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Impact of blood lead and manganese levels on metabolic dysfunction-associated steatotic liver disease prevalence: insights from NHANES (2017–2020)

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Abstract

Background The metabolic dysfunction-associated steatotic liver disease (MASLD) paradigm represents a significant departure from the previous nonalcoholic fatty liver disease (NAFLD) framework, offering a non-stigmatizing approach that enhances awareness and accelerates patient understanding. Our primary aim was to investigate the potential relationship between blood lead and manganese exposure and the onset of MASLD.

Methods Using data from the National Health and Nutrition Examination Survey (NHANES) database spanning from 2017 to 2020, a cross-sectional study included 4,475 participants was performed to assess the relationship. The statistical analysis used throughout the study included multivariable linear regression and multiple logistic regression models, adjusted for potential confounders to ensure robust and reliable results. We applied a thorough multivariable analysis, examining various factors including age, sex, and ethnicity to enhance the robustness of our findings.

Results Employing linear regression models in our study, we observed a clear positive correlation between elevated levels of blood lead and manganese and Controlled attenuation parameter (CAP). Additionally, employing multiple logistic regression models for detailed analysis, we noted a significant increase in the likelihood of MASLD with higher levels of blood lead and manganese.

Conclusion The findings of this study strongly suggest a notable correlation between increased levels of blood lead and manganese with both CAP and the presence of MASLD. This study represents a population-based approach, enhancing the generalizability of the findings to the broader U.S. population.

Keywords MASLD, NHANES, CAP, VCTE, Lead, Manganese

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as a significant worldwide health issue due to the excessive buildup of fat in the liver [1]. In recent times, the concept of metabolic associated fatty liver disease (MAFLD) has gained prominence, seeking to broaden the scope of liver conditions beyond those linked solely to alcohol consumption [2]. The diagnostic criteria for MAFLD encompass evidence of hepatic fat accumulation coupled with one or more metabolic risk factors, such as obesity, type 2 diabetes, or dyslipidemia. This paradigm shift reshapes our comprehension of liver disorders within the framework of metabolic dysfunction [3]. Nevertheless, as scientific inquiry delves deeper into the multifaceted etiology and pathophysiology of this condition, there has been scrutiny regarding the term "fatty" due to its potential stigmatizing connotations. Consequently, the concept of metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged [4]. Revised diagnostic guidelines for MASLD now require the presence of at least one of the five cardiometabolic risk factors, depending on whether liver steatosis is present. The updated framework emphasizes our focus on metabolic factors and a nuanced understanding of the intricate interplay between liver health [5].

Lead is pervasive in the natural environment and everyday settings, originating from sources including natural soil enrichment, historical deposits, current mining emissions, and the use of lead-based paints. Known for its accumulative nature and resistance to degradation, lead is acknowledged as a significant environmental toxin [6, 7]. Lead is recognized as an endocrine-disrupting agent, with certain exposure scenarios in humans being linked to the onset of diabetes and metabolic syndrome (MetS) [8]. Furthermore, lead can affect lipid metabolism, which may result in hepatic fat accumulation and the progression of MAFLD [9].

Manganese, a vital transition metal known for its varied oxidation states, finds broad application in battery production, alloy fabrication, and environmental studies [10]. Beyond its industrial uses, manganese is crucial for human health, acting as a cofactor in numerous enzymes and playing a significant role in antioxidant defense mechanisms [10]. Notably, increased exposure to manganese is associated with MetS, suggesting a possible connection to MASLD [11]. Epidemiological studies suggest a possible connection between elevated manganese concentrations in the blood and the prevalence of NAFLD [11–13]. Due to its critical role in activating enzymes involved in metabolic processes, manganese exposure levels might be utilized as a biomarker for predicting the onset of MASLD.

MASLD is a liver condition that has been increasingly linked to environmental exposures, yet the role of these metals in its development has not been fully explored [14]. The impact of blood lead and manganese on MASLD has been the subject of previous research [14]. Vibration-controlled transient elastography (VCTE) provides a reliable and non-invasive method for assessing liver health, eliminating the need for invasive procedures. However, the relationship between these metals and MASLD has not yet been explored using VCTE. NHANES (www.cdc.gov/nchs/nhanes) is a nationally representative survey designed to assess the health and nutritional status of the U.S. population. It combines physical examinations and health interviews to gather data on a wide range of factors, including demographics, lifestyle, medical history, and environmental exposures. The NHANES dataset is particularly valuable for studying the impact of environmental toxins, as it includes laboratory data on metals like blood lead and manganese, which are known to affect various health conditions, including liver disease. This study aims to address this gap by utilizing the controlled attenuation parameter (CAP) data obtained through VCTE from National Health and Nutrition Examination Survey (NHANES) data, to examine the cross-sectional association between blood lead and manganese levels and MASLD. By integrating these advanced diagnostic tools and nationally representative data, this study provides new insights into the potential environmental contributions to MASLD.

Materials and methods

Study population

The dataset used in this study was derived from the NHANES cycle spanning 2017 to 2020. The initial cohort comprised 15,560 participants, with exclusions made based on the following criteria: (1) incomplete liver elastography measurements ($n = 6,539$), (2) presence of hepatitis B or C ($n = 665$), (3) heavy alcohol consumption, defined as ≥ 3 drinks per day for males and ≥ 2 drinks per day for females ($n = 1,220$), (4) incomplete basic characteristic data ($n = 2,213$) and (5) incomplete data on blood lead and manganese ($n = 448$). After these exclusions, the final sample size was 4,475 participants. For a detailed overview, see Fig. 1.

Measurement of blood lead and manganese

Throughout the examination, blood samples were collected, frozen at -30 °C, and sent to the CDC in Atlanta, Georgia, for analysis. Lead and manganese concentrations in the blood were measured using inductively coupled plasma dynamic reaction cell mass spectrometry, following NHANES quality assurance and quality control protocols. The lower limit of detection (LLOD) was 0.07 μg/L for lead and 0.99 μg/L for manganese. Notably, the blood lead and manganese levels in this study exceeded these LLOD values. For ease of analysis,

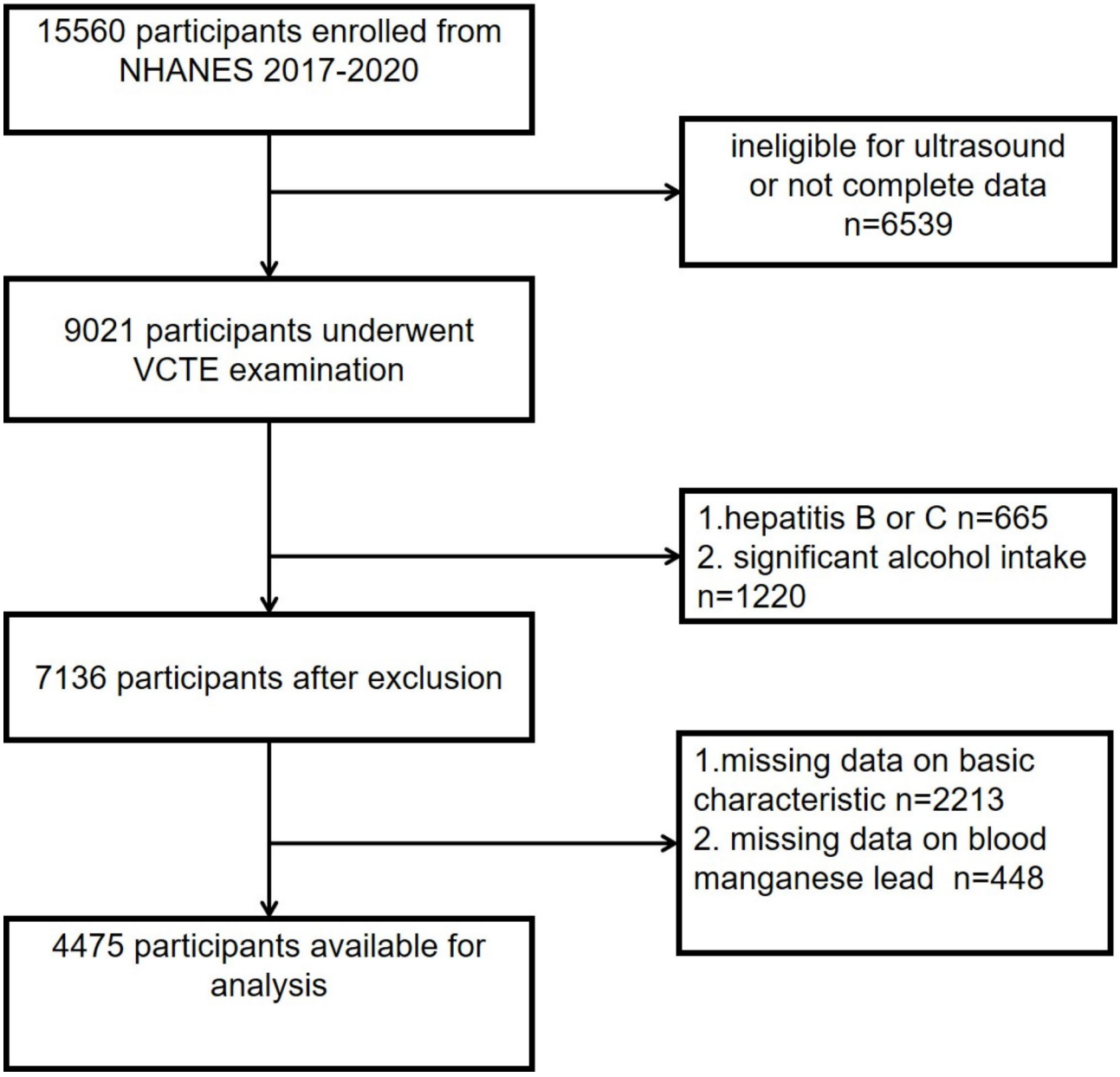

Fig. 1 Participant screening flowchart

participants were stratified into four cohorts based on the quartile concentrations of blood lead and manganese level (the detail could be found in Supplementary Table 1).

Non-invasive evaluation of hepatic steatosis

This study employed VCTE to evaluate hepatic steatosis. Participants were required to fast for a minimum of three hours and collect more than ten liver measurements, with the aim of achieving an interquartile range/median ratio < 30% to ensure accuracy. Consistent with previous research, hepatic steatosis was determined by a CAP score equal to or greater than 260 dB/m [13, 15, 16].

The definition of MASLD

The diagnosis of MASLD was confirmed by the presence of hepatic steatosis and the exclusion of significant alcohol consumption and viral hepatitis. The following diagnostic criteria were applied: (1) body mass index (BMI) ≥ 25 kg/m² or waist circumference (WC) ≥ 94 cm for males and ≥ 80 cm for females. (2) fasting plasma glucose (FPG) levels ≥ 6 mmol/L, hemoglobin A1c (HbA1c) levels ≥ 5.7%, a prior diagnosis of diabetes, or ongoing diabetes treatment. (3) blood pressure ≥ 130/85 mmHg or current antihypertensive treatment. (4) triglyceride (TG) levels ≥ 1.70 mmol/L or current lipid-lowering therapy. (5) low levels of high-density lipoprotein cholesterol

(HDL) (< 1.0 mmol/L for males and < 1.3 mmol/L for females) or lipid-lowering therapy [5].

Covariate assessment

The laboratory conducted measurements on WC, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL), HDL, FPG, and HbA1c. Information regarding age, sex, race, education level, marital status, poverty income ratio (PIR), alcohol intake, and medication usage was obtained through standardized self-administered surveys. The PIR was categorized into three groups: less than 1.30, between 1.30 and 3.50, and greater than 3.50 [17]. Physical activity (PA) was quantified using the formula PA = Metabolic equivalent of task(MET) × weekly frequency × duration of each activity. A PA value of zero indicated no physical activity. Participants were categorized according to their adherence to the American Physical Activity guidelines, defined as achieving at least 600 MET-minutes per week for adults [18]. Diabetes was defined following the American Diabetes Association's criteria, which include FPG ≥ 7 mmol/L, HbA1c ≥ 6.5%, self-reported clinician-diagnosed diabetes, or diabetes medication use [19]. Hypertension was classified with criteria including blood pressure exceeding 130/80 mm Hg or the use of antihypertensive drugs [20]. The participants were divided into two groups based on their alcohol consumption: those who never drank alcohol and those who consumed alcohol moderately (1–2 drinks per day for males, 1 drink per day for females). Smoking status was assessed by measuring cotinine levels [21, 22].

Statistical analysis

Continuous variables were represented using mean values and standard deviations (mean ± SD), while categorical variables were expressed as percentages. A weighted t-test was used to compare continuous variables, and a chi-squared test was employed for evaluating categorical variables, with results presented as counts (n) and percentages (%). Research into the relationship between blood lead and manganese levels with CAP utilized a linear regression framework. Three models were developed to explore the interplay between covariates and the analysis results, each introducing incremental adjustments. The initial model was unchanged, but the second model made some adjustments for certain variables like age, race, sex, education level, marital status, PIR, PA, and BMI. The fully adjusted third model also included extra factors such as smoking habits, alcohol intake, diabetes, and hypertension. To ensure no multicollinearity among independent variables, the Variance Inflation Factor (VIF) was calculated for all covariates, and all VIF values were below 5, indicating no significant multicollinearity issues. Assessing the correlation between blood lead and manganese in MASLD was achieved through a multivariable logistic regression model, as previously outlined. Subgroup analyses were performed to investigate variations in effect measures, taking into account sex, age, and BMI as potential influencing factors. Furthermore, restricted cubic spline (RCS) analysis was utilized to explore potential nonlinear relationships between blood lead and manganese in MASLD. A significance threshold of less than 0.05 was set for all statistical analyses, with R (version 4.1.0, Vienna, Austria) serving as the analytical tool.

Results

Baseline characteristic

In our research, a total of 4475 individuals were involved. Additional details about the baseline characteristics of the group can be found in Supplementary Table 2. A comparative analysis between non-MASLD individuals and MASLD patients showed significant discrepancies in sex, race, education, alcohol consumption habits, prevalence of diabetes and hypertension, as well as BMI. Additionally, MASLD patients had higher levels of age, WC, TG, TC, FPG, Hb1Ac, CAP, lead and manganese while showing lower levels of HDL.

Association between blood lead and manganese with CAP

The results in Table 1 show the findings from a series of multiple linear regression models investigating the potential relationship between blood lead and manganese levels and CAP. In the initial model, a significant positive correlation was found between blood lead and manganese levels with CAP ($p < 0.001$, 0.029, respectively). Subsequently, Model 2 showed a notable positive link between blood manganese levels and CAP ($p = 0.015$) after adjustments, while no significant correlation was detected between blood lead levels and CAP. Finally, in Model 3, the analysis consistently indicated a positive correlation between blood lead and manganese levels with CAP ($p = 0.021$, 0.005, respectively).

Association between blood lead and manganese with MASLD

Table 2 presents the results from multiple logistic regression models investigating the independent relationships between blood manganese and MASLD. Notably, significant associations were found in Model 1 for blood lead (Q2, Q3, Q4) and manganese (Q4) levels with MASLD ($P < 0.05$ for all). Model 2 further confirmed positive correlations, revealing significant relationships between MASLD and the highest blood lead and manganese levels (Q4, $p = 0.032$, 0.044, respectively). In the final model, Model 3, an analysis demonstrated a substantial increase in MASLD probability with rising concentrations of serum lead and manganese (Q4, $p = 0.022$, 0.034, respectively).

Table 1 Linear regression analysis of the relationship between blood lead and manganese with CAP

		model1		model2		model3	
		β, (95% CI)	P value	β, (95% CI)	P value	β, (95% CI)	P value
Lead	Continuous	4.268(2.807,5.729)	**< 0.001**	0.864(-0.564,2.291)	0.236	1.398(0.215,2.580)	**0.021**
	Q1	ref	ref	ref	ref	ref	ref
	Q2	11.009(4.628,17.390)	**0.001**	-1.659(-7.111,3.792)	0.551	-2.294(-7.332,2.745)	0.372
	Q3	18.352(11.714,24.990)	**< 0.001**	0.034(-5.970,6.037)	0.991	0.668(-4.847,6.182)	0.812
	Q4	18.709(12.386,25.032)	**< 0.001**	0.407(-5.860,6.675)	0.899	2.150(-3.774,8.074)	0.477
Manganese	Continuous	0.630(0.063,1.197)	**0.029**	0.633(0.122,1.143)	**0.015**	0.713(0.214,1.212)	**0.005**
	Q1	ref	ref	ref	ref	ref	ref
	Q2	1.225(-4.989,7.439)	0.699	1.489(-3.609,6.586)	0.567	1.781(-3.048,6.610)	0.470
	Q3	0.240(-5.795,6.275)	0.938	.-2.892(-8.077,2.293)	0.274	2.439(-7.359,2.480)	0.331
	Q4	4.302(-1.888,10.492)	0.173	4.742(-0.801,10.284)	0.094	5.188(-0.233,10.609)	0.061

Table 2 Logistic regression analysis of the relationship between blood lead and manganese level with MASLD

		MASLD					
		Q1	Q2		Q3		Q4	
			OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Lead	model1	ref	1.515(1.234,1.859)	**< 0.001**	2.099(1.692,2.604)	**< 0.001**	2.313(1.883,2.842)	**< 0.001**
	model2	ref	1.054(0.815,1.363)	0.687	1.244(0.934,1.657)	0.135	1.395(1.028,1.892)	**0.032**
	model3	ref	1.032(0.796,1.337)	0.813	1.246(0.931,1.666)	0.139	1.445(1.054,1.982)	**0.022**
Manganese	model1	ref	1.150(0.930,1.422)	0.198	1.149(0.928,1.423)	0.203	1.263(1.020,1.563)	**0.032**
	model2	ref	1.131(0.876,1.462)	0.345	0.933(0.718,1.212)	0.605	1.321(1.008,1.731)	**0.044**
	model3	ref	1.138(0.878,1.477)	0.329	0.942(0.721,1.229)	0.658	1.351(1.024,1.783)	**0.034**

Following comprehensive multivariable adjustments in Model 3, a distinctive and statistically significant nonlinear association surfaced in RCS analysis between blood manganese levels and MASLD occurrence (p overall = 0.0001; p nonlinear = 0.0321). Conversely, no significant nonlinear relationship was detected between blood lead levels and MASLD (p overall = 0.0286; p nonlinear = 0.6747), as illustrated in Fig. 2. The p-overall values for both lead and manganese were less than 0.05, indicating significant overall associations with MASLD. The p-nonlinear value for manganese suggests a nonlinear relationship with MASLD, where the effect varies with exposure levels. In contrast, the p-nonlinear value for lead indicates a linear relationship, with a consistent increase in MASLD risk across the exposure range.

Subgroup analysis

A multivariate regression analysis was conducted, stratified by distinct population subgroups categorized by sex, age, and BMI, to examine the relationship between blood lead and manganese with MASLD. As shown in Fig. 3, no significant associations were found between blood lead, manganese with MASLD in any subgroup.

Discussion

Our study aimed to explore the relationship between blood lead and manganese levels and the likelihood of MASLD, addressing gaps in previous research. Previous studies have primarily focused on examining the relationship between blood lead and manganese levels and the likelihood of NAFLD [13]. While previous studies have explored the relationship between blood lead, manganese, and MASLD, they did not employ the more innovative VCTE method to assess steatosis [14]. To build upon these findings, we conducted a comprehensive investigation utilizing data from the NHANES cycles spanning 2017 to 2020, allowing us to include a broader and more diverse cohort. Through this exploration, we discovered a significant and consistent positive correlation between blood lead and manganese levels and MASLD. This aligns with some previous studies suggesting a link between metal exposure and liver disease, though the mechanisms remain unclear. However, subgroup analyses did not reveal any significant differences across grouping factors such as age, sex, or BMI. This suggests that the relationship between blood lead, manganese, and MASLD may be consistent across different demographic groups, though potential limitations such as sample size and unmeasured confounders should be considered.

While earlier epidemiological studies have suggested an inverse relationship between heightened blood manganese levels and NAFLD [23], further research supports a direct correlation between elevated blood manganese concentration and fatty liver [11–13]. Lower levels of manganese could decrease the efficacy of key superoxide dismutase enzymes, affecting lipid and glucose metabolism, potentially resulting in metabolic disorders

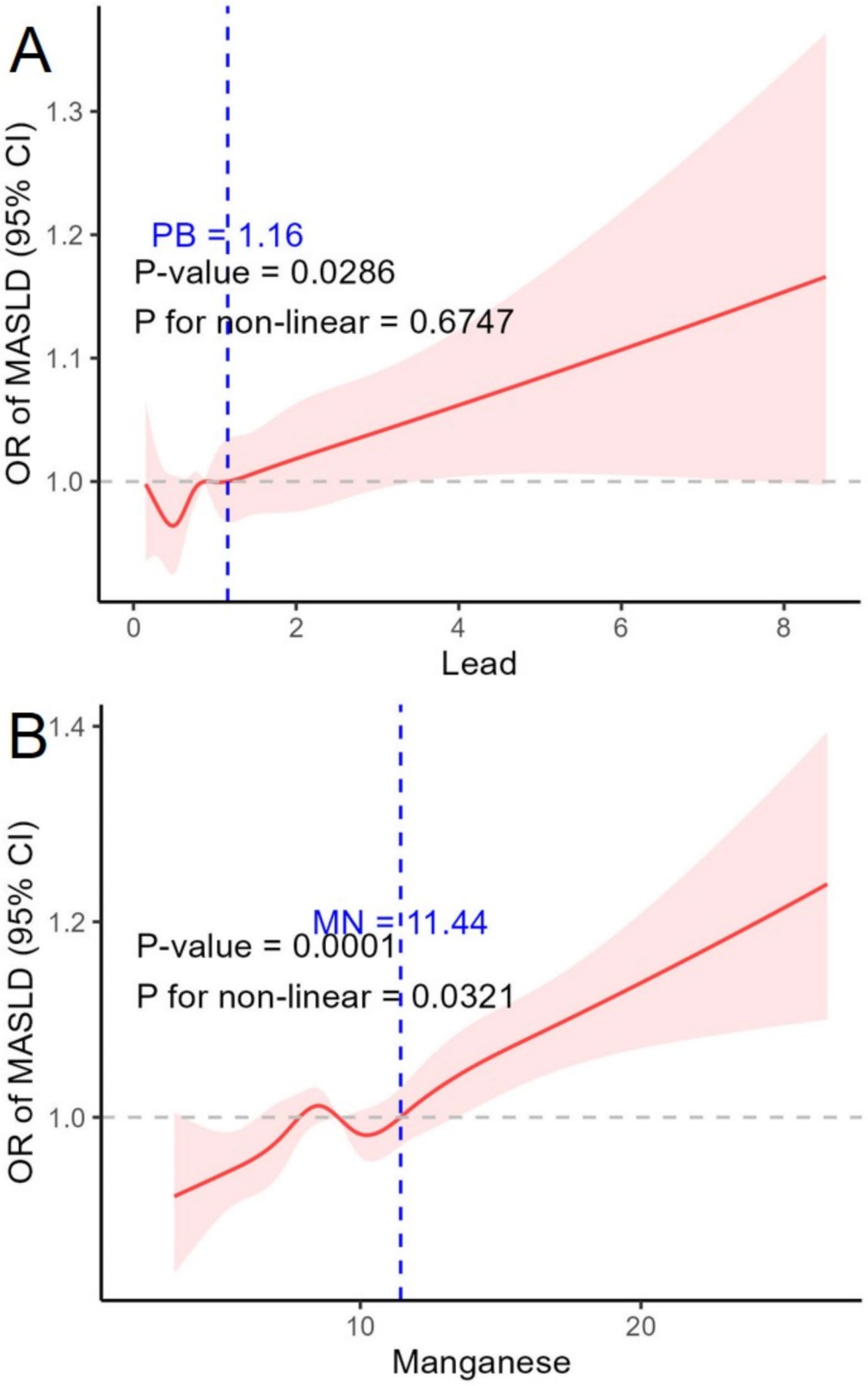

Fig. 2 RCS plots depicting the association of blood (**A**) lead and (**B**) manganese with MASLD

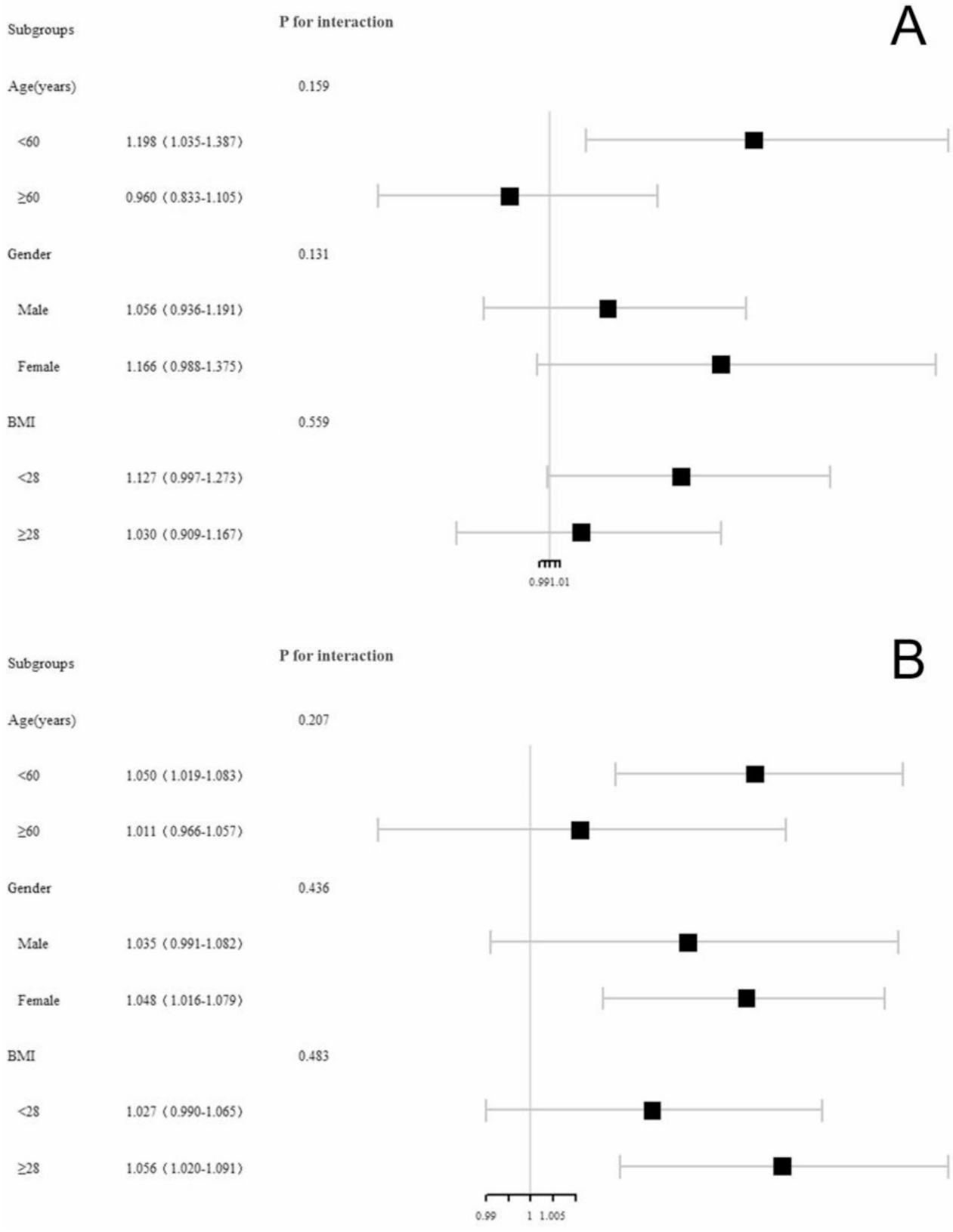

Fig. 3 Subgroup analysis of blood (**A**) lead and (**B**) manganese in relation to MASLD

[24]. Conversely, elevated manganese levels may disrupt normal mitochondrial processes by increasing reactive oxygen species (ROS), hindering ATP synthesis, and triggering mitochondrial disorders. This disruption exacerbates oxidative stress and raises the likelihood of NAFLD [25]. Additionally, heightened manganese exposure exacerbated hepatic lipid accumulation through Mancozeb, a fungicide rich in manganese, within an NAFLD cellular model [26]. Furthermore, manganese acted as the principal stimulant for prolidase, the key enzyme implicated in extracellular matrix alteration and hepatic stellate cell activation [27]. Lastly, mutations in the manganese transporter gene were found to increase the levels of 12 alpha-hydroxylated bile acids, leading to insulin resistance and hypercholesterolemia [28, 29].

The specific cause of lead exposure and its association with MASLD remains elusive, likely stemming from a complex interplay of genetic, endocrine, and oxidative stress pathways [30]. Lead exposure disrupts thiol-containing antioxidants and intracellular enzymes, leading to heightened generation of reactive oxygen species and diminished antioxidant function [31]. Past investigations have delved into lead's function as an endocrine-disrupting chemical (EDC), setting off a series of metabolic repercussions [32–34]. EDCs engage with nuclear hormone receptors, impeding lipid metabolism and potentially heightening vulnerability to NAFLD [33]. Furthermore, lead-induced hypercholesterolemia correlates with the upregulation of enzymes governing cholesterol synthesis while downregulating catabolic counterparts, leading to escalated levels of cellular and overall cholesterol. This effect is ascribed to the amplified hepatic expression of cytochrome P450 isoform, specifically lanosterol 14-demethylase (CYP51) [35, 36].

In our subgroup analysis, no significant correlation emerged between blood lead, manganese, and MASLD concerning age, sex, and BMI. Yang et al. emphasized a trend where mean blood lead concentration rises with age, potentially attributed to prior exposure to leaded gasoline or the use of leaded alloys among older individuals, leading to accumulated lead levels predating policy changes [30]. Previous research has highlighted a greater likelihood of the association between blood manganese and NAFLD being influenced in females compared to males [13, 23]. This observation could be attributed to several factors. Firstly, the difference in manganese-superoxide dismutase (Mn-SOD) levels between sex may contribute to these sex-specific differences. Research has indicated that Mn-SOD levels were notably decreased in males with NAFLD, whereas this trend was not observed in females. Consequently, decreased manganese levels may accelerate Mn-SOD impairment in males, thus potentially contributing to the onset and progression of NAFLD [37]. Accumulation of manganese in hepatic mitochondria might correlate with NAFLD. A sex-specific manganese exposure pattern could impact liver mitochondrial function, potentially indicating a sex-related disparity in manganese-NAFLD association [10, 38]. Besides, manganese might induce sex-specific alterations in the gut microbiome. Manganese-exposed mice displayed increased relative abundance of the Firmicutes phylum, linked to obesity and metabolic disorders, as well as the Bacteroidetes phylum, associated with anti-inflammatory properties. However, female mice exhibited reduced Firmicutes levels [39]. Prior research suggests that while both males and females experience similar levels of lead exposure, males typically display elevated blood lead levels and may be more vulnerable to the negative effects of lead toxicity compared to females [40]. Previous studies have also found a positive association between blood manganese levels and BMI [41]. Moreover, investigations have demonstrated that individuals with higher BMI are at increased risk of NAFLD due to elevated blood manganese levels [11, 13]. These discoveries underscore the importance of further exploration into how different populations may vary in their susceptibility to liver damage from manganese exposure.

To the best of our knowledge, this investigation represents the first foray into examining the correlation between blood lead and manganese levels in relation to MASLD using VCTE. Employing a comprehensive methodology that incorporates multifactor regression analysis alongside subgroup analysis, we assessed the influence of blood lead and manganese on MASLD. Despite the robustness of our approach, it is essential to acknowledge certain limitations. Even after meticulous adjustments for various variables within the model, the presence of unmeasured confounding factors remains a possibility. These factors, whether overlooked or excluded due to incomplete information within the NHANES database during model construction, could exert influence. Additionally, it is important to note that bias may arise from the use of self-reported outcome variables, as participants might provide inaccurate or incomplete information regarding their health status. This could potentially affect the validity of our results. Moreover, the study's cross-sectional nature imposes constraints inherent to its experimental design, precluding a deeper investigation into the causal linkage between blood lead and manganese and MASLD. Potential confounders, such as lifestyle factors and underlying health conditions, could not be fully accounted for in the analysis due to data limitations. These confounders may influence the observed associations and should be considered when interpreting the results. Finally, it's noteworthy that the data utilized in this investigation originated from the participants exclusively comprising residents of the United States. Care

must be taken when extrapolating the research outcomes to diverse populations across various countries.

The positive correlation between blood lead and manganese levels with MASLD highlights a significant public health concern, as both of these metals are widely prevalent in environmental exposures. Understanding these associations can inform future prevention strategies, particularly in high-risk populations who may be exposed to lead or manganese through occupational or environmental sources. While previous studies using NHANES data have explored the effects of lead and manganese on liver disease, none have specifically focused on MASLD with VCTE as the diagnostic tool. Our study is novel in employing this advanced method to assess liver steatosis, providing a more accurate measure of liver health compared to traditional biomarkers. Additionally, the inclusion of NHANES data spanning from 2017 to 2020 ensures that our findings represent a more current and diverse cohort. Future research should aim to explore the underlying mechanisms linking blood lead and manganese to MASLD, particularly through longitudinal studies that can establish causality. Additionally, studies investigating the role of other potential confounders, such as diet, lifestyle, and genetic predispositions, would help refine our understanding of how these metals contribute to liver disease. Our study has important practical implications for public health, as it underscores the need for policies that mitigate exposure to toxic metals like lead and manganese. For example, stricter regulations on occupational safety and environmental contaminants may be essential to reduce the risk of MASLD in vulnerable populations. Further, healthcare providers should be aware of these associations and consider monitoring individuals with high levels of metal exposure for liver health.

Conclusion

In this comprehensive cross-sectional study involving a sizable population, a notable correlation has been identified between elevated blood levels of lead, manganese and an elevated CAP, suggesting a more prominent presence of steatosis. Additionally, a positive relationship has been observed between increased concentrations of blood lead, manganese and a higher prevalence of MASLD. Our findings have been meticulously adjusted for various potential confounding factors, confirming the strength of this correlation. Our study highlights the potential health risks associated with exposure to lead and manganese, suggesting their role in the development of MASLD. These results emphasize the need for further research to explore the underlying mechanisms and the broader public health implications of these metal exposures.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
MAFLD	Metabolic associated fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetS	Metabolic syndrome
VCTE	Vibration-controlled transient elastography
CAP	Controlled attenuation parameter
NHANES	National Health and Nutrition Examination Survey
LLOD	Lower limit of detection
BMI	Body mass index
WC	Waist circumference
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
TG	Triglyceride
HDL	High-density lipoprotein cholesterol
TC	Total cholesterol
LDL	Low-density lipoprotein cholesterol
PA	Physical activity
MET	Metabolic equivalent of task
VIF	Variance inflation factor
RCS	Restricted cubic spline
ROS	Reactive oxygen species
EDC	Endocrine-disrupting chemical

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03731-3.

Supplementary Material 1

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Author contributions

WYG: searched the database, extracted data, analyzing data and manuscript writing; TW: writing—review and editing; YFS: supervision, project administration, writing—review and editing.

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Data availability

https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Declarations

Ethics approval and consent to participate

The study was supported by the National Centre for Health Statistics Research Ethics Review Board. Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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