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EDITED BY

Liu Zhirong,
East China University of Technology,
China

REVIEWED BY

Mohamed Helal,
National Institute of Oceanography and
Fisheries, Egypt
Augusta Chinyere Nsonwu-Anyanwu,
University of Calabar, Nigeria

*CORRESPONDENCE

Dongliang Li,
ldliang900@163.com

[†]These authors have contributed equally
to this work and share first authorship

SPECIALTY SECTION

This article was submitted to
Toxicology, Pollution and the
Environment,
a section of the journal
Frontiers in Environmental Science

RECEIVED 16 July 2022

ACCEPTED 20 September 2022

PUBLISHED 17 October 2022

CITATION

Zhang Z, Li Z, Lin H, Zeng Z, Huang J and
Li D (2022), Lead exposure was
associated with liver fibrosis in subjects
without known chronic liver disease: An
analysis of NHANES 2017–2020.
Front. Environ. Sci. 10:995795.
doi: 10.3389/fenvs.2022.995795

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Lead exposure was associated with liver fibrosis in subjects without known chronic liver disease: An analysis of NHANES 2017–2020

Zhiqiang Zhang ^{1,2†}, Zhangping Li ^{3†}, Haiyan Lin ^{1,2},
Zhiyu Zeng ^{1,2}, Jiaofeng Huang ² and Dongliang Li ^{1,2*}

¹Department of Hepatobiliary Disease, The 900th Hospital of Joint Logistics Support Force, Fuzhou, China, ²Department of Hepatobiliary Disease, Fuzong Clinical Medical College of Fujian Medical University, Fuzhou, China, ³Department of Hepatobiliary Disease, Cangshan District of the 900th Hospital of Joint Logistics Support Force, Fuzhou, China

Lead is one of the most important toxic heavy metals in the environment; however, the relationship between blood lead levels and liver fibrosis in individuals without chronic liver diseases (CLD) is unclear. This study used data obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2020. Multivariate logistic regression was used to explore the relationship between the blood lead level and significant liver fibrosis. A total of 1962 cases without underlying CLD were included, 77 (3.9%) of whom were diagnosed with advanced liver fibrosis by transient elastography. The proportion of advanced fibrosis significantly increased with the blood lead level ($p < 0.001$), and the blood lead level was higher in the fibrosis group than in the non-fibrosis group (1.2 $\mu\text{g}/\text{dl}$ vs 0.9 $\mu\text{g}/\text{dl}$, $p < 0.001$). After adjusting for relevant confounding factors, the blood lead level was found to be independently associated with advanced liver fibrosis (OR = 1.168; 95% CI, 1.006–1.356; $p = 0.041$). The blood lead level remained an independent risk factor for advanced liver fibrosis (OR = 1.249; 95% CI, 1.048–1.489; $p = 0.013$) after controlling for age and sex through propensity score matching. In conclusion, the blood lead level is associated with liver fibrosis in individuals without known CLD.

KEYWORDS

lead, fibrosis, environment, liver, NHANES

Abbreviations: NHANES, National Health and Nutrition Examination Surveys; NAFLD, nonalcoholic fatty liver disease; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; BMI, body mass index; FBG, fasting blood-glucose; TCHO, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; PSM, propensity score matching; FIB-4, Fibrosis-4 index; NFS, NAFLD fibrosis score.

Introduction

Liver fibrosis/cirrhosis is defined as the excessive accumulation of extracellular matrix proteins in liver tissue in response to chronic liver injury (Guo and Lu, 2020; Cheng et al., 2021; Ginès et al., 2021). Chronic viral hepatitis, fatty liver disease, and alcoholic liver disease are the three leading causes of fibrosis. However, for a small group of patients, the cause of fibrosis is difficult to identify (Nalbantoglu and Jain, 2019; Ginès et al., 2021).

Lead is one of the most important toxic heavy metals that are released from exhaust gas, paints, and industrial wastes. In the United States, the sources of lead include paint, batteries, and the industrial legacy of lead exposure (Obeng-Gyasi, 2019). Due to the historically widespread use of lead in gasoline and paint and the persistence of lead in the environment, lead exposure is common in the modern society, and the legacy of lead exposure remains a major health problem worldwide (Meyer et al., 2008).

Lead can affect nearly all organs and systems of the human body. A high blood lead concentration is a causative factor of renal impairment, anemia, cognitive dysfunction, and neurological diseases (Boskabady et al., 2018; El-Naggar et al., 2018). The importance of liver lead toxicity has been acknowledged recently (Kasperczyk et al., 2013), and the association between lead level and liver fibrosis has been reported in two survey-based studies from the United States and Korea, respectively (Reja et al., 2020; Kim et al., 2021). However, these two studies did not exclude patients with chronic liver diseases, especially non-alcoholic fatty liver disease

(NAFLD), which is a known cause of liver fibrosis (Lin et al., 2021). Previous studies have suggested that blood lead level is also significantly associated with higher prevalence of NAFLD (Chung et al., 2020; Reja et al., 2020; Betanzos-Robledo et al., 2021). As preexisting chronic liver disease, especially NAFLD, might act as a mediating factor, it is difficult to conclude that lead exposure directly increases the risk of fibrosis. Moreover, in previous studies, fibrosis was assessed using noninvasive fibrosis score, which is not as accurate as liver elasticity (Xiao et al., 2017; Staufer et al., 2019; Chuah et al., 2020).

Therefore, the relationship between lead level and liver fibrosis requires further clarification. In this context, this study aimed to evaluate the relationship between blood lead level and liver fibrosis assessed by liver elasticity based on data from the NHANES 2017–2020 database.

Methods

Study population

The study dataset was obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 database. NHANES is a national survey conducted by the Centers for Disease Control and Prevention of the United States. It is designed to assess the health and nutrition status of the non-institutionalized population in the United States. The inclusion criterion for this study was a blood lead test. The exclusion criteria were as follows: age <18 years; hepatic steatosis assessed based on the controlled attenuation parameter (CAP); hepatitis B or C virus infection; excessive alcohol consumption; history of chronic liver disease; ineligibility to liver fibrosis test; and with missing key data.

Assessment of liver steatosis and fibrosis

Liver steatosis and liver fibrosis were assessed based on the CAP and liver stiffness measurement (LSM), respectively, which were obtained using FibroScan®. Liver steatosis was defined as CAP ≥ 248 dB/m (Karlas et al., 2017), and significant liver fibrosis was defined as LSM ≥ 8.2 kPa (Cassinotto et al., 2016).

Definition

The following demographic variables were obtained from the original database: age, sex, race, body mass index (BMI), waist circumference, and history of hypertension and diabetes. BMI was calculated as weight (in kilograms) divided by the square of the height (in meters). Hypertension was defined as resting blood pressure persistently at or above 140/90 mmHg according to the international standard (Gabb et al., 2016). Diabetes was defined as a fasting blood glucose (FBG) level ≥ 7.0 mmol/L, a glycosylated hemoglobin

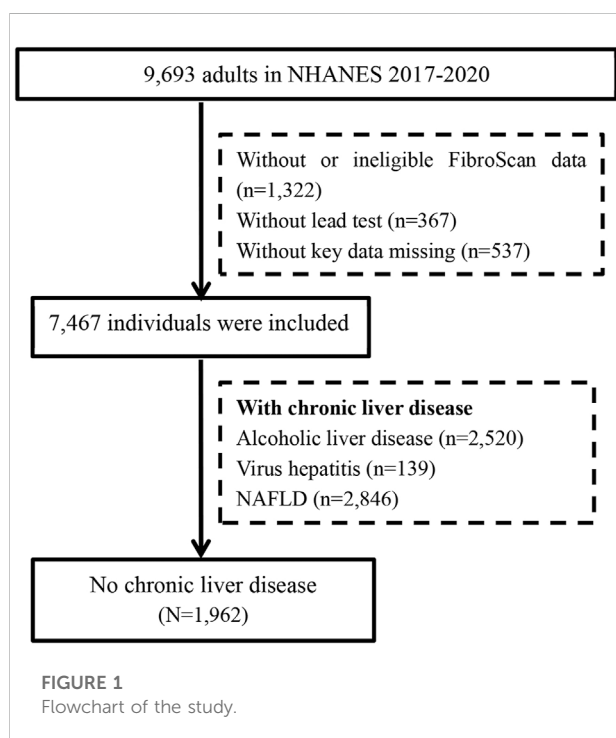


TABLE 1 The Characteristics of patients without CLD.

Variables	Total
N	1962
Male (%)	938 (47.8)
Age (years)	48.4 ± 19.8
Race, n (%)	
Mexican American	148 (7.5)
Other Hispanic	182 (9.3)
Non-Hispanic White	618 (31.5)
Non-Hispanic Black	604 (30.8)
Other Race	410 (20.9)
Hypertension (%)	676 (34.5)
Diabetes, n (%)	194 (9.9)
Smoker, n (%)	620 (31.6)
BMI (kg/m ²)	25.8 ± 5.2
Waist circumference (cm)	90.0 ± 13.2
FBG (mmol/L)	5.2 ± 1.3
TCHO (mmol/L)	4.7 ± 1.0
TG (mmol/L)	1.2 ± 0.8
ALT (U/L)	15 (12, 21)
AST (U/L)	19 (16, 22)
Creatinine (μmol/L)	75.1 (62.8, 90.2)
eGFR (ml/min)	95.4 ± 25.4
BUN (mmol/L)	5.3 ± 2.1
Uric acid (μmol/L)	299.4 ± 79.7
LSM (kPa)	5.1 ± 4.3
Lead (μg/dl)	0.9 (0.5, 1.5)

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range]. Abbreviations: CLD, chronic liver diseases; LSM, liver stiffness measurement; BMI, body mass index; FBG, fasting blood-glucose; TCHO, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

(HbA1c) level ≥6.5%, a previous diagnosis of diabetes, or treatment with oral hypoglycemic drugs or insulin (American Diabetes Association, 2020). The estimated glomerular filtration rate (eGFR) was calculated according to the 2009 CKD-EPI eGFR formula (Levey et al., 2009). A smoker was defined as having smoked at least 100 cigarettes in their entire life (Horne et al., 2012). Fibrosis-4 score (FIB-4) and NAFLD fibrosis score (NFS) were used for noninvasive assessment of fibrosis. The cutoff values of FIB-4 and NFS to diagnose advanced fibrosis were 2.670 and 0.676, respectively (Kabbany et al., 2017).

Laboratory parameters

Whole blood specimens were processed, stored, and shipped to the National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. All biochemical parameter assessments were performed using standard methods with automated techniques (Roche Calibrator for Automated Systems),

including those for FBG, total cholesterol (TCHO), total triglycerides (TG), aspartate aminotransferase (AST), alanine transaminase (ALT), serum creatinine, blood urea nitrogen (BUN), and uric acid. The blood lead concentration was detected using inductively coupled plasma mass spectrometry with a dynamic reaction cell. Quality controls were applied throughout all these assays. For a detailed description of the laboratory methods used, please see 'https://www.cdc.gov/Nchs/Nhanes/2017-2018/P_BIOPRO.htm'.

Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD), and categorical variables were expressed as percentages. The Student t-test (for normally distributed variables), Mann-Whitney *U* test (for non-normally distributed variables) and chi-squared test (for categorical variables) were used to investigate the differences between groups. Propensity score matching (PSM) was applied to match the age and sex between two groups. Multivariate logistic regression was used to explore the independent factors for significant liver fibrosis. All tests were two-tailed, and results with a *p*-value < 0.05 were considered statistically significant. All analyses were conducted using R 3.6.2 (<https://www.r-project.org/>).

Results

Baseline characteristics of the study subjects

A total of 9,693 adults participated the survey from 2017 to 2020. After excluding 2,226 cases with ineligible data and 5,505 cases with chronic liver diseases, 1962 patients without underlying liver disease were included in the final analysis (Figure 1). The proportion of men was 47.8% (938/1962), and the mean age was 48.4 ± 19.8 years. Overall, 9.9% of cases had diabetes, and 34.5% had hypertension. The liver enzyme (ALT and AST) levels of the study population were within normal range. The mean LSM was 5.1 ± 4.3 kPa. A total of 77 (3.9%) participants were diagnosed with advanced liver fibrosis by LSM. The other details are shown in Table 1.

Characteristics of individuals with different blood lead levels (quartiles 1–4)

The study subjects were divided into four groups according to the quartile of blood lead level (<0.52, 0.52–0.87, 0.87–1.47, and ≥1.47 μg/dl). The comparisons of the four groups are shown in Table 2. Higher lead levels were associated with higher age and more metabolic derangements such as hypertension, diabetes, obesity and hyperlipidemia (all with a *P* for trend value < 0.05).

TABLE 2 Baseline characteristics of individuals with different blood lead level (quartiles 1–4).

Variables	Lead ($\mu\text{g}/\text{dl}$)				P	P For trend
	<0.52	0.52–0.87	0.87–1.47	≥ 1.47		
N	498	486	490	488		
Male (%)	177 (35.5)	251 (51.6)	236 (48.2)	274 (56.1)	<0.001	<0.001
Age (years)	32.5 \pm 14.9	45.9 \pm 18.5	55.1 \pm 17.2	60.5 \pm 16.3	<0.001	<0.001
Race, n (%)					<0.001	<0.001
Mexican American	54 (10.8)	35 (7.2)	30 (6.1)	29 (5.9)		
Other Hispanic	68 (13.7)	56 (11.5)	32 (6.5)	26 (5.3)		
Non-Hispanic White	149 (29.9)	149 (30.7)	166 (33.9)	154 (31.6)		
Non-Hispanic Black	172 (34.5)	146 (30.0)	130 (26.5)	156 (32.0)		
Other Race	55 (11.0)	100 (20.6)	132 (26.9)	123 (25.2)		
Hypertension (%)	78 (15.7)	148 (30.5)	203 (41.4)	247 (50.6)	<0.001	<0.001
Diabetes, n (%)	21 (4.2)	47 (9.7)	60 (12.2)	66 (13.5)	<0.001	<0.001
Smoker, n (%)	71 (14.3)	144 (29.6)	173 (35.3)	232 (47.5)	<0.001	<0.001
BMI (kg/m^2)	26.0 \pm 6.2	26.1 \pm 5.3	25.7 \pm 4.7	25.2 \pm 4.6	0.046	0.012
Waist circumference (cm)	87.4 \pm 13.7	90.2 \pm 13.4	91.3 \pm 12.9	91.0 \pm 12.3	<0.001	<0.001
FBG (mmol/L)	5.0 \pm 0.8	5.2 \pm 1.3	5.3 \pm 1.5	5.3 \pm 1.6	<0.001	<0.001
TCHO (mmol/L)	4.4 \pm 0.9	4.7 \pm 1.1	4.8 \pm 1.1	4.9 \pm 1.1	<0.001	<0.001
TG (mmol/L)	1.1 \pm 0.6	1.2 \pm 0.7	1.2 \pm 0.6	1.3 \pm 1.0	<0.001	<0.001
ALT (U/L)	14 (11, 20)	16 (12, 20)	15 (12, 21)	15 (12, 20)	0.998	0.936
AST (U/L)	17 (15, 21)	19 (16, 22)	19 (16, 23)	19 (16, 24)	0.645	0.305
Creatinine ($\mu\text{mol}/\text{L}$)	69.0 (60.1, 83.1)	76.0 (64.5, 91.1)	76.9 (64.5, 90.2)	80.4 (66.3, 95.5)	<0.001	<0.001
eGFR (ml/min)	111.1 \pm 21.1	97.1 \pm 24.1	89.1 \pm 23.2	84.1 \pm 24.5	<0.001	<0.001
BUN (mmol/L)	4.7 \pm 1.5	5.2 \pm 2.0	5.5 \pm 2.2	5.7 \pm 2.4	<0.001	<0.001
Uric acid ($\mu\text{mol}/\text{L}$)	277 \pm 74.1	300.2 \pm 78.3	306.1 \pm 76.3	314.9 \pm 85.1	<0.001	<0.001
Advanced fibrosis, n (%)	13 (2.6)	13 (2.7)	21 (4.3)	30 (6.1)	0.013	0.002
Noninvasive blood markers						
FIB4 >2.67	5 (1)	14 (2.9)	21 (4.3)	40 (8.2)	<0.001	<0.001
NFS >0.676	11 (2.2)	21 (4.3)	26 (5.3)	46 (9.4)	<0.001	<0.001

Categorical values are shown as n (%). Continuous variables are shown as mean \pm standard deviation or median [interquartile range]. Abbreviations: CLD, chronic liver diseases; LSM, liver stiffness measurement; BMI, body mass index; FBG, fasting blood-glucose; TCHO, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; FIB-4, Fibrosis-4 score; NFS, NAFLD, fibrosis score.

Conversely, the eGFR decreased with the increase in lead concentration ($p < 0.05$). The proportion of advanced fibrosis assessed by LSM also significantly increased with blood lead levels (Figure 2 and Table 2).

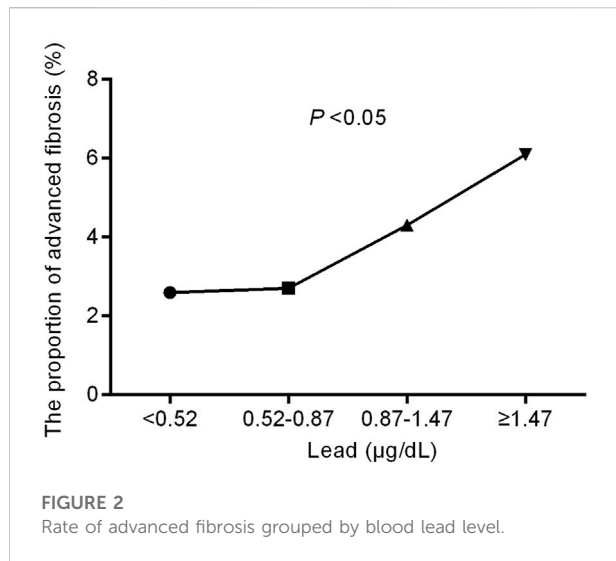
Characteristics of individual with and without advanced liver fibrosis

Overall, 77 (3.9%) cases had an LSM ≥ 8.2 kPa and were diagnosed with advanced liver fibrosis. The comparison between advanced liver fibrosis (LSM ≥ 8.2 kPa) and non-fibrosis (LSM < 8.2 kPa) is shown in Table 3. Patients with fibrosis were relatively older than those without (57.9 ± 20.0 vs 48.0 ± 19.7 , $p < 0.001$). The fibrosis group had a higher proportion of

men (63.6% vs 47.2%, $p = 0.007$) and significantly higher proportions of hypertension, diabetes, and smoking history. Liver injury indicators, including ALT and AST levels, were higher in the fibrotic individuals (both with a p -value < 0.05). There was no statistical difference in BMI and FBG and TG levels between the two groups (all with a p -value > 0.05); however, the blood lead level was higher in the fibrosis group than in the non-fibrosis group (1.2 $\mu\text{g}/\text{dl}$ vs 0.9 $\mu\text{g}/\text{dl}$, $p < 0.001$).

Binary logistic regression analysis of the association between lead level and fibrosis

Univariate logistic regression analysis showed that blood lead level was a risk factor for advanced liver fibrosis (OR = 1.227; 95%



CI, 1.087–1.385, $p = 0.001$, Table 4). The factors with a p -value < 0.05 in the univariate analysis were set as candidate parameters for the multivariate regression. A co-linearity test revealed that ALT and AST, creatinine, eGFR, and BUN showed collinearity. We selected the parameters with the largest area under the receiver operating characteristic curve for multivariate regression. After adjusting for sex, age, smoking history, presence of metabolic profiles (diabetes, hypertension, waist circumference, TCHO), AST, and eGFR, the blood lead level was still independently associated with advanced liver fibrosis (OR = 1.168; 95% CI, 1.006–1.356; $p = 0.041$).

Results of the age- and sex-matched cohort

As the risk of liver fibrosis increases with age, we used PSM to match age and sex between the fibrosis and non-fibrosis groups. The comparison after PSM is summarized in Supplementary Table S1. No difference in age and sex was detected between individuals with and without advanced liver fibrosis after PSM. The blood lead levels in the fibrosis group were significantly higher than those of the non-fibrosis group (1.2 µg/dl vs 1.0 µg/dl, $p < 0.001$). Univariate logistic regression analysis showed that blood lead level was a risk factor for advanced liver fibrosis (OR = 1.273; 95% CI, 1.079–1.502, $p = 0.004$). After adjusting for hypertension, diabetes, TCHO, ALT and AST, the blood lead level remained as an independent risk factor for advanced liver fibrosis (OR = 1.249; 95% CI, 1.048–1.489, $p = 0.013$) (Supplementary Table S2).

Discussion

Utilizing the data from NHANES 2017–2020, this study showed that higher blood lead was independently associated

TABLE 3 Comparison between the fibrosis and non-fibrosis groups.

Variables	Non-fibrosis	Fibrosis	<i>P</i>
N	1885	77	
Male (%)	889 (47.2)	49 (63.6)	0.007
Age (years)	48.0 ± 19.7	57.9 ± 20.0	<0.001
Race, n (%)			0.064
Mexican American	144 (7.6)	4 (5.2)	
Other Hispanic	175 (9.3)	7 (9.1)	
Non-Hispanic White	590 (31.3)	28 (36.4)	
Non-Hispanic Black	573 (30.4)	31 (40.3)	
Other Race	403 (21.4)	7 (9.1)	
Hypertension (%)	635 (33.7)	41 (53.2)	<0.001
Diabetes, n (%)	178 (9.4)	16 (20.8)	0.002
Smoker, n (%)	584 (31.0)	36 (46.8)	0.005
BMI (kg/m ²)	25.7 ± 5.1	26.6 ± 8.5	0.359
Waist circumference (cm)	89.8 ± 13	94 ± 16.4	0.029
FBG (mmol/L)	5.2 ± 1.3	5.4 ± 1.6	0.39
TCHO (mmol/L)	4.7 ± 1.0	4.2 ± 1.1	<0.001
TG (mmol/L)	1.2 ± 0.8	1.1 ± 0.6	0.208
ALT (U/L)	15 (12, 20)	16 (12, 26)	0.044
AST (U/L)	19 (16, 22)	20 (17, 31)	<0.001
Creatinine (µmol/L)	75.1 (62.8, 89.3)	79.6 (69.8, 100.8)	0.005
eGFR (ml/min)	95.8 ± 25	86.4 ± 31.9	0.012
BUN (mmol/L)	5.3 ± 2.0	5.9 ± 3.0	0.06
Uric acid (µmol/L)	299 ± 80.1	310.6 ± 69.7	0.158
Lead (µg/dl)	0.9 (0.5, 1.5)	1.2 (0.6, 2.1)	<0.001

Categorical values are shown as n (%). Continuous variables are shown as mean ± standard deviation or median [interquartile range]. Abbreviations: CLD, chronic liver diseases; LSM, liver stiffness measurement; BMI, body mass index; FBG, fasting blood-glucose; TCHO, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

with the risk of liver fibrosis in adults without underlying chronic liver disease.

In the present study, liver fibrosis was assessed as the liver elasticity measured using FibroScan. This method was completely different from those used in previous studies, in which a noninvasive model was used to diagnose fibrosis. For example, (Reja et al., 2020) used the NAFLD Fibrosis Score (NFS) and (Chung et al., 2020) used the fibrosis-4 index (FIB-4) to diagnose fibrosis. The accuracy of liver elasticity *via* FibroScan has been consistently reported to be better than those of noninvasive models (Ragazzo et al., 2017; Petta et al., 2019; Stauffer et al., 2019).

In line with many previous studies, which have shown that long-term lead exposure was significantly associated with liver injury (Can et al., 2008; Chen et al., 2019; Nakhaee et al., 2019) and fibrosis (Chung et al., 2020; Reja et al., 2020) in both the overall and NAFLD populations, we also demonstrated that the proportion of advanced liver fibrosis was related to blood lead level. In contrast to the published literature, we ruled out cases

TABLE 4 Binary logistic regression analysis of blood lead and significant fibrosis.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Lead ($\mu\text{g}/\text{dl}$)	1.227	1.087–1.385	0.001	1.168	1.006–1.356	0.041
Male	1.961	1.222–3.147	0.005	1.333	0.793–2.242	0.278
Age (years)	1.026	1.014–1.039	<0.001	1.023	1.003–1.043	0.023
Race, n (%)						
Mexican American	1.000					
Other Hispanic	1.440	0.413–5.017	0.567			
Non-Hispanic White	1.708	0.590–4.948	0.324			
Non-Hispanic Black	1.948	0.677–5.606	0.217			
Other Race	0.625	0.180–2.168	0.459			
Hypertension (%)	2.242	1.418–3.543	0.001	1.349	0.765–2.380	0.301
Diabetes, n (%)	2.515	1.420–4.456	0.002	1.044	0.538–2.023	0.900
Smoker, n (%)	1.956	1.237–3.093	0.004	1.377	0.832–2.278	0.214
BMI (kg/m^2)	1.029	0.991–1.068	0.139			
Waist circumference (cm)	1.022	1.006–1.039	0.006	1.012	0.993–1.031	0.229
FBG (mmol/L)	1.062	0.944–1.195	0.316			
TCHO (mmol/L)	0.598	0.463–0.774	<0.001	0.608	0.466–0.792	<0.001
TG (mmol/L)	0.831	0.569–1.214	0.337			
ALT (U/L)	1.012	1.002–1.023	0.017			
AST (U/L)	1.024	1.014–1.035	<0.001	1.028	1.017–1.040	<0.001
Creatinine ($\mu\text{mol}/\text{L}$)	1.004	1.001–1.007	0.007			
eGFR (ml/min)	0.986	0.978–0.995	0.002	1.002	0.989–1.016	0.746
BUN (mmol/L)	1.118	1.030–1.214	0.007			
Uric acid ($\mu\text{mol}/\text{L}$)	1.002	0.999–1.005	0.210			

Abbreviations: CLD, chronic liver diseases; LSM, liver stiffness measurement; BMI, body mass index; FBG, fasting blood-glucose; TCHO, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

known to have an increased risk of chronic liver disease, such as those with viral hepatitis, alcoholic liver disease, or fatty liver disease. By excluding patients with preexisting chronic liver disease, we minimized the fibrogenetic effect of known etiology. The results of this study further confirmed the association between blood lead concentration and risk of liver fibrosis.

The exact pathogenesis of chronic blood lead exposure and liver fibrosis remains unclear. Previous studies have shown that blood lead could cause hepatic damage by increasing the inflammatory response and oxidative stress (Berrahal et al., 2011). Moreover, lead is a divalent cation, which can replace calcium at multiple levels in the human body and therefore interfere with cell signaling pathways (Mitra et al., 2017). Furthermore, the molecular level of lead exposure resulting in various systemic effects is being extensively explored (Qian et al., 2020).

The suggestive safe blood lead level has declined dramatically from 60 $\mu\text{g}/\text{dl}$ in 1960 to 5 $\mu\text{g}/\text{dl}$ in 2012 (Ruckart et al., 2021). In 2021, this number was 5 $\mu\text{g}/\text{dl}$, as recommended by the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry of the United States (Ruckart et al., 2021). In

the present study, the median blood lead level was 0.9 $\mu\text{g}/\text{dl}$, which was much lower than the suggestive “safe” level. The results indicated that even a very low dose exposure might cause liver injury. This also raised concerns regarding the “real safe” blood lead level. As indicated by a previous study, there may in fact be no safe blood lead level for humans (Lanphear et al., 2018).

To the best of our knowledge, this is the first study to use liver elasticity to explore the relationship between liver fibrosis and blood lead level. The diagnostic accuracy for fibrosis has been greatly improved by using this new method. However, the current study should be interpreted in light of several limitations. First, as it was a cross-sectional study, we could not draw a causal relationship between lead exposure and liver fibrosis. Second, we were not able to rule out cases with undiagnosed liver disease as no data was provided in the database. However, the liver enzyme levels of this study population were within the normal range, and it has been comprehensively shown that normal liver enzymes are uncommon in patients with chronic liver disease. Therefore, although we may have missed some cases with undiagnosed chronic liver disease, this would not be common and therefore should not have greatly influenced the conclusion of

this study. Nevertheless, the results of this study need to be confirmed in prospective studies.

In conclusion, this study demonstrated an association between blood lead level and liver fibrosis in individuals without known chronic liver disease. However, the causal relationship and underlying mechanism between lead and fibrosis requires further investigation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

ZZh, ZL, HL conducted the formal statistical analysis and data management. ZZe and ZL drafted the paper. DL and JH edited and revised the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the Startup Fund for scientific research of Fujian Medical University (No. 2020QH1252).

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Acknowledgments

The authors thank the National Health and Nutrition Examination Survey program for providing the data for this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fenvs.2022.995795/full#supplementary-material>

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