consistent with the present analysis which concluded that Cd could be related to liver injury in the US population (Hong et al. 2021; Xu et al. 2022).

ROS is a key factor that Pb affects liver function. Pb induces ROS formation by inhibiting the enzyme activity of respiratory complex. In addition, studies have shown that Pb can also reduce the activities of many other key enzymes in the cells (Lakka et al. 2023). Other studies have shown that Pb binds to structural proteins or any cytoplasmic proteins, which leads to the decline of antioxidant defense performance of cell membranes (Quan et al. 2020).

At present, through animal experiments, it is considered that Co may cause oxidative stress in the mitochondria of hepatocytes to produce reactive oxygen species, which in turn leads to permeability transformation and apoptosis of hepatocytes (Díaz-de-Alba et al. 2021). In addition, there are also studies showing that Co could be hepatotoxic through lysosomes (Briffa et al. 2020). The epidemiological study on Co remains limited. Similarly, Cs is a metal recognized to be harmful to the human body. It can affect several human functions, including the weight of newborns (Zhang et al 2022). However, there are few reports about the effect of Cs on human liver function.

Our results showed that urinary Co and Cs was negatively correlated with LFTs, which was contrary to the previous studies that suggested metal hepatotoxicity. We think that this negative correlation may because of the antagonistic relationship between metals (Feng et al. 2018; Xie et al. 2023). Due to the competition of metabolic pathways and metal carriers, Cs has a negative correlation with LFTs.

Ba, Mo, and Tl show negative correlation with some LFTs. This may also be due to the competitive relationship between metals. Similar to this study, there are many studies that show that some metals are negatively correlated with LFTs or non-alcoholic fatty liver disease (Li et al. 2023; Xie et al. 2023). However, there is no better explanation except the competition relationship between metals, and its

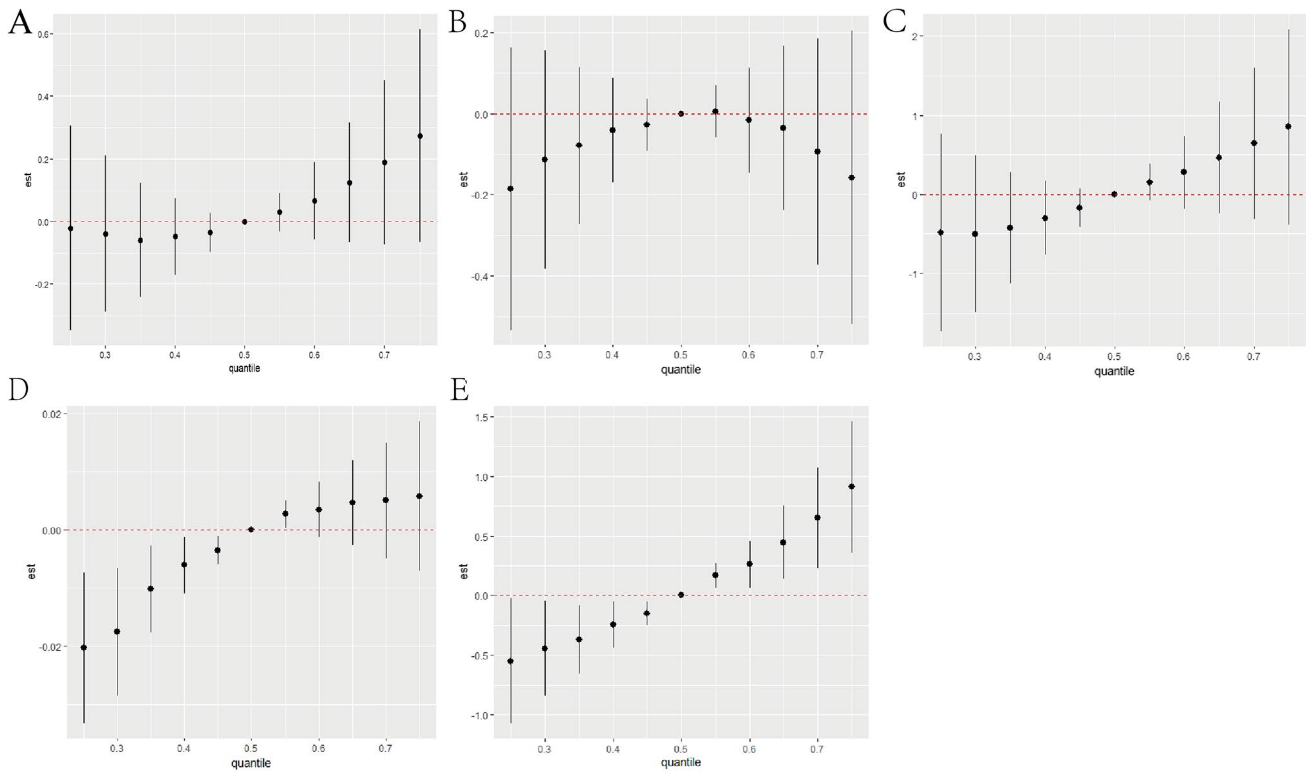

Fig. 2 Overall effect of metal content in urine on LFT based on BKMR. Associations between overall urinary metal content with AST (**A**), ALT (**B**), GGT (**C**), TBIL (**D**), and ALP (**E**) levels based on Bayesian kernel machine regression. All models were adjusted for age, sex, education level, race, poverty, smoker, alcohol user, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes, and hypertension

mechanism needs to be further studied and discussed in the future.

A previous study, which was also based on NHANES data, found a clear association between the content of five metals in blood and liver function (Li et al. 2023). Although the metal in urine is not as accurate as that in blood, its simplicity in terms of sample collection represents an advantage. Supposing that technology to analyze the metal content in urine will become available, screening out individuals with liver function damage and reminding them to seek medical treatment in time will be easier.

Research shows that among the types of man-made garbage (Stanton et al. 2022), metals are second only to plastics, accounting for 14%. Environment, society, and governance (ESG) are very important in the development of metal projects and resource transformation (Lèbre et al. 2019). More and more studies suggest that enterprises need to fulfill their social and environmental responsibilities while showing green development (Khan and Liu 2023, Yang et al. 2023), to reduce the impact of metals on human health.

A recent study found that mixed metal exposure may be negatively correlated with liver function markers by qgcomp (Tang et al. 2023). It is consistent with the conclusion of this study. Another study found that exposure to volatile organic compounds had a significant effect on LFT (Liu et al. 2023b). These studies show that various environmental pollutants are potentially dangerous to the liver.

The present study has the following advantages. First, the present is the first study to evaluate the correlation between the urine levels of nine metal and LFTs. Second, the present analysis was based on the NHANES database, which consists of several representative samples of the general population in the USA. The generated evidence is highly reliable. Thirdly, several advanced statistical methods were to ensure the reliability of the results.

However, the present analysis had the following shortcomings. First, although the analysis was adjusted for several confounding factors, some potential confounding factors were not included in the statistical model because they were not easy to calculate. Secondly, NHANES utilized random urine samples to detect the metal concentration in urine instead of using 24-h urine mental analysis. The measurement of metal content in urine still needs to be fixed. Third, NHANES utilized a cross-sectional design, so the causal relationship could not be further judged; the present analysis could only conclude that some metals in urine were related to LFTs. Fourthly, we cannot discuss the influence of participants taking hepatotoxic drugs on

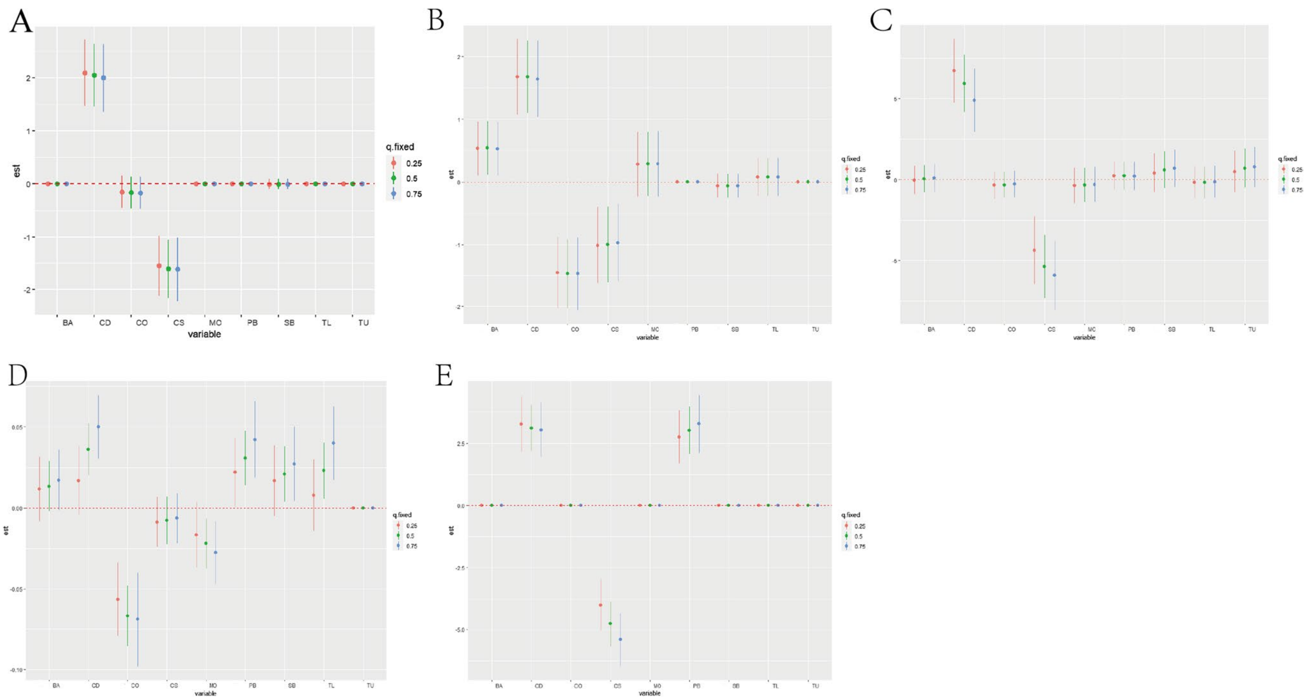

Fig. 3 Individual effect of each metal content in urine on LFT based on BKMR. Associations between individual urinary metal content with AST (**A**), ALT (**B**), GGT (**C**), TBIL (**D**), and ALP (**E**) levels based on Bayesian kernel machine regression. All models were adjusted for age, sex, education level, race, poverty, smoker, alcohol user, BMI, total cholesterol, high-density lipoprotein cholesterol, diabetes, and hypertension. Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; Tu, tungsten

patients' LFTs and hope that this factor can be fully considered in future research.

Using NHANES data of the American population from 2005 to 2018, it was found that Cd and Cs contents in urine significantly correlated with LFTs. The present results showed that exposure to metals may be related to liver dysfunction and the metal content in urine may be a marker for predicting liver dysfunction. However, further research is needed to verify the present findings.

Conclusion

Using NHANES data of the American population from 2005 to 2018, we found that Cd and Co contents in urine significantly correlated with LFTs. Our results show that exposure to metals may be related to liver dysfunction, and the metal content in urine may be a marker for predicting liver dysfunction. More research is needed to verify our findings in the future.

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Author contribution All authors contributed to the study conception and design. Data collection and analysis were performed by B. Z. and H. X. The first draft of the manuscript was written by X. Z. and Y. L., and all authors revised the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate This study uses NHANES data. The participants in this study provided consent, and NCHS Research Ethics Review Board approved the study protocol.

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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