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**Original Article**

# Urinary Arsenic Exposure and Metabolic Dysfunction-associated Steatotic Liver Disease: A NHANES Analysis

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## Abstract

**Background and objectives:** While metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with obesity, the cause of its rapidly rising prevalence is not well understood. In this study, we aimed to examine the association between arsenic exposure and MASLD in humans.

**Methods:** Urinary inorganic arsenic data from the National Health and Nutrition Examination Survey, 2011–2020, were used. These were combined with death certificate data from the National Death Index of the National Center for Health Statistics to ascertain mortality rates. Weighted linear regression and chi-squared analysis were performed.

**Results:** The analysis included 6,386 participants after exclusions. The mean urinary arsenic level was 5.92 μg/L in participants with MASLD versus 5.59 μg/L in those without. Alanine aminotransferase levels exhibited a statistically significant increasing trend across both continuous arsenic levels and arsenic quintiles. A statistically significant upward trend was observed for the income-to-poverty ratio and body mass index but not for education status. MASLD prevalence was highest among the white population, while an increasing trend was observed in the Hispanic population over the years ($p < 0.001$). The proportion of Mexican Americans increased to 12.6% in the MASLD group versus 8.09% in the non-MASLD cohort ($p < 0.001$). There was a statistically significant increase in the odds of MASLD across arsenic exposure levels, with individuals in the highest quintile having a 32% greater likelihood compared to those in the lowest quintile ($p$-trend = 0.002). The odds further increased to 55% in the highest quintile (odds ratio 1.55, 95% confidence interval: 1.19–2.03; $p$-trend < 0.001). MASLD was more prevalent in females than males (57.9% vs. 47.6%; $p < 0.001$), and the mean age increased from 46.9 years to 49.9 years ($p = 0.016$).

**Conclusions:** Our findings reveal a positive association between urinary arsenic exposure and MASLD, with increasing trends particularly observed among Hispanics and those with higher income-to-poverty ratios and body mass index.

## Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease, is characterized by macrovesicular steatosis in hepatocytes occurring in the absence of excessive alcohol consumption, steatogenic medications, or other secondary causes of hepatic fat accumulation.[1] While often asymptomatic in its early stages, MASLD can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma, representing a growing global health burden.[2] The pathophysiology of MASLD is intricately linked to metabolic dysregulation, including insulin resistance, obesity, and type 2 diabetes mellitus, which drive hepatic lipid accumulation and inflammation.[3] However, emerging evidence suggests that environmental factors, such as exposure to toxic heavy metals, may independently contribute to MASLD pathogenesis, even in individuals without traditional metabolic risk factors.[4]

Among environmental hepatotoxins, arsenic, a pervasive contaminant in groundwater, soil, and food, has garnered increasing attention due to its potential role in liver injury. Experimental studies have demonstrated that arsenic exposure disrupts hepatic lipid

**Keywords:** Metabolic dysfunction-associated steatotic liver disease; MASLD; Metabolic dysfunction-associated fatty liver disease; MAFLD; Arsenic; Obesity; National Health and Nutrition Examination Survey; NHANES; Alanine.

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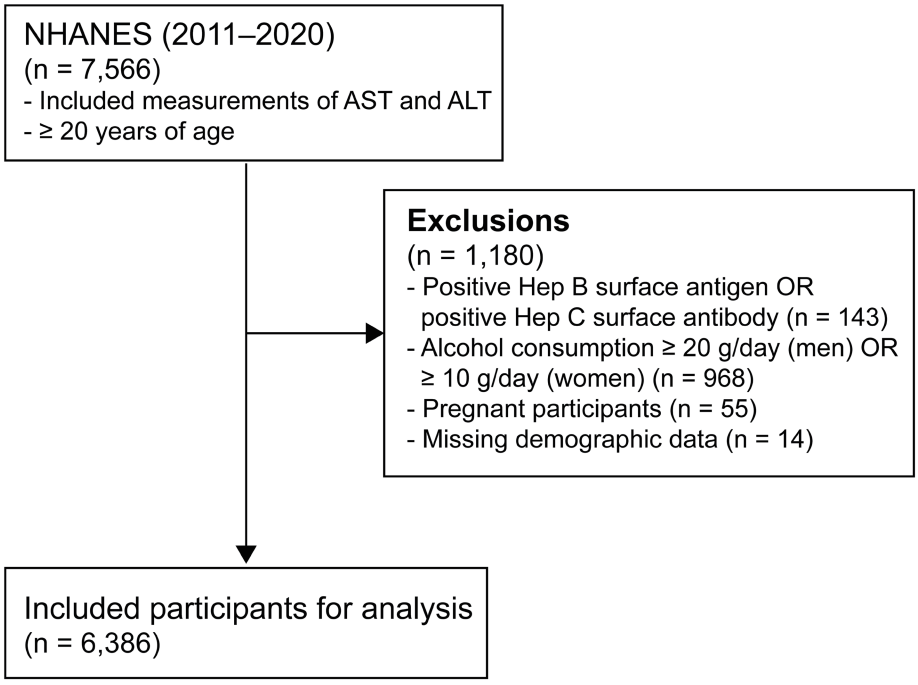


**Fig. 1. Inclusion/exclusion criteria.** ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHANES, National Health and Nutrition Examination Survey.

metabolism through multiple mechanisms, including oxidative stress induction, mitochondrial dysfunction, and activation of lipogenic pathways (e.g., PPAR-γ and *SREBP-1c*).[5] However, these studies are often limited to highly exposed cohorts, leaving a gap in our understanding of the effects of moderate, environmentally relevant arsenic levels, such as those typical in the U.S. population, on MASLD risk. The goal of this experiment was to use National Health and Nutrition Examination Survey (NHANES) data to determine whether the association between arsenic exposure and MASLD observed in animal models also applies to humans.

## Materials and methods

### *Study design*

NHANES is a nationwide, cross-sectional survey that collects demographic, questionnaire, and laboratory data using a stratified, multistage probability cluster design to provide a representative sample of the civilian, non-institutionalized U.S. population.[6] The current study utilizes four consecutive cycles (2011–2012, 2013–2014, 2015–2016, and 2017–2020). Since data collection was paused in March 2020, the 2019–2020 data were combined with the 2017–2018 cycle to ensure accurate population weighting. All data and methods are publicly available at the National Center for Health Statistics website (https://www.cdc.gov/nchs/nhanes/index.htm). The Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention, approved all NHANES protocols, and informed consent was obtained from all participants.

A total of 7,566 participants aged 20 years or older had recorded arsenic and alanine aminotransferase (ALT) levels. Participants with common risk factors for liver disease, such as positive Hep B surface antigen (hepatitis B) and positive Hep C surface antibody (hepatitis C), were excluded (n = 143). Additionally, participants who reported high alcohol consumption (≥20 g/day for men and ≥10 g/day for women (n = 968)) and those who were pregnant (n = 55) were excluded. This resulted in 6,386 participants included in the current study (Fig. 1).

### *Arsenic evaluation*

Arsenic exposure was assessed using urine samples from participants. Total arsenic and speciated forms, such as arsenobetaine and arsenocholine, were measured using inductively coupled plasma dynamic reaction cell–mass spectrometry. The lower limits of detection for arsenic were 1.25 µg/L in 2011–2012, 0.26 µg/L in 2013–2016, and 0.23 µg/L in 2017–2020 (Centers for Disease Control and Prevention/National Center for Health Statistics, 2011–2020). All arsenic values below these thresholds were adjusted by dividing the lower limits of detection by the square root of 2.[7] Identical calculations were applied to speciated arsenobetaine and arsenocholine. This study focuses solely on inorganic arsenic. Inorganic arsenic levels were calculated by subtracting speciated arsenic compounds from total arsenic values. Negative concentrations resulting from measurement error were replaced by imputing 0.01 µg/L.[8] To account for variability due to urine dilution, arsenic concentrations were standardized by dividing by creatinine concentrations.[8] Standardized arsenic measurements were then categorized into quintiles based on population estimates (<2.036, 2.037–3.29, 3.30–5.00, 5.01–8.72, >8.72µg/L).

### *Metabolic dysfunction-associated steatotic liver disease evaluation*

Serum ALT was used to determine the presence of MASLD, as it is a common screening and monitoring biomarker.[9] From 2011–2016, serum ALT was measured using the Beckman UniCel DxC800 Synchron (Beckman Coulter, Brea, CA). During the

2017–2020 NHANES cycle, ALT was measured using the Roche Cobas 6000 Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN 46250). Both instruments used a kinetic rate reaction to determine serum ALT levels. MASLD status was defined as serum ALT activity >30 IU/L in men and >19 IU/L in women, assuming no other identifiable causes of liver disease were present.[10]

### *Statistical analysis*

NHANES utilizes a complex survey design; therefore, recommended subsample weights, strata, and primary sampling units were applied to all descriptive statistics and regression models. Continuous variables were reported as means (95% confidence interval (CI)), while categorical variables were reported as proportions (95% CI). Weighted linear regression was used to compare continuous variables between groups, and chi-squared analysis was used to compare categorical variables. Generalized additive models (GAMs) with cubic splines were used to assess the linearity between arsenic levels and ALT. ALT values were natural-log-transformed, and arsenic levels were log base 10-transformed to reduce right skewness. Additionally, weighted linear regression and logistic regression were used to calculate percent differences in ALT and the odds of MASLD across arsenic level quintiles. Both regression models included an initial model adjusted for age, sex, race/ethnicity, and NHANES survey cycle. The full model was further adjusted for education, income-to-poverty ratio, body mass index (BMI), smoking status, and alcohol consumption. All *p*-values were two-sided, and $p < 0.05$ was considered statistically significant. GAM analyses with smoothing plots were created using the mgcv package in R version 4.3.1 (www.R-project.org). All other analyses were conducted using Stata version 18 (StataCorp; College Station, TX).

### *Methodological considerations*

This study relied on elevated ALT levels as a surrogate marker for MASLD due to the absence of liver imaging or biopsy data in NHANES. While ALT elevation is a practical and widely used indicator of hepatic injury, it does not directly assess steatosis, inflammation, or fibrosis, key features of MASLD. Liver biopsy and imaging (e.g., transient elastography or magnetic resonance imaging-based techniques) remain the gold standards for diagnosis but were not feasible in this large, population-based cohort. We acknowledge this as a limitation; however, elevated ALT has been validated in prior epidemiological studies as a reasonable proxy for MASLD in the absence of advanced diagnostic modalities.

## Results

### *Study population*

A total of 7,566 participants aged 20 years or older were initially considered. Participants who had hepatitis B or hepatitis C (n = 143), those who reported high levels of alcohol consumption (≥20 g/day for men and ≥10 g/day for women; n = 968), and pregnant women (n = 55) were excluded. Finally, 6,386 participants were included in the current study.

The overall unweighted sample of 6,386 survey respondents (weighted n = 230,489,807) was included in the analysis (Table 1). Across the NHANES cycles, the mean age increased from 46.9 years to 49.9 years ($p = 0.016$). Statistically significant increasing trends were observed in the income-to-poverty ratio and BMI. From 2011–2012 to the 2017–2020 NHANES cycle, the proportion of the population with a ratio greater than or equal to 1 increased from 83.3% to 89.5% ($p = 0.014$). Additionally, mean BMI increased from 28.9 kg/m$^2$ to 30.0 kg/m$^2$ over the same period. No statistically significant trends were observed for sex, race/ethnicity, or smoking status. Furthermore, mean arsenic levels did not demonstrate a statistically significant trend across the cycles. Conversely, the prevalence of MASLD showed an increasing trend from 2011–2016, followed by a noticeable decrease in the final cycle ($p < 0.001$).

Within the population, the prevalence of MASLD was 32.8% (Table 2). The overall mean (95% CI) age of the weighted population was 47.9 years (47.0, 48.7). Comparisons reported no statistically significant difference in mean age between participants with and without MASLD ($p = 0.31$). However, notable statistical differences were observed in terms of sex and race/ethnicity. Among those with MASLD, there was a 10% higher proportion of female individuals (47.6% vs. 57.9%; $p < 0.001$). Differences were also observed among non-Hispanic blacks and Mexican Americans. Participants in the MASLD cohort reported a smaller proportion of non-Hispanic blacks (12.6% vs. 7.56%), while the proportion of Mexican Americans increased to 12.6% in the MASLD group compared to 8.09% in the non-MASLD cohort ($p < 0.001$). In addition, a larger proportion of "Never" smokers was observed within the MASLD group, while the proportion of "Current" smokers was lower. The proportions by education status or income-to-poverty ratio did not differ significantly by MASLD status.

### *Arsenic levels and ALT*

The overall mean arsenic level was 5.69 µg/L. Relative to MASLD status, the mean arsenic level among participants with MASLD was 5.92 µg/L, whereas the mean level among those without MASLD was 5.59 µg/L; no statistically significant difference was observed. However, there was a statistically significant increasing trend in ALT levels across continuous arsenic levels and arsenic quintiles. The GAM plots indicate that the increasing trend in natural log ALT begins at an arsenic level of log base 10 of 0 = 1 µg/L (Fig. 2a). Across the arsenic quintiles, a 3.43% increase in ALT was observed from the first to the last quintile in the initial model (Beta (95% CI) = 3.43 (−1.88, 9.03); $p = 0.036$) (Table 3). After further adjustment for education, poverty-income ratio, body mass index, smoking status, and alcohol consumption, ALT levels increased by 7.22% in the last arsenic quintile compared to the first quintile ($p = 0.001$).

### *Arsenic levels and MASLD prevalence*

The relationship between arsenic levels and MASLD status was similar to that between arsenic levels and ALT. The GAM plots (Fig. 2) also show that the natural log of the odds of MASLD begins to increase shortly after log base 10 of 0 = 1 µg/L. Across the arsenic quintiles, the prevalence of MASLD increased from 29.9% in the first quintile to 35.9% in the last quintile. In the initial model, an increasing trend in the odds of MASLD was statistically significant. The odds of MASLD were 32% higher in the last quintile compared to the first (*p*-trend = 0.002). In the fully adjusted model, the odds increased by 55% in the last quintile compared to the first (odds ratio 95%CI = 1.55 (1.19, 2.03); *p*-trend <0.001) (Table 4).

## Discussion

MASLD, previously known as non-alcoholic fatty liver disease, is currently the most common chronic liver disease worldwide, with a rising prevalence. A series of studies from NHANES, which represents the general US population, illustrate a steady increase

**Table 1. Trends in arsenic levels by NHANES cycle**

| Variables (n = 6,386; weighted = 230,489,807) | 2011–2012 (n = 1,336) | 2013–2014 (n = 1,430) | 2015–2016 (n = 1,434) | 2017–2020 (n = 2,186) | *p*-trend[1] |
|---|---|---|---|---|---|
| Weighted sample size | 53,793,186 | 57,566,604 | 59,183,029 | 59,964,988 | |
| Age (years), mean (95% CI) | 46.9 (45.0, 48.8) | 46.9 (45.4, 48.3) | 47.6 (45.7, 49.5) | 49.9 (47.9, 51.7) | 0.016 |
| Sex, % (95% CI) | | | | | 0.97 |
| Male | 48.3 (44.6, 52.1) | 49.4 (45.6, 53.1) | 49.5 (45.8, 53.2) | 48.9 (45.1, 52.7) | |
| Female | 51.7 (47.9, 55.4) | 50.6 (46.9, 54.4) | 50.5 (46.8, 54.1) | 51.1 (47.2, 54.9) | |
| Race, % (95% CI) | | | | | 0.91 |
| Non-Hispanic White | 65.1 (55.9, 73.4) | 64.3 (56.5, 71.3) | 62.5 (52.9, 71.3) | 59.9 (53.8, 65.7) | |
| Non-Hispanic Black | 11.3 (7.09, 17.5) | 10.2 (7.30, 13.9) | 11.0 (7.40, 16.0) | 11.3 (8.86, 14.3) | |
| Non-Hispanic Asian | 6.19 (3.98, 9.54) | 5.58 (4.05, 7.66) | 6.60 (3.90, 10.9) | 6.66 (4.59, 9.58) | |
| Mexican American | 7.61 (4.53, 12.5) | 11.2 (7.10, 17.3) | 9.41 (5.45, 15.8) | 9.86 (7.09, 13.6) | |
| Other Hispanic | 7.66 (4.68, 12.3) | 5.99 (3.83, 9.24) | 7.27 (4.36, 11.9) | 7.71 (6.16, 9.60) | |
| Multiracial | 2.11 (1.28, 3.44) | 2.75 (1.65, 4.53) | 3.19 (1.86, 5.39) | 4.56 (3.11, 6.64) | |
| Education, % (95% CI) | | | | | 0.22 |
| <High school | 16.6 (13.4, 20.3) | 15.7 (11.9, 20.3) | 15.7 (11.5, 21.1) | 12.5 (10.5, 14.8) | |
| High school | 20.4 (15.5, 26.3) | 23.7 (21.2, 26.3) | 20.3 (17.6, 23.3) | 28.8 (25.4, 32.5) | |
| Some college | 32.6 (28.5, 37.0) | 32.4 (29.2, 35.7) | 32.4 (28.4, 36.6) | 29.4 (26.4, 32.6) | |
| College and above | 30.4 (24.6, 36.9) | 28.2 (23.9, 32.9) | 31.6 (26.0, 37.7) | 29.2 (23.9, 35.1) | |
| Income-to-poverty ratio, % (95% CI) | | | | | 0.014 |
| <1 | 16.7 (13.1, 21.1) | 14.9 (12.2, 18.2) | 12.6 (10.1, 15.6) | 10.5 (8.51, 12.9) | |
| ≥1 | 83.3 (78.9, 86.9) | 85.1 (81.7, 87.8) | 87.4 (84.4, 89.9) | 89.5 (87.0, 91.5) | |
| Smoking status, % (95% CI) | | | | | 0.36 |
| Never | 62.1 (59.2, 65.9) | 58.7 (54.3, 62.9) | 58.0 (54.4, 61.6) | 59.8 (55.7, 63.8) | |
| Former | 20.9 (18.6, 23.5) | 23.8 (20.3, 27.7) | 25.3 (22.3, 28.7) | 25.6 (21.8, 29.9) | |
| Current | 16.9 (14.0, 20.2) | 17.5 (15.2, 19.9) | 16.7 (13.7, 20.1) | 14.6 (11.4, 18.5) | |
| Alcohol consumption (g/day), mean (95% CI) | 1.55 (1.10, 1.99) | 1.68 (1.24, 2.12) | 1.65 (1.28, 2.02) | 1.47 (1.11, 1.84) | 0.76 |
| BMI (kg/m$^2$), mean (95% CI) | 28.9 (28.2, 29.6) | 29.1 (28.6, 29.6) | 29.5 (28.9, 30.2) | 30.0 (29.5, 30.5) | 0.004 |
| HOMA-IR, mean (95% CI) | 3.93 (3.23, 4.63) | 3.98 (3.37, 4.59) | 4.27 (3.48, 5.06) | 5.14 (3.97, 6.31) | 0.056 |
| Total urine arsenic (ug/L), mean (95% CI) | 6.15 (5.15, 7.14) | 5.45 (4.73, 6.17) | 5.16 (4.61, 5.72) | 6.05 (5.44, 6.66) | 0.78 |
| Prevalence of MASLD, % (95% CI) | 32.4 (28.4, 36.7) | 35.2 (31.0, 39.5) | 37.0 (34.2, 39.9) | 26.7 (24.5, 29.0) | <0.001 |
| Alanine aminotransferase (U/L) mean (95% CI) | 24.5 (23.4, 25.6) | 25.3 (24.2, 26.5) | 26.3 (25.3, 27.2) | 21.8 (20.9, 22.6) | <0.001 |

[1]Weighted linear regression was used to compare continuous variables between participants with and without MASLD. Weighted chi-squared analysis was used to compare categorical variables between groups. BMI, body mass index; CI, confidence interval; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey.

**Table 2. Survey-weighted characteristics of the study population by MASLD status**

| Variables | Total (n = 6,386) | No MASLD (n = 4,419) | Yes MASLD (n = 1,967) | *p*-value[1] |
|---|---|---|---|---|
| Weighted sample size (%) | 230,489,807 | 154,872,371 (67.2) | 75,617,436 (32.8) | |
| | | | | |
| Age (years), mean (95% CI) | 47.9 (47.0, 48.7) | 48.1 (47.1, 49.1) | 47.4 (46.4, 48.5) | 0.31 |
| Sex, % (95% CI) | | | | <0.001 |
| Male | 49.0 (47.3, 50.8) | 52.4 (49.9, 54.9) | 42.1 (39.1, 45.2) | |
| Female | 51.0 (49.2, 52.7) | 47.6 (45.1, 50.0) | 57.9 (54.8, 60.9) | |
| Race, % (95% CI) | | | | <0.001 |
| Non-Hispanic White | 62.9 (59.1, 66.6) | 63.7 (60.0, 67.2) | 61.2 (56.1, 66.3) | |
| Non-Hispanic Black | 10.9 (9.22, 12.9) | 12.6 (10.5, 14.9) | 7.56 (6.16, 9.23) | |
| Non-Hispanic Asian | 6.27 (5.12, 7.65) | 6.12 (4.89, 7.63) | 6.58 (5.38, 8.02) | |
| Mexican American | 9.56 (7.69, 11.8) | 8.09 (6.50, 10.0) | 12.6 (9.72, 16.1) | |
| Other Hispanic | 7.15 (5.86, 8.71) | 6.19 (4.94, 7.72) | 9.13 (7.33, 11.3) | |
| Multiracial | 3.18 (2.54, 3.98) | 3.34 (2.57, 4.32) | 2.86 (2.05, 3.99) | |
| Education, % (95% CI) | | | | 0.80 |
| <High school | 15.1 (13.4, 16.9) | 15.1 (13.4, 16.9) | 15.0 (12.8, 17.6) | |
| High school | 23.4 (21.7, 25.2) | 23.8 (21.8, 25.9) | 22.5 (19.9, 25.4) | |
| Some college | 31.7 (29.9, 33.5) | 31.4 (29.4, 33.4) | 32.2 (29.6, 34.9) | |
| College and above | 29.9 (27.3, 32.6) | 29.7 (27.2, 32.3) | 30.2 (26.4, 34.3) | |
| Income-to-poverty ratio, % (95% CI) | | | | 0.21 |
| <1 | 13.6 (12.3, 15.1) | 14.1 (12.6, 15.7) | 12.7 (10.8, 14.9) | |
| ≥1 | 86.4 (84.9, 87.7) | 85.9 (84.3, 87.4) | 87.3 (85.1, 89.2) | |
| Smoking status, % (95% CI) | | | | 0.014 |
| Never | 59.6 (57.7, 61.5) | 58.6 (56.5, 60.7) | 61.7 (58.8, 64.4) | |
| Former | 23.9 (22.4, 25.7) | 23.9 (22.1, 25.8) | 24.3 (21.6, 27.2) | |
| Current | 16.4 (14.9, 17.9) | 17.5 (15.8, 19.4) | 14.0 (12.6, 15.6) | |
| Alcohol consumption (g/day), mean (95% CI) | 1.59 (1.39, 1.78) | 1.59 (1.38, 1.81) | 1.58 (1.26, 1.90) | 0.94 |
| BMI (kg/m$^2$), mean (95% CI) | 29.4 (29.1, 29.7) | 28.3 (28.1, 28.6) | 31.6 (30.9, 32.1) | <0.001 |
| HOMA-IR, mean (95% CI) | 4.35 (3.94, 4.76) | 3.92 (3.36, 4.48) | 5.27 (3.37, 4.48) | <0.001 |
| Total urine arsenic (ug/L), mean (95% CI) | 5.69 (5.36, 6.03) | 5.59 (5.25, 5.92) | 5.92 (5.42, 6.41) | 0.13 |
| Alanine aminotransferase (U/L) mean (95% CI) | 24.5 (23.9, 24.9) | 17.8 (17.5, 18.1) | 38.1 (36.8, 39.4) | <0.001 |

[1]Weighted linear regression was used to compare continuous variables between participants with and without MASLD. Weighted chi-squared analysis was used to compare categorical variables between groups. BMI, body mass index; CI, confidence interval; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MASLD, metabolic dysfunction-associated steatotic liver disease.

in MASLD prevalence over the last three decades: 19% in 1988–1994, 32% in 1999–2016, and 54% in 2005–2016.[11] It is currently estimated that 25% of adults in the U.S. have MASLD.[12] While it often occurs with other metabolic conditions such as obesity, diabetes, and hypercholesterolemia,[13] its pathogenesis remains poorly understood. Animal experiments demonstrate that arsenic exposure contributes to liver injury.[14] Therefore, our aim in this study was to examine the association between arsenic exposure and MASLD in humans.

Using NHANES 2011–2020 data, we evaluated a total of 6,386 participants (after exclusions) with elevated levels of urinary inorganic arsenic and ALT but without other common risk factors for liver disease, including hepatitis B, hepatitis C, or alcohol use. Results showed higher mean arsenic levels of 5.92 µg/L in participants with MASLD versus 5.59 µg/L in those without. Other findings included a positive association between urinary arsenic exposure and MASLD, as well as increasing trends observed among Hispanics and among those with higher poverty-to-income ratios and higher BMI.

These results are consistent with literature indicating that Hispanics are especially susceptible to MASLD. A recent study found a MASLD prevalence of 41% among U.S. Hispanic adults, demonstrating a significantly higher risk for developing MASLD than among non-Hispanic adults.[15] Risk factors for developing

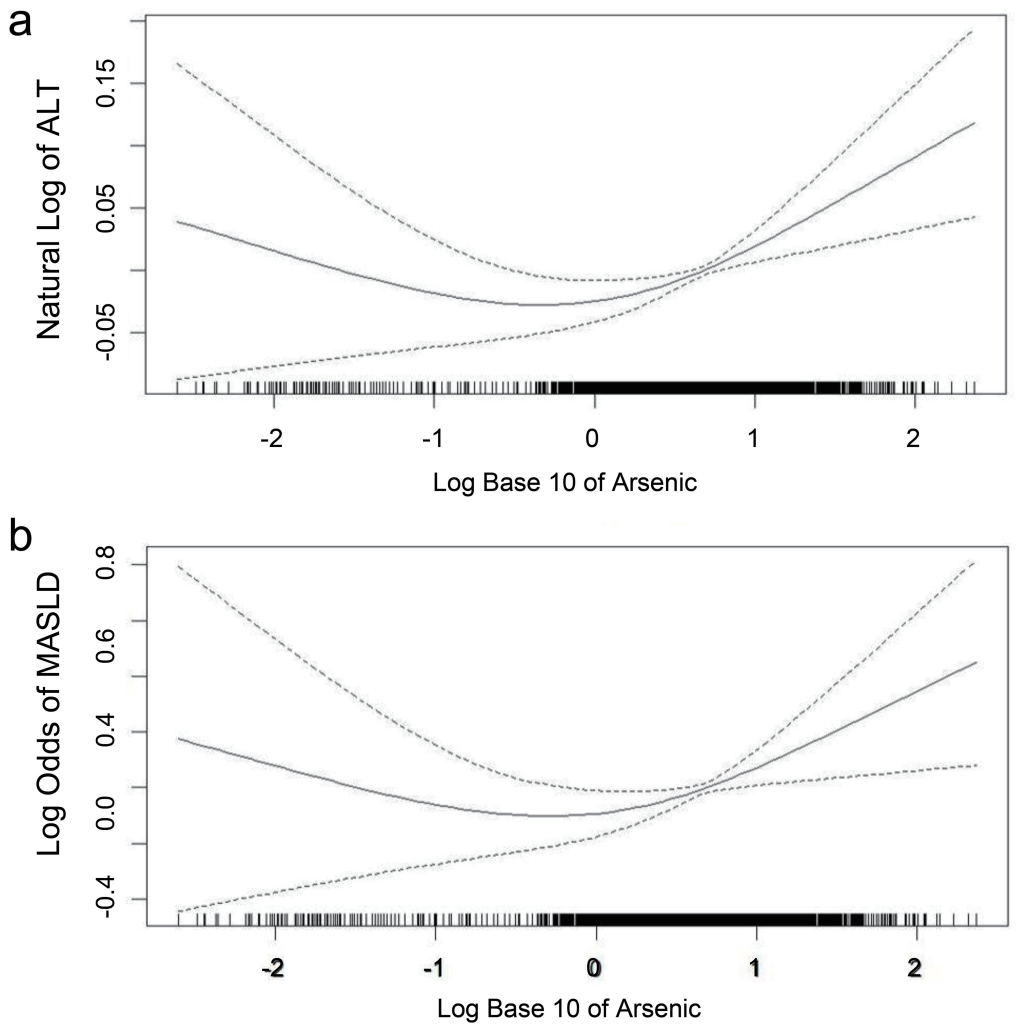


**Fig. 2. Generalized additive models assessing linearity between arsenic levels and ALT (a) and prevalence of MASLD (b), respectively.** Models were adjusted for age, sex, race/ethnicity, NHANES survey cycles, education, poverty-income ratio, body mass index, smoking status, and alcohol consumption. ALT, alanine aminotransferase; MASLD, metabolic dysfunction-associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey.

MASLD, such as obesity, diabetes, and poor diet, are common in Hispanic populations, as are associations with higher poverty-to-income ratios and higher BMI.[16] While these factors likely contribute to this disparity, little is known about how they specifically influence the development of MASLD. Recent research has shown a positive association between heavy metal exposure, including arsenic, and metabolic syndrome.[17] Furthermore, other research has demonstrated mechanisms by which arsenic may trigger metabolic

**Table 3. Adjusted percentage changes (95% CI) in serum ALT activity with quintile changes in urinary arsenic levels in the survey-weighted multivariable-adjusted linear regressions**

| ALT as outcome | Quintiles of urine arsenic levels (ug/L) | | | | | *p*-trend |
|---|---|---|---|---|---|---|
| | Quintile 1 (<2.036) | Quintile 2 (2.037–3.29) | Quintile 3 (3.30–5.00) | Quintile 4 (5.01–8.72) | Quintile 5 (>8.72) | |
| ALT mean (95% CI) | 24.7 (23.3, 26.1) | 24.1 (23.0, 25.2) | 25.1 (23.7, 26.4) | 24.7 (23.3, 26.1) | 23.4 (22.5, 24.3) | |
| Models[1] | | | | | | |
| Initial model[a] | REF | −0.53 (−5.53, 4.72) | 2.10 (−2.64, 7.08) | 3.43 (−0.93, 7.99) | 3.43 (−1.88, 9.03) | 0.036 |
| Full model[b] | REF | −1.13 (−6.41, 4.45) | 2.36 (−2.28, 7.21) | 5.80 (0.53, 11.4) | 7.22 (1.28, 13.5) | 0.001 |

[1]ALT has been log-transformed; [a]Initial model: adjusted for age, sex, race/ethnicity, and NHANES survey cycles; [b]Full model: initial model with additional adjustments for education, poverty-income ratio, body mass index, smoking status, and alcohol consumption. ALT, alanine aminotransferase; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

**Table 4. Adjusted ORs (95% CI) for the prevalence of MASLD with quintile changes in urinary arsenic levels in the survey-weighted multivariable-adjusted logistic regressions**

| MASLD as outcome | Quintiles of urine arsenic levels (ug/L) | | | | | *p*-trend |
|---|---|---|---|---|---|---|
| | Quintile 1 (<2.036) | Quintile 2 (2.037–3.29) | Quintile 3 (3.30–5.00) | Quintile 4 (5.01–8.72) | Quintile 5 (>8.72) | |
| MASLD, % (95% CI) | 29.9 (26.4, 33.7) | 30.9 (27.7, 34.4) | 33.1 (29.8, 36.6) | 35.7 (31.7, 39.9) | 35.9 (32.1, 39.8) | |
| Models | | | | | | |
| Initial model[a] | REF | 1.03 (0.78, 1.35) | 1.12 (0.89, 1.41) | 1.23 (0.98, 1.55) | 1.32 (1.04, 1.67) | 0.002 |
| Full model[b] | REF | 1.01 (0.75, 1.38) | 1.20 (0.92, 1.56) | 1.35 (1.02, 1.79) | 1.55 (1.19, 2.03) | <0.001 |

[a]Initial model: adjusted for age, sex, race/ethnicity, and NHANES survey cycles; [b]Full model: initial model with additional adjustments for education, poverty-income ratio, body mass index, smoking status, and alcohol consumption. CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey; ORs, odds ratios.

syndrome. In the liver, arsenic causes insulin resistance by reducing glucose transporter 2 protein levels and glycogen synthesis through inflammasome activation, as well as by promoting hepatic lipogenesis, which contributes to MASLD.[18–20]

The observed association between urinary arsenic and MASLD warrants consideration of exposure routes, particularly among high-risk populations such as Mexican Americans in our cohort. In the U.S., inorganic arsenic exposure occurs primarily through contaminated drinking water (notably private wells unregulated by the Safe Drinking Water Act) and dietary sources, including rice, cereals, and certain juices. Mexican Americans may face disproportionate exposure due to cultural dietary practices (e.g., higher rice consumption) and geographic factors (e.g., residing in regions with groundwater arsenic contamination). This aligns with NHANES data showing higher urinary arsenic levels in Mexican Americans compared to non-Hispanic whites.[21–23]

While our study lacked granular dietary or residential water data, prior work links these exposure pathways to liver injury. For example, experimental studies suggest that inorganic arsenic exacerbates hepatic steatosis by disrupting lipid metabolism and promoting oxidative stress. Public health interventions, such as targeted screening of groundwater, dietary education, and regulatory action on food arsenic limits, could help mitigate risks in vulnerable subgroups. Future studies should integrate geospatial water quality data and food frequency questionnaires to refine exposure assessment.[24,25]

These findings suggest arsenic may play a role in the multifactorial origins of metabolic syndrome.[26] In conjunction with our findings that factors associated with metabolic syndrome are showing increasing trends in MASLD, continued research is warranted to better understand the pathogenesis of this disease process, to study different levels of arsenic exposure, and to monitor for early signs of metabolic dysfunction that could prevent progression to MASLD. Additionally, research into the development of pharmacotherapy targeting the metabolic issues central to MASLD is needed to help slow disease progression.

Urinary arsenic concentrations below the limit of detection (LOD) were imputed as LOD/√2, consistent with the approach recommended by Hornung and Reed (1990) for left-censored data in environmental exposure studies. This method assumes a log-normal distribution of exposure values below the LOD and minimizes bias in mean estimates compared to alternatives (e.g., substitution with zero or LOD). However, misclassification may still occur if the true distribution deviates from this assumption, particularly for analytes with high proportions of non-detects. Sensitivity analyses using alternative substitution methods (e.g., LOD/2 or multiple imputation) were explored and yielded materially similar results (data not shown), supporting the robustness of our primary approach.[27]

The NHANES data are cross-sectional, precluding temporal assessments of arsenic exposure and MASLD development. While our findings align with experimental evidence linking arsenic to hepatic steatosis, reverse causality (e.g., MASLD altering arsenic metabolism) cannot be ruled out. Longitudinal studies with repeated exposure measurements are needed to establish causality. Reliance on ALT elevation as a surrogate for MASLD may underestimate prevalence, as ALT levels can be normal in early steatosis or fluctuate with non-metabolic conditions (e.g., viral hepatitis). Imaging- or biopsy-confirmed MASLD would improve specificity but was unavailable in NHANES. NHANES lacks data on occupational arsenic exposure (e.g., mining, agriculture), which could covary with both dietary intake and liver injury. Polymorphisms in arsenic-metabolizing genes (*AS3MT*, *GSTO1*) influence toxicity risk but were not assessed. NHANES excludes institutionalized populations (e.g., incarcerated individuals, long-term care residents) and underrepresents rural communities with high arsenic exposure (e.g., well-dependent households). Mexican Americans were oversampled, but results may not extend to other Hispanic subgroups or global populations with differing exposure patterns.

Longitudinal designs with repeated arsenic measurements and imaging-confirmed MASLD (e.g., FibroScan, magnetic resonance imaging-proton density fat fraction) are needed to establish temporality and dose-response relationships. Mechanistic studies should clarify arsenic's role in hepatic lipid metabolism (e.g., PPAR-γ activation, mitochondrial dysfunction). Gene-environment interaction studies exploring polymorphisms in arsenic metabolism (AS3MT) and MASLD susceptibility are warranted. While limited by its cross-sectional design, this study underscores the need to integrate environmental hepatotoxins into MASLD risk stratification frameworks.

## Conclusions

In this nationally representative study, higher urinary arsenic levels were significantly associated with a 55% increased odds of MASLD (95% CI: 1.2–2.0) in the highest quintile, independent of traditional metabolic risk factors. These findings persist across key subgroups, suggesting arsenic may contribute to hepatic steatosis even at moderate exposure levels typical in the U.S. population. Screening for arsenic exposure (e.g., urinary biomarkers, well-water testing) in high-risk regions (e.g., Southwest U.S.) could identify populations for targeted liver disease prevention. Regulatory efforts to reduce arsenic in food and water supplies (e.g.,

U.S. Food and Drug Administration limits for rice products) may concurrently mitigate the MASLD burden.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

Reference collection, writing of the manuscript (SC), writing of the discussion section (AJ, WG), data statistics (PK), table generation (SC, PK), review, and revision (JR). All authors reviewed and approved the final manuscript.

## Ethical statement

This study was carried out in accordance with the Helsinki Declaration (as revised in 2024). Institutional Review Board approval and the individual consent were waived as the data were collected from public databases.

## Data sharing statement

Data were collected from PubMed and Google Scholar.

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