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ORIGINAL RESEARCH ARTICLE

Mediating role of systemic inflammation in heavy metal-induced metabolic dysfunction-associated steatotic liver disease: Insights from NHANES 2017 to 2020

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Abstract

Introduction: Inflammatory responses play an essential role in metabolic dysfunction-associated steatotic liver disease (MASLD).

Objective: This study investigates the mediating role of systemic inflammation in the pathophysiology of heavy metal-induced MASLD.

Methods: We employed data from the National Health and Nutrition Examination Survey from 2017 to 2020 to examine the relationship between 16 heavy metals and MASLD. Vibration-controlled transient elastography was used to evaluate hepatic steatosis and determine the Systemic Immune Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI). Data analysis was conducted using linear or logistic regressions, weighted quantile sum regression (WQS), restricted cubic spline, and mediation effect models.

Results: The study involved 2,934 patients, with an average age of 44.86 ± 20.58 years, of whom 50.23% were female. Urinary cadmium (Cd), lead (Pb), arsenic, mercury, and tungsten were all positively associated with MASLD risk. The WQS model showed a strong positive correlation between a high amount of urea-metal mixtures and higher SII, SIRI, and MASLD (p<0.01). Mediation analysis found that systemic inflammation mediated the effects of single metals (Cd, cesium [Cs], and Pb) on MASLD risk. The mediation proportions of urinary metal mixtures on MASLD risk, mediated by SII and SIRI, were 57.84% and 65.21%, respectively.

Conclusion: Based on the findings, systemic inflammation partially mediates the association between metals such as Cd, Cs, and Pb—and their combined effects—and metabolic dysfunction and steatosis. Hence, reducing systemic inflammation could help prevent and treat metal-related steatohepatitis caused by environmental exposure.

Keywords: Metabolically-dysfunction-associated steatotic liver disease; Heavy metals; Mediation analysis; Systemic inflammation; National Health and Nutrition Examination Survey

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a clinical–pathological condition characterized by impaired liver function in the presence of ≥5% hepatocellular steatosis. Regardless of alcohol intake, excessive lipid deposition in the liver may lead to fibrosis, cirrhosis, or even primary liver carcinoma.[1] MASLD pathogenesis is complex and related to insulin resistance, obesity, dyslipidemia, and genetic factors.[2,3] It affects almost a quarter of the world; its occurrence has been steadily increasing. The number of people with MASLD globally in 2021 was more than twice that in 1990, with an increase of >50%.[4] MASLD now impacts about 30% of Americans, highlighting a rising public health burden over the last several decades.[5] Given the poor outcomes in medical care and the continually growing disease burden, it is crucial to identify MASLD and adopt effective strategies to manage it.[6]

A growing body of evidence suggests that exposure to environmental contaminants plays a significant role in the pathogenesis of a broad spectrum of chronic illnesses. Due to their considerable bioaccumulation potential, resistance to degradation, and multi-system toxicity, heavy metals are strongly associated with the development of tumors, hypertension, diabetes, and kidney diseases.[7-9] A connection between urinary metal concentrations, such as cadmium (Cd), chromium, and lead (Pb), and MASLD has been identified in existing studies. Once the body absorbs heavy metals, the liver, as a primary target organ, may exhibit abnormal function and progressive hepatitis due to potential toxic effects.[10-12] However, the exact mechanisms by which metals induce MASLD remain elusive, and there is a pressing need for a more comprehensive investigation into its underlying biological pathways.

According to multiple studies, the inflammatory response represents a pivotal pathological characteristic of MASLD, which may initially manifest as benign liver steatosis and subsequently progress to hepatocyte injury. The severity of hepatic steatosis inflammation is closely associated with the activation of immune cells, including T lymphocytes and neutrophils, as well as the secretion of inflammatory mediators such as interleukin-8.[13] By effectively reflecting the inflammatory-immune homeostasis in patients with metabolic diseases, the Systemic Immune Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI) function as quantitative instruments for evaluating systemic inflammatory status.[14,15] Demonstrating considerable predictive value for diabetes patients,[16] SIRI has been corroborated as a reliable indicator of chronic inflammation. Notably, the toxic effects of heavy metals can actively change inflammatory markers: prolonged Cd exposure is especially detrimental to the elderly and female animals, inducing oxidative stress, endoplasmic reticulum stress, and liver inflammation;[17] Pb exposure causes continuous immune-inflammatory responses in hepatic and renal tissues;[18] and arsenic (As) poisoning induces inflammatory liver damage through inflammasomes and autophagy.[19,20] In the development of MASLD, inflammatory responses in hepatocytes and mitochondrial dysfunction induced by insulin resistance, metabolic disorders, and cellular aging play pivotal roles.[21,22] Therefore, inflammation is considered a key mechanism underlying heavy metal-induced MASLD.

However, the mediating role of systemic inflammatory markers in the association between urinary metals and MASLD remains unclear. Wang *et al.*[23] found that SII might be involved in the association between As and cesium (Cs) exposure and liver fibrosis indicators, including the Fibrosis-4 index and the Non-Alcoholic Fatty Liver Disease Fibrosis Score. However, no significant correlation was observed with hepatic steatosis, as represented by the Fatty Liver Index.[23] This study innovatively used two systemic inflammation markers, SII and SIRI, based on the National Health and Nutrition Examination Survey (NHANES) 2017–2020 data from the United States. The severity of accumulated liver fat in participants was assessed using vibration-controlled transient elastography (VCTE). We included data on 16 urinary heavy metals and evaluated whether systemic inflammation mediates the association between urinary metal exposure and MASLD.

2. Materials and methods

2.1. Study population

Employing a stratified, multistage, probability-cluster design, the NHANES is a population-based survey that comprehensively assesses the health and nutritional status of the United States' population, while ensuring statistical robustness and representativeness. The study protocol was approved by the National Center for Health Statistics Ethics Review Board, and all participants provided written informed consent. The data obtained contributed to the development of national health promotion and disease prevention strategies. During the 2017–2020 NHANES cycle, this survey recruited participants and gathered comprehensive data through physical examinations, imaging studies, and urine tests, thereby ensuring a robust methodological approach. The detailed survey results can be accessed on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Initially, this study included a cohort of 4,890 participants who completed urinary heavy metal testing. Following a stringent screening process, the sequential

exclusions were performed based on the following criteria: (i) Incomplete urinary heavy metal data (n = 295); (ii) Absent liver elastography measurements (n = 1,417); (iii) Undetected systemic inflammation markers (SII/SIRI) (n = 31); (iv) Participants with viral hepatitis infections (positive for Hepatitis B surface antigen or antibodies to Hepatitis C, n = 133); and (v) Individuals exhibiting excessive alcohol consumption (n = 80), as these factors are known to potentially influence liver function parameters. Following a series of rigorous screening procedures, our study ultimately included 2,934 participants, of whom 1,603 were diagnosed with MASLD, as illustrated in Figure 1.

2.2. Assessment of metal exposure

Following standardized procedures, the concentrations of 16 trace elements were determined using inductively coupled plasma mass spectrometry (iCAP Q, Thermo Fisher Scientific, Germany) at the National Center for Environmental Health, with a focus on precision and accuracy in analytical methodology. The analytical framework encompassed a comprehensive set of elements, including As, barium (Ba), Cs, cobalt (Co), chromium (Cr), mercury (Hg), nickel (Ni), iodine (I), manganese (Mn), molybdenum (Mo), antimony, Pb, thallium (Tl), tin, and tungsten (W), thereby providing a robust foundation for subsequent investigations. The detection limits for each metal element were determined to be 0.230, 0.190, 2.400, 0.130, 0.310, 0.060, 0.036, 0.086, 0.023, and 0.013 μg/mL, respectively, under the specified experimental conditions. To address non-detectable values, we imputed them as the limit of detection divided by the square root of two.

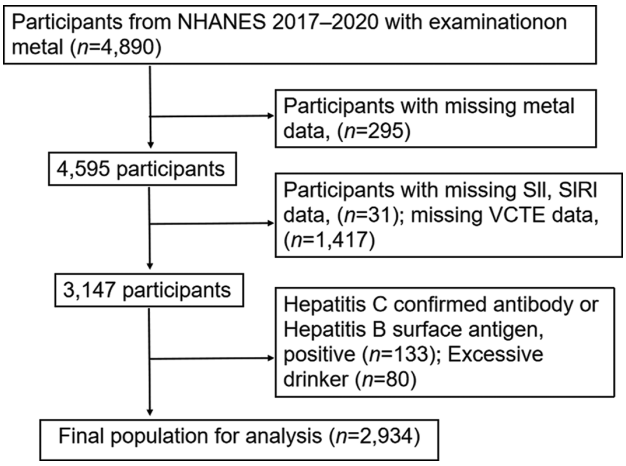

Figure 1. Flow chart of participant selection
Abbreviations: NHANES: National Health and Nutrition Examination Survey; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; VCTE: Vibration-controlled transient elastography.

Subsequently, all metal concentrations were adjusted for urinary creatinine and presented in micrograms per gram of creatinine.

2.3. Evaluation of systemic inflammation

Using the Beckman Coulter (United States) DxH 900 automated blood analyzer and adhering to NHANES whole blood cell count (complete blood count [CBC]) testing procedures, a comprehensive quantitative analysis of hematological parameters was performed on the subjects. The detection indicators include lymphocyte, neutrophil, monocyte, and platelet counts, measured in 1 × 10^3/μL. Sourced from the publicly accessible "Complete Blood Count with 5-Part Differential-Whole Blood" data file within the NHANES 2017-March 2020 Pre-Pandemic Laboratory Data module,[24] the essential CBC parameters served as the foundation for calculating systemic inflammation indices. As detailed below, the SII and SIRI were calculated through well-established formulas: Equations (I) and (II):[16]

SII = (Platelet count × Neutrophil count)/Lymphocyte count (I)

SIRI = (Neutrophil count × Monocyte count)/Lymphocyte count (II)

2.4. Assessment of metabolic dysfunction-associated steatotic liver disease

Since 2017, NHANES has added liver ultrasound transient elastography examinations to assess hepatic steatosis. By measuring ultrasonic attenuation to evaluate hepatic steatosis, this technology integrates the controlled attenuation parameter (CAP) with VCTE, providing a reliable, non-invasive approach for quantifying liver fat content. According to clinical diagnostic criteria, a CAP value ≥246 dB/m indicates hepatic steatosis.[25,26] The demonstration of hepatic steatosis, in the absence of significant alcohol intake, is essential for the diagnosis of MASLD. To confirm the diagnosis, it is pivotal to appropriately exclude other etiologies of liver disease, particularly viral hepatitis B, as evidenced by a positive hepatitis B surface antigen, and hepatitis C, indicated by a positive antibody test. It excludes heavy alcohol use (more than two drinks daily for men and over one for women) and drug-related causes.

2.5. Covariates

Through an online survey, participants provided self-reported data on a range of covariates, such as age, gender, race (non-Hispanic White, non-Hispanic Black, Mexican American, Other), marital status (married/cohabiting, divorced/separated, unmarried), education (below 9th,

9–11th, high school, college, college+), and lifestyle-related factors including smoking behavior and physical activity levels. A comprehensive set of anthropometric measurements, including height, weight, and waist circumference, was systematically obtained. Body mass index (BMI) was derived as weight in kilograms divided by the square of height in meters (kg/m^2). Laboratory analysis further measured liver enzyme levels, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are crucial indicators of hepatic function. Through self-reported interviews, medical history, and diagnostic details (e.g., hypertension and diabetes) were systematically gathered. Based on the diagnostic criteria, a participant was identified as having hypertension if their systolic blood pressure exceeded 140 mmHg or their diastolic blood pressure surpassed 90 mmHg, whereas the diagnosis of diabetes was determined from questionnaire responses, particularly concerning the use of insulin or other antihyperglycemic medications.

2.6. Statistical analysis

Continuous variables were presented as mean±standard deviation, while categorical variables were presented in terms of frequency (n) and percentage (%). The t-test and the Chi-square test were employed to compare the demographic characteristics of MASLD patients. The metal concentration in urine was divided into quartiles and analyzed as a categorical variable. Pearson's analysis was used to assess the correlation structure among urinary metals, with the strengths being dichotomized into low ($r \leq 0.3$) and moderate ($0.3 < r \leq 0.6$). Using a covariate-adjusted regression model, the link between urinary metal levels and MASLD was subsequently examined, while accounting for a comprehensive set of demographics, anthropometric, and clinical variables, including age, sex, race, education, marital status, BMI, smoking, alcohol consumption, hypertension, and diabetes. To investigate the associations between metal concentrations and quantified systemic inflammation markers, a multiple linear regression analysis was employed.

To estimate the cumulative effect of the urinary metal mix on the risk of MASLD, weighted quantile sum (WQS) regression analyses were performed using the "gWQS" package in R. The existence of linear or non-linear relationships between the heavy metal concentrations and MASLD was determined using restricted cubic splines produced from the "RMS" package. Using R, a mediation analysis was conducted to further explore the potential causal pathway linking metal exposure to MASLD. This analysis quantified the direct effect, which denotes the impact of metal exposure on MASLD in the absence of mediators, and the indirect effect, which captures pathways mediated by factors such as inflammatory markers. By dividing the indirect effect by the total effect, the mediation proportion was calculated, effectively quantifying the mediator's contribution to the overall association. All statistical analyses were conducted in R version 3.3.3, with a two-sided significance threshold of $p<0.05$.

3. Results

3.1. Basic demographics and urinary metal concentrations

A total of 2,934 adults were included, of whom 1,063 had MASLD (Table 1). In the survey of participants' demographic characteristics, patients with liver steatosis were more likely to be older and have higher waist circumference, BMI, ALT, AST, and C-reactive protein, but lower high-density lipoprotein cholesterol ($p<0.05$). Participants were predominantly male, hypertensive, diabetic, smokers, and non-Hispanic White with lower levels of education ($p<0.05$). After controlling for urinary creatinine concentration, we found a significant correlation (Pearson's r = 0.65) between urinary Tl and urinary Cs. In addition, there was a moderate correlation between urinary Cs and urinary Mo (0.42), as well as between urinary TI and urinary Mo (0.41) and between urinary Pb and Cd (0.36). The results for other metals were less correlated (Figure 2).

3.2. The relationship between single heavy metal exposure, systemic inflammation, and metabolic dysfunction-associated steatotic liver disease risk

Figure 3 shows the quartile grouping of urine metal concentrations after creatinine correction to assess their relationship with MASLD, using logistic regression. The highest quartiles (Q4) of Co, Cd, Pb, As, Hg, and W were robustly associated with increased MASLD risk relative to the lowest quartile (Q1), with a significant trend ($p<0.05$), as seen in Figure 3A. It is worth noting that the urinary Co concentration showed a significant negative correlation with the risk of MASLD. We performed a linear regression to assess the correlation between urinalysis metals and inflammatory markers. The relevance results showed that the highest quartile of urine concentrations for Ba, Cd, Co, Hg, and Cr (compared to the lowest quartile Q1) correlated with the SII index ($p<0.05$). It is worth noting that urine Ba and Hg concentrations showed a negative correlation with the SII index (Figure 3B). Moreover, the SIRI index rose with increasing quartiles of urinary Cd, I, Mo, and Tl concentrations ($p<0.05$). Notably, the urine Tl concentration exhibited a negative correlation with the SIRI index, as illustrated in Figure 3C.

Table 1. The baseline characteristics of participants

Variables	Overall, *n*=2,934	Non-MASLD, *n*=1,331	MASLD, *n*=1,603	*p*-value
[a]Age, years	44.86 (20.58)	38.04 (20.86)	50.53 (18.53)	<0.001***
[b]Sex				0.002**
Female	1,474 (50.23)	710 (53.34)	764 (47.66)	
Male	1,460 (49.77)	621 (46.66)	839 (52.34)	
[b]Race				<0.001***
Non-Hispanic White	975 (33.23)	431 (32.38)	544 (33.94)	
Non-Hispanic Black	756 (25.77)	379 (28.47)	377 (23.51)	
Mexican American	394 (19.43)	144 (10.82)	250 (15.60)	
Others	809 (27.57)	377 (28.32)	432 (26.95)	
[b]Marital status				<0.001***
Married or living with a partner	1,618 (55.15)	677 (50.86)	941 (58.70)	
Widowed/divorced/separated	620 (21.13)	255 (19.16)	365 (22.77)	
Unmarried	696 (23.72)	399 (29.98)	297 (18.53)	
[b]Education level				0.005**
Less than 9th grade	199 (6.80)	72 (5.44)	127 (7.93)	
High school	1,083 (37.04)	495 (37.39)	588 (36.75)	
Some college or AA degree	898 (30.71)	391 (29.53)	507 (31.69)	
College graduate or above	744 (25.44)	366 (27.64)	378 (23.63)	
[b]Poverty income ratio				0.088
1.3 or less	890 (30.35)	432 (32.46)	460 (28.70)	
1.3–3.5	937 (31.96)	412 (30.95)	525 (32.75)	
>3.5	1105 (37.69)	487 (36.59)	618 (38.55)	
[a]WC (cm)	96.28 (18.21)	86.27 (13.85)	106.69 (16.08)	<0.001***
[b]BMI (kg/m^2)				<0.001***
<18.5	101 (3.44)	92 (6.91)	9 (0.56)	
18.5–24.9	861 (29.34)	670 (50.34)	191 (11.92)	
25.0–29.9	881 (30.03)	367 (27.57)	514 (32.06)	
≥30.0	1,091 (37.18)	202 (15.18)	889 (55.46)	
[b]Smoke status				<0.001***
Yes	1,046 (35.65)	409 (30.73)	637 (39.74)	
No	1,888 (64.35)	922 (69.27)	966 (60.26)	
[b]Alcohol use				<0.001***
Yes	2,159 (73.59)	1,021 (76.71)	1,138 (70.99)	
No	775 (26.41)	310 (23.29)	465 (29.01)	
[b]Activity level				0.304
Vigorous	794 (27.06)	376 (28.25)	418 (26.08)	
Moderate	671 (22.87)	308 (23.14)	363 (22.64)	
Inactive	1,469 (50.07)	647 (48.61)	822 (51.28)	
[b]Hypertension				<0.001***
Yes	606 (20.65)	208 (15.63)	398 (24.83)	
No	2,328 (79.35)	1,123 (84.37)	1,205 (75.17)	

(*Cont'd...*)

Table 1. (*Continued*)

Variables	Overall, *n*=2,934	Non-MASLD, *n*=1,331	MASLD, *n*=1,603	*p*-value
[b]Diabetes				<0.001***
Yes	397 (13.53)	69 (5.18)	328 (20.46)	
No	2,537 (86.47)	1,262 (94.82)	1,275 (79.54)	
[a]ALT (U/L)	21.37 (16.66)	17.18 (15.38)	24.39 (17.00)	<0.001***
[a]AST (U/L)	21.29 (11.47)	20.04 (10.23)	22.27 (12.29)	<0.001***
[a]TC (mg/dL)	183.84 (39.86)	172.77 (38.52)	186.02 (39.93)	<0.001***
[a]HDL-C (mg/dL)	53.97 (15.00)	56.83 (14.30)	50.29 (14.91)	<0.001***
[a]CRP (mg/L)	3.27 (1.44)	2.69 (1.20)	4.78 (1.54)	<0.001***
[a]SII	546.34 (305.82)	484.43 (219.33)	523.24 (230.56)	<0.001***
[a]SIRI	1.29 (1.01)	1.16 (0.95)	1.27 (0.97)	<0.001***
[a]CAP (dB/m)	261.09 (62.26)	202.88 (30.83)	303.86 (45.62)	<0.001***

Notes: [a]Continuous variables are presented as the mean±standard deviation (SD). [b]Categorical variables are presented as *n* (%). All participants were divided into two groups: no metabolic dysfunction-associated fatty liver disease (non-MASLD) and MASLD. Statistical significance determined at *** ***$p<0.001$.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CAP: Controlled attenuation parameter; CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; SII: Systemic Immune Inflammation Index; SIRI: Systemic Inflammatory Response Index; TC: Total cholesterol; WC: Waist circumference.

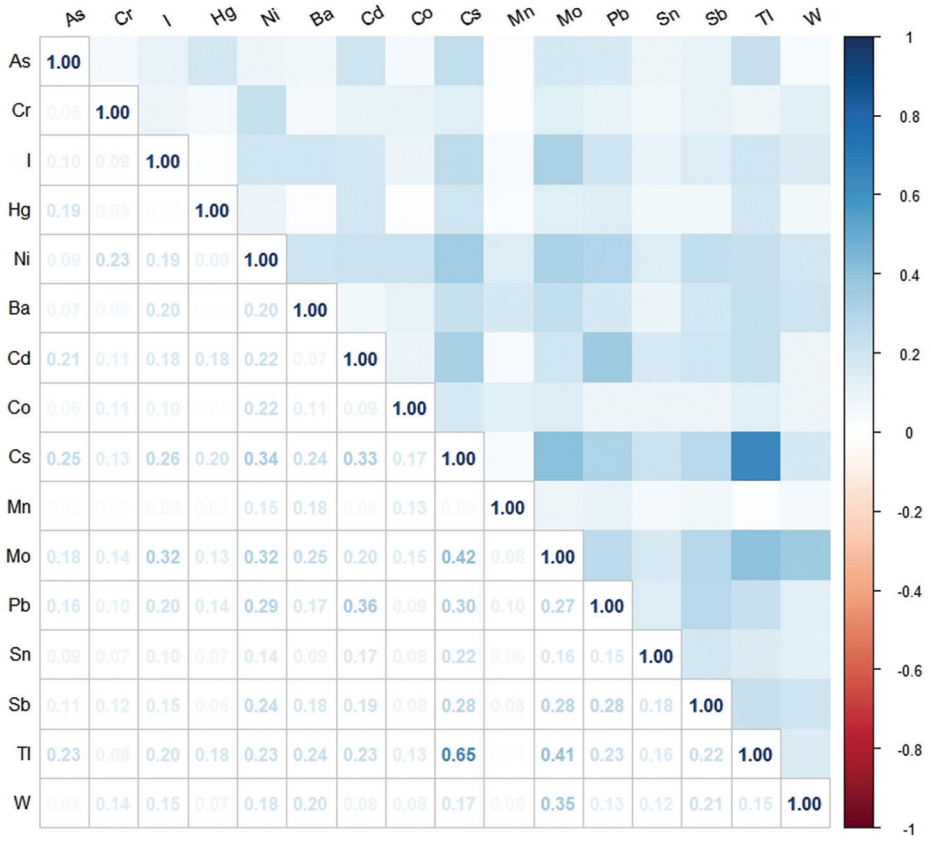

Figure 2. Pearson's correlation matrix among urinary metals corrected for urinary creatinine in the study population

Abbreviations: As: Arsenic; Ba: Barium; Cd: Cadmium; Co: Cobalt; Cr: Chromium; Cs: Cesium; Hg: Mercury; I: Iodine; Mn: Manganese; Mo: Molybdenum; Ni: Nickel; Pb: Lead; Sb: Antimony; Sn: Tin; Tl: Thallium; W: Tungsten.

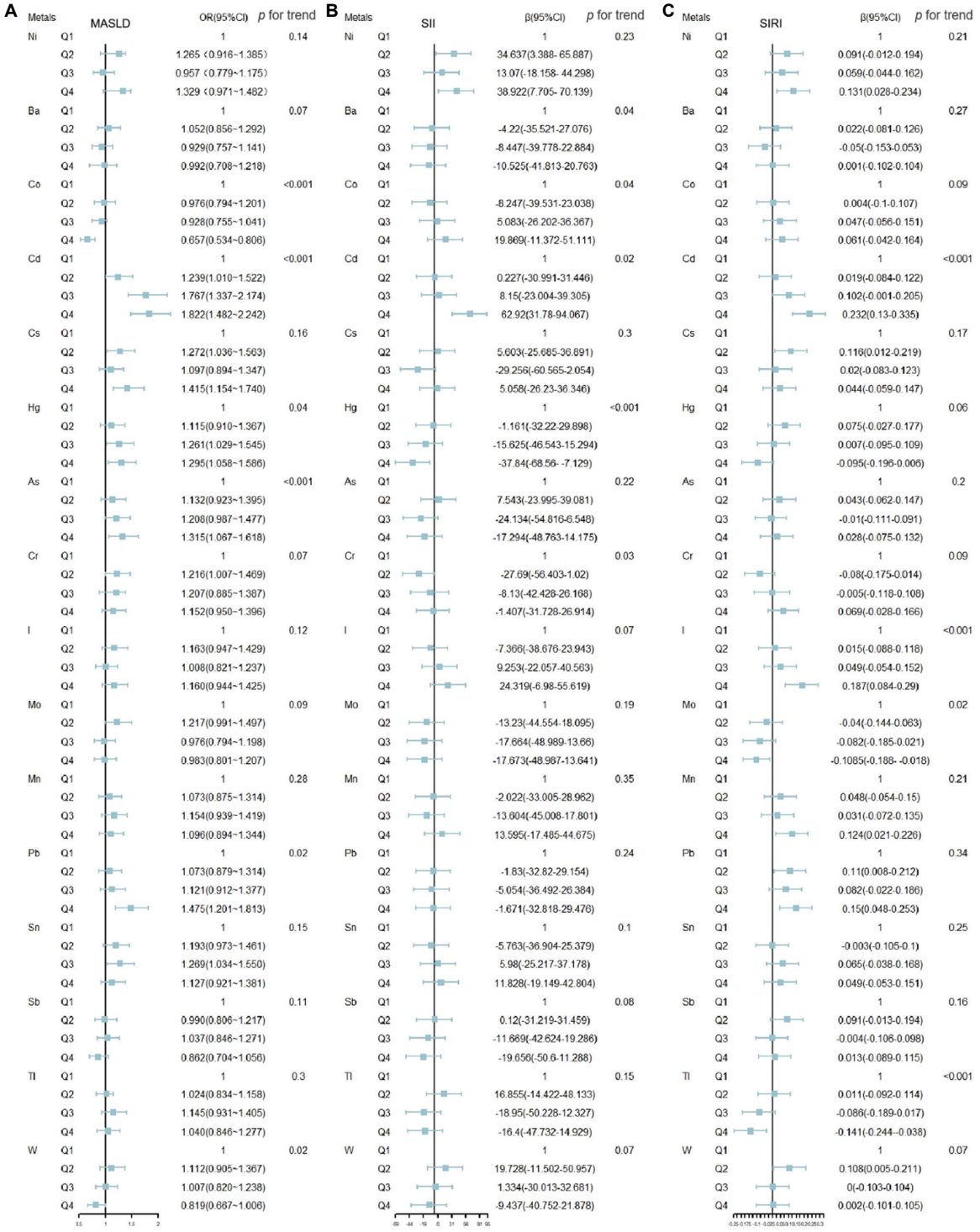

Figure 3. The relationship between single heavy metal exposure and systemic inflammation or metabolic dysfunction-associated steatotic liver disease. (A) Odds ratios (95 % confidence intervals [CI]) for the associations between urinary concentrations of single metals and the risk of MASLD. Regression coefficients (95% confidence intervals) for the associations between urinary concentrations of single metals and inflammatory biomarkers in (B)SII, and (C)SIRI. Q1 was used as the reference when comparing the associations of Q2, Q3, and Q4 with systemic inflammation. Adjusted for age (continuous), sex, race, marital status, education, body mass index(continuous), smoking status, and alcohol use.

Abbreviations: As: Arsenic; Ba: Barium; Cd: Cadmium; Co: Cobalt; Cr: Chromium; Cs: Cesium; Hg: Mercury; I: Iodine; MASLD: Metabolic dysfunction-associated steatotic liver disease; Mn: Manganese; Mo: Molybdenum; Ni: Nickel; OR: Odds ratio; Pb: Lead; Sb: Antimony; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; Sn: Tin; Tl: Thallium; W: Tungsten.

3.3. The association between metal mixture, metabolic dysfunction-associated steatotic liver disease risk, and systemic inflammation

The WQS models determined a weighted value for exposure to the metal mixture in the blood sample. The metals in the WQS model that had the most influence on MASLD risk were Cd (0.53), As (0.187), Cr (0.083), Mn (0.054), and Cs (0.036), as shown in Figure 4A. Regarding inflammatory markers, the metals with the most significant impact on SII were Cd (0.31), Mn (0.274), I (0.136), and Ni (0.117), as illustrated in Figure 4B. For the SIRI index, the most influential metals were Mn (0.37), Cd (0.231), I (0.185), and Pb (0.066), as shown in Figure 4C. Table 2 shows a strong positive association between the combination of urinary mixtures and MASLD risk, after accounting for all possible covariates using WQS models (p<0.001). In line with this, the combined impact of urinary metals showed a strong positive correlation with inflammatory markers (p_{SII}<0.001, p_{SIRI}=0.007).

Table 2. The association between the weighted quantile sum regression index of combined heavy metal exposure, metabolic dysfunction-associated steatotic liver disease, and inflammatory indices

Indicator	Categorical	Estimate	Standard error	*t*-value	*p*-value
MASLD	Model I	0.387	0.071	5.492	<0.001***
	Model II	0.258	0.082	3.938	<0.001***
SII	Model I	35.050	11.161	3.891	<0.001***
	Model II	19.873	11.034	3.701	<0.001***
SIRI	Model I	0.185	0.044	4.229	<0.001***
	Model II	0.116	0.043	2.658	0.007**

Notes: Model I was the crude regression before adjusting for covariates. Model II was the regression model for adjustment age (continuous), sex, race, marital status, education, body mass index (continuous), smoking status, and alcohol use. Statistical significance determined at **p<0.01, ***p<0.001.
Abbreviations: MASLD: Metabolic dysfunction-associated steatotic liver disease; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index.

3.4. The connection between systemic inflammation and the risk of metabolic dysfunction-associated steatotic liver disease

Table 3 presents the correlation between inflammatory markers and the risk of MASLD, as identified by logistic regression. Individuals in the highest SII quartile (Q4) had a higher MASLD risk than those in the lowest quartile (Q1) (odds ratio [OR]: 1.362; 95% confidence interval [CI]: 1.108–1.674; p<0.001), highlighting potential inflammatory mechanisms underlying this association. In line with this finding, the fourth quartile of the SIRI index demonstrated a statistically significant correlation with an elevated risk of MASLD (OR: 1.720; 95% CI: 1.399–2.117; p<0.001).

3.5. Dose-response analysis of metals and inflammatory indices in metabolic dysfunction-associated steatotic liver disease

Based on the findings from the logistic regression and WQS analysis, several heavy metals—Cd, Cs, Co, Hg, Cr, and Pb—showing strong correlations with MASLD were selected for further investigation. The possible non-linear relationships among these metals were then examined using restricted cubic spline analysis. The findings revealed that, with increasing Cs concentration and the SII index, the associated risks exhibited a monotonic upward trajectory; in contrast, Cd and Pb exhibited a U-shaped escalation (non-linear

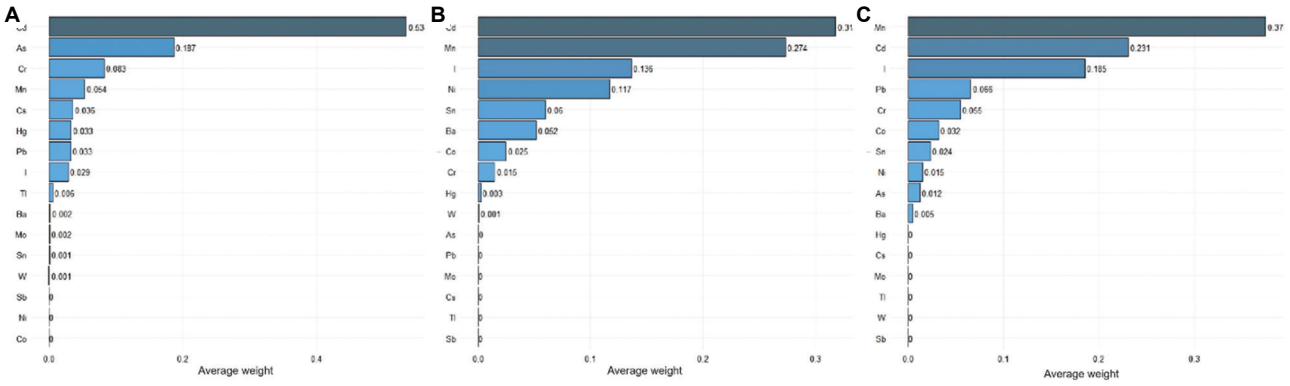

Figure 4. Estimated weights assigned to each exposure based on WQS regression modeled in the positive direction with respect to the (A) MASLD, (B) SII, and (C) SIRI. Adjusted for age (continuous), sex, race, marital status, education, body mass index(continuous), smoking status, and alcohol use.
Abbreviations: As: Arsenic; Ba: Barium; Cd: Cadmium; Co: Cobalt; Cr: Chromium; Cs: Cesium; Hg: Mercury; I: Iodine; MASLD: Metabolic dysfunction-associated steatotic liver disease; Mn: Manganese; Mo: Molybdenum; Ni: Nickel; OR: Odds ratio; Pb: Lead; Sb: Antimony; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; Sn: Tin; Tl: Thallium; W: Tungsten.

p<0.05). It is noteworthy that, with increasing SIRI index, the impact on MASLD risk followed a reversed J-shaped pattern (non-linear p=0.026). Furthermore, no significant non-linear relationships between MASLD and other metals, such as As, Co, and Cr, were identified (Figure 5).

3.6. Mediation analysis

To examine the hypothesis that systemic inflammation underlies this association, we conducted mediation analyses to assess whether inflammatory markers (SII/SIRI) mediate the association between metal exposure and MASLD. Following adjustment for confounders, the SII demonstrated a significant mediating role in the relationships between Cd, Cs, and Pb and MASLD. The indirect mediation effects, as indicated by the beta coefficients (βs), were 0.0909 (95% CI: 0.0449–0.1377), 0.0096 (95% CI: 0.0081–0.0125), and 0.068 (95% CI: 0.0315–0.1114), respectively. The corresponding proportions mediated by SII were 39.8%, 29.1%, and 8.9%, respectively.

Similarly, the SIRI served as a mediator in the associations between exposure to Cd, Cs, and Pb and the risk of MASLD. The βs corresponding to the indirect mediation effects were 0.0928 (95% CI: 0.0443–0.1391), 0.0064 (95% CI: 0.0013–0.0117), and 0.0659 (95% CI: 0.0306–0.1124), respectively, each representing a distinct pathway in the analysis. Respectively, the proportions of the total effect mediated by SIRI were determined to be 40.5%, 26.6%, and 27.2%, as illustrated in Table S1 and Figure S1.

Table 3. The association between inflammatory indices and metabolic dysfunction-associated steatotic liver disease

Indicator	Odds ratio (95% confidence interval)					p
	Continuous	Q1	Q2	Q3	Q4	
SII	1.044 (1.019–1.071)	1.00 reference	1.137 (0.926–1.396)	1.169 (1.015–1.435)	1.362 (1.108–1.674)	<0.001***
SIRI	1.128 (1.043–1.227)	1.00 reference	1.323 (1.078–1.624)	1.590 (1.294–1.956)	1.720 (1.399–2.117)	<0.001***

Notes: The regression model included adjustment for age (continuous), sex, race, marital status, education, body mass index (continuous), smoking status, and alcohol use. Statistical significance determined at ***p<0.001.
Abbreviations: SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index.

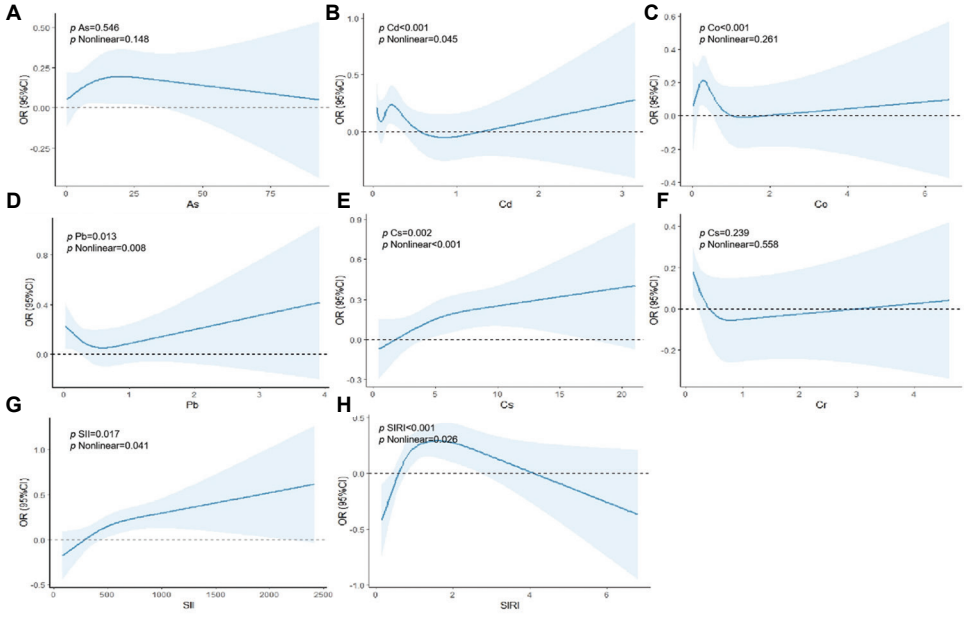

Figure 5. Estimated the dose-response relationship between urine heavy metals, systemic inflammation, and MASLD risk in the general population using the restricted cubic spline model. (A) As-MASLD; (B) Cd-MASLD; (C) Co-MASLD; (D) Pb-MASLD; (E) Cs-MASLD; (F) Cr-MASLD; (G) SII-MASLD; and (H) SIRI-MASLD. Adjusted for age (continuous), sex, race, marital status, education, body mass index (continuous), smoking status, and alcohol use
Abbreviations: As: Arsenic; Ba: Barium; Cd: Cadmium; CI: Confidence interval; Co: Cobalt; Cr: Chromium; Cs: Cesium; Hg: Mercury; I: Iodine; MASLD: Metabolic dysfunction-associated steatotic liver disease; Mn: Manganese; Mo: Molybdenum; Ni: Nickel; OR: Odds ratio; Pb: Lead; Sb: Antimony; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; Sn: Tin; Tl: Thallium; W: Tungsten.

Furthermore, the association between mixed-metal concentration and MASLD risk was mediated by both the SII and SIRI indices. The βs associated with the indirect mediation effects were determined to be 0.0561 (95% CI: 0.0155–0.1392) for SII and 0.0551 (95% CI: 0.0007–0.1279) for SIRI. As illustrated in Figure 6, the proportions of the total effect of the metal mixture on MASLD mediated by SII and SIRI were 57.84% and 65.21%, respectively, which sequentially explain 57.84% and 65.21% of the effect of mixed-metal exposure on MASLD through these inflammatory indices (Figure 6). These findings underscore the notion that inflammatory markers serve as a modifiable target with the potential to alleviate the disease burden associated with environmental factors.

4. Discussion

Within the general adult population of the United States, urinary Cd, Cs, and Pb have emerged as substantial risk factors for MASLD, and mixed metal exposure further demonstrates a significant association with increased susceptibility to MASLD. Furthermore, within the WQS framework, urinary C demerged as the predominant metal associated with MASLD among mixed-metal exposures. Our mediation analysis further indicated that inflammatory markers partly mediate the link between heavy metal exposure and MASLD risk. These findings deepen understanding of the detrimental effects of heavy metals on MASLD, suggesting that modulation of systemic inflammatory marker levels may represent a potential biological pathway and serve as a preventive strategy.

Experimental data and a substantial body of epidemiological research indicate that the risk of MASLD is potentially associated with heavy metal exposure. Recent experimental studies have unraveled the fundamental mechanisms by which heavy metals trigger hepatic damage. According to recent reports, the induction of excessive reactive oxygen species (ROS) production in hepatic tissues by metal ions has been shown to result in significant oxidative stress and subsequent cellular damage. While triggering inflammatory responses and ultimately resulting in cell and tissue damage, this also decreases the stability of biomolecules such as proteins and lipids.[27-29] Second, oxidative stress serves as a crucial mechanism underlying NLRP3 inflammasome activation, which is achieved through the induction of organelle damage, including mitochondrial DNA release and potassium ion efflux, thereby subsequently initiating programmed cell death pathways.[30] Heavy metals are simultaneously recognized as potent activators of various pathogenic pathways, such as endoplasmic reticulum stress, ferroptosis, pyroptosis, and autophagy, which further exacerbate hepatocyte apoptosis and amplify inflammatory signaling cascades.[31,32] During the progression of MASLD, hepatic lipid accumulation and advancing hepatitis are collectively induced by these synergistic mechanisms. Moreover, extensive epidemiological investigations conducted by Wang *et al.*[33] demonstrated that, during a follow-up period of 3–6 years, every one-unit increase in the logarithmically transformed concentrations of W and copper (Cu) was independently associated with an annual elevation of ALT levels by 1.3% (95% CI: 0.7–1.8%) and 1.3% (95% CI: 0.7–2.0%), respectively.[32] A positive correlation was observed between plasma C-reactive protein concentration and urinary Cu, Cd, and ALT levels. These studies demonstrate that inflammatory responses play a pivotal role in the biological mechanisms associated with heavy metal-induced hepatic injury.

Prior research has shown a link between inflammatory markers and the risk of MASLD. While Liu *et al.*[34] reported the levels of the NLR proteins, Wang *et al.*[35] identified

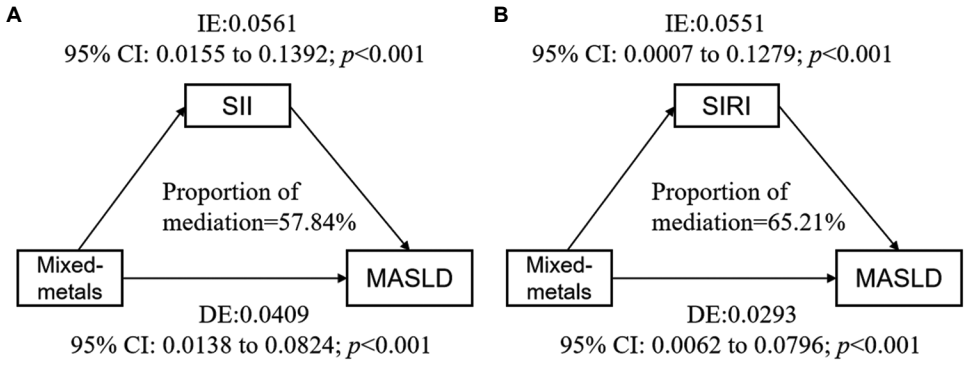

Figure 6. The mediating effects of the relationship between the urine metal mixture and MASLD risk. In this figure, the SII indexes were used as intermediaries in (A), and the SIRI indexes were used as intermediaries in (B). The indirect effect (IE) and the direct effect (DE) were estimated. The models were adjusted for sex, age (continuous), race, marital status, education, body mass index(continuous), alcohol use, and smoking status.
Abbreviations: MASLD: Metabolic dysfunction-associated steatotic liver disease; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index.

six inflammatory markers as potential tools for assessing the risk of hepatic steatosis.[34,35] Derived from platelet, neutrophil, and lymphocyte counts, the SII index serves as a composite biomarker that quantitatively reflects the intricate balance between pro-inflammatory mechanisms and immune-regulatory responses. Consistent with previous research, our study demonstrates that both SII and SIRI are significantly associated with the risk of developing MASLD. Recent studies have revealed that the SII may play a crucial role in the pathophysiological mechanisms underlying heavy metal-induced liver dysfunction, which is noteworthy. The study demonstrated significant associations between SII and hepatic fibrosis markers, such as Fibrosis-4 index and the Non-Alcoholic Fatty Liver Disease Fibrosis Score, whereas no such relationship was identified with hepatocyte steatosis indicators, including the Fatty Liver Index and the Liver Fat Score.[23] It is widely acknowledged that the utilization of the Fatty Liver Index and the Liver Fat Score scoring for diagnosing MASLD demonstrates insufficient validation against imaging or histological evidence, particularly in the context of evaluating hepatocyte steatosis.[36] Utilizing the accessible data from VCTE, our study conducted a comprehensive assessment of liver steatosis, demonstrating enhanced diagnostic accuracy and precision in clinical applications. This study demonstrated that inflammation markers SII and SIRI mediate the relationship between urinary Cd, Cs, and Pb exposure and MASLD risk, incorporating multiple metals. The discrepancy between this finding and the study by Wang *et al.*[23] may be attributed to variations in outcome assessment methods and in the characteristics of the included research populations. More importantly, within the context of mixed-metal exposure, a prominent association between these inflammatory indices and the risk of MASLD has been demonstrated. This insight is further corroborated by animal experiments demonstrating that infiltration of inflammatory cells into hepatocytes induced by heavy metals can lead to lipid accumulation in hepatic tissues. Under hepatic lipid overload, a marked increase in the production of key inflammatory cytokines (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6) is driven by the activation and accumulation of resident immune cells, particularly Kupffer cells. These factors intensify the inflammatory process, triggering inflammatory apoptosis in hepatocytes and enhancing the proliferation of immune cells within the organism.[37]

A significant positive association was identified between urinary Cd concentrations and systemic inflammation indices (SII and SIRI), suggesting a potential mechanistic link. Within the WQS model, Cd was identified as the metal with the greatest influence on MASLD. Cd-induced liver damage has been demonstrated in previous studies to involve an inflammatory response as a critical mechanism, triggering acute and/or chronic inflammatory infiltrative reactions in hepatocytes through innate immune pathways.[38] Considered the biological basis for the initiation of hepatic damage, this process plays a vital role in the pathogenesis of hepatic injury. Numerous *in vivo* experiments have demonstrated that Cd can directly bind to the thiol groups of crucial molecules, such as glutathione, involved in antioxidant defense, thereby triggering ROS generation. Throughout this process, both activated Kupffer cells and recruited neutrophils persistently release ROS.[39,40] The activation of the NLRP3 inflammasome by Cd can lead to significant infiltration of inflammatory cells into the livers of pubertal mice, suggesting a potential mechanism of hepatotoxicity. As evidenced by elevated ALT and AST levels, hepatic injury occurs concurrently with the activation of M1 and M2 macrophages, subsequently promoting the release of various inflammatory mediators. The accumulation of Cd in the liver may induce a range of pathological conditions, including MASLD, through mechanisms that include oxidative stress promotion, activation of the inflammatory response, induction of DNA damage, and initiation of apoptosis.[41]

To date, only a limited body of research has investigated the precise impacts of non-radioactive Cs exposure on hepatic metabolic function. The existing body of literature predominantly focuses on the application of radioactive Cs (e.g., Cs-137) at specific dosage levels to enhance localized radiation therapy, particularly in the treatment of tumors such as brain and neck cancers.[42,43] A significant positive correlation between plasma Cs levels and the severity of fatty liver disease was identified in a case-control study involving 189 Greek participants, revealing a progressively increasing trend across the mild, moderate, and severe stages of the condition.[44] Our analysis also shows a positive link between Cs and MASLD. Investigations conducted within Chinese community settings reveal that Cs interferes with the equilibrium of inflammatory regulatory mechanisms, as evidenced by an inverse correlation between urinary Cs concentrations and interleukin-6 levels.[45] The adverse effects of Cs on maintaining immune homeostasis might be associated with this phenomenon. Consistent with trends observed in earlier Greek studies,[43] both SII and SIRI demonstrated a positive mediating effect on the relationship between Cs and MASLD, a finding that is particularly noteworthy. This result suggests that Cs may affect liver metabolic function through immune-metabolic regulatory pathways, and it is crucial to conduct further prospective studies to validate the association between Cs exposure and MASLD while exploring the underlying biological mechanisms.

In the past, due to predominant occupational exposure to Pb, workers in industries such as the production of Pb-containing paints and battery manufacturing faced significantly higher risks of hepatic injuries.[46,47] However, in recent years, the surge of the electric vehicle industry has resulted in Pb, a crucial raw material for battery production, emerging as an increasingly prevalent pollutant that the public frequently encounters in daily life. An inverse correlation between blood Pb levels and the incidence of hepatic steatosis in men was identified through a nationwide survey conducted across South Korea.[48] Compared to the lowest quartile, our study revealed a significant positive association between urinary Pb levels in the highest quartile (Q4) and the risk of MASLD, indicating a potential dose-response relationship. Further non-linear analysis revealed that the risk of MASLD exhibited a U-shaped relationship with increasing urinary Pb concentrations. Although Pb chelators have been demonstrated to effectively reduce liver stiffness, lower proinflammatory cytokine levels, and enhance circulating glutathione concentrations, these beneficial effects fail to mitigate hepatic steatosis during the progressive stages of inflammatory liver injury caused by chronic Pb accumulation.[49] Our findings revealed that the SIRI index played a crucial role as a significant mediator in the association between Pb exposure and MASLD risk, although no considerable mediation effect was observed for the SII index. Research demonstrates that exposure to Pb is associated with T helper 2-type cytokines, and prolonged interaction with Pb may trigger the secretion of diverse cytokines, such as interleukin-6 and tumor necrosis factor alpha, through complex immunological mechanisms. At the same time, humoral immune mechanisms mediated by T helper 2 cells can induce eosinophil differentiation, thereby strengthening anti-inflammatory responses.[50] The functional roles of immune pathways in their processes might be partially revealed by these mechanisms.

This study offers several notable advantages. First, a remarkable strength of this study lies in its utilization of the NHANES data, which, through a rigorous sampling design, offers a high-quality, nationally representative sample. Secondly, we employed VCTE, which, unlike traditional diagnostic imaging techniques, provides more reliable and robust results. Finally, to explore potential modifiable biological mechanisms of MASLD, the study performed a mediation analysis, thereby providing novel insights into preventive strategies. Nevertheless, a significant constraint of this study lies in the employment of single-time-point measurements, which, due to temporal variability, may fail to comprehensively represent long-term exposure dynamics, thus potentially compromising the precision of estimated metal concentrations. Second, while this study solely evaluated two systemic inflammatory markers, future research could integrate additional inflammation-related indicators to provide a more comprehensive assessment of the mediating role of systemic inflammation in the relationship between metal exposure and MASLD. Overall, to elucidate the relationships and potential mechanisms connecting metal exposure, inflammatory markers, and MASLD, further investigations employing longitudinal designs and prospective trials with larger sample sizes are warranted.

5. Conclusion

Our findings, derived from analysis of large-scale NHANES data, reveal a significant association between exposure to specific metals, particularly Cd, and metal mixtures, and an elevated risk of developing MASLD. For the 1st time, this study demonstrates that the inflammatory markers SII and SIRI serve as mediators between heavy metal exposure (particularly Cd, Cs, and Pb) and MASLD, providing a novel insight into mitigating the burden of environmentally-associated diseases. To summarize, the study's conclusion underscores the critical role of these metals as risk indicators for MASLD, while also proposing that the regulation of systemic inflammation marker levels could represent a promising strategy for preventing metabolic liver dysfunction associated with environmental heavy metal exposure.

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Conflict of interest

The authors declare that they have no competing interests.

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Writing–review & editing: Somchai Bovornkitti, Sarisak Soontornchai

Ethics approval and consent to participate

The study was approved by the National Center for Health Statistics (approval number: Protocol #2011-17 with continuing approval #2018-01) and followed the Tenets of the Declaration of Helsinki. All participants provided informed written consent.

Consent for publication

All participants provided informed written consent for publication.

Availability of data

The datasets presented in this study are available in online repositories. All data can be downloaded and used on the official NHANES database website. (https://www.cdc.gov/nchs/nhanes/index.htm).

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