



# Associations of arsenic exposure with liver injury in US adults: NHANES 2003–2018

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## Abstract

Arsenic is a natural element with complex toxicity. Long-term exposure to arsenic can cause a variety of health damage. In recent years, there are some studies on arsenic exposure and liver injury. But few of them tried to measure the quantitative relationship between arsenic exposure and indicators of liver injury in adult. Therefore, this study aimed to elucidate the relationship between them. This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) in 2003–2018. Arsenic exposure was assessed using total urinary arsenic and dimethylarsenate acid (DMA). We selected alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total protein (TP), ALT/AST, total bilirubin (TBIL), and albumin (ALB) as markers of liver injury. Multiple linear regression was used to explore the relationship between urinary arsenic concentrations and these markers of liver function injury. In addition, six covariables (age, sex, smoker, alcohol user, BMI, diabetes) were further analyzed in subgroups. A total of 13,420 adults were included in the analysis. The multivariate linear regression analyses showed that urinary DMA was positively correlated with ALT ( $\beta$  0.135, 95%CI 0.090, 0.180,  $p < 0.001$ ), AST ( $\beta$  0.053, 95%CI 0.014, 0.092,  $p < 0.01$ ), ALT/AST ( $\beta$  0.052, 95%CI 0.030, 0.074,  $p < 0.001$ ), TBIL ( $\beta$  0.061, 95%CI 0.034, 0.089,  $p < 0.001$ ), and GGT ( $\beta$  0.178, 95%CI 0.110, 0.246,  $p < 0.001$ ). Similar results were observed for total urinary arsenic, suggesting a positive association with AST ( $\beta$  0.048, 95%CI 0.016, 0.081,  $p < 0.01$ ), ALT ( $\beta$  0.090, 95%CI 0.049, 0.132,  $p < 0.001$ ), and TBIL ( $\beta$  0.062, 95%CI 0.037, 0.088,  $p < 0.001$ ). In subgroup analysis, sex and smoker showed significant differences between subgroups. Our results demonstrate a positive association between urinary arsenic exposure and liver injury in adults. Sex and smokers may be related to arsenic pathogenicity.

**Keywords** Urinary arsenic · DMA · Liver injury · NHANES · Adults

## Abbreviations

ALB	Albumin	GGT	Gamma-glutamyl transferase
ALT	Alanine aminotransferase	HDL-C	High-density lipoprotein cholesterol
AST	Aspartate aminotransferase	LFTs	Liver function tests
BMI	Body mass index	NHANES	National Health and Nutrition Examination Survey
DMA	Dimethylarsenate acid	TBIL	Total bilirubin

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## Introduction

The liver is the largest anabolic organ in the human body, as well as the largest and most complex enzymatic activity system, responsible for the decomposition, transformation, and detoxification of various endogenous and exogenous substances (Trefts et al. 2017). Studies have shown that genetics and lifestyle can lead to liver injury, but in recent years, environmental chemicals may play an important role in liver function injury, such as urinary phthalate

metabolism and fluoride exposure. There are some studies on arsenic exposure and liver injury, but few of them tried to measure the quantitative relationship between arsenic exposure and indicators of liver injury in adult (Malin et al. 2019; Yu et al. 2021).

Arsenic, one of the heavy metals, is known for its oxide arsenic trioxide, which is effective in the treatment of acute promyelocytic leukemia. However, in today's era of rapid industrial development and severe environmental damage, it has become the most common environmental toxin (Garbinski et al. 2019). According to a prospective cohort study in Bangladesh, high levels of arsenic exposure in drinking water were associated with an increased risk of cardiovascular disease (Chen et al. 2011). Ana Navas-Acien et al. found that total urinary arsenic was associated with an increased incidence of diabetes in a cross-sectional study in the USA (Navas-Acien et al. 2008). Arsenic can cause liver injury through a variety of ways, including oxidative stress, and inducing apoptosis, etc. (Garcia-Nino and Pedraza-Chaverri 2014). A large number of studies have shown that long-term exposure to arsenic can promote liver fibrosis in human liver, leading to non-alcoholic fatty liver, hepatitis, and even liver cancer. Several large-scale epidemiological studies in Taiwan (Lin et al. 2013), the USA (Garcia-Esquinas et al. 2013), and northern Chile (Liaw et al. 2008) have shown that long-term exposure to arsenic increased the risk of liver cancer death. However, in the current study, there is still a lack of large-scale, standardized epidemiological studies to deeply observe the specific quantitative relationship between arsenic exposure and liver injury.

The National Health and Nutrition Examination Survey (NHANES) (<https://www.cdc.gov/nchs/nhanes/index.htm>) is a large crowd research project dominated by the National Center for Health Statistics (NCHS) to assess the adults and children health and nutrition. In our study, we used this large, multi-stage, nationally representative study to determine whether there is a clear relationship between arsenic exposure and liver injury in the adults, hoping to provide reference for the prevention of such hazards in the future.

## Materials and methods

### Study population

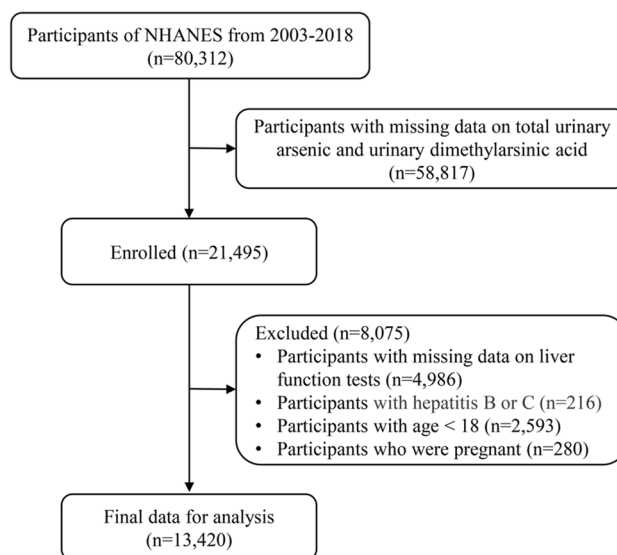
The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey to assess the health and nutritional status of non-institutionalized people in the USA. The survey used a stratified, multi-stage probability design to recruit a representative sample of the US adults (<https://www.cdc.gov/nchs/nhanes/default.aspx>). All participants provided written informed consent, and study

procedures were approved by the National Center for Health Statistics Research Ethics Review Board.

There were totally 80,312 subjects participated in NHANES from 2003 to 2018. We screened out 21495 samples with complete data of total urinary arsenic and urine DMA. We excluded participants with self-reported pregnancy ( $n=280$ ), with hepatitis B or C ( $n=216$ ), with missing data on liver function tests (LFTs,  $n=4986$ ), or under 18 years of age ( $n=2593$ ). A total of 13,420 participants were included in the final analysis (Fig. 1).

### Measurement of urinary arsenic

Urine samples for heavy metal analysis were obtained at the physical examination site, packed in arsenic-free containers, transported with dry ice, frozen at  $-70^{\circ}\text{C}$  or lower, and analyzed within 3 weeks of sampling (Davis et al. 2012). Total arsenic and arsenic species were measured at the Environmental Health Sciences Laboratory of the National Center for Environmental Health following a standardized protocol (Centers for Disease Control and Prevention (CDC)) (Chen et al. 2011). Total urinary arsenic concentrations were determined via inductively coupled plasma-mass spectrometry with dynamic reaction cell (ICP-DRC-MS), and speciated arsenic concentrations were measured via high performance liquid chromatography (HPLC) coupled to ICP-MS (Sanders et al. 2019). We used DMA, a major metabolite of inorganic arsenic in humans, and total urinary arsenic to reflect people's exposure to arsenic. Inter-assay coefficients of variation for DMA and total arsenic were 2.2–6.0% and 1.0–19.4%,



**Fig. 1** Study flowchart. Eligible participants and those included in the analyses of the associations between arsenic exposure and liver function parameters in adults. NHANES, National Health and Nutrition Examination Survey

respectively. The limit of detection (LOD) of DMA varied ranged from 1.70 to 1.91  $\mu\text{g/L}$  and total arsenic from 0.26 to 0.74  $\mu\text{g/L}$ . Samples that cannot be measured below the LOD were estimated as the LOD divided by the square root of two. The NHANES database also provides five other indicators (arsenobetaine, arsenocholine, monomethylarsonic acid, arsenous (III) acid, and arsenic (V) acid) of arsenic exposure. However, due to their high limit of detection (LOD) or their excessive low concentrations in human body, we did not choose them as primary biomarkers of arsenic exposure.

### Measurement of liver function

ALT and AST were liver enzyme parameters, and when hepatocytes were necrotic or hepatocyte membranes were damaged, they were released into the blood in large quantities, raising their concentration in serum. ALT/AST was the ratio of ALT and AST concentration, which was a sensitive indicator of liver injury (Xie et al. 2019). Serum TBIL concentration was affected by the balance between bilirubin production and clearance, and hepatocytes were the main site of bilirubin clearance (Yu et al. 2021). Therefore, elevated serum bilirubin levels usually indicate liver injury or obstruction of the bile duct. GGT were markers of cholestasis (Lozano-Paniagua et al. 2021). ALB reflected the synthetic ability of the liver, and its expression decreases significantly with the decrease of the synthetic ability of the liver (Woreta and Alqahtani 2014).

Serum LFTs were determined by Beckman Coulter DxS 800 Synchron clinical system. ALT, AST, and GGT activities were measured by kinetic rate method, TBIL was measured by timing end point diazo method, ALB was quantified by two-color digital end point method, and TP was measured by timing rate biuret method (Xiang et al. 2022).

### Assessment of covariates

Based on the results of previous studies, our study included three types of covariates, including demographic variables, lifestyle variables, and some clinical characteristics related to liver function. Finally, we selected age, sex, education level, race/ethnicity, poverty, smoker, alcohol user, diabetes, body mass index (BMI), high-density lipoprotein cholesterol (HDL-C), total cholesterol, energy intake, and urinary creatinine. The information of the first eight covariates was obtained through questionnaires and family interviews. The education level was divided into below high school, high school, and above high school. And race includes Mexican American, Other Hispanic, non-Hispanic White, non-Hispanic Black, and other race. When the value of the family was less than 1, the family income-to-poverty ratio was introduced to measure poverty. Alcohol users were defined as those who consumed at least 12 alcoholic beverages in a

year (Lazo et al. 2011). Smokers were defined as having a serum cotinine value  $> 14 \text{ ng/mL}$  (Lin et al. 2014). BMI was weight divided by height squared. BMI, HDL-C, total cholesterol, and urinary creatinine were evaluated by authoritative medical personnel and institutions. Participants were interviewed by certified dietary interviewers and completed a 24-h dietary recall. Their energy intake was calculated based on nutritional database data from the University of Minnesota Nutrition Coordinating Center. Description of each variable can be found in <https://wwwn.cdc.gov/Nchs/Nhanes/continuousnhanes/>.

### Statistical analysis

According to the CDC guidelines (<https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx>), weighted analysis was used to generate accurate estimates nationally, adjusting for the oversampling of minority subgroups. Continuous variables were expressed in median (quartile range) and categorical variables in absolute value (percentage).

Two sequential multiple linear regression models with increasing levels of adjustment for confounding variables were used to calculate the regression coefficient ( $\beta$ ) and 95% confidence intervals (CIs) for the association between urinary arsenic and several liver function indicators: Model 1 was adjusted for age, sex, education level, and race; model 2 was adjusted as model 1 plus poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, HDL-C, urinary creatinine, and diabetes. Crude model (unadjusted model) was also built at the same time. We used two indexes of urine DMA and total urine arsenic for regression analysis, respectively. Two linear regression analyses with Log2 converted continuous and categorical variables were performed to explore the association of arsenic exposure with liver injury. The concentrations of arsenic compounds were divided into four gradients by quartile and median, and the liver function indicator corresponding to the lowest quartile was used as a reference value to judge the trend of change and the amount of liver function indicator with increasing content. Furthermore, by observing the  $\beta$  values obtained by comparing quartiles 2–4 with 1, a trend analysis was conducted for liver injury indexes with obvious gradient changes, and the  $P$  values for the trend were also plotted in the table.

Subgroup analysis was then performed to investigate whether several covariables affected the relationship between urinary DMA or total urinary arsenic and liver function test results. Age, sex, smoker, alcohol user, BMI, and diabetes were selected as grouping variables. Age was divided into “ $> 60$  years old” and “ $< 60$  years old.” BMI was divided into “ $< 24.9$ ,” “ $24.9\text{--}29.9$ ,” and “ $> 29.9$ .” The regression coefficient ( $\beta$ ) and the 95%CI for the association between urinary arsenic and several indicators of liver

function were also calculated. All analyses were adjusted for covariates age, sex, education level, race, poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, HDL-C, urinary creatinine, diabetes, and hypertension when they were not the stratified variables.

All statistical analyses were conducted by using R Statistical Software (version 4.1.0). Significance was set at  $P < 0.05$  (two-sided).

## Results

### Subjects' characteristics

A total of 13,420 samples were included in our study. In addition to collecting basic data, we also used sample weights to recalculate demographic data to make our sample more representative of the population. Table 1 lists the general characteristics, clinical indicators, and urinary arsenic metabolites of the study participants. The median age (IQR) of the study population was 46.0 (32.0, 59.0), and the number of men and women was almost the same. And most of the subjects had received high school education (59.8%). In terms of race, non-Hispanic White (68.0%) dominated. In addition, smoker and average BMI levels were higher in this group. In terms of liver function indicators, the median values of ALT, AST, ALT/AST, and GGT were 23.0, 21.0, 0.9, and 19.0, respectively. Other secondary indicators (total bilirubin, albumin, total protein) were also within the normal range (Table 1).

### Multiple linear regression associations of urinary DMA with LFTs in adults

Firstly, log<sub>2</sub>-transformed urinary DMA was used as a continuous variable to explore its relationship with liver function. In the crude model, we found that AST ( $\beta$  0.021, 95%CI 0.012, 0.031,  $p < 0.001$ ), ALT ( $\beta$  0.049, 95%CI 0.037, 0.062,  $p < 0.001$ ), ALT/AST ( $\beta$  0.020, 95%CI 0.014, 0.026,  $p < 0.001$ ), GGT ( $\beta$  0.065, 95%CI 0.046, 0.084,  $p < 0.001$ ), TBIL ( $\beta$  0.025, 95%CI 0.017, 0.032,  $p < 0.001$ ), and TP ( $\beta$  0.021, 95%CI 0.012, 0.030,  $p < 0.001$ ) were positively related to DMA. In model 2, AST ( $\beta$  0.022, 95%CI 0.009, 0.034,  $p < 0.001$ ), ALT ( $\beta$  0.049, 95%CI 0.035, 0.064,  $p < 0.001$ ), ALT/AST ( $\beta$  0.017, 95%CI 0.010, 0.025,  $p < 0.001$ ), GGT ( $\beta$  0.051, 95%CI 0.029, 0.073,  $p < 0.001$ ), and TBIL ( $\beta$  0.024, 95%CI 0.015, 0.032,  $p < 0.001$ ) were all found having positive relationship with urinary DMA. Then, this independent variable was divided into quartiles, and the lowest quartile was used as a reference class to assess the relationship between levels and various indicators of liver function. We used quartile 4 to compare with the reference group (quartile 1) in model 1 and found that

**Table 1** Survey-weighted, sociodemographic and health status characteristics of adult NHANES 2003–2018 participants with available data ( $n = 13,420$ )

Variable	Median (IQR) or N (%)
Age, years	46.0 (32.0, 59.0)
Male, %	6719 (48.9)
Education level, %	
Below high school	3415 (16.4)
High school	3091 (23.8)
Above high school	6914 (59.8)
Race/ethnicity, %	
Mexican American	2317 (8.7)
Other Hispanic	1211 (5.4)
Non-Hispanic White	5705 (68.0)
Non-Hispanic Black	2799 (10.8)
Other race	1388 (7.1)
Poverty, %	2846 (14.4)
Smoker, %	3191 (24.6)
Alcohol user, %	9351 (75.0)
Body mass index, kg/m <sup>2</sup>	27.7 (24.0, 32.3)
HDL-C, mg/dL	51.0 (42.2, 63.0)
Total cholesterol, mg/dL	191.0 (164.0, 219.0)
Energy intake, kcal/day	2026.0 (1514.0, 2692.0)
Urinary creatinine, mg/dL	104.0 (58.0, 164.0)
Diabetes, %	1579 (8.8)
AST, U/L	23.0 (19.0, 27.0)
ALT, U/L	21.0 (16.0, 28.0)
ALT/AST	0.9 (0.8, 1.1)
GGT, U/L	19.0 (14.0, 29.0)
Total bilirubin, mg/dL	0.6 (0.5, 0.8)
Albumin, g/dL	4.3 (4.1, 4.5)
Total protein, g/dL	7.1 (6.8, 7.4)
Total urinary arsenic, ug/L	6.9 (3.5, 14.8)
Urinary dimethylarsinic acid, ug/L	3.3 (1.9, 5.6)

Data are presented as median (IQR) or  $n$  (%); Sampling weights were applied for calculation of demographic descriptive statistics;  $N$  reflect the study sample, while percentages reflect the survey-weighted. *IQR*, interquartile range; *HDL-C*, high-density lipoprotein cholesterol; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *GGT*, gamma-glutamyl transferase

urinary DMA was significantly positively associated with ALT, AST, ALT/AST, TBIL, and GGT and negatively correlated with ALB. After further adjustment to model 2, all liver function markers still maintained the same relationship with urinary DMA (ALT ( $\beta$  0.135, 95%CI 0.090, 0.180,  $p < 0.001$ ), AST ( $\beta$  0.053, 95%CI 0.014, 0.092,  $p < 0.01$ ), ALT/AST ( $\beta$  0.052, 95%CI 0.030, 0.074,  $p < 0.001$ ), TBIL ( $\beta$  0.061, 95%CI 0.034, 0.089,  $p < 0.001$ ), and GGT ( $\beta$  0.178, 95%CI 0.110, 0.246,  $p < 0.001$ )). Significance remained even when quartile 3 was used for comparison with the reference group. Except for ALB, the negative correlation with

urinary DMA disappeared after further adjustment. Notably, TP levels were never associated with urinary dimethylarsinic (Table 2).

### Multiple linear regression associations of total urinary arsenic with LFTs in adults

Next, the relationship between total urinary arsenic and liver injury was explored. When set to a continuous variable, log<sub>2</sub>-transformed total urinary arsenic was positively related to AST ( $\beta$  0.011, 95%CI 0.005, 0.018,  $p < 0.01$ ), ALT ( $\beta$  0.022, 95%CI 0.014, 0.031,  $p < 0.001$ ), ALT/AST ( $\beta$  0.007, 95%CI 0.003, 0.011,  $p < 0.001$ ), and GGT ( $\beta$  0.029, 95%CI 0.016, 0.041,  $p < 0.001$ ) and negatively related to ALB ( $\beta$  -0.005, 95%CI -0.009, -0.001,  $p < 0.05$ ) in the crude model. When adjusted to model 2, we found AST ( $\beta$  0.009, 95%CI 0.002, 0.017,  $p < 0.05$ ), ALT ( $\beta$  0.021, 95%CI 0.012, 0.030,  $p < 0.001$ ), ALT/AST ( $\beta$  0.007, 95%CI 0.002, 0.012,  $p < 0.01$ ), GGT ( $\beta$  0.017, 95%CI 0.003, 0.030,  $p < 0.05$ ), and TBIL ( $\beta$  0.014, 95%CI 0.009, 0.020,  $p < 0.001$ ) having

positive relationship with total urinary arsenic. Then we divided log<sub>2</sub>-transformed total urinary arsenic into quartiles, too. In model 1, when quartile 4 was compared with reference quartile, total urinary arsenic was still positively correlated with AST, ALT, and TBIL, but negatively correlated with ALB. ALT/AST, GGT, and TP levels did not fluctuate significantly with the change of total urinary arsenic. The results were similar in model 2, as AST ( $\beta$  0.048, 95%CI 0.016, 0.081,  $p < 0.01$ ), ALT ( $\beta$  0.090, 95%CI 0.049, 0.132,  $p < 0.001$ ) and TBIL ( $\beta$  0.062, 95%CI 0.037, 0.088,  $p < 0.001$ ) also increased when total arsenic upgraded, but ALB did not decrease significantly (Table 3).

### Subgroup analysis for the associations between urinary arsenic and LFTs in adults

We have fully found a positive association between elevated urinary arsenic levels and liver injury in the population. Given the heterogeneity of the population, it was necessary to clarify whether various demographic

**Table 2** Multiple linear regression associations of urinary dimethylarsinic acid (DMA) with liver function tests (LFTs) in adults

LFTs	Model	Continuous log <sub>2</sub> -transformed DMA	Quartile 1 $\beta$	Quartile 2 $\beta$ (95%CI)	Quartile 3 $\beta$ (95%CI)	Quartile 4 $\beta$ (95%CI)	<i>p</i> - <i>t</i>
AST	Crude	0.021 (0.012, 0.031) <sup>***</sup>	0.00 (Ref.)	0.018 (-0.010, 0.047)	0.052 (0.023, 0.081) <sup>***</sup>	0.054 (0.023, 0.084) <sup>***</sup>	<0.001
	Model 1	0.015 (0.006, 0.025) <sup>**</sup>	0.00 (Ref.)	0.003 (-0.025, 0.032)	0.027 (-0.001, 0.055)	0.036 (0.006, 0.066) <sup>*</sup>	0.008
	Model 2	0.022 (0.009, 0.034) <sup>***</sup>	0.00 (Ref.)	0.015 (-0.016, 0.046)	0.041 (0.006, 0.077) <sup>*</sup>	0.053 (0.014, 0.092) <sup>**</sup>	0.004
ALT	Crude	0.049 (0.037, 0.062) <sup>***</sup>	0.00 (Ref.)	0.069 (0.028, 0.111) <sup>**</sup>	0.125 (0.082, 0.167) <sup>***</sup>	0.141 (0.101, 0.181) <sup>***</sup>	<0.001
	Model 1	0.032 (0.020, 0.045) <sup>***</sup>	0.00 (Ref.)	0.034 (-0.005, 0.073)	0.063 (0.022, 0.103) <sup>**</sup>	0.092 (0.053, 0.129) <sup>***</sup>	<0.001
	Model 2	0.049 (0.035, 0.064) <sup>***</sup>	0.00 (Ref.)	0.053 (0.012, 0.094) <sup>*</sup>	0.094 (0.047, 0.141) <sup>***</sup>	0.135 (0.090, 0.180) <sup>***</sup>	<0.001
ALT/AST	Crude	0.020 (0.014, 0.026) <sup>***</sup>	0.00 (Ref.)	0.006 (0.020, 0.059) <sup>***</sup>	0.049 (0.030, 0.068) <sup>***</sup>	0.062 (0.044, 0.081) <sup>***</sup>	<0.001
	Model 1	0.012 (0.006, 0.018) <sup>***</sup>	0.00 (Ref.)	0.024 (0.005, 0.042) <sup>*</sup>	0.022 (0.004, 0.040) <sup>*</sup>	0.038 (0.020, 0.056) <sup>***</sup>	<0.001
	Model 2	0.017 (0.010, 0.025) <sup>***</sup>	0.00 (Ref.)	0.027 (0.008, 0.045) <sup>**</sup>	0.030 (0.009, 0.050) <sup>***</sup>	0.052 (0.030, 0.074) <sup>***</sup>	<0.001
GGT	Crude	0.065 (0.046, 0.084) <sup>***</sup>	0.00 (Ref.)	0.109 (0.052, 0.166) <sup>***</sup>	0.122 (0.070, 0.175) <sup>***</sup>	0.220 (0.158, 0.282) <sup>***</sup>	<0.001
	Model 1	0.039 (0.021, 0.058) <sup>***</sup>	0.00 (Ref.)	0.062 (0.009, 0.116) <sup>*</sup>	0.047 (-0.004, 0.099)	0.147 (0.088, 0.205) <sup>***</sup>	<0.001
	Model 2	0.051 (0.029, 0.073) <sup>***</sup>	0.00 (Ref.)	0.070 (0.014, 0.127) <sup>*</sup>	0.064 (0.005, 0.122) <sup>*</sup>	0.178 (0.110, 0.246) <sup>***</sup>	<0.001
TBIL	Crude	0.025 (0.017, 0.032) <sup>***</sup>	0.00 (Ref.)	0.017 (-0.002, 0.037)	0.062 (0.043, 0.080) <sup>***</sup>	0.064 (0.041, 0.088) <sup>***</sup>	<0.001
	Model 1	0.022 (0.016, 0.029) <sup>***</sup>	0.00 (Ref.)	0.006 (-0.013, 0.026)	0.045 (0.027, 0.063) <sup>***</sup>	0.058 (0.036, 0.079) <sup>***</sup>	<0.001
	Model 2	0.024 (0.015, 0.032) <sup>***</sup>	0.00 (Ref.)	0.014 (-0.007, 0.035)	0.051 (0.028, 0.075) <sup>***</sup>	0.061 (0.034, 0.089) <sup>***</sup>	<0.001
TP	Crude	0.021 (0.012, 0.030) <sup>***</sup>	0.00 (Ref.)	0.001 (-0.025, 0.028)	0.013 (-0.013, 0.041)	0.061 (0.033, 0.090) <sup>***</sup>	<0.001
	Model 1	-0.001 (-0.010, 0.007)	0.00 (Ref.)	-0.023 (-0.049, 0.002)	-0.022 (-0.047, 0.004)	-0.006 (-0.032, 0.021)	-
	Model 2	0.006 (-0.005, 0.017)	0.00 (Ref.)	-0.008 (-0.038, 0.022)	-0.002 (-0.034, 0.031)	-0.014 (-0.020, 0.043)	-
ALB	Crude	-0.005 (-0.011, 0.001)	0.00 (Ref.)	-0.020 (-0.040, -0.001) <sup>*</sup>	0.001 (-0.016, 0.020)	-0.021 (-0.043, -0.001) <sup>*</sup>	--
	Model 1	-0.010 (-0.016, -0.005) <sup>***</sup>	0.00 (Ref.)	-0.036 (-0.054, -0.018) <sup>***</sup>	-0.021 (-0.038, -0.004) <sup>*</sup>	-0.039 (-0.058, -0.020) <sup>***</sup>	-
	Model 2	0.003 (-0.007, 0.007)	0.00 (Ref.)	-0.004 (-0.024, 0.015)	-0.018 (-0.034, 0.039)	-0.001 (-0.024, 0.025)	-

Model 1 was adjusted for age, sex, education level, and race. Model 2 was adjusted as model 1 plus poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, high-density lipoprotein cholesterol, urinary creatinine, and diabetes. LFTs include aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALT/AST, gamma-glutamyl transferase (GGT), total bilirubin (TBIL), albumin (ALB), and total protein (TP). CI, confidence interval; Ref., reference; *p*-*t*, *p* for trend;

\*  $p < 0.05$ , \*\*  $p < 0.01$ , and \*\*\*  $p < 0.001$



**Table 3** Multiple linear regression associations of total urinary arsenic with liver function tests (LFTs) in adults

LFTs	Model	Continuous log2-trans- formed total urinary arsenic	Quartile 1 $\beta$	Quartile 2 $\beta$ (95%CI)	Quartile 3 $\beta$ (95%CI)	Quartile 4 $\beta$ (95%CI)	<i>p-t</i>
AST	Crude	0.011 (0.005, 0.018)**	0.00 (Ref.)	0.013 (−0.015, 0.042)	0.044 (0.010, 0.078)*	0.055 (0.026, 0.085)***	<0.001
	Model 1	0.007 (0.001, 0.013)*	0.00 (Ref.)	0.001 (−0.026, 0.028)	0.022 (−0.009, 0.054)	0.037 (0.009, 0.065)**	0.006
	Model 2	0.009 (0.002, 0.017)*	0.00 (Ref.)	0.009 (−0.021, 0.040)	0.030 (−0.007, 0.066)	0.048 (0.016, 0.081)**	0.002
ALT	Crude	0.022 (0.014, 0.031)***	0.00 (Ref.)	0.043 (−0.006, 0.093)	0.084 (0.037, 0.132)***	0.096 (0.055, 0.137)***	<0.001
	Model 1	0.013 (0.004, 0.021)**	0.00 (Ref.)	0.012 (−0.035, 0.059)	0.035 (−0.007, 0.077)	0.057 (0.017, 0.096)**	0.003
	Model 2	0.021 (0.012, 0.030)***	0.00 (Ref.)	0.022 (−0.026, 0.070)	0.053 (0.007, 0.099)*	0.090 (0.049, 0.132)***	<0.001
ALT/AST	Crude	0.007 (0.003, 0.011)***	0.00 (Ref.)	0.024 (−0.002, 0.051)	0.027 (0.004, 0.049)*	0.026 (0.005, 0.047)*	-
	Model 1	0.003 (−0.001, 0.008)	0.00 (Ref.)	0.010 (−0.017, 0.036)	0.006 (−0.016, 0.027)	0.010 (−0.011, 0.031)	-
	Model 2	0.007 (0.002, 0.012)**	0.00 (Ref.)	0.008 (−0.017, 0.034)	0.010 (−0.013, 0.034)	0.022 (−0.001, 0.046)	-
GGT	Crude	0.029 (0.016, 0.041)***	0.00 (Ref.)	0.039 (−0.015, 0.095)	0.075 (0.014, 0.136)*	0.117 (0.061, 0.172)***	<0.001
	Model 1	0.010 (−0.002, 0.022)	0.00 (Ref.)	−0.006 (−0.057, 0.045)	−0.001 (−0.056, 0.054)	0.038 (−0.013, 0.088)	-
	Model 2	0.017 (0.003, 0.030)*	0.00 (Ref.)	−0.016 (−0.069, 0.036)	−0.007 (−0.068, 0.054)	0.054 (−0.003, 0.112)	-
TBIL	Crude	0.018 (0.013, 0.023)	0.00 (Ref.)	0.012 (−0.008, 0.033)	0.058 (0.038, 0.079)***	0.080 (0.057, 0.102)***	<0.001
	Model 1	0.016 (0.011, 0.020)***	0.00 (Ref.)	0.004 (−0.017, 0.024)	0.046 (0.027, 0.064)***	0.070 (0.050, 0.091)***	<0.001
	Model 2	0.014 (0.009, 0.020)***	0.00 (Ref.)	0.004 (−0.021, 0.029)	0.042 (0.018, 0.066)***	0.062 (0.037, 0.088)***	<0.001
TP	Crude	0.006 (−0.001, 0.0125)	0.00 (Ref.)	0.018 (−0.006, 0.043)	0.023 (−0.002, 0.049)	0.039 (0.009, 0.068)**	<0.001
	Model 1	−0.004 (−0.010, 0.002)	0.00 (Ref.)	−0.013 (−0.037, 0.011)	−0.010 (−0.036, 0.014)	−0.005 (−0.032, 0.022)	-
	Model 2	−0.001 (−0.008, 0.006)	0.00 (Ref.)	−0.001 (−0.029, 0.028)	0.005 (−0.026, 0.035)	0.011 (−0.020, 0.043)	-
ALB	Crude	−0.005 (−0.009, −0.001)*	0.00 (Ref.)	−0.019 (−0.044, 0.005)	0.001 (−0.020, 0.021)	−0.013 (−0.033, 0.007)	-
	Model 1	−0.006 (−0.010, −0.003)**	0.00 (Ref.)	−0.032 (−0.056, −0.009)**	−0.012 (−0.033, 0.009)	−0.021 (−0.040, −0.002)*	-
	Model 2	−0.002 (−0.007, 0.003)	0.00 (Ref.)	−0.007 (−0.031, 0.017)	0.015 (−0.009, 0.038)	−0.002 (−0.022, 0.026)	-

Model 1 was adjusted for age, sex, education level, and race. Model 2 was adjusted as model 1 plus poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, high-density lipoprotein cholesterol, urinary creatinine, and diabetes. LFTs include aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALT/AST, gamma-glutamyl transferase (GGT), total bilirubin (TBIL), albumin (ALB), and total protein (TP). *CI*, confidence interval; *Ref.*, reference; *p-t*, *p* for trend

\*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$

and clinical characteristics have a synergistic or antagonistic role in the process of arsenic-induced liver injury. Therefore, age, sex, smoker, alcohol user, BMI, diabetes, and other factors were selected as the basis for grouping, and subgroup analysis was performed to clarify differences between groups. We first explored the relationship between urinary DMA and liver function. Interestingly, we did find significant differences between urinary DMA and liver function when grouped by sex and smokers. The levels of ALT, AST, and TBIL in both male and female groups increased with the increase of urinary DMA, and the changes of liver function in male group were greater than that in female group. Furthermore, ALT and AST increased more with urinary DMA in smokers compared with non-smokers. However, subgroup analyses of other covariates found no significant differences (Table 4). In addition, we also obtained results consistent with urinary DMA in the subgroup analysis of total urinary arsenic and liver function (Table 5).

## Discussion

This study revealed a positive correlation between urinary arsenic concentrations and the degree of liver injury in adults using the NHANES database (2003–2018). It was observed that ALT, AST, ALT/AST, TBIL, GGT, and urinary DMA were consistently significantly positively correlated before and after adjustment. However, ALB decreased with the increase of urinary DMA concentration. We also used total urinary arsenic as an independent variable to discuss the changes in LFTs. We found that with the increase of total urine arsenic concentration, ALT, AST, TBIL increased, while ALB decreased. The changes of these indicators all indicated that arsenic was related to the impairment of liver function. Subgroup analysis was used to further investigate whether covariates affected the linear relationship between urinary arsenic and LFTs. The results showed that, with the change of urinary arsenic, ALT, AST, and TBIL had significant differences between sex and smoker. These results

**Table 4** Subgroups analysis for the associations between urinary dimethylarsinic acid (DMA) and liver function tests (LFTs) in adults

Variables	Subgroups	N	AST		ALT		TBIL	
			$\beta$ (95%CI)	<i>p-int</i>	$\beta$ (95%CI)	<i>p-int</i>	$\beta$ (95%CI)	<i>p-int</i>
Age	<60	9310	0.024 (0.011, 0.038)	0.165	0.046 (0.030, 0.062)	0.720	0.021 (0.011, 0.030)	0.861
	$\geq 60$	4110	0.009 (−0.015, 0.032)		0.041 (0.012, 0.070)		0.032 (0.016, 0.048)	
Sex	Male	6719	0.030 (0.013, 0.047)	0.003	0.061 (0.037, 0.084)	0.001	0.032 (0.019, 0.046)	<0.001
	Female	6701	0.012 (−0.006, 0.029)		0.034 (0.015, 0.054)		0.015 (0.006, 0.024)	
Smoker	Yes	3191	0.038 (0.015, 0.062)	0.001	0.062 (0.032, 0.093)	0.003	0.030 (0.017, 0.043)	0.063
	No	10229	0.015 (0.001, 0.030)		0.044 (0.028, 0.061)		0.021 (0.011, 0.031)	
Alcohol user	Yes	4069	0.022 (0.008, 0.037)	0.895	0.052 (0.036, 0.070)	0.565	0.023 (0.013, 0.034)	0.517
	No	9351	0.015 (−0.009, 0.040)		0.033 (0.004, 0.063)		0.023 (0.010, 0.037)	
BMI	<24.9	4078	0.034 (0.013, 0.054)	0.752	0.055 (0.032, 0.077)	0.384	0.021 (0.008, 0.034)	0.392
	24.9–29.9	4444	0.021 (0.002, 0.040)		0.045 (0.021, 0.070)		0.031 (0.016, 0.046)	
	>29.9	4898	0.010 (−0.011, 0.031)		0.042 (0.021, 0.064)		0.020 (0.007, 0.034)	
Diabetes	Yes	1579	−0.018 (−0.063, 0.029)	0.188	0.020 (−0.030, 0.071)	0.690	0.021 (0.001, 0.041)	0.716
	No	11841	0.025 (0.012, 0.037)		0.051 (0.035, 0.066)		0.024 (0.015, 0.032)	

Analyses were adjusted for covariates age, sex, education level, race, poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, high-density lipoprotein cholesterol, urinary creatinine, diabetes, and hypertension when they were not the strata variables

*BMI*, body mass index; *CI*, confidence interval; *p-int*, *p* for interaction

**Table 5** Subgroups analysis for the associations between total urinary arsenic and liver function tests (LFTs) in adults

Variables	Subgroups	N	AST		ALT		TBIL	
			$\beta$ (95%CI)	<i>p-int</i>	$\beta$ (95%CI)	<i>p-int</i>	$\beta$ (95%CI)	<i>p-int</i>
Age	<60	9310	0.011 (0.003, 0.019)	0.257	0.022 (0.013, 0.032)	0.508	0.013 (0.006, 0.020)	0.810
	$\geq 60$	4110	0.006 (−0.008, 0.019)		0.016 (0.001, 0.032)		0.017 (0.008, 0.025)	
Sex	Male	6719	0.015 (0.005, 0.026)	0.011	0.030 (0.017, 0.044)	0.009	0.018 (0.011, 0.026)	0.001
	Female	6701	0.005 (−0.004, 0.014)		0.015 (0.002, 0.027)		0.011 (0.004, 0.018)	
Smoker	Yes	3191	0.016 (0.001, 0.032)	0.009	0.026 (0.005, 0.047)	0.025	0.017 (0.009, 0.027)	0.238
	No	10229	0.007 (−0.002, 0.015)		0.019 (0.009, 0.029)		0.013 (0.007, 0.020)	
Alcohol user	Yes	4069	0.009 (0.001, 0.017)	0.690	0.021 (0.011, 0.032)	0.959	0.015 (0.009, 0.021)	0.301
	No	9351	0.009 (−0.006, 0.023)		0.018 (0.001, 0.036)		0.012 (0.002, 0.021)	
BMI	<24.9	4078	0.015 (0.003, 0.027)	0.874	0.031 (0.018, 0.045)	0.798	0.018 (0.009, 0.026)	0.610
	24.9–29.9	4444	0.002 (−0.009, 0.014)		0.012 (−0.004, 0.029)		0.011 (0.002, 0.020)	
	>29.9	4898	0.010 (−0.004, 0.023)		0.017 (0.003, 0.031)		0.014 (0.007, 0.022)	
Diabetes	Yes	1579	−0.002 (−0.033, 0.029)	0.477	0.009 (−0.026, 0.052)	0.684	0.015 (0.001, 0.029)	0.835
	No	11841	0.010 (0.003, 0.017)		0.022 (0.013, 0.031)		0.014 (0.009, 0.020)	

Analyses were adjusted for covariates age, sex, education level, race, poverty, smoker, alcohol user, BMI, energy intake levels, total cholesterol, high-density lipoprotein cholesterol, urinary creatinine, diabetes, and hypertension when they were not the strata variables

*BMI*, body mass index; *CI*, confidence interval; *p-int*, *p* for interaction

suggested that sex and smoker may play a role in the mechanism of arsenic-induced liver injury.

In a cohort of 8518 samples from the NHANES database, urinary inorganic arsenic was found to be positively associated with elevated blood ALT, and the extent of the positive association varied by race and obesity, which is consistent with our study, but the evaluation indicators of arsenic exposure and liver function were relatively single and incomplete

(Frediani et al. 2018). A cross-sectional study conducted in Italy by Casale et al. (Casale et al. 2014). found that 130 outdoor workers were divided into two groups with significantly different levels of arsenic exposure. Multiple linear regression analysis showed that high arsenic exposure could lead to significant increases in ALT, AST, and GGT in the population. Although the sample used in this study were fewer and less representative, the results were also similar

to ours. Mazumder et al. (Mazumder 2005) conducted a cross-sectional epidemiological study of 7683 people living in arsenic-affected areas in West Bengal, measuring people's exposure to arsenic based on arsenic levels in drinking water. The incidence of hepatomegaly was positively linear with the increase of arsenic exposure in drinking water, and the level of ALB detected in drinking water samples with high arsenic content was lower, while the level of ALT was higher. It can be seen that our findings were consistent with those of previous studies.

Arsenic has previously been reported to be toxic mainly by inactivating enzyme systems (Hughes 2002; Bahrami et al. 2020). Trivalent arsenic interferes with enzymes activity by binding to sulfhydryl and hydroxyl groups, especially in the tricarboxylic acid cycle that provides energy to cells, mainly by inactivating pyruvate dehydrogenase, a key node in the Krebs cycle (Hughes 2002). As a result, cellular energy production is sharply reduced, and eventually the cells are slowly damaged. Current studies on the mechanism of arsenic-induced hepatotoxicity is mainly because it can cause oxidative stress and mitochondria are the main targets of arsenic. By destroying enzymes in the mitochondrial respiratory chain, a large amount of ROS is generated, and then ROS attacks the DNA and phospholipid membranes of cells (Renu et al. 2020). At present, the mechanism of arsenic-induced liver injury is still in its infancy, and more basic research and clinical validation are still needed. Although there have been many previous studies on arsenic exposure and liver injury, most of the samples collected are limited and not well-represented. In addition, most previous studies focused on liver fibrosis and tumors, tending to histomorphological studies, while few studies on the damage of liver function biochemical indicators.

In our study, we found that sex and smoking were also related to liver function injury. Our study showed that when exposed to arsenic, males were more likely to suffer liver injury than females. Maggi et al. showed that compared to males, adult fertile females have higher rates of hepatic fatty acid uptake, esterification, very low-density lipoprotein triglyceride synthesis and release rates, and lower fatty acid oxidation, which may indicate that liver injury was related to sex (Maggi and Della 2018). Another study showed that estrogen promoted the regeneration and differentiation of liver cells, making females more resistant to liver injury under stress than males (Kao et al. 2018). These studies may partially explain our results, but more research is needed to support the results. In addition, our results also showed that arsenic had greater damage to the liver of smokers than non-smokers, but few studies have directly focused on the relationship between smoking and liver injury. However, some studies have shown that smoking can promote the occurrence and development of hepatitis C, primary biliary cirrhosis, and hepatocellular

carcinoma (Mizoue et al. 2000; Zein et al. 2011). Previous studies have shown that chemicals produced by smoking could induce oxidative stress associated with lipid peroxidation, which may mediated liver injury (El-Zayadi 2006).

Compared to previous studies, our research has some advantages. First of all, with the help of the NHANES project, we obtained a group of large-scale randomly selected samples from the USA, which were well represented. Secondly, the LFTs data was selected as the indicators of liver injury, which made the analysis of arsenic-induced liver injury more objective and intuitive. Moreover, we also included many covariables in addition to the main independent variables and dependent variables and created two models in the process of multiple linear regression, using covariables to adjust layer by layer to reduce the interference of confounding factors. Finally, we also conducted subgroup analysis using covariates to discuss in detail the population differences in arsenic hepatotoxicity.

Our study also has several limitations. First, arsenic-induced liver injury is often based on its chronic toxicity, but the urinary arsenic we used was only a measure of recent arsenic exposure. Second, our study is a cross-sectional study, and since temporality cannot be determined, an exact causal relationship cannot be determined. In addition, although we performed an adjusted analysis for some covariates, there may still be some unknown factors that were not considered. In recent years, there has been a growing awareness that seafood may be the largest contributor to arsenic (As) exposure in human populations. Most of the arsenic in the human body comes from seafood. Although studies have shown that organic arsenic in seafood is much less toxic than inorganic arsenic in the environment, it is still likely to have inestimable effects on the human body given the large amounts (Chen et al. 2010; Taylor et al. 2017). Due to the lack of relevant information in the NHANES database, our study did not include the seafood consumption of the population, which was a large limitation. In fact, if adjustments can be included, perhaps we could gain a better understanding of the effects of arsenic exposure on liver injury. Also, we did not discuss the specific liver disease caused by arsenic, but compared the changes in liver function test results caused by arsenic, which requires further basic and clinical research to clarify and verify.

## Conclusions

High levels of arsenic exposure have been associated with liver injury, and the degree of liver injury aggravates with the increase of arsenic exposure, and sex and smoking may be related to arsenic pathogenicity. Further longitudinal studies are needed to verify the exact relationship between arsenic and liver function and to explore the underlying mechanisms.



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**Author contribution** WJL and XL designed the study. WJL, XZJ, and HSQ completed data analysis and wrote the manuscript. XYL and JS checked the statistical method and helped conduct the literature review. GXZ and XL reviewed and edited the manuscript. All authors read, edited, and approved the final manuscript.

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**Data availability** The datasets used and analyzed during the current study are available at <https://www.cdc.gov/nchs/nhanes/index.htm>.

## Declarations

**Ethics approval and consent to participate** Institutional Review Board approval was not required as the NHANES represents an adequately de-identified and publicly available dataset.

**Consent for publication** Not applicable

**Competing interests** The authors declare no competing interests.

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