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Article

The Association of Arsenic Exposure and Metabolism Biomarkers with Subclinical Measures of Liver Disease: A Cross-Sectional Investigation in the Multi-Ethnic Study of Atherosclerosis

Hui-Chen Wu,* Ronald A. Glabonjat, Kathrin Schilling, William A. Anderson, Siyue Gao, Arce Domingo Relloso, Nancy LoIacono, Monique Slowly, Anne E Nigra, Tiffany Sanchez, Marisa H. Sobel, Marta Galvez-Fernandez, Matthew J. Budoff, Mary V Gamble, Ana Navas-Acien, and Mariana Lazo

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ABSTRACT: **BACKGROUND:** Long-term exposure to arsenic (As) can cause many health effects, and As metabolism is key in the detoxification and elimination of As. We hypothesize that hepatic steatosis might affect As metabolism efficiency. We evaluated the association of As exposure and As metabolism biomarkers with hepatic steatosis. **METHODS:** In this cross-sectional analysis, we analyzed data from 3,577 participants in the Multi-Ethnic Study of Atherosclerosis (MESA), an ethnically diverse US adult population, with urinary metals and liver CT scan data available. We measured total As and As species in urine and summarized As methylation biomarkers as inorganic (iAs%), monomethylarsonic acid (MMA%), and dimethylarsinic acid (DMA%). The ratio of liver-to-spleen (L/S) Hounsfield units (HU) < 1.0 and liver attenuation <40 HU were used to assess the presence and severity of liver fat content. We used logistic regression to estimate the odds ratio (OR) (95%CI) of steatosis per higher interquartile range (IQR) of log-transformed total urinary As levels ($\sum$As, μg/L) and per 5% higher in log-transformed As species (iAs%, MMA%, DMA%). **RESULTS:** The adjusted ORs (95%CI) for L/S < 1.0 were 1.09 (0.91, 1.30) per higher IQR of $\sum$As and 0.80 (0.68, 0.95), 0.69 (0.61, 0.77), and 1.24 (1.15, 1.34) per 5% higher iAs%, MMA%, and DMA%, respectively. The corresponding ORs (95% CI) for HU < 40 were 0.99 (0.75, 1.30) per higher IQR of increase $\sum$As and 0.70 (0.50, 0.91), 0.65 (0.55, 0.78), and 1.31 (1.16, 1.48) per 5% higher iAs%, MMA%, and DMA%, respectively. The associations were consistent by self-reported race/ethnicity and sex. **CONCLUSIONS:** Arsenic methylation capacity, but not exposure, was associated with the prevalence of hepatic steatosis. Studies are needed to examine the longitudinal association between the progression of hepatic steatosis with As metabolism biomarkers and As-related disease.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease, is characterized by excessive hepatic fat accumulation (steatosis). MASLD manifests itself as a spectrum of diseases, ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and liver cancer.[1] MASLD has become the leading cause of liver disease, affecting up to 30% of adults globally.[2] Beyond its hepatic impact, MASLD is an independent risk factor for cardiovascular disease and all-cause mortality.[3] The pathogenesis of MASLD is multifaceted, involving interactions between genetic and environmental factors, yet the empirical evidence of the role of environmental factors is extremely limited.[1] The liver's crucial functions include detecting, detoxifying, and eliminating xenobiotics to shield against potential chemical insults.[4] Given the significant public health burden of the disease, identifying risk factors involved in disease progression becomes paramount for implementing prevention strategies at both individual and population levels.

Inorganic arsenic (iAs) is a potent toxic and carcinogenic metalloid.[5] The main sources of iAs exposure are naturally contaminated drinking water[6−8] and food, especially rice and grains.[9−11] Between 2006 and 2011, 45.5% of community water systems (CWS) in the US reported detectable amounts of As, and 2.6% were above the US Environmental Protection Agency's (EPA) maximum contaminant level of 10 μg/L.[12] Chronic iAs exposure is a critical public health issue, as iAs is a carcinogen, an established cause of cardiovascular disease, and is associated with numerous adverse health outcomes.[13,14] Almost all consumed iAs is absorbed in the gastrointestinal tract, transformed through a series of methylation and reduction processes in the liver, and excreted primarily through the urine.[15] The average distribution of As metabolites in urine is 10−30% iAs, 10−20% monomethylarsonic acid (MMA), and 60−80% dimethylarsinic acid (DMA), with substantial interindividual variation.[16−18] This variation in the capacity to convert iAs into MMA and DMA has been

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proposed as an important determinant of the risk associated with iAs toxicity.[19] In most populations, diabetes and diabetes-related outcomes, including excess adiposity, have been associated with higher levels of DMA%.[20−23] The presence of MASLD is tightly linked to diabetes, obesity, and other cardiometabolic risk factors.[24] MASLD affects ∼70% of patients with diabetes.[25] The association of liver steatosis with As metabolism biomarkers is largely unknown.

Arsenic metabolism, particularly methylation, is linked to one-carbon metabolism in the liver, which provides methyl groups for various processes, including As detoxification. In addition, toxic metabolites generated during the metabolism of As can induce liver damage.[26−29] Imaging technology, such as computed tomography (CT) scans, can be used as a noninvasive approach to assess the presence and quantify the severity of fatty infiltration of the liver.[30] In this study, we examined the associations of iAs exposure and As metabolism biomarkers, as measured in urine, with hepatic steatosis. We used data from 3,577 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based study of adults 45 to 84 years of age with CT scans available for diagnosis of steatosis and urine available for As speciation. We hypothesize that higher levels of As exposure (measured as the sum of inorganic and methylated species in urine) are associated with a higher prevalence of hepatic steatosis and hepatic steatosis might affect As metabolism efficiency, characterized by higher DMA% and lower MMA%.

METHODS

Study Population

MESA is a cohort of 6,814 adults aged 45 to 84 years without known cardiovascular disease (asymptomatic) at the time of enrollment (2000 to 2002).[31] Participants were enrolled at 6 academic field centers in Baltimore, MD, Chicago, IL, Los Angeles, CA, New York, NY, St. Paul, MN, and Winston-Salem, NC. At baseline (exam 1), participants provided data on demographics, lifestyle factors, and medical history using standardized questionnaires.[31] Participant race/ethnicity was assessed by self-report and categorized as non-Hispanic White (37%), non-Hispanic Black (30%), Hispanic/Latino (23%) and Chinese/Chinese American (10%). The study was approved by the institutional review board of Columbia University (IRB-AAAC945), and all participants gave written informed consent.

Of the 6,814 MESA participants at baseline, 6,734 had urinary As measured at baseline (Figure S1). We included participants who underwent baseline noncontrast cardiac CT between July 17, 2000 and August 29, 2002, and had adequate hepatic and splenic imaging for fatty liver determination (n = 4,337). Participants with heavy alcohol intake (n = 219) (>7 drinks/week for women and >14 drinks/week for men) were excluded. Additionally, we excluded participants with a self-reported history of hepatitis B (n = 23) or hepatitis C (n = 22) virus infection.

Medical history, anthropometric measurements, laboratory testing, and coronary calcium CT scans were taken during the first examination (July 2000 to August 2002). Information regarding demographic data, education status, rice consumption, tobacco usage, passive smoke exposure, alcohol consumption, medical conditions, and current use of prescription and nonprescription medications and supplements was obtained through a questionnaire at the baseline visit of the study. Weekly rice consumption was determined using food frequency questionnaires.[32] Cigarette smoking status and alcohol consumption were classified as never, former, or current. Participants who had not smoked 100 cigarettes in their lifetime were classified as never smokers. Participants who answered "yes" were classified as current smokers if they had smoked in the last 30 days or classified as former smokers if they had not smoked in the last 30 days. Heavy alcohol consumption was defined as >7 drinks/week for women and 14 drinks/week for men. Height and weight were measured with participants wearing light clothing and no shoes, and body mass index (BMI) was calculated in kilograms per meters squared. Metabolic syndrome was defined by the American Heart Association/National Heart, Lung, and Blood Institute criteria as at least 3 of the following: waist circumference ≥ 102 cm for men and ≥ 88 cm for women; triglycerides (TG) ≥ 150 mg/dL or drug treatment for elevated TG; high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl for men and < 50 mg/dL for women or drug treatment for reduced HDL-C; systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or drug treatment for hypertension; and fasting blood glucose level ≥ 100 mg/dL or drug treatment for elevated glucose. Participants' estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation based on age, sex, and serum creatinine levels without considering race/ethnicity.[33]

Outcomes

At exam 1, each participant underwent two consecutive nonenhanced cardiac CT scans covering the liver and spleen. The protocol of scanner parameters and scanning details was reported previously.[34] CT scans were evaluated for liver fat measurement by two independent, experienced readers blinded to the demographic data, the details of which were published previously.[35] Hepatic and splenic attenuation were measured in Hounsfield units (HU). The liver/spleen (L/S) ratio was calculated using the mean of the hepatic measurements divided by the splenic attenuation value. L/S ratio < 1.0 was used as the cutoff point for the diagnosis of presence of liver fat (primary outcome). Liver attenuation <40 HU was used as a cutoff that would correspond with > 30% liver fat content, which is considered to represent severe hepatic steatosis (secondary outcome).[35]

Urinary Arsenic Biomarkers

Spot urine samples, collected into cups during mid to late morning at exams 1 and 5, were aliquoted into small vials, shipped frozen on dry ice, and stored at −80 °C at the MESA biorepository at the University of Vermont MESA Central Laboratory. Aliquots of 0.8 mL urine were shipped on dry ice to the Trace Metals Core Laboratory at Columbia University. Detailed information on the analytical protocol to measure metals and metalloids in MESA has been described.[36] Briefly, all trace elements were analyzed using a PerkinElmer NexION 350S inductively coupled plasma mass spectrometry with dynamic reaction cell (ICP-DRC-MS) instrument. At least five multielement standard solutions were used for external instrument calibration, and internal standards were used for matrix and instrumental drift correction. The same diluent used for urine samples was used for calibration standards. Trace element concentrations of the calibration solutions were chosen to cover the expected ranges of urine analyte concentrations. Urinary As species concentrations were determined after anion-exchange chromatographic separation (Hamilton PRP-X100 column) with high-performance liquid chromatography (HPLC, Agilent 1260 bioinert system) and coupled directly to elemental specific detection with inductively coupled plasma triple quadrupole mass spectrometry (ICPMS,[2] Agilent 8900 series system) in oxygen reaction mode as described previously.[37] External calibration for the As species was performed using seven standard solutions containing iAs, MMA, DMA, and arsenobetaine in the expected urinary analyte range. Quality control was performed by addition of matrix-matched method blanks and five urine certified reference materials. Samples were analyzed for total element and As species concentrations, blinded to participants' characteristics, along with sample preparation blanks, and commercially available certified urine reference materials with a broad range of trace element concentrations. Approximately 10% of the samples were prepared and measured in duplicate to determine intra-assay precision, and another 10% were prepared and measured on different days to determine interassay precision. The intra-assay coefficients of variation (CV) for urinary iAs, MMA, DMA, and arsenobetaine (together with other cationic and neutral As species) were 4.7%, 5.0%, 3.1%, and 2.6%, respectively; the interassay CVs were 5.8%, 5.6%, 4.7%, and 4.6%,

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Table 1. Participant Characteristics Based on L/S Ratio < 1.0 and Liver Attenuation < 40 HU Cutoffs in the Multi-Ethnic Study of Atherosclerosis at Baseline Exam 1 (2000–2002) (n = 3,577)[a]

Variable, n	L/S < 1, N = 598	L/S ≥ 1, N = 2,979	p-value[c]	HU < 40,N = 219	HU ≥ 40, N = 3,358	p-value[c]
Age, years[b]	61 (53, 69)	65 (54, 72)	<0.001	60 (52, 67)	64 (54, 72)	<0.001
Male, n (%),n = 1,588	270 (45%)	1,318 (44%)	0.70	100 (46%)	1,488 (44%)	0.70
Race/ethnicity			<0.001			<0.001
White, n = 1,373	200 (33%)	1,173 (39%)		78 (36%)	1,295 (39%)	
Black, n = 1,009	108 (18%)	901 (30%)		28 (13%)	981 (29%)	
Hispanic/Latino, n = 825	219 (37%)	606 (20%)		88 (40%)	737 (22%)	
Chinese, n = 370	71 (12%)	299 (10%)		25 (11%)	345 (10%)	
Center			<0.001			<0.001
Winston-Salem, NC, n = 577	63 (11%)	514 (17%)		13 (5.9%)	564 (17%)	
New York, NY, n = 563	78 (13%)	485 (16%)		17 (7.8%)	546 (16%)	
Baltimore, MD, n = 540	70 (12%)	470 (16%)		26 (12%)	514 (15%)	
St Paul, MN, n = 681	161 (27%)	520 (17%)		74 (34%)	607 (18%)	
Chicago, IL, n = 602	85 (14%)	517 (17%)		39 (18%)	563 (17%)	
Los Angeles, CA, n = 614	141 (24%)	473 (16%)		50 (23%)	564 (17%)	
Education			<0.001			0.07
High School or less, n = 1,356	266 (44%)	1,090 (37%)		99 (45%)	1,257 (37%)	
Some college, n = 800	127 (21%)	673 (23%)		45 (21%)	755 (22%)	
College degree or more, n = 1,421	205 (34%)	1,216 (41%)		75 (34%)	1,346 (40%)	
Cigarette smoking			0.04			0.06
Never, n = 1,909	347 (58%)	1,562 (52%)		133 (61%)	1,776 (53%)	
Former, n = 1,297	198 (33%)	1,099 (37%)		64 (29%)	1,233 (37%)	
Current, n = 371	53 (8.9%)	318 (11%)		22 (10%)	349 (10%)	
Alcohol consumption			0.01			0.20
Never, n = 792	160 (27%)	632 (21%)		58 (26%)	734 (22%)	
Former, n = 867	133 (22%)	734 (25%)		44 (20%)	823 (25%)	
Current, n = 1,918	305 (51%)	1,613 (54%)		117 (53%)	1,801 (54%)	
Diabetes			<0.001			<0.001
Nondiabetic, n = 2,642	334 (56%)	2,308 (77%)		113 (52%)	2,529 (75%)	
Prediabetic, n = 478	140 (23%)	338 (11%)		58 (26%)	420 (13%)	
Untreated diabetes, n = 96	33 (5.5%)	63 (2.1%)		15 (6.8%)	81 (2.4%)	
Treated diabetes, n = 361	91 (15%)	270 (9.1%)		33 (15%)	328 (9.8%)	
Rice consumption			0.15			0.20
<1 serving/week, n = 1,484	229 (38%)	1,255 (42%)		82 (37%)	1,402 (42%)	
1–6 servings/week, n = 1,696	293 (49%)	1,403 (47%)		106 (48%)	1,590 (47%)	
≥1 serving/day, n = 397	76 (13%)	321 (11%)		31 (14%)	366 (11%)	
Metabolic syndrome (Yes)	379 (63%)	973 (33%)	<0.001	164 (75%)	1,188 (35%)	<0.001
Hypertension (Yes)	314 (53%)	1,366 (46%)	0.003	122 (56%)	1,558 (46%)	0.007
BMI[b], **kg/m^2**	30.3 (27.4, 34.4)	27.2 (24.4, 30.6)	<0.001	32.0 (28.4, 35.6)	27.5 (24.6, 30.9)	<0.001
LDL-C[b], **mg/dL**	115 (94, 136)	116 (97, 137)	0.30	116 (96, 136)	116 (96, 136)	0.80
HDL-C[b], **mg/dL**	43 (37, 51)	49 (41, 60)	<0.001	42 (37, 51)	48 (41, 59)	<0.001
TG[b], **mg/dL**	152 (104, 202)	104 (75, 150)	<0.001	160 (119, 205)	108 (76, 156)	<0.001
eGFR, mL/min/1.73 m^2			0.06			0.02
<60, n = 187	22 (3.7%)	165 (5.5%)		4 (1.8%)	183 (5.4%)	
≥60, n = 3,390	576 (96%)	2,814 (94%)		215 (98%)	3,175 (95%)	

[a]Abbreviations: L/S, liver/spleen ratio; HU, Hounsfield units; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate. [b]Median (25th percentile, 75th percentile). [c]p-Values were from Wilcoxon Rank-sum test for continuous variables or Pearson's chi-squared test for categorical variables.

respectively.[37] The method detection limit (MDL) for arsenobetaine was 0.02 μg As/L urine and 0.03 μg As/L urine for iAs, MMA and DMA. Among the 3,577 participants, 5.6% had urinary As species concentrations below the MDL. Urinary As species concentrations below the MDL were imputed by dividing the MDL by the square root of two.[38] Urine creatinine was measured using the kinetic Jaffé method. In this study, we used only data from exam 1.

We defined As exposure not derived from seafood as the sum of concentration of iAs, MMA, and DMA ($\sum$As = iAs + MMA + DMA) corrected for arsenobetaine using a residual based method.[38] To define As metabolism biomarkers, we used the relative proportions of iAs, MMA, and DMA over the sum of the three (expressed as iAs%, MMA%, and DMA%) and the methylation efficiency ratios MMA/iAs and DMA/MMA, known as the primary methylation index (PMI) and secondary methylation index (SMI), respectively.

Water Arsenic Assignment

Each MESA participant was assigned to zip code–level estimates of community water systems (CWS) As by baseline residential zip code.[39] CWS As estimates represent population-weighted average concentrations (μg/L) from 2006 to 2011. Among 6,722 MESA participants at baseline, the median (interquartile range) As concentration in CWS was 0.35 (0.35, 0.38) μg/L between 2006 and 2011.[39]

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Table 2. Distribution of As in Water, Urinary ∑As Levels and As Metabolism Biomarkers by L/S < 1.0 and HU < 40 in the Multi-Ethnic Study of Atherosclerosis at Baseline Exam 1 (2000−2002)[a]

		Presence of hepatic steatosis			Severity of hepatic steatosis		
		Yes (L/S < 1.0)	No (L/S ≥ 1.0)		Yes (HU< 40)	No (HU ≥ 40)	
Variable	*n*	*N* = 598	*N* = 2,979	*p*-value[f]	*N* = 219	*N* = 3,358	*p*-value[f]
∑As[b,e], μg/L	3,577	3.2 (2.0, 5.4)	2.6 (1.6, 4.5)	<0.001	3.2 (2.0, 5.5)	2.7 (1.6, 4.6)	0.002
iAs%[c,e]	3,577	6.1 (4.6, 8.3)	6.6 (4.7, 8.7)	0.005	5.9 (4.4, 8.0)	6.6 (4.7, 8.7)	0.01
MMA%[c,e]	3,577	10.5 (7.4, 13.5)	12.1 (9.1, 15.7)	<0.001	9.8 (7.3, 13.1)	12.0 (8.9, 15.5)	<0.001
DMA%[c,e]	3,577	83.3 (78.2, 87.6)	81.0 (76.1, 85.7)	<0.001	83.6 (79.2, 88.0)	81.2 (76.3, 86.0)	<0.001
Methylation efficiency ratio							
PMI[d,e]	3,577	1.7 (1.4, 2.0)	1.8 (1.5, 2.3)	<0.001	1.6 (1.4, 2.0)	1.8 (1.5, 2.2)	<0.001
SMI[d,e]	3,577	7.9 (5.7, 11.8)	6.7 (4.8, 9.5)	<0.001	8.5 (6.0, 12.1)	6.8 (4.9, 9.7)	<0.001
CWS As[f], μg/L	3,484			<0.001			<0.001
<1	3,077	480 (83%)	2,597 (89%)		171 (81%)	2,906 (89%)	
1−2	208	48 (8.3%)	160 (5.5%)		17 (8.0%)	191 (5.8%)	
>2	199	51 (8.8%)	148 (5.1%)		24 (11%)	175 (5.3%)	

[a]Abbreviations: L/S, liver/spleen ratio; HU, Hounsfield units; ∑As, total urinary arsenic; iAs, urinary inorganic arsenic; MMA, urinary monomethylarsonic acid; DMA, urinary dimethylarsinic acid; PMI, primary methylation index; SMI, secondary methylation index; CWS As, community water system arsenic. [b]∑As is the sum of iAs, MMA, and DMA urine concentrations corrected for arsenobetaine. [c]iAs% is iAs/∑As*100; MMA% is MMA/∑As*100; DMA% is DMA/∑As*100. [d]PMI is MMA/iAs; SMI is DMA/MMA. [e]Median (25th percentile, 75th percentile). [f]*p*-Values were from the Wilcoxon Rank-sum test for continuous variables or Pearson's chi-squared test for categorical variables.

Statistical Analysis

All analyses were conducted using R (version 4.4.1, R foundation for Statistical Computing). A two-tailed p-value below 0.05 was considered statistically significant. Baseline characteristics were described as median (interquartile range) for continuous variables according to their distributions and number (percentage) for categorical variables. Differences between outcome groups (L/S < 1.0 vs ≥1.0; HU < 40 vs ≥40) were compared using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables.

We used multivariable-adjusted logistic regression models to estimate the odds ratio (OR) of presence and severity of hepatic steatosis (L/S < 1.0 and HU < 40) by As exposure levels (∑As in urine) and As metabolism biomarkers (iAs%, MMA%, DMA%, PMI, and SMI). Because diabetes-related outcomes and adiposity appear to be determinants of As metabolism biomarkers based on previous studies,[20,21,40] Model 1 adjusted for age (years), sex (male/female), MESA field center (Winston-Salem, NC, New York, NY, Baltimore, MD, St. Paul, MN, Chicago, IL, Los Angeles, CA), highest level of education completed (high school or less, some college, college degree or more), rice consumption (<1 serving/week, 1−6 servings/week, ≥ 1 serving/day), eGFR (mL/min/1.73 m^2), BMI (kg/m^2), metabolic syndrome (yes/no), and urinary creatinine concentrations (mg/L; log-transformed). eGFR was included because kidney function has been shown to interfere with the excretion of iAs.[41,42] Rice consumption was included to account for the increased As exposure from frequent rice intake.[9,32] Model 2 included variables in Model 1 as well as cigarette smoking (never, former, current), and alcohol consumption (never, former, current). Model 3 adjusted for metabolic variables individually (instead of together as the metabolic syndrome) as BMI (kg/m^2), low-density lipoprotein cholesterol (LDL-C; mg/dL), HDL-C (mg/dL), TG (mg/dL), and diabetes status based on fasting glucose levels (nondiabetic, prediabetic, untreated or treated diabetes), and was considered the final model. We excluded 17 participants missing education, 402 missing rice consumption, 8 missing eGFR, 1 missing urinary creatinine, 16 missing alcohol consumption, and 52 missing LDL-C, resulting in 3,577 participants for analysis. For As exposure, ORs for the outcomes were estimated in terms of per higher interquartile range (IQR) in log-transformed urine ∑As levels. For As metabolism biomarkers, ORs for the outcomes were estimated in terms of per 5% higher urinary iAs%, MMA%, DMA% because *a* 1% unit change in As metabolism markers could be a small change. We also estimated ORs per higher IQR in log-transformed levels of PMI and SMI. In models using urinary iAs%, MMA%, DMA%, PMI, or SMI as the predictor of interest, Model 1 included adjustment for urine ∑As levels (log-transformed). We did not adjust for self-reported race/ethnicity. One of the complexities regarding As exposure and the interpretation of the As metabolism biomarkers in MESA is that the sources of As exposure are very different in the different race/ethnicities for multiple reasons including geography (with different race/ethnic groups recruited at each center) as well as cultural.[43] In particular seafood intake, rice, and also inorganic As exposure through drinking water was higher for the Chinese participants in MESA (recruited only in Chicago and L.A.). Rice is also very common for Hispanics/Latinos from the New York MESA center. Given these differences, which can impact the interpretation of the As metabolism biomarkers, we also assessed effect modification, stratified by sex and self-reported race/ethnicity.

We further performed the same logistic regression models as described above but modeled ∑As and As methylation biomarkers (iAs%, MMA%, and DMA%) using restricted cubic spline regression to evaluate the potential nonlinearity of As exposure and As metabolism biomarkers, in separate models, with odds of presence and severity of hepatic steatosis. In 3,484 participants with CWS As measurements,[39] the ORs were estimated using generalized estimating equations with an independent working correlation structure to account for clustering within zip code measurements of CWS As levels.[44] The ORs were interpreted per higher IQR of log-transformed CWS As. This analysis was implemented to assess the possibility of reverse causality for the associations between the urinary As methylation biomarkers and the presence and severity of hepatic steatosis.

We performed a sensitivity analysis estimating the average differences in liver attenuation scores in HU from CT scans per higher IQR of log-transformed urinary ∑As, PMI, SMI, and CWS As levels, and per 5% higher urinary iAs%, MMA%, and DMA% by excluding participants with chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), and those with untreated or treated diabetes, resulting in a sample size of 2,977 participants.

We performed a secondary analysis that estimated prevalence ratios using Poisson regression with robust variance estimation for the binary presence and severity of hepatic steatosis outcomes per higher IQR of urinary ∑As, PMI, SMI, and CWS As levels, and per 5% higher urinary iAs%, MMA%, and DMA%.[45] Prevalence ratios estimated from Poisson regression can be preferable to ORs when the disease outcome is not considered rare.[46,47] The Poisson models had the same covariate adjustments as the primary analysis. The goal

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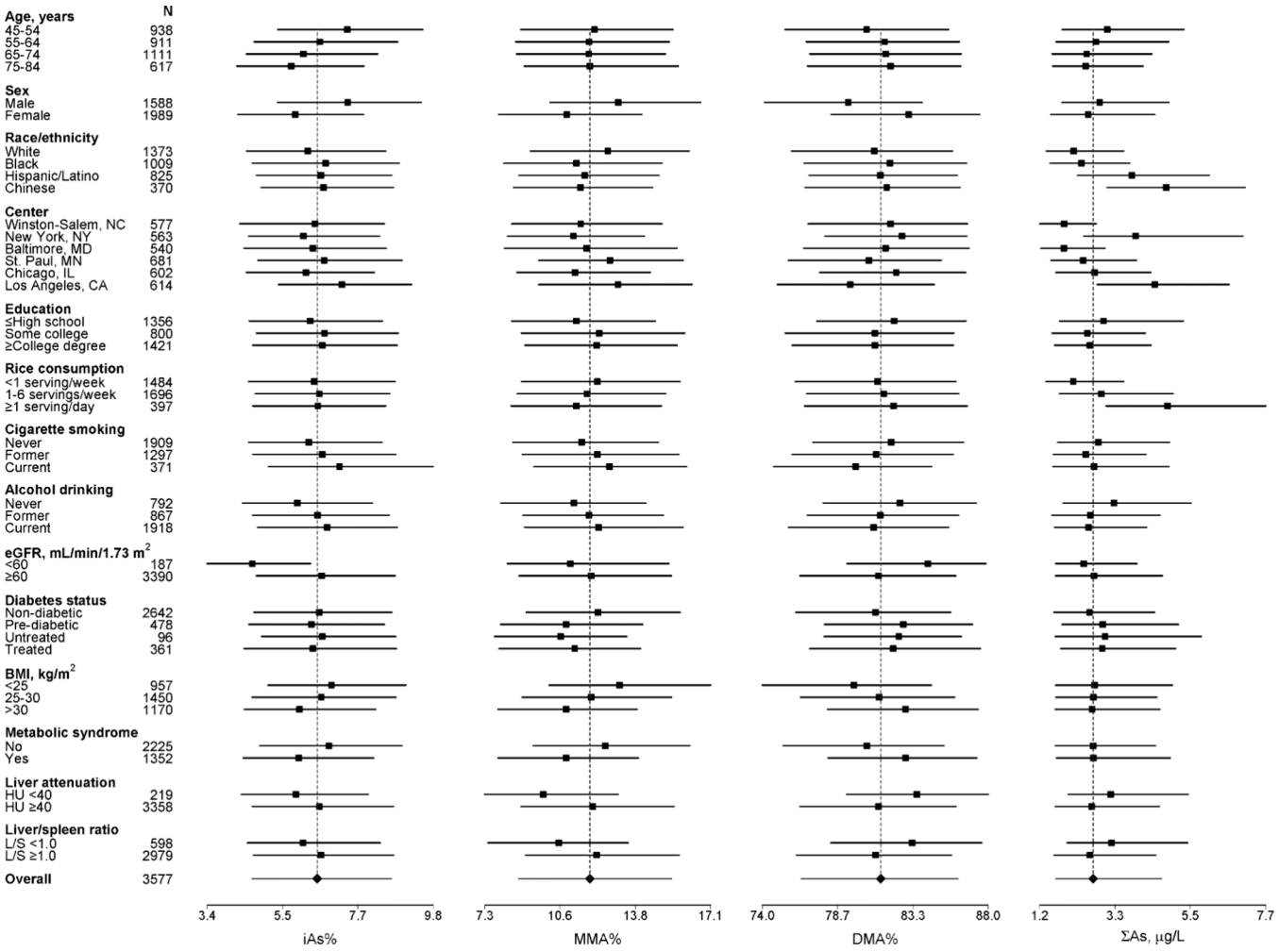

Figure 1. Distribution of urinary arsenic levels (sum of inorganic and methylated arsenic, ∑As) and arsenic metabolism biomarkers (iAs%, MMA %, DMA%) by participant characteristics in the Multi-Ethnic Study of Atherosclerosis at baseline exam 1 (2000–2002) (n = 3,577). Points represent the median of urinary concentrations for arsenic biomarkers. Horizontal lines represent the interquartile range.

of this secondary analysis was to evaluate the consistency of the ORs in the primary analysis by comparing them to the point estimates and confidence intervals of the prevalence ratios.

RESULTS

Among the 3,577 participants, 44% were male (Table 1). The MESA field centers were 16% Winston-Salem, NC, 16% New York, NY, 15% Baltimore, MD, 19% St. Paul, MN, 17% Chicago, IL, 17% Los Angeles, CA, and 40% of participants reported having a college degree or more (Table 1). 598 participants (17%) had L/S < 1.0 (steatosis present) and 219 (6.1%) had HU < 40 (severe hepatic steatosis) (Table 1). The median (IQR) age was 61 (53, 69) years for L/S < 1.0 and 60 (52, 67) years for HU < 40 (Table 1). Hispanic/Latino participants had the highest prevalence of hepatic steatosis (37%) and severe hepatic steatosis (40%), compared to White, Black, and Chinese participants (Table 1). Participants with hepatic steatosis showed higher burden of metabolic-related risk factors, including diabetes, metabolic syndrome, hypertension, BMI, HDL, cholesterol, and TG.

Distributions of As exposure and As metabolism biomarkers by hepatic steatosis status are summarized in Table 2 and Figure 1. Participants with hepatic steatosis and severe liver fat content had higher urinary ∑As levels than individuals without these conditions. The median levels of iAs%, MMA%, and DMA% were 6.1%, 10.5%, and 83.3%, respectively, for participants with L/S < 1.0, and 6.6%, 12.1%, and 81.0%, respectively, for L/S ≥ 1.0. Participants with hepatic steatosis and severe liver fat content had lower PMI and higher SMI levels than individuals without these conditions. Participants with hepatic steatosis and severe liver fat content had higher CWS As levels.

In the fully adjusted model, we found an association between measures of As metabolism biomarkers and hepatic steatosis. The ORs (95% CI) for L/S < 1.0 were 1.09 (0.91, 1.30) per higher IQR of ∑As and 0.80 (0.68, 0.95), 0.69 (0.61, 0.77), and 1.24 (1.15, 1.34) per 5% higher iAs%, MMA%, and DMA%, respectively (Table 3, Model 3). The results for HU < 40 were similar. The corresponding ORs (95% CI) for HU < 40 were 0.99 (0.75, 1.30) per higher IQR of ∑As and 0.70 (0.53, 0.91), 0.65 (0.54, 0.78), and 1.31 (1.16, 1.48) per 5% higher iAs%, MMA%, and DMA%, respectively. Regarding methylation efficiency ratios, the ORs (95% CI) per higher IQR of PMI were 0.92 (0.84, 1.00) for L/S < 1.0 and 0.91 (0.80, 1.05) for HU < 40. The corresponding OR (95% CI) per higher IQR of SMI was 1.47 (1.30, 1.66) for L/S < 1.0 and 1.49 (1.25, 1.78) for HU < 40. There was no association between the odds of L/S < 1.0 or HU < 40 per higher IQR of

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Table 3. Odds Ratio (95%CI) of L/S < 1.0 and HU < 40 by As in Water, Urinary ∑As Levels, and As Metabolism Biomarkers in the Multi-Ethnic Study of Atherosclerosis at Baseline Exam 1 (2000−2002)[a]

			Model 1[b]		Model 2[c]		Model 3[d]	
		n	OR (95% CI)[e,f]	p-value	OR (95% CI)[e,f]	p-value	OR (95% CI)[e,f]	p-value
	L/S < 1.0 (n = 598)							
per IQR	∑As, μg/L[g]	3,577	1.18 (0.99, 1.41)	0.06	1.16 (0.98, 1.38)	0.09	1.09 (0.91, 1.30)	0.35
per 5%	iAs%	3,577	0.79 (0.67, 0.94)	0.01	0.80 (0.67, 0.94)	0.01	0.80 (0.68, 0.95)	0.01
	MMA%	3,577	0.68 (0.61, 0.77)	<0.001	0.68 (0.61, 0.77)	<0.001	0.69 (0.61, 0.77)	<0.001
	DMA%	3,577	1.25 (1.16, 1.35)	<0.001	1.25 (1.15, 1.35)	<0.001	1.24 (1.15, 1.34)	<0.001
per IQR	PMI[g]	3,577	0.92 (0.85, 1.00)	0.05	0.92 (0.85, 1.00)	0.05	0.92 (0.84, 1.00)	0.05
	SMI[g]	3,577	1.47 (1.30, 1.65)	<0.001	1.47 (1.30, 1.65)	<0.001	1.47 (1.30, 1.66)	<0.001
per IQR	CWS As[h], μg/L	3,484	1.00 (0.98, 1.02)	0.72	1.00 (0.98, 1.02)	0.74	1.00 (0.98, 1.02)	0.87
	HU < 40 (n = 219)							
per IQR	∑As, μg/L[g]	3,577	1.08 (0.83, 1.42)	0.56	1.07 (0.81, 1.40)	0.65	0.99 (0.75, 1.30)	0.93
per 5%	iAs%	3,577	0.69 (0.53, 0.91)	0.01	0.70 (0.53, 0.92)	0.01	0.70 (0.53, 0.91)	0.01
	MMA%	3,577	0.64 (0.53, 0.78)	<0.001	0.64 (0.53, 0.78)	<0.001	0.65 (0.54, 0.78)	<0.001
	DMA%	3,577	1.32 (1.16, 1.49)	<0.001	1.31 (1.16, 1.49)	<0.001	1.31 (1.16, 1.48)	<0.001
per IQR	PMI[g]	3,577	0.92 (0.80, 1.04)	0.18	0.92 (0.80, 1.04)	0.19	0.91 (0.80, 1.05)	0.19
	SMI[g]	3,577	1.50 (1.27, 1.78)	<0.001	1.51 (1.27, 1.79)	<0.001	1.49 (1.25, 1.78)	<0.001
per IQR	CWS As[h], μg/L	3,484	1.02 (0.99, 1.05)	0.11	1.02 (1.00, 1.05)	0.11	1.02 (0.99, 1.05)	0.15

[a]Abbreviations: L/S, liver/spleen ratio; HU, Hounsfield units; ∑As, total urinary arsenic; iAs, urinary inorganic arsenic; MMA, urinary monomethylarsonic acid; DMA, urinary dimethylarsinic acid; PMI, primary methylation index; SMI, secondary methylation index; CWS As, community water system arsenic. [b]Model 1: adjust for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), and metabolic syndrome (yes/no). [c]Model 2: adjust for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), metabolic syndrome (yes/no), smoking status (never, former, current), and alcohol consumption (never, former, current). [d]Model 3: adjust for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), smoking status (never, former, current), alcohol consumption (never, former, current), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), and diabetes status (nondiabetic, prediabetic, untreated diabetes, treated diabetes). [e]OR and CIs for ∑As, PMI, SMI, and CWS As are reported per higher log IQR. [f]OR and CIs for iAs%, MMA%, and DMA% are reported per higher 5%. [g]Total urinary arsenic is the sum of urinary iAs + MMA + DMA corrected for arsenobetaine; PMI is MMA/iAs; SMI is DMA/MMA. [h]Odds ratio estimates were from generalized estimating equations with a random effect for zip code level community water system arsenic levels.

log-transformed CWS As levels (Table 3). Modeling As metabolism biomarkers as restricted cubic splines showed both that higher levels of iAs% and MMA% were inversely associated with L/S < 1.0 (Figure 2) and HU < 40 (Figure 3), while DMA% was positively associated with odds of presence and severity of hepatic steatosis, with associations being markedly linear for both outcomes. For ∑As, there was a positive association, although nonstatistically significant, with odds of hepatic steatosis presence (Figure 2) but no clear trends were observed for odds of having severe hepatic steatosis (Figure 3) in flexible dose−response analyses.

The association of As metabolism biomarkers with hepatic steatosis by different self-reported race/ethnicities showed consistent trends, although the associations were weaker for Hispanic/Latino participants (Table 4). The associations between As metabolism biomarkers and hepatic steatosis also showed consistent patterns by sex, although the association with the presence of hepatic steatosis tended to be stronger in women, and with severe liver fat content, it tended to be stronger in men (Table 5). The associations between ∑As and As metabolism biomarkers were also consistent when excluding participants with chronic kidney disease and diabetes (Table S1) and when estimating the prevalence ratios from Poisson regression (Table S2).

DISCUSSION

About two to five million people in the rural and suburban US drink water contaminated with As at levels higher than the US EPA's maximum contaminant level of 10 μg/L.[48,49] However, many more millions drink water with measurable As levels below 10 μg/L.[42,50,51] MESA is a multiethnic, population-based cohort study that included adults from urban and suburban communities in the US with As exposure levels in drinking water markedly below the US EPA maximum contaminant level.[39] The liver is a known target of As toxicity and also serves as the primary organ for As methylation.[28] Arsenic exposure, quantified by the aggregate of inorganic and methylated As levels in urine and corrected for arsenobetaine, was not associated with hepatic steatosis. The presence of liver steatosis and more severe liver fat content, however, were associated with As methylation biomarkers: higher DMA% and lower iAs%. Risk for most As-related health outcomes, such as cancers of the bladder, breast, lung, and skin, and peripheral vascular disease are associated with reduced As methylation capacity.[23] The profile was marked by lower levels of iAs% and MMA% coupled with higher levels of DMA% and SMI. These associations remained robust after adjustment for BMI and metabolic syndrome as well as after adjustment for diabetes, hypertension, BMI, and lipids. Although these findings are cross-sectional, they suggest that iAs metabolism is affected in

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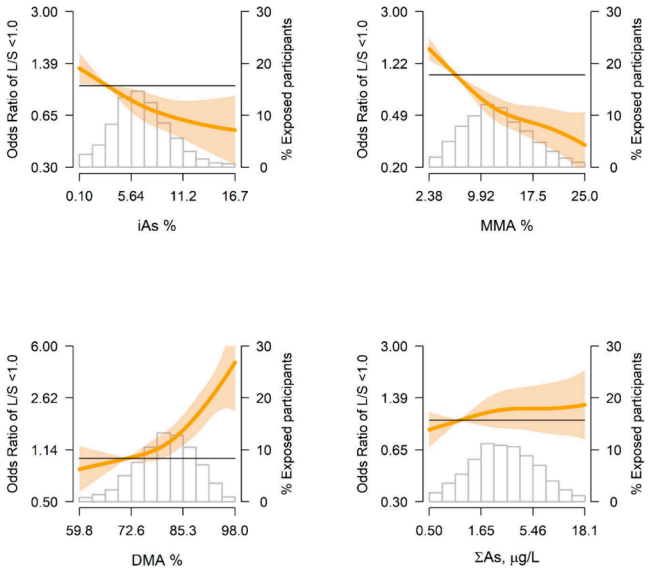

Figure 2. Odds ratios for the associations between urinary As levels (∑As) and As metabolism biomarkers (iAs%, MMA%, DMA%) with hepatic steatosis (L/S < 1.0) in the Multi-Ethnic Study of Atherosclerosis at baseline exam 1 (2000−2002). Lines (shaded areas) represent the adjusted odds ratio (95% confidence interval) of steatosis, based on restricted cubic splines for log-transformed ∑As and As metabolism biomarker distributions with knots at the 10th, 50th, and 90th percentiles. The reference value was set at the 10th percentile. Models were adjusted for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), smoking status (never, former, current), alcohol consumption (never, former, current), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), and diabetes status (nondiabetic, prediabetic, untreated diabetes, treated diabetes) (n = 3,577). The histograms in the background represent the distribution of iAs%, MMA%, DMA%, and ∑As, corrected for arsenobetaine.

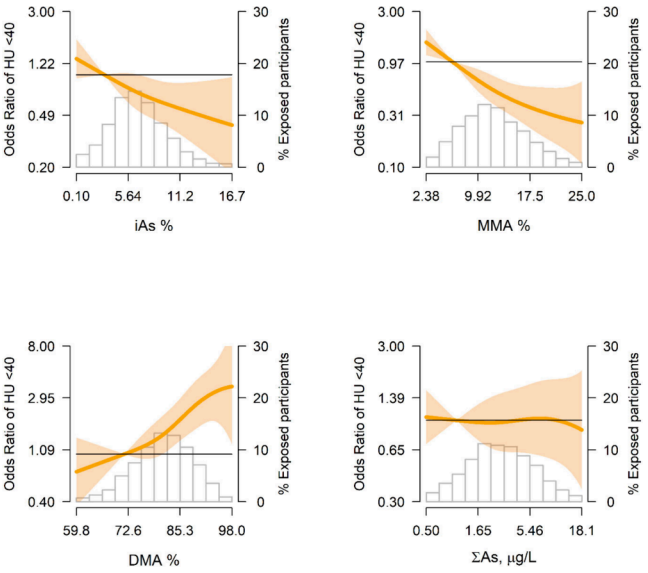

Figure 3. Odds ratios for the associations between urinary As levels (∑As) and As metabolism biomarkers (iAs%, MMA%, DMA%) with hepatic steatosis (HU < 40) in the Multi-Ethnic Study of Atherosclerosis at baseline exam 1 (2000−2002). Lines (shaded areas) represent the adjusted odds ratio (95% confidence interval) of steatosis, based on restricted cubic splines for log-transformed ∑As and As metabolism biomarker distributions with knots at the 10th, 50th, and 90th percentiles. The reference value was set at the 10th percentile. Models were adjusted for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), smoking status (never, former, current), alcohol consumption (never, former, current), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), and diabetes status (nondiabetic, prediabetic, untreated diabetes, treated diabetes) (n = 3,577). The histograms in the background represent the distribution of iAs%, MMA%, DMA%, and ∑As, corrected for arsenobetaine.

the presence of hepatic steatosis and characterized by accelerated methylation and higher DMA% levels in urine.

MASLD is a multisystem disease where systemic insulin resistance, oxidative stress, and related metabolic dysfunction play a role in its development.[52,53] Despite its high prevalence, the pathogenesis of MASLD is not fully understood. Limited literature on the topic has investigated the link between As exposure, As metabolism, and MASLD.[54,55] In NHANES 2003−2018,[54] DMA% was positively associated with MASLD, defined by fatty liver index, a score incorporating age, race, and ethnicity, waist circumference, gamma-glutamyl transferase, fasting insulin, and fasting glucose (OR = 1.17, 95% CI = 1.07, 1.27) after adjusting for other risk factors and urinary metals. Another cross-sectional study from China assessed the relationship between As exposure and As metabolism biomarkers with MASLD, ascertained by abdominal ultrasonography (mild, moderate, and severe).[55] This study found positive associations for both iAs% (OR per standard deviation (SD) = 1.16, 95% CI = 1.03, 1.30) and SMI (OR per log-SD = 1.16, 95% CI = 1.03, 1.31), while MMA% (OR per SD = 0.80, 95% CI = 0.70, 0.91) and PMI (OR per log-SD = 0.86, 95% CI = 0.77, 0.96) were inversely associated with MASLD. We also observed both MMA% and PMI were inversely associated with steatosis while both DMA% and SMI showed positive associations. These findings, including those from our current study, underscore the importance of assessing the connection development of MASLD and As methylation biomarkers.

Emerging research indicates that adiposity may be driving shifts in As metabolism biomarkers.[56,57] During pregnancy, DMA% in urine tends to rise as pregnancy advances, a phenomenon that could be related to changes in adiposity levels and adiposity distribution during pregnancy,[58] although one-carbon metabolism might change during pregnancy (i.e., due to upregulation of phosphatidylethanolamine *N*-methyltransferase (PEMT) and thus methylation capacity).[59,60] Furthermore, body composition indicators such as BMI and percent body fat have shown a direct positive correlation with urinary DMA% and SMI while inversely correlated with urinary MMA%.[56,61,62] Our observations also link elevated urinary DMA% and SMI with the prevalence of MASLD. While the present cross-sectional study does not confirm the direction of the association, findings from the Strong Heart Study, which include 3,792 American Indian adults, suggest that higher urinary DMA% and a lower MMA% are prospectively associated with an increased risk of metabolic syndrome and diabetes.[20,57,63] Thus, adiposity, or other metabolic changes related to adiposity, may influence As metabolism alterations rather than As metabolism influencing

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Table 4. Odds Ratio (95%CI) of L/S < 1.0 and HU < 40 by Urinary ∑As Levels and As Metabolism Biomarkers in the Multi-Ethnic Study of Atherosclerosis by Race/Ethnic Group at Baseline Exam 1 (2000−2002)[a]

			White	Black	Hispanic/Latino	Chinese
		n	OR (95% CI)[b,c]	OR (95% CI)[b,c]	OR (95% CI)[b,c]	OR (95% CI)[b,c]
	L/S < 1.0 (n = 598)		1,373	1,009	825	370
per IQR	**∑As, μg/L[d]**	3,577	0.99 (0.72, 1.38)	1.32 (0.89, 1.95)	0.98 (0.72, 1.35)	1.04 (0.58, 1.85)
per 5%	**iAs%**	3,577	0.87 (0.65, 1.16)	0.73 (0.52, 1.04)	0.99 (0.70, 1.39)	0.38 (0.20, 0.74)
	MMA%	3,577	0.69 (0.57, 0.83)	0.52 (0.39, 0.69)	0.82 (0.65, 1.03)	0.55 (0.36, 0.83)
	DMA%	3,577	1.23 (1.08, 1.40)	1.42 (1.19, 1.69)	1.10 (0.94, 1.28)	1.51 (1.16, 1.97)
per IQR	**PMI[d]**	3,577	0.92 (0.80, 1.05)	0.88 (0.74, 1.05)	0.90 (0.76, 1.08)	1.02 (0.63, 1.66)
	SMI[d]	3,577	1.49 (1.21, 1.83)	1.88 (1.46, 2.42)	1.16 (0.90, 1.49)	2.10 (1.31, 3.38)
	HU < 40 (n = 219)		1,373	1,009	825	370
per IQR	**∑As, μg/L[d]**	3,577	0.86 (0.53, 1.41)	0.90 (0.38, 2.14)	0.87 (0.55, 1.36)	1.62 (0.72, 3.66)
per 5%	**iAs%**	3,577	0.96 (0.63, 1.47)	0.55 (0.24, 1.24)	0.71 (0.42, 1.19)	0.22 (0.07, 0.69)
	MMA%	3,577	0.63 (0.47, 0.84)	0.44 (0.24, 0.79)	0.78 (0.55, 1.10)	0.42 (0.21, 0.85)
	DMA%	3,577	1.26 (1.03, 1.53)	1.61 (1.11, 2.33)	1.20 (0.95, 1.51)	1.85 (1.16, 2.94)
per IQR	**PMI[d]**	3,577	0.78 (0.62, 0.98)	0.84 (0.56, 1.26)	1.01 (0.76, 1.35)	1.22 (0.52, 2.83)
	SMI[d]	3,577	1.60 (1.19, 2.15)	2.17 (1.34, 3.50)	1.22 (0.86, 1.73)	2.64 (1.27, 5.47)

[a]Model: adjust for age (years), sex, center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), smoking status (never, former, current), alcohol consumption (never, former, current), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), and diabetes status (nondiabetic, prediabetic, untreated diabetes, treated diabetes). Abbreviations: L/S, liver/spleen ratio; HU, Hounsfield units; ∑As, total urinary arsenic; iAs, urinary inorganic arsenic; MMA, urinary monomethylarsonic acid; DMA, urinary dimethylarsinic acid; PMI, primary methylation index; SMI, secondary methylation index. [b]OR and CIs for ∑As, PMI, and SMI are reported per higher log IQR. [c]OR and CIs for iAs%, MMA%, and DMA% are reported per higher 5%. [d]Total urinary arsenic is the sum of urinary iAs + MMA + DMA corrected for arsenobetaine; PMI is MMA/iAs; SMI is DMA/MMA.

adiposity. In our study, the association of liver steatosis with As metabolism biomarkers persisted after adjusting BMI, diabetes and other metabolic factors. The impact of liver steatosis in As metabolism biomarkers could also influence As toxicology and health effects, including cancer, cardiovascular disease, and other outcomes.

The association of As metabolism biomarkers with MASLD, might be related to one-carbon metabolism given that *S*-adenosylmethionine serves as the main methyl donor for As metabolism.[64,65] One-carbon metabolism encompasses the interconnected methionine and folate cycles. Alterations in one-carbon metabolism have been implicated in hepatic lipid metabolism.[66−68] In a cross-sectional analysis of As exposure and lipid metabolism in NHANES 2003−2020, the ORs for elevated total cholesterol were 1.47 (1.23, 1.78) for DMA% (80th vs 20th) and 1.36 (1.15, 1.62) for MMA% (80th vs 20th).[69] Animal models have shown that one-carbon metabolism is strongly associated with MASLD.[67,6870] Nutrigenomic analyses have uncovered significant changes in key metabolites and transcript levels of enzymes within hepatic one-carbon metabolism and its associated pathways.[70] A deficiency in dietary folates leads to upregulation of genes involved in lipogenesis, thereby facilitating lipid accumulation.[71] One carbon metabolism, which involves folate, choline, and other nutrients, further research is needed to elucidate the interconnection between methylation processes and As methylation tied to one-carbon metabolism and MASLD.[72,73]

Hispanic/Latinos are disproportionally impacted by MASLD,[74,75] and although genetic factors contribute to racial and ethnic differences in this condition,[76,77] the role of environmental pollutants has not been thoroughly explored. In MESA, Chinese and Hispanic/Latino individuals exhibited average total urine As concentrations that were 82% and 37% higher, respectively, compared to their White counterparts, possibly related to higher rice intake and also higher water As exposure in Los Angeles, a MESA study site that recruited both Chinese and Hispanic participants.[39,78] The association of As metabolism biomarkers with hepatic steatosis among Hispanic/Latinos was weaker compared to other race/ethnic groups, although the trend and the direction of the association was similar. Hispanic/Latinos in MESA are a group highly diverse by ancestry, geography and culture. Genetic factors are believed to account for a considerable proportion of the interindividual variations in As metabolism biomarkers.[79−82] In addition, As metabolism is influenced by a variety of factors, such as nutrition and smoking status, which might vary by culture.[22,83]

This study acknowledges several limitations. First, we have presented cross-sectional data from the MESA cohort, thus temporality cannot be inferred. Second, the diagnosis of MASLD relied on CT scans, an accepted tool used to determine hepatic steatosis noninvasively[84,85] but that does not allow for staging of liver damage or assessment of hepatic inflammation. Hepatic steatosis represents the most pre-eminent preclinical histopathological manifestation of MASLD (e.g., presence of fat and inflammation) and our results yield important information for setting priorities informing prevention efforts designed to tackle MASLD at the population level and reduce disparities. Arsenic exposure assessment was based on a single urinary measurement through speciation. In a recent study from our group, the intraclass correlation coefficient for total urinary As and individual As species measured over 10 years ranged from 0.66 to 0.76.[36,37] While we used arsenobetaine to correct for seafood arsenicals, we cannot discard that DMA still reflects seafood intake in MESA.[86] Another limitation is the lack of representation from rural populations in the U.S. who are more likely to be exposed to elevated As in drinking water due to a

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Table 5. Odds Ratio (95%CI) of the Inorganic Arsenic and the Metabolism Biomarkers with L/S < 1.0 and HU < 40 by Sex in the Multi-Ethnic Study of Atherosclerosis at Baseline Exam 1 (2000−2002)[a]

		n	Males OR (95% CI)[c,d]	Females OR (95% CI)[c,d]
	L/S < 1.0 (*n* = 598)		1,588	1,989
per IQR	∑As, μg/L[e]	3,577	1.00 (0.76, 1.32)	1.16 (0.91, 1.48)
per 5%	iAs%	3,577	0.95 (0.78, 1.17)	0.62 (0.48, 0.80)
	MMA%	3,577	0.81 (0.68, 0.95)	0.56 (0.47, 0.67)
	DMA%	3,577	1.11 (1.00, 1.23)	1.43 (1.27, 1.61)
per IQR	PMI[b,e]	3,577	0.94 (0.82, 1.06)	0.91 (0.81, 1.02)
	SMI[b,e]	3,577	1.29 (1.07, 1.55)	1.73 (1.45, 2.06)
	HU < 40 (*n* = 219)		1,588	1,989
per IQR	∑As, μg/L[e]	3,577	0.96 (0.63, 1.48)	1.00 (0.70, 1.45)
per 5%	iAs%	3,577	0.86 (0.59, 1.25)	0.59 (0.40, 0.87)
	MMA%	3,577	0.72 (0.54, 0.94)	0.58 (0.44, 0.76)
	DMA%	3,577	1.20 (1.00, 1.44)	1.43 (1.19, 1.71)
per IQR	PMI[b,e]	3,577	0.87 (0.71, 1.06)	0.95 (0.79, 1.13)
	SMI[b,e]	3,577	1.45 (1.11, 1.91)	1.59 (1.24, 2.04)

[a]Model: adjust for age (years), center, education (high school or less, some college, college degree or more), rice consumption (< 1 serving/week, 1−6 servings/week, ≥ 1 serving/day), estimated glomerular filtration rate (mL/min/1.73 m^2), total urinary arsenic (log-transformed), urinary creatinine (log-transformed), body mass index (kg/m^2), smoking status (never, former, current), alcohol consumption (never, former, current), low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), and diabetes status (nondiabetic, prediabetic, untreated diabetes, treated diabetes). Abbreviations: L/S, liver/spleen ratio; HU, Hounsfield units; ∑As, total urinary arsenic; iAs, urinary inorganic arsenic; MMA, urinary monomethylarsonic acid; DMA, urinary dimethylarsinic acid; PMI, primary methylation index; SMI, secondary methylation index. [b]PMI is MMA/iAs; SMI is DMA/MMA. [c]OR and CIs for ∑As, PMI, and SMI are reported per higher log IQR. [d]OR and CIs for iAs%, MMA%, and DMA% are reported per higher 5%. [e]Total urinary arsenic is the sum of urinary iAs + MMA + DMA corrected for arsenobetaine.

higher likelihood of using private unregulated drinking water. Strengths include the rigorous protocol and laboratory methods,[36,37] the comprehensive assessment of As species to explore the impact of As metabolites on MASLD and the inclusion of a racially and ethnically diverse cohort of participants across the US.

CONCLUSIONS

MASLD is a highly prevalent liver condition and an independent risk factor for cardiovascular disease and end-stage liver disease. In populations characterized by low-moderate levels of As exposure through consumption of drinking water and food, As exposure as measured in urine was not associated with CT-assessed-hepatic steatosis. However, specific patterns of As metabolism biomarkers, particularly a lower MMA% and a higher DMA%, characterized also with higher SMI, were linked to higher levels of hepatic steatosis. Future prospective studies, in cohorts with well-defined MASLD over time and with longitudinal data on iAs exposure, As metabolism biomarkers, and biomarkers of liver damage, are essential to delineate the association between MASLD and As metabolism biomarkers and As-related disease.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/ehp.6c00759.

Figure S1 and Tables S1 and S2 (PDF)

AUTHOR INFORMATION

Corresponding Author

Hui-Chen Wu − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*; Phone: 212-305-6960; Email: hw2057@cumc.columbia.edu

Authors

Ronald A. Glabonjat − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Kathrin Schilling − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

William A. Anderson − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Siyue Gao − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Arce Domingo Relloso − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States; Department of Biostatistics, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Nancy LoIacono − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Monique Slowly − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Anne E Nigra − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Tiffany Sanchez − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Marisa H. Sobel − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

Marta Galvez-Fernandez − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*

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Matthew J. Budoff − *Lundquist Institute at Harbor-UCLA, Department of Medicine, Torrance, California 90502, United States*
Mary V Gamble − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*
Ana Navas-Acien − *Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, New York 10032, United States*
Mariana Lazo − *Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania 19104, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/EHP.6c00759

Author Contributions

HCW, ANA, and ML conceived and designed the study. ANA funded the project. MB, ANA, and ML provided their expertise regarding the MESA cohort. RAG and KS conducted the arsenic measurements. WA, SG, ADR, MS, MS, and MGF assisted the data cleaning and data analysis. HCW, WA, SG, and ANA lead the manuscript writing. All of the authors discussed the study design, the interpretation of the results, and reviewed and approved the final manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATION

ALT, alanine aminotransferase
(ALT), AsB, arsenobetaine
BMI, body mass index
CI, confidence interval
CT, computed tomography
CV, coefficients of variation
CWS, community water systems
DBP, diastolic blood pressure
DMA, dimethylarsinic acid
DMA%, dimethylarsinic acid percentage
eGFR, estimated glomerular filtration rate
HDL-C, high-density lipoprotein cholesterol
HU, Hounsfield unit
iAs, inorganic arsenic
iAs%, inorganic arsenic percentage
IQR, interquartile range
LOD, limit of detection
L/S, liver/spleen
MASLD, metabolic-associated steatotic liver disease
MCL, maximum contaminant level
MESA, Multi-Ethnic Study of Atherosclerosis
MMA, monomethylarsonic acid
MMA%, monomethylarsonic acid percentage
NHANES, National Health and Nutrition Examination Survey
ORs, odds ratios
PMI, primary methylation index
SBP, systolic blood pressure
SMI, secondary methylation index
TG, triglycerides
∑As, sum of urinary arsenic metabolites

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