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Elevated Arsenic Exposure Is Associated with an Increased Risk of Chronic Hepatitis B Virus Infection: NHANES (2003—2014) in U.S. Adults*

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Summary: Studies concerning the association between arsenic exposure and hepatitis B virus (HBV) infection have been lacking. The present study aimed to examine the association between total urinary arsenic (TUA) and infection of HBV. A total of 5186 participants from National Health and Nutrition Examination Survey (NHANES) 2003–2014 were included in the analysis. We used logistic regression to evaluate the association. We defined two measures of TUA. TUA1 was the sum of arsenous acid, arsenicacid, monomethylarsonic acid and dimethylarsenic acid. TUA2 was defined as TUA minus arsenobetaine and arsenocholine. The results showed that the weighted overall prevalence of HBV infection was 6.08%. For NHANES 2003–2014, the medians (interquartile range) of TUA1 and TUA2 were 5.60 μg/L (3.97–8.09 μg/L) and 4.91 μg/L (2.36–9.11 μg/L), respectively. Comparing the highest quartile to the lowest quartile after multivariable adjustment showed that the odds ratios (ORs) and 95% confidence intervals (CIs) for TUA1 and TUA2 were 2.44 (1.40–4.27) and 2.84 (1.60–5.05), respectively. In conclusion, elevated urinary arsenic was associated with the risk of HBV infection. Further studies, especially prospective studies, are needed to confirm the causal relationship between arsenic exposure and HBV infection.
Key words: arsenic; exposure; hepatitis B; infection; National Health and Nutrition Examination Survey

As a class A human carcinogen, arsenic poses a great threat to public health worldwide. Arsenic-contaminated drinking water has affected over 200 million people in the world[1]. It is estimated that approximately 17 million Americans are at risk of arsenic exposure through contaminated drinking water, chicken, and wine in USA[2, 3]. Some epidemiological studies have demonstrated the association of arsenic exposure with the high risk of infectious diseases in addition to the carcinogenic effect of arsenic[4, 5]. It has been reported that arsenic exposure in early life is associated with an increased risk of lower respiratory tract infections, diarrhea and acute respiratory infections in infants[4, 5]. In addition, arsenic exposure was reported to increase susceptibility to hepatitis E virus infection during pregnancy[6]. Urinary arsenic concentration was associated with the positive seroprevalence of total

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hepatitis A antibodies in the population in the USA[7]. Furthermore, high-dose arsenic exposure was inversely associated with varicella zoster virus IgG antibody levels in the U.S. population[8].

Hepatitis B virus (HBV) is the leading infectious disease in the world. It is estimated that approximately 248 million people worldwide were chronically infected by HBV in 2010[9]. Among them, approximately 1/3 of HBV-infected people will develop serious HBV sequalae, such as cirrhosis and hepatocellular carcinoma (HCC)[10, 11]. Despite the infant vaccination initiated in 1991 in the USA, it has been reported that adults over 21 years of age has the highest prevalence of HBV infection, which reflects lower HBV vaccine coverage among these individuals[12].

There is a paucity of studies that seek to examine the impact of arsenic exposure on the risk of HBV infection. In the present study, we explored the association between arsenic exposure and HBV infection in a nationally representative sample of the U.S. population. Our hypothesis was that elevated urinary arsenic levels may be associated with an increased prevalence of HBV infection.

1 MATERIALS AND METHODS

1.1 Study Population

The population that underwent urinary arsenic tests in the six cycles of the National Health and Nutrition Examination Survey (NHANES, 2003–2014) was included in the present study. NHANES is a program that assesses the health and nutritional status of residents in the United States. More details of the program could be found somewhere[13]. In brief, the survey used a complex multistage, stratified design to obtain a representative sample of the US population. Demographic and socioeconomic information and data from a medical examination, including laboratory test results of the blood, urine and other samples, were collected from participants.

In total, 61 087 participants completed the in-home interview and the medical examination in NHANES 2003–2014. The response rates for the 6 cycles were 76%, 77.36, 75.4%, 77.3%, 69.5% and 68.5%[14]. Among 10 468 participants aged 20 years and older who had arsenic measurements, 3266 participants having HBV vaccination, 1244 participants with unknown vaccine status, 287 participants without serology test results for HBV and 485 participants with missing values for covariates were excluded from the analysis. Additionally, 354 participants who were negative for anti-HBc but positive for anti-HBs, and were considered to have both natural and vaccine-induced immunity, were excluded from the analysis as a previous study[15]. Thus, eventually, a total of 5186 participants were included in our analysis.

1.2 HBV Serological Testing

In NHANES, there are tests for hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs) and hepatitis B surface antigen (HBsAg). Anti-HBc was taken as a key indicator in this study since the outcome of interest in our study was naturally acquired HBV infections and anti-HBc is a more accurate serological marker than the others[15]. The Ortho HBc ELISA, a commercially qualitative ELISA, was used to detect anti-HBc in NHANES[16].

1.3 Urinary Arsenic Assessment

According to the standardized protocol of NHANES, urine arsenic samples were obtained at the time of the physical examinations into arsenic-free containers, shipped in dried ice, stored at –70°C and analyzed within 3 weeks of collection[17]. The method for the measurement of arsenics was consistent across survey cycles. A one-third random subsample of NHANES participants aged 6 years and over was measured for urinary arsenic concentrations. Urinary total arsenic and speciated arsenics were determined. The speciated urinary arsenics included arsenous acid (AsIII), arsenicacid (AsV), arsenobetaine (AsB), arsenocholine (AsC), monomethylarsonic acid (MMA), dimethylarsenic acid (DMA), and trimethylarsine oxide (TMAO). Total arsenic was measured using inductively coupled plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS)[18]. The lower limit of detection (LLOD, in μg/L) for total arsenic was 0.6 μg/L in NHANES 2003–2004, 0.74 μg/L in 2005–2010, 1.25 μg/L in 2011–2012 and 0.26 μg/L in 2013–2014. The urinary speciated arsenics were analyzed by using high-performance liquid chromatography (HPLC) to separate the species coupled to an ICP-DRC-MS to detect the arsenic species[19]. The corresponding LLOD was as follows in NHANES 2003–2010: AsIII (1.2 μg/L), AsV (1.0 μg/L), AsB (0.4 μg/L), AsC (0.6 μg/L), DMA (1.7 μg/L) and MMA (0.9 μg/L). In the 2011–2012 cycle, the LLOD was 0.48, 0.87, 1.19, 0.28, 1.80, and 0.89 μg/L for AsIII, AsV, AsB, AsC, DMA, and MMA, respectively. In the 2013–2014 cycle, the LLOD was 0.21, 0.79, 0.16, 0.11, 1.91 μg/L for AsIII, AsV, AsB, AsC, DMA, and MMA, respectively. The arsenic measurements below LLOD were assigned a value as corresponding LLOD divided by square root of 2[20]. The proportion of total arsenic, AsIII, AsV, MMA, DMA, AsB and AsC below LLOD varied from 0–3.50%, 35.72%–97.78%, 93.54%–99.16%, 30.64%–76.50%, 13.47%–25.95%, 25.49%–52.57%, and 80.44%–98.20%, respectively, for 2003–2014 cycles.

Previous studies have demonstrated that AsB and AsC, two kinds of arsenosugars found in seafood, are nontoxic[21]. In the present study, two indicators were used to define total urinary arsenic (TUA). The first indicator, TUA1, equals the sum of AsIII, AsV, MMA and DMA. As a complement, the second indicator,

TUA2, was defined as total arsenic minus the sum of the two non-toxic arsenosugars, as reported in the previous literature[8]. In total, 121 participants yielded a negative value of TUA2, because the sum of AsB and AsC were greater than the total arsenic. We excluded these participants from the analysis.

Urine creatine concentration was used to account for urine dilution. Urine creatine was determined using the Jaffe rate reaction on a CX3 analyzer prior to 2007 and using an enzymatic method on a Roche ModP Chemistry Analyzer from 2007 onwards[22].

1.4 Covariates

Based on biological considerations and previous studies, potential confounders were extracted from the NHANES database[15, 23], including the NHANES survey cycle, age (categorized into quartiles), sex, race/ethnicity, birth place (USA and elsewhere), body mass index (BMI), poverty index (ratio of family income to poverty ≤1 *vs*. ratio of family income to poverty >1), education (lower than high school, high school or equivalent, above high school), general health condition (excellent/very good, good, fair/poor), smoking status (never, former smoker and current smoker), use of illegal injected drugs (yes, no/unknown).

Race information was extracted from the demographic questionnaire based on self-report and was categorized as Mexican-American, non-Hispanic white, non-Hispanic black, other Hispanic and other race. We derived a single category that included other Hispanic and other race to produce adequate sample sizes for analysis. BMI was classified into four groups: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30 kg/m^2). We combined the underweight and normal weight groups into a new category. Poverty index is an indicator of economic status and we used 1 as cutoff point as described in previous studies[7, 8]. Smoking status was categorized into three groups, which were never, former smoker and current smoker.

1.5 Statistical Analysis

All analyses were performed for TUA1 and TUA2 separately. In the descriptive analysis, unweighted sample sizes and weighted proportions were presented by population characteristics. The distribution of TUA (μg/L) was represented as the median [interquartile range (IQR)]. A linear regression model was used to test the difference of the distribution of TUA across population characteristics.

The weighted logistic regression models were used to estimate the associations between arsenic exposure levels and the risk of HBV. TUA1 and TUA2 were categorized into quartiles according to the weighted distribution in the population, and the data were entered into the models in both continuous (log-transformed) form and in quartiles. Three models with different adjusted covariables were used to estimate the associations between TUA levels and the risk of HBV. Model 1 was a crude model adjusted for urine creatinine and survey cycles. In model 2, we further adjusted for age, sex, and race/ethnicity. In model 3, the full adjusted model, we further adjusted for birth place, poverty index, smoking status, general health condition and use of illegal injected drugs (traditional HBV risk factors). Tests for trends across quartiles were conducted by entering TUA median concentrations in each quartile into the regression models[24]. All models were adjusted for log-transformed creatine to account for urine dilution and for the survey cycle to account for differences resulting from the survey year. In addition, we also reported effect of arsenic exposure on HBV risk by comparing arsenic levels in individuals with creatinine above 10 μg/g and below, as current criterion of drinking water is 10 μg/L in U.S[25]. The approach made a risk assessment of arsenic exposure from the perspective of policy making. To avoid spurious associations caused by heavy weights attached to few individuals, an unweighted logistic regression was also analyzed.

To examine the consistency of the estimates, we also performed estimates of odds ratios (ORs) and 95% confidence intervals (CIs) of HBV infection across the population by doubling the TUA for subgroups defined by each covariate. Tests for interactions were used to examine the interaction effect between arsenic exposure and population characteristics. The interaction *P* value was obtained by adding a product of TUA (log-transformed) and corresponding population characteristics in the fully adjusted model.

All analyses were conducted using the SURVEY procedure in SAS v9.4 (SAS, Inc., USA) to account for the complex sampling design. A new sample weight was calculated by dividing subsample weights by 6, according to the recommendation of the National Center for Health Statistics[14]. We set α=0.05 as the statistical significance level, and all of the tests were 2-tailed.

2 RESULTS

2.1 Characteristics of Participants

In the combined 6 NHANES cycles (2003–2014), a total of 5174 participants had TUA1 measurements and 5040 had TUA2 measurements. The difference in sample sizes between TUA1 and TUA2 measurements resulted from the missing values of TUA2. Eventually, 444 participants were found positive for HBV infection, and the overall weighted seroprevalence was 6.08% in terms of the sample sizes for TUA1. Four hundred thirty-one participants were positive for HBV infection, and the overall weighted seroprevalence was 6.08% in the sample sizes for TUA2. The population characteristics are shown in table 1.

Table 1 Participant characteristics in the present study for the combined NHANES, 2003–2014

Characteristic	TUA1[a] N=5174 (%)[c]	TUA2[b] N=5040 (%)[c]
Age (years)		
20–39	1122 (24.01)	1095 (24.11)
40–50	1001 (23.42)	976 (23.59)
51–62	1158 (25.25)	1122 (25.02)
63 and over	1893 (27.32)	1847 (27.28)
Sex		
Male	2693 (50.53)	2636 (50.89)
Female	2481 (49.47)	2404 (49.11)
BMI (kg/m^2)		
Underweight /normal weight	1474 (29.41)	1431 (29.27)
Overweight	1835 (36.73)	1789 (36.64)
Obese	1865 (33.86)	1820 (34.09)
Race/ethnicity		
Non-Hispanic white	2666 (74.26)	2590 (74.12)
Non-Hispanic black	1034 (9.80)	1009 (9.87)
Mexican American	813 (7.30)	797 (7.40)
Other/Other Hispanic	661 (8.64)	644 (8.61)
Birth place		
USA	3994 (85.83)	3884 (85.75)
Elsewhere	1180 (14.17)	1156 (14.25)
Education		
<High school	1512 (18.99)	1476 (19.10)
High school	1302 (26.71)	1262 (26.62)
>High school	2360 (54.30)	2302 (54.28)
Poverty index		
≤1	1004 (12.07)	981 (12.16)
>1	4170 (87.93)	4059 (87.84)
Smoking status		
Never	2595 (50.01)	2523 (49.81)
Former	1546 (29.21)	1510 (29.29)
Current	1033 (20.78)	1007 (20.90)
General health condition		
Excellent/very good	2002 (47.49)	1967 (47.72)
Good	1855 (33.41)	1797 (33.14)
Fair poor	1317 (19.10)	1276 (19.14)
Injected drug user		
No/Unknown	5098 (98.14)	4965 (98.08)
Yes	76 (1.86)	75 (1.92)
HBV		
Seropositive	444 (6.08)	431 (6.08)
Seronegative	4730 (93.92)	4609 (93.92)

[a]TUA1=AsIII+AsV+MMA+DMA; [b]TUA2=Total As – AsC – AsB; [c]weighted percentages

2.2 Distribution of TUA Levels by Participant Characteristics

As shown in table 2, the overall medians (IQR) of TUA1 and TUA2 were 5.60 μg/L (3.97–8.09 μg/L) and 4.91 μg/L (2.36–9.11 μg/L), respectively. After adjusting for creatinine, TUA1 and TUA2 were found to be significantly associated with BMI, race/ethnicity, birth place, and HBV infections (all P<0.05). TUA1 and TUA2 were higher among the population with HBV infections than those without HBV infections (7.03 *vs*. 5.52 μg/L, P<0.001; and 6.58 *vs*. 4.80 μg/L, P<0.001).

2.3 TUA Levels and HBV Infection

As shown in table 3, the ORs (95% CI) for the association between 2-fold increases in TUA1 and TUA2 and HBV infection risk in the model 1 were 1.90 (1.59–2.26) and 1.50 (1.36–1.66), respectively. Similar results were found in model 2 and model 3 after adjustment for more covariables. In addition, after full adjustment for TUA1, the adjusted ORs and 95% CI of quartile 4, quartile 3 and quartile 2 as compared to the lowest quartile were1.09 (0.65–1.81), 1.61 (0.88–2.93), and 2.44 (1.40–4.27), and for TUA2 were 1.43 (0.86–2.39), 2.49 (1.38–4.49) and 2.84 (1.60–5.05), respectively. The adjusted ORs and 95% CI for HBV risk by comparing TUA1 in individuals with creatinine above *vs*. below 10 μg/g was 1.62 (1.19–2.21). The adjusted ORs and 95% CI for HBV risk by comparing TUA2 in individuals with creatinine above *vs*. below 10 μg/g was 1.93 (1.42–2.62).

For subgroup analyses, the association between TUA and HBV infection was consistent in most subgroups. In addition, there was a significant interaction effect between TUA and age, race or BMI (table 4). Additionally, we also performed unweighted analysis to avoid spurious associations caused by heavy weights attached to few individuals, and the results were consistent (data not shown).

3 DISCUSSION

The findings of our study suggest that elevated arsenic exposure is associated with an increased risk of HBV infection in the U.S. population. Our findings demonstrated that the effect of arsenic exposure, even at low to moderate arsenic levels, on HBV infection is not to be neglected in the general population.

The observed effect of arsenic exposure on the risk of HBV infection was supported by findings from *in vivo* and *in vitro* studies. A number of studies demonstrated that arsenic exposure may induce both innate and adaptive immune response. Macrophages play critical roles in immune defense and they are involved in the onset of inflammation and activation of the innate immune response[26]. Comparing the capacity of macrophages between individuals with and without chronic arsenic exposure showed that arsenic exposure can deregulate the function of macrophages[26]. Arsenic can also inhibit the adaptive antigen-driven T-cell immune response, including the development, activation and proliferation of T-cells[27, 28]. In addition, arsenic can inhibit cytokine secretion in children and adults and induce the incidence of opportunistic infections[29, 30]. Arsenic exposure in childhood can reduce cell-mediated immunity via decreased Th1 cytokines[31]. Blood arsenic concentration was also found to be correlated with levels of several vaccine

antibodies in children in electrical waste recycling areas of China[32]. Additionally, several previous studies indicated that arsenic may also alter the invasiveness and virulence of viruses[33, 34]. Although the evidence focusing on the association between arsenic exposure and HBV infection risk is limited, the findings of arsenic-induced immunotoxicity have suggested the biological plausibility between arsenic exposure and HBV infection in the present study.

Another potential mechanism by which arsenic exposure increases HBV infection risk is that arsenic may induce liver injury and interact with HBV infection. The liver plays a key role in inorganic arsenic metabolism[35]. An earlier study has demonstrated that the arsenic concentration in the liver is higher than that in other organs after acute intoxication[36]. Furthermore, a high tissue concentration of arsenic affects the methylation of key proteins in the liver and leads to serious adverse effects[37–39]. Animal model studies have shown that when mice were fed on arsenic-contaminated water for 15 months, fatty infiltration and hepatic fibrosis were observed in liver

Table 2 Distribution of TUA levels (μg/L) among included participants, NHANES 2003-2014

Characteristic	TUA1[a] Median (IQR)	*P*	TUA2[b] Median (IQR)	*P*
Overall	5.60 (3.97−8.09)		4.91 (2.36−9.11)	
Age (years)				
20–39	6.10 (4.16−8.83)	0.772	5.52 (2.69−10.07)	0.112
40–50	5.65 (4.05−8.12)		4.93 (2.48−8.97)	
51–62	5.21 (3.44−7.86)		4.69 (2.22−9.08)	
63 and over	5.24 (3.89−7.63)		4.52 (2.18−8.52)	
Sex		0.023		0.092
Male	6.09 (4.25−8.59)		5.53 (2.86−9.90)	
Female	5.10 (3.40−7.55)		4.29 (1.99−8.09)	
BMI		<0.001		<0.001
Underweight /normal weight	5.48 (3.78−7.91)		4.70 (2.24−9.12)	
Overweight	5.62 (4.01−8.17)		4.97 (2.38−9.13)	
Obese	5.67 (4.04−8.09)		5.05 (2.49−9.07)	
Race/ethnicity		<0.001		<0.001
Non-Hispanic white	5.30 (3.77−7.59)		4.51 (2.16−8.30)	
Non-Hispanic black	6.22 (4.32−9.30)		5.91 (3.36−11.16)	
Mexican American	6.24 (4.32−9.36)		5.83 (3.04−10.13)	
Other/Other Hispanic	7.59 (4.91−14.19)		8.07 (3.76−16.77)	
Birth place		<0.001		<0.001
USA	5.36 (3.86−7.69)		4.59 (2.24−8.39)	
Elsewhere	7.42 (4.92−12.38)		7.80 (3.76−14.73)	
Education		0.088		<0.001
<High school	5.35 (3.87−8.19)		4.76 (2.29−9.12)	
High school	5.64 (4.02−7.79)		4.69 (2.39−8.33)	
>High school	5.64 (3.97−8.17)		5.09 (2.38−9.43)	
Poverty index		0.874		0.542
≤1	5.56 (4.03−8.44)		4.72 (2.41−9.40)	
>1	5.60 (3.96−8.04)		4.93 (2.33−9.10)	
Smoking status		0.082		0.007
Never	5.54 (3.94−8.10)		4.90 (2.38−8.78)	
Former	5.62 (4.07−8.09)		5.10 (2.40−9.88)	
Current	5.63 (3.78−8.00)		4.70 (2.29−8.79)	
General health condition		0.570		0.273
Excellent/very good	5.63 (3.99−7.99)		4.93 (2.38−9.11)	
Good	5.66 (3.93−8.29)		5.10 (2.30−9.24)	
Fair poor	5.35 (3.98−7.90)		4.47 (2.39−8.85)	
Injected drug user		0.828		0.769
No/Unknown	5.59 (3.95−8.09)		4.91 (2.33−9.14)	
Yes	5.86 (4.51−7.80)		4.94 (3.38−7.25)	
HBV		<0.001		<0.001
Seropositive	7.03 (4.29−10.71)		6.58 (3.47−14.15)	
Seronegative	5.52 (3.94−7.91)		4.80 (2.31−8.91)	

[a]TUA1=AsIII +AsIV+MMA+DMA; [b]TUA2=Total As – AsC – AsB; [c]*P* value is calculated after adjusted for Log-transformed creatine using linear regression.

Table 3 Adjusted ORs and 95% CIs for association between TUA and HBV risk in participants in NHANES 2003-2014

		Quartile				
	Per doubling of arsenic OR (95% CI)	1[g] OR (95% CI)	2 OR (95% CI)	3 OR (95% CI)	4 OR (95% CI)	Test for trend[h]
TUA1[a]		<3.97	3.97–5.60	5.60-8.09	>8.09	
C/NCc	444/4730	76/1073	79/1218	89/1176	200/1264	
Model 1[d]	1.90 (1.59–2.26)	1.00	1.32 (0.80–2.17)	2.06 (1.18–3.59)	4.17 (2.40–7.26)	<0.001
Model 2[e]	1.61 (1.36–1.89)	1.00	1.15 (0.69–1.92)	1.77 (0.97–3.21)	2.88 (1.67–4.95)	<0.001
Model 3[f]	1.47 (1.24–1.75)	1.00	1.09 (0.65–1.81)	1.61 (0.88–2.93)	2.44 (1.40–4.27)	<0.001
TUA2[b]		<2.36	2.36–4.91	4.91-9.11	>9.11	
C/NC[c]	431/4609	62/1035	84/1163	106/1183	179/1228	
Model 1[d]	1.50 (1.36–1.66)	1.00	1.82 (1.14–2.91)	3.26 (1.92–5.53)	4.98 (2.97–8.36)	<0.001
Model 2[e]	1.36 (1.24–1.49)	1.00	1.56 (0.95–2.56)	2.69 (1.51–4.82)	3.32 (1.95–5.67)	<0.001
Model 3[f]	1.31(1.18–1.44)	1.00	1.43 (0.86–2.39)	2.49 (1.38–4.49)	2.84 (1.60–5.05)	0.0005

[a]TUA1=AsIII +AsV+MMA+DMA; [b]TUA2=Total As – AsC – AsB; [c]NC: non-cases; [d]Adjusted for urine creatinine and survey cycles; [e]Further adjusted for age, sex, race; [f]Further adjusted for birth place, family poverty-income ratio, smoking status, general health condition and use of illegal injected drugs; [g]Reference category; [h]Based on TUA median concentrations in each quartile

Table 4 OR (95% CI) of HBV risk with 2-fold increase of TUA by population characteristics

Subgroup	TUA1[a]		TUA2[b]	
	Adjusted OR[c] (95% CI)	*P*[d]	Adjusted OR[a] (95% CI)	*P*[d]
Age (years)		0.054		0.013
20–39	2.13 (1.37−3.32)		1.77 (1.34−2.34)	
40–50	1.44 (1.06−1.94)		1.26 (1.03−1.56)	
51–62	1.57 (1.20−2.06)		1.34 (1.14−1.58)	
63 and over	1.16 (0.82−1.63)		1.14 (0.96−1.36)	
Sex		0.084		0.453
Male	1.36 (1.08−1.73)		1.28 (1.11−1.46)	
Female	1.65 (1.32−2.06)		1.37 (1.18−1.59)	
BMI(kg/m^2)		0.011		0.039
Underweight /normal weight weight	1.78 (1.31−2.41)		1.29 (1.07−1.57)	
Overweight	1.35 (1.07−1.72)		1.33 (1.14−1.54)	
Obese	1.22 (0.80−1.85)		1.27 (1.03−1.56)	
Race/ethnicity		0.005		0.003
Non-Hispanic white	1.08 (0.73−1.59)		1.12 (0.93−1.36)	
Non-Hispanic black	1.23 (0.93−1.63)		1.23 (1.02−1.48)	
Mexican American	1.51 (0.91−2.54)		1.42 (0.97−2.08)	
Other/Other Hispanic	2.47 (1.87−3.26)		1.96 (1.57−2.44)	
Birth place		0.028		0.106
USA	1.12 (0.86−1.46)		1.19 (1.03−1.36)	
Elsewhere				
Education		0.215		0.067
<High school	1.89 (1.40−2.54)		1.61 (1.35−1.91)	
High school	1.09 (0.80−1.48)		1.07 (0.90−1.27)	
>High school	1.58 (1.19−2.09)		1.38 (1.15−1.65)	
Poverty index		0.316		0.475
≤1	1.78 (1.28−2.49)		1.44 (1.17−1.76)	
>1	1.40 (1.14−1.73)		1.28 (1.14−1.45)	
Smoking status		0.261		0.228
Never	1.72 (1.36−2.18)		1.44 (1.22−1.69)	
Former	1.15 (0.75−1.77)		1.12 (0.90−1.39)	
Current	1.35 (0.97−1.86)		1.28 (1.04−1.57)	
General Health Condition		0.242		0.707
Excellent/very good	1.58 (1.13−2.20)		1.39 (1.14−1.68)	
Good	1.19 (0.96−1.48)		1.19 (1.03−1.36)	
Fair poor	1.83 (1.32−2.55)		1.40 (1.15−1.72)	
Injected drug user		0.700		0.836
No/Unknown	1.50 (1.26−1.78)		1.32 (1.19−1.46)	
Yes	0.71 (0.29−1.71)		1.03 (0.48−2.23)	

[a]TUA1=AsIII +AsV+MMA+DMA ; [b]TUA2=Total As – AsC – AsB; [c]OR were adjusted for age, sex, race, birth place, family poverty-income ratio, smoking status, general health condition and use of illegal injected drugs; [d]Test for interaction between arsenic level and subgroups with adjustment for other covariables

histology[40]. For mice given a high-fat diet and arsenic-contaminated water, researchers observed increases in inflammation and cell death in the livers[41]. Based on the liver injury induced by low arsenic exposure, people who have arsenic exposure may have a greater chance of HBV infection.

There are several limitations in our study. First, this study is cross-sectional. It is hard to infer the causality between arsenic exposure and HBV infection risk, because urine arsenic concentrations and HBV status were determined at the same time in the NHANES. However, the evidence for the immunotoxicity of arsenic may support the causal relationship. Second, inorganic arsenics have a short half-life, which may limit their role in chronic arsenic exposure. Nevertheless, an earlier study has shown that the urine arsenic measure adequately represented the cumulative arsenic exposure in drinking water[42]. Third, the presence of other chronic infections may also lead to HBV infection by immunosuppression[43]. Considering the relatively low prevalence of these chronic diseases in the population in the USA, we think that the effect is limited. Additionally, the effect of co-exposure of multiple metals on HBV was not considered in the present study.

Despite these limitations, the present study provides evidence that arsenic exposure increases the potential risk of HBV infection. Such a finding requires further prospective studies to verify the causality between arsenic exposure and HBV infection. More attention needs to be given to the risk of HBV infection in the general population, which may be potentially affected by arsenic exposure.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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