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# Contribution of arsenic and uranium in private wells and community water systems to urinary biomarkers in US adults: The Strong Heart Study and the Multi-Ethnic Study of Atherosclerosis

**Maya Spaur**[1], **Ronald A. Glabonjat**[1], **Kathrin Schilling**[1], **Melissa A. Lombard**[2], **Marta Galvez-Fernandez**[1], **Wil Lieberman-Cribbin**[1], **Carolyn Hayek**[3], **Vesna Ilievski**[1], **Olgica Balac**[1], **Chiugo Izuchukwu**[1], **Kevin Patterson**[1], **Anirban Basu**[1], **Benjamin C. Bostick**[4], **Qixuan Chen**[5], **Tiffany Sanchez**[1], **Ana Navas-Acien**[1], **Anne E. Nigra**[1]

[1]Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY, USA

[2]U.S. Geological Survey, New England Water Science Center, Pembroke, NH, USA

[3]Columbia Water Center, Columbia Climate School, New York, NY, USA

[4]Lamont-Doherty Earth Observatory of Columbia University, Palisades, NY, USA

[5]Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY, USA

## Abstract

**Background:** Chronic exposure to inorganic arsenic (As) and uranium (U) in the United States (US) occurs from unregulated private wells and federally regulated community water systems (CWSs). The contribution of water to total exposure is assumed to be low when water As and U concentrations are low.

**Objective:** We examined the contribution of water As and U to urinary biomarkers in the Strong Heart Family Study (SHFS), a prospective study of American Indian communities, and the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective study of racially/ethnically diverse urban U.S. communities.

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**Corresponding author:** Maya Spaur. mss2284@cumc.columbia.edu. (240) 422-7881. 722 W 168th St, Room 1107, New York, NY.

Author Contribution Statement:

**Ronald A. Glabonjat, Kathrin Schilling, Vesna Ilievski, Olgica Balac,** and **Chiugo Izuchukwu** conducted the urine arsenic and uranium measurements. **Maya Spaur, Marta Galvez-Fernandez**, **Wil Lieberman-Cribbin, Carolyn Hayek,** and **Anne E. Nigra** contributed data preparation, management, and statistical code. **Melissa A. Lombard, Benjamin C. Bostick, Qixuan Chen, Ana Navas-Acien,** and **Anne E. Nigra** contributed to conceptualization and writing-review & editing. **Ronald A. Glabonjat** and **Kathrin Schilling** contributed to writing-original draft & editing. **Kevin Patterson, Anirban Basu,** and **Tiffany Sanchez** contributed to conceptualization. **Maya Spaur** conducted writing-original draft & editing, visualization, and statistical analysis.

**Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

This research was approved by the Institutional Review Boards at the participating institutions, and written informed consent was given by all participants. This manuscript has been cleared by the respective Tribal Research Review Boards and area Indian Health Service IRBs for the SHFS and by the Publications and Presentations Committee for MESA.

Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

**Methods:** We assigned residential zip code-level estimates in CWSs (μg/L) and private wells (90$^{th}$ percentile probability of As >10 μg/L) to up to 1,485 and 6,722 participants with dietary information and urinary biomarkers in the SHFS (2001–2003) and MESA (2000–2002; 2010–2011), respectively. Urine As was estimated as the sum of inorganic and methylated species, and urine U was total uranium. We used linear mixed-effects models to account for participant clustering and removed the effect of dietary sources via regression adjustment.

**Results:** The median (interquartile range) urine As was 5.32 (3.29, 8.53) and 6.32 (3.34, 12.48) μg/L for SHFS and MESA, respectively, and urine U was 0.037 (0.014, 0.071) and 0.007 (0.003, 0.018) μg/L. In a meta-analysis across both studies, urine As was 11% (95% CI: 3, 20%) higher and urine U was 35% (5, 73%) higher per 2-fold higher CWS As and U, respectively. In the SHFS, zip-code level factors such as private well and CWS As contributed 46% of variation in urine As, while in MESA, zip-code level factors, e.g. CWS As and U, contribute 30 and 49% of variation in urine As and U, respectively.

**Significance:** Water from public water supplies and private wells represents a major contributor to inorganic As and U exposure in diverse US populations.

### Keywords

metals; epidemiology; exposure modeling

## 1. Introduction

In the United States (US), drinking water, diet, and in some places dust are the major sources of inorganic arsenic (As) and uranium (U), which are potent toxicants and carcinogens.[1–8] Approximately 90% of US residents are reliant on community water systems (CWSs), which are public water systems regulated by the US Environmental Protection Agency (EPA). When establishing maximum contaminant levels (MCLs) for regulated contaminants, EPA considers technological feasibility, cost, and public health benefit.[9, 10] The current MCLs for As and U are 10 and 30 μg/L, respectively; these are consistent with the World Health Organization (WHO) recommended limits for these elements in drinking water. The EPA also sets the MCL goal, a non-enforceable level below which there is no known or expected health risk, at 0 μg/L for both elements.[9, 10] The WHO's recommendation to have As levels as low as possible is also consistent with the EPA's MCL goal of zero.[11, 12]

Approximately 40 million people in the US rely on unregulated private wells for drinking water.[13, 14] Private wells usually serve individual households, and the well or home owner is responsible for testing for contaminants of concern, installing treatment systems, and maintaining those systems over time. Regulated public water has traditionally been less studied as a source of As and U exposure in the US compared to unregulated private wells. Private wells are infrequently tested and treated and have an increased likelihood of high concentrations of arsenic or uranium.[3, 15–17] Moreover, the epidemiologic association of public water As and U with relevant adverse health outcomes remains insufficient because estimates of public water As and U are not readily available for most epidemiologic cohorts.

A current gap in the science is understanding the association and relative contribution of CWS and private well As and U to urine biomarkers in US epidemiologic cohorts. Previous studies have estimated that diet (particularly rice) is a major contributor to total inorganic As exposure when water As concentrations are below 10 μg/L.[18, 19] These studies leveraged tap water samples for some participants, but also modeled water as nationwide mean As concentrations and were limited by the lack of robust, speciated urine As measurements which can isolate inorganic As from less or non-toxic and food derived organic species.[20] Assigning participants area-level water concentration estimates can also capture drinking water consumed outside of the home. For U, no studies have yet assessed the contribution of drinking water to biomarkers in general US populations. Differences in the concentration of As and U in drinking water may result in differences in the relative contribution of water to total exposure. Regional variation in drinking water levels may be due to differences in geogenic As and U in groundwater, driven by differences in geochemistry, hydrology, aquifer material, and climate.[21–24] In addition, high water As and U can occur due to contamination from U mining and milling, often on/near tribal lands.[25–27] As and U are known to co-occur in unregulated groundwater sources, untreated public supply wells, and in finished CWS supplies.[28–30] Groundwater As and U can be mobilized by similar processes, and occurrence is driven by the geologic composition of the aquifer; in particular, As, U, and manganese (Mn) are the most common trace elements that exceeded human health benchmarks in glacial and nonglacial unconsolidated sand and gravel aquifers.[29]

Differences in water As and U levels across race/ethnic subgroups are rooted in inequalities in the built, natural, and sociopolitical environments (e.g., selective enforcement, access to regulated public systems, access to water treatment technologies, challenges to effectively implement private well testing and treatment, etc.).[31, 32] Differences in the relative contribution of water to total exposure are likely influenced by diet, geography, socioeconomic factors (e.g. treatment systems) and other sources of exposure such as dust.[17, 18, 32]

Our objectives were to evaluate the association of water As and U levels assigned at the zip-code level with urine biomarkers, and to quantify the percent of variability in urine As and U explained by assigned levels in water, in the Strong Heart Family Study (SHFS) and in the Multi-Ethnic Study of Atherosclerosis (MESA). The SHFS includes participants reliant on both private wells and regulated CWSs whereas participants in MESA are almost entirely in urban areas that rely primarily on CWSs; we thus assigned both private well and CWS As and U levels to SHFS participants, and only CWS As and U levels to MESA participants. Information from this study can potentially inform equitable drinking water interventions and regulations to reduce total As and U exposure for the most highly exposed populations and advance environmental justice in drinking water quality.

## 2. Materials and Methods

### 2.1 Study population

We included participants from the SHFS and MESA, two prospective epidemiologic cohorts. The SHFS is a study of cardiovascular disease and its risk factors in American Indians.[33] Participants are family members of participants enrolled in the Strong Heart Study, which

enrolled members from 12 American Indian Nations at field centers in Arizona, Oklahoma, and North Dakota and South Dakota.[33] MESA is a study of cardiovascular disease and its risk factors in a racially/ethnically diverse, community-based sample, and participants were free of clinical cardiovascular disease at baseline.[34] Participants were enrolled from six urban centers (Baltimore, MD, Chicago, IL, Los Angeles, CA, New York City, NY, Saint Paul, MN, and Winston-Salem, NC), with approximately 38% Non-Hispanic White, 25% Non-Hispanic Black, 23% Hispanic, and 11% Chinese-American participants.[34] Participants in both cohorts completed an in-person interview, physical examination, and food frequency questionnaire, and provided spot urine samples during physical examination during in person study visits for further analysis.

Data management and analysis were conducted in R version 4.1.0.[35] A total of 1,881 SHFS participants in 2001–2003 had urinary As and creatinine (to control for urine dilution) data available. We excluded participants missing body mass index (BMI, N=8), missing smoking status and pack years (N=40; pack years is defined as the number of cigarettes smoked per day multiplied by the number of years smoking), missing dietary data about As containing foods (N=98), missing assigned zip code-level CWS As concentration (N=422) or private well As probability (N=35), for a final total of 1,278 SHFS participants in As analyses (Supplemental Figure S1). A total of 1,882 SHFS participants had urinary U and creatinine data available. We excluded participants missing BMI (N=8), missing smoking status and pack years (N=40), missing dietary data about U (N=98), missing assigned CWS U (N=251), for a final total of 1,485 SHFS participants in U analyses (Figure S2). Of these, N=899 had an assigned private well U estimate available. Private well U was not available for participants in North Dakota.

MESA participants had urinary As measured in spot urine samples from multiple study visits. Across both the 2000–2002 and 2010–2011 visits, a total of 6,739 MESA participants had spot urine samples with both urinary creatinine and As data available (N=7,672 samples). We excluded samples from participants missing smoking status and pack years (N=101), missing dietary data relevant for As (N=711), missing residential zip code (N=41) and missing assigned CWS As (N=97), for a final total of 6,722 MESA samples (from N=5,903 participants) in As analyses (Figure S1). A total of 7,672 MESA samples (from N=6,739 participants) in 2000–2002 and 2010–2011 had urinary creatinine and U data available. We excluded samples from participants missing smoking status and pack years (N=101), missing dietary data relevant for U (N=621), missing residential zip code (N=41) and missing assigned CWS U (N=3,277), for a final total of 3,632 MESA samples (from N=3,203 participants) in U analyses (Figure S2). Many participants were missing assigned CWS U because CWS U records and concentration estimates are less complete than those for As nationwide, reflecting the EPA's compliance monitoring requirements.[30]Across the SHFS and MESA, we included data for 410 zip codes for As analyses and 313 zip codes for U analyses.

### 2.2 Urinary arsenic and uranium measurement

Urinary metals and metalloids (including As and U) from MESA participants were analyzed at the Trace Metals Core Laboratory at Columbia University. Total As and U concentrations

were quantified together with a panel of 15 other metals and metalloids using a PerkinElmer NexION 350S Quadrupole Inductively Coupled Plasma-Mass Spectrometer (Q-ICP-MS) equipped with an Elemental Scientific (Omaha, USA) SC-4 DX FAST autosampler enclosure with ULPA Filter system and operated with the PerkinElmer Syngistix software. Urine arsenic species (inorganic As (iAs), monomethyl arsonate (MMA), dimethylarsinate (DMA), and other neutral and cationic arsenic species including arsenobetaine (AB; referred to as AB throughout the remaining article) were analyzed on an Agilent 1260 Infinity II Bio-inert high performance liquid chromatography (HPLC) system coupled to an Agilent 8900 inductively coupled plasma triple quadrupole mass spectrometer (ICP-MS/MS). To minimize the percent of samples undetectable for iAs, the urine sample was treated with hydrogen peroxide to convert arsenite to arsenate and reported as "total iAs".[36] To evaluate urine dilution, creatinine was measured using the Jaffé reaction method and specific gravity was measured using Total Solids Refractometer model Atago IC-PAL-10S. For 7,672 MESA urine samples analyzed for As and U with creatinine available, the N (%) >LOD was 7,345 (95.7%) for iAs (LOD=0.03 μg/L), 7,599 (99%) for MMA (LOD=0.03 μg/L), 7,671 (100%) for DMA (LOD=0.03 μg/L), 7,637 (99.5%) for AB (LOD=0.02 μg/L), and 6,778 (88.3%) for U (LOD U=0.001 μg/L). For the SHFS, concentrations of iAs, MMA, DMA, and AB were determined by anion-exchange high performance liquid chromatography (HPLC; Agilent 1100, Agilent Technologies) coupled to ICPMS (Agilent 7700x) at Graz University.[36] For 1,881 SHFS urine samples with As and creatinine available, the N (%) >LOD was 1,678 (89.2%) for iAs (LOD=0.1 μg/L), 1,821 (96.8%) for MMA (LOD=0.1 μg/L), 1,881 (100%) for DMA (LOD=0.1 μg/L), and 1,769 (94%) for AB (LOD=0.1 μg/L). For 1,882 SHFS urine samples with urine U and creatinine, N (% >LOD) of U samples was 1,542 (81.9%) (LOD U=0.008 μg/L). All sample concentrations measured below the limit of detection (LOD) were replaced by the LOD divided by the square root of two. This standard method is used by the US Centers for Disease Control and Prevention (CDC) in reporting environmental biomarkers and concentrations below the LOD.[37] For As, our main analyses evaluated iAs (sum of arsenite and arsenate) and sumAs (sum of iAs, MMA, and DMA) as biomarkers of total inorganic arsenic internal dose.

### 2.3 Water arsenic and uranium variables

We assigned zip code level CWS and private well As and U estimates based on participant residential zip code at baseline, which might have resulted in additional measurement error in MESA participants at exam 5 if they had changed their address from baseline. We relied on previously developed and published estimates of As and U in both CWSs and private wells.[30, 38–40]

For CWS As and U, we developed population-weighted average CWS concentrations for each zip code tabulation area (ZCTA) using estimates previously developed by Nigra et al.[24] and Ravalli et al.[30] These CWS-level estimates (2006–2011 for As and 2000–2011 for U) were generated from routine compliance monitoring records in the US EPA's Six Year Review of Contaminant Occurrence Database, which represents over 95% of all public systems nationwide.[38] The states of Arizona and Oklahoma (SHFS), California, Illinois, Minnesota, and North Carolina (MESA) publish publicly available shapefiles of CWS distribution boundaries (Supplemental Table S1). Because some ZCTAs may be served

by multiple CWSs, we overlapped CWS distribution boundaries with 2010 Census ZCTA boundaries using the "st_intersection" function in the "sf" R package,[41] and calculated the area of overlap between CWS service areas and ZCTAs and between CWS service areas and Census blocks. Census data was sourced from "tigris" and "tidycensus" packages in R. Census block-level population attribute data was applied to the overlapping CWS service area, and aggregated to generate population weights for each CWS within a ZCTA. Population weights were only generated for CWSs serving an area with a population > 0. Population weights were applied using the "weighted.mean" function to create population-weighted average estimates of CWS As and U grouped at the ZCTA level.

We assigned CWSs to participants living in the states of North Dakota and South Dakota (SHFS) and New York and Maryland (MESA) because these states do not publish shapefiles of CWS distribution boundaries (detailed methods provided in Appendix). For participants in South Dakota, we matched residential zip code to the corresponding CWS based on town name and published .pdf maps of rural water system service area boundaries.[42] For participants in North Dakota, we matched residential zip code to the corresponding CWS based on town name and personal communication with the North Dakota Water Resources and Environmental Quality departments (Ann Fritz and Greg Wavra, email communication, October 2021). For participants in New York, we matched residential zip code to the corresponding CWS based on town name.[43] We assigned participants residing in Baltimore City and areas of the surrounding counties that are expected to be served by the City of Baltimore CWS[44] to the estimates for the City of Baltimore CWS.[24, 43]

For private wells, Lombard et al.[22] has estimated the probability of water As exceeding 10 μg/L throughout the US using boosted regression tree models based on over 20,000 private supply well samples collected and analyzed between 1970 and 2013.[39] Private well estimates were generated for 1 $km^2$ grids across the conterminous US and grouped at the zip code level. We calculated the $90^{th}$ percentile for the probability of private well As exceeding 10 μg/L for each zip code (hereafter referred to as "private well As"). The National Uranium Resource Evaluation (NURE) program, under the Department of Energy, collected and analyzed uranium in water sources across the US from 1975–1980.[40] 335,547 samples were collected, as previously described.[40, 45] Uranium concentrations (μg/L) were reported in the NURE Hydrogeochemical and Stream Sediment Reconnaissance database with longitudinal coordinates of sample locations. Sample locations were grouped by ZCTA and uranium concentrations were averaged (hereafter referred to as "private well U").[40, 45]

Water estimates for the SHFS were merged to participant data at the Center for American Indian Health Research at the University of Oklahoma Health Sciences Center located in Oklahoma City, Oklahoma. To protect the confidentiality of SHFS participants, all private well and CWS estimates were jittered by 20% (default, computed as the smallest difference between estimates per study center / 5) and rounded to 2 decimal points.

### 2.4 Additional variables

Information on sociodemographic (age, sex, education, race/ethnicity), anthropometric (body mass index, BMI calculated from measured height and weight), and lifestyle (smoking status, pack-years) characteristics were collected during the exam visits, as

previously defined.[46, 47] Smoking status was determined by self-report questionnaires and was categorized as never, former, and current.

Dietary information from SHFS and MESA participants was collected using a food frequency questionnaire. In the SHFS, self-reported frequency of intake of As- and U-containing foods was combined with serving sizes to calculate the grams per day of rice or dishes with rice (relevant for As), organ meat (relevant for As and U), processed meat (relevant for As), and fish/seafood (relevant for As), as previously described.[46] For MESA participants, self-reported frequency of weekly intake was used to calculate grams of fish (relevant for As) and red meat (relevant for As and U) consumed per week, and the number of weekly servings of rice (relevant for As), categorized as < 1 serving per week (reference), 1–6 servings per week, and 1 or more servings per day, as previously described.[47] Values of zero grams were imputed with the minimum non-zero value divided by 10.

### 2.5 Statistical analysis

All statistical analyses were conducted at the individual level separately for SHFS and MESA participants. Descriptive analyses were conducted overall and stratified by sex and race/ethnicity.

We performed linear mixed-effects model analyses for the association of assigned water As and U with the corresponding urinary As or U concentrations using the “lmer” function in R package “lme4”.[48] Random effects were included for zip code identifier to account for correlation within zip code (both SHFS and MESA), for family identifier to account for the clustered family design (SHFS), and for participant identifier to account for repeated measurements (MESA). Fully adjusted models were adjusted for age, sex, BMI, smoking status, pack years, natural log transformed urine creatinine to account for urine dilution, urine AB (μg/L) in As models to account for seafood intake, and self-reported dietary intake of As and U containing foods. Self-reported dietary intake of As was defined as the number of weekly servings of rice and grams/week of fish and red meat for MESA, and defined as grams/day of rice, organ meat, processed meat, and fish for SHFS. Self-reported dietary intake of U was defined as grams/week of red meat for MESA, and defined as grams/day of organ meat for SHFS.

We estimated the geometric mean ratio (GMR, 95% confidence interval, CI) of urinary As and U (μg/L, natural log transformed) per 2-fold higher (log-2 transformed) CWS As and U (μg/L) and private well As (probability >10 μg/L) and private well U (μg/L). We also report the corresponding percent change defined as ((GMR-1)*100%). Model 1 was adjusted for urinary creatinine and urine AB (As models only), and included random effects for zip code (SHFS, MESA), participant identifier (MESA, to maximize repeated data in a subset at exams 1 and 5), and family identifier (SHFS). Model 2 (fully adjusted) included further adjustment for age, sex, BMI, smoking status, pack years, and dietary sources of As and U. To evaluate the contribution of water As and U to total estimated As and U exposure as measured by urinary biomarkers (modeled in μg/g creatinine, to enable direct interpretation of water contributions while also accounting for urine dilution), we used the “r.squaredGLMM” function in the MuMIN package of R to compute the conditional $R^2$ for

progressively adjusted models.[49] We additionally calculated the proportion of variance in urine As and U explained by zip code level random effects, such as zip code-level As and U.

To evaluate the change in the contribution of water to urine As and U at intervals directly relevant for regulatory standards, we repeated our main analyses with CWS As and U as categorical variables. For SHFS participants, we calculated the GMR for participants with CWS As > 1–5 and > 5 μg/L compared to those with CWS As ≤ 1 (reference). For MESA (where the distribution of CWS As is lower), we categorized CWS As concentrations ≤ 1 (reference) and > 1 μg/L. For CWS U, we categorized CWS U concentrations as ≤ 1 (reference), > 1–10, and > 10 μg/L for the SHFS, and ≤ 1 (reference), > 1–5, and > 5 μg/L for MESA (lower distribution of CWS U).

Finally, we pooled the effect estimates for CWS As and U across SHFS and MESA using a random-effects meta-analysis, using the “metagen” function in the “meta” package in R.[50, 51]

### 2.6 Sensitivity Analyses

We performed several sensitivity analyses (detailed methods provided in Appendix). To make our findings informative for future risk assessment efforts, we repeated our analyses after transforming assigned water As and U into estimated average daily dose using a standard exposure assessment framework used by US EPA.[52, 53] We also compared findings assigning area-weighted ZCTA-level CWS As and U estimates (instead of population-weighted ZCTA-level CWS estimates), also with similar findings (data not shown). To assess the impact of adjusting for urine dilution with creatinine, we repeated our analyses a) after dividing urinary As and U by urinary creatinine concentrations (μg As/g creatinine or μg U/g creatinine), and b) after correcting for specific gravity.[54] We additionally evaluated whether the associations between CWS As and U and urinary As and U were stable across monitoring periods in MESA. We assigned MESA participants with urinary biomarkers collected at Exams 1 (2000–2002) or 5 (2010–2011) to the period-specific CWS As concentrations (2006–2008 or 2009–2011) and CWS U concentrations (2000–2007 or 2008–2011).

We evaluated potential non-linearity in associations between water As and U and urinary As and U using cubic regression splines and generalized additive models (GAMs) with the mgcv package in R.[55–57] To reduce computation time, we restricted MESA analyses to exam 5 urine As (N=827) and U (N=433) samples. Finally, we explored potential effect measure modification by sex and by race/ethnicity (the latter within MESA) to determine if potential differences in sources of exposure or metabolic processes would influence the relative contribution of water to total exposures across sociodemographic groups.

## 3. Results

### 3.1 Descriptive characteristics

The median (interquartile range, IQR) among SHFS and MESA participants was, respectively, 0.47 (0.25, 0.84) and 0.33 (0.17, 0.60) μg/L for urinary iAs; 5.32 (3.29, 8.53) and 6.32 (3.34, 12.48) μg/L for sumAs; 3.10 (1.99, 4.79) and 0.35 (0.35, 0.38) μg/L for

CWS As; and 5.6 (4.2, 9.5) % for private well As probability (this value only in SHFS) (Tables 1 and 2). For U, the median (IQR) among SHFS and MESA participants was 0.037 (0.014, 0.071) and 0.007 (0.003, 0.018) μg/L, respectively, for urinary U; and 0.59 (0.36, 1.08) and 1.14 (0.63, 5.22) μg/L for CWS U (Tables S2A and S2B). Among SHFS participants, the median (IQR) of private well water U was 4.21 (3.75, 11.83) μg/L.

### 3.2 Linear mixed-effects model results

In adjusted analyses, urine iAs of SHFS participants was 26% (95% CI: 19, 34%) higher and urine sumAs was 16% (95% CI: 10, 22%) higher per 2-fold higher CWS As (μg/L). Urine iAs was 12% (95% CI: 2, 23%) higher per 2-fold higher private well As (Figure 1, Table S3). Among MESA participants, urine iAs was 13% (95% CI: 9, 17%) higher and urine sumAs was 7% (95% CI: 3, 11%) higher per 2-fold higher CWS As (μg/L). In the meta-analysis, the pooled percent change of urinary As per 2-fold higher CWS As was 19% (7, 33%) higher for iAs, and 11% (3, 20%) higher for urine sumAs, across SHFS and MESA participants.

In adjusted analyses, urine U was 18% (95% CI: 11, 26%) higher and 53% (95% CI: 48, 58%) higher per 2-fold higher CWS U (μg/L) among SHFS and MESA participants, respectively (Figure 1, Table S4). Two-fold higher private well U was associated with 8% (95% CI: −1, 19%) higher urinary U in the SHFS. The corresponding pooled percent change in urinary U per 2-fold higher CWS U was 35% (5, 73%) across the SHFS and MESA.

The associations between water As and U and urinary biomarkers were largely consistent by sex in both the SHFS and MESA (data not shown). We found evidence for effect measure modification and statistical interaction ($p<0.05$) by race/ethnicity in MESA; specifically, the association between water As and urinary As was attenuated among Hispanic participants, and the association between water U and urinary U was attenuated among Chinese American participants (Tables S3, S4).

### 3.3 Categorical analyses

Findings from our analyses modeling CWS As and U as categorical variables are provided in Table 3. The GMR of urine sumAs comparing SHFS participants with CWS As >1–5 and > 5 μg/L to those with CWS As ≤ 1 μg/L was 1.22 (95% CI 1.02, 1.46; difference in unadjusted GMs=1.63 μg/L) and 1.88 (95% CI 1.51, 2.34; difference=4.01 μg/L), respectively. In MESA, the GMR of urine sumAs comparing those with CWS As >1 vs CWS As ≤ 1 μg/L was 1.18 (95% CI 1.08, 1.28; difference=4.72 μg/L). In the SHFS, the GMR of urine U comparing those with CWS U >1–10 and > 10 vs. those with CWS U ≤ 1 μg/L was 1.21 (95% CI 0.95, 1.52; difference=0.003 μg/L) and 3.53 (95% CI 95% CI 2.51, 4.96; difference=0.084 μg/L), respectively. In MESA, the GMR of urine U comparing those with CWS U > 1–5 and > 5 vs. ≤ 1 μg/L was 2.17 (95% CI 1.81, 2.62; difference=0.001 μg/L) and 5.05 (95% CI 4.23, 6.02; difference=0.019 μg/L), respectively.

We estimated the contribution of water As and U to urinary As and U using the conditional $R^2$ (Table 4). In crude analyses (predictors: water As or U with random effects for zip code and participant (MESA) or family (SHFS) identifier), the conditional $R^2$ for urinary sumAs was 0.54 in MESA. In the SHFS, the conditional $R^2$ was 0.46 for private well As

and 0.43 for CWS As. Inclusion of urine AB increased the conditional $R^2$ for urine sumAs analyses by 0.05 to 0.06 for both the SHFS and MESA. For U, the conditional $R^2$ for urine U was 0.60 in MESA. In the SHFS, it was 0.22 for CWS U and 0.17 for private well U. Adjustment for additional factors (e.g., age, sex, BMI, smoking, and dietary sources) had a small (0.01–0.02 increase) or negligible impact on the conditional $R^2$ for all analyses. Based on variance estimates of random-effects only models (provided in Table S5), approximately 30% and 46% of the variation in urine sumAs in MESA and the SHFS, respectively, can be explained by zip code level factors such as water As. 49% and 17% of the variation in urine U in MESA and SHFS, respectively, can be explained by zip code level factors such as water U.

### 3.4 Sensitivity analyses

**Average daily dose—**Results for analyses modeling the exposure as the average daily dose of water As and U from CWSs using standard intake rates of water consumption are provided in Supplemental Tables S6 and S7, respectively. In fully adjusted analyses, per 2-fold higher average daily dose of water As, urinary iAs was 28% (95% CI: 21, 36%) and 20% (95% CI: 16, 24%) higher among SHFS and MESA participants, respectively. In fully adjusted analyses, per 2-fold higher average daily dose of CWS U, urinary U was 21% (95% CI: 14, 28%) and 49% (95% CI: 45, 54%) higher among SHFS and MESA participants, respectively. Similar to our main analyses, the associations between average daily dose of water As or U and urinary As or U were similar by sex and across race/ethnicity group, though attenuated among Hispanic participants for As analyses.

To assess the impact of the urine dilution correction method, we repeated our analyses using urinary As and U in units of μg/g creatinine and after correcting for specific gravity. Our results were consistent with our main analyses (Supplemental Tables S8 and S9). We also evaluated whether the associations between CWS As and U and urine As and U were stable over time in MESA; we found that the corresponding associations were similar across time periods.

**Non-linear associations—**There was no evidence of non-linearity in As analyses in MESA. In the SHFS, the association between water As and urinary As was generally positive at CWS As concentrations > 3.5 μg/L. In the SHFS and MESA, the association between CWS U and urinary U was generally positive at CWS U > 1.5 μg/L (Figure S3).

## 4. Discussion

Our findings support As in drinking water as a major contributor to As exposure and total internal dose in racially/ethnically diverse US populations in both urban and rural settings. For U, our findings indicate that regulated public drinking water is a major source of U exposure in urban populations. Our estimates of water U explained less of the variability in urine U in the SHFS, either because we lacked appropriate water U estimates in rural areas or because ingestion of U-containing foods or inhalation and dust U exposures are more important in rural settings.[27] This represents the first study to model drinking water As and U for SHFS and MESA participants, and to examine the association of these environmental measures with biomarker data as a measure of internal dose. These findings also indicate

that water As and U data assigned at the zip-code level can be used as estimates of water exposure in epidemiologic studies of US populations.

Contrary to prior estimates from prediction modeling studies, we observed that drinking water is a major contributor to total inorganic As exposure even at CWS As levels < 10 μg/L.[18, 19] Prior studies did not match assigned water estimates to biomarker data at the individual level.[18, 58] Although diet remains a source of inorganic As exposure and As in food remains largely unregulated, our findings indicate that reducing water As concentrations is likely to reduce total inorganic As exposure more than reducing dietary intake for SHFS and MESA communities, even when water As is below the MCL. Higher levels of seafood consumption in MESA may also contribute to the attenuated association observed for urinary sumAs (and also observed in analyses specific to DMA, data not shown); however, our results remained positive and significant.[59] These findings have major implications for drinking water regulations and interventions in the US, and support that interventions to reduce water As below the current US EPA MCL of 10 μg/L are likely to meaningfully decrease total inorganic As exposure. Compared to CWS As levels ≤ 1 μg/L, urinary iAs was 50% higher at CWS As levels >1–5 μg/L in the SHFS and 32% higher at CWS As levels > 1 μg/L in MESA. At CWS As > 5 μg/L, urinary iAs was 156% higher among SHFS participants. These findings indicate that a lower MCL, such as the MCLs of 5 μg/L in New Jersey and New Hampshire, may significantly reduce inorganic As exposure nationwide.[60, 61] Our findings also underscore the importance of testing private wells and mitigation measures: urinary iAs was 54% higher when the probability of private well As > 10 μg/L was > 25%, vs. probability ≤ 25% (Table S10). For private wells with elevated arsenic concentrations, when point-of-use exposure reduction measures are not effective or feasible, alternative interventions, such as the use of bottled water or connection to the nearest CWS, may reduce exposure. Similarly, a lower MCL for U may substantially reduce exposure in urban and rural communities: compared to CWS U levels ≤ 1 μg/L, urinary U was 253% higher at CWS U > 10 μg/L in the SHFS and 405% higher at CWS U > 5 μg/L in MESA.

We found evidence of effect measure modification for As by race/ethnicity in MESA in stratified analyses. In MESA, results stratified by race/ethnicity may reflect the geographic distribution of participants: Hispanic participants in MESA generally reside in California, New York and Minnesota, while Chinese American participants generally reside in California and Illinois, and Non-Hispanic White and Black participants are more distributed throughout the study sites (providing greater variability in water exposures for stratified analyses) (Figure S4). The association between CWS As and urinary As was attenuated among Hispanic participants, likely due to relatively low CWS As concentrations in New York City and the surrounding areas where rice consumption is likely the dominant source of inorganic As exposure. In post hoc analyses excluding New York participants, a positive and statistically significant association between CWS and urinary As was observed among Hispanic participants. After further stratification by country/region of origin, we observed a positive and statistically significant association for Hispanic participants of Mexican origin (who largely reside in California and Minnesota) but not for Hispanic participants of Cuban, Dominican, Puerto Rican/Caribbean or Other Hispanic origin. As almost all Hispanic participants of Mexican origin resided in California and Minnesota, this further

underscores the importance of regional variability in drinking water arsenic contributions. The association between CWS U and urinary U was attenuated among Chinese American participants, likely due to limited variability in CWS U exposure assignment: because CWS U data were missing for most areas of Illinois where participants resided, most (97%) Chinese American participants included in our U analyses were in California. Although we adjusted for dietary sources of As and U, residual confounding by diet could partially explain differences observed across racial/ethnic groups.

We estimated lower CWS As and U for Non-Hispanic White participants, which is consistent with several studies finding significant racial/ethnic and regional inequalities in CWS concentrations of As and U nationwide.[24, 30, 32, 62] Specifically, higher proportions of Non-Hispanic White residents are associated with lower concentrations of As and U in regulated CWSs. Together with our findings, this suggests that reducing water As and U concentrations for the most highly exposed populations may improve environmental health and racial equity nationwide.

Levels of U in water were two orders of magnitude higher than those estimated in urine. There are several explanations for this relative difference comparing water and urine for As versus U. The ratio of As in drinking water and urine is estimated to be approximately 1:1 because iAs is absorbed completely in the gastrointestinal tract after ingestion and most excretion occurs through urine.[63, 64] However, this is not true for U; a substantial portion of ingested U is not absorbed through the gastrointestinal tract, and previous studies suspect that only 1 to 1.5% is absorbed.[65, 66] Also, not all U absorbed through the gastro-intestinal track or other routes is eliminated through the urine, as part of U accumulates in bone.[67] Potential non-linear associations between drinking water U exposures and U internal dose may reflect measurement error in CWS U estimate and assignment, and noise from other U sources (e.g., dust, air, food), that might be more relevant at lower U levels in drinking water.[27] In addition, the wide 95% CIs in the pooled effect estimate for CWS U (GMR=1.35, 95% CI 1.05, 1.73) reflect variability in water U across and within study populations; for instance, CWS U levels for California participants (geometric mean=6.22 μg/L) were much higher than for other MESA states (geometric mean=0.87 μg/L). These results are consistent with previous studies and highlight the need for future research to evaluate absorption, metabolism, and excretion of ingested U for the general US population.[67]

The water U measurements underlying the final drinking water estimates for U are often sparser in the SHFS areas than in the MESA urban communities, excluding Maryland which reported no CWS U data (Figure S5). We used the most comprehensive, nationwide database of estimated CWS As and U concentrations available, which is based on the EPA's Six Year Review database covering over 95% of all public water systems nationwide.[24, 30] For example, out of approximately 52,110 CWSs nationwide,[68] U estimates were available for only 14,503 CWSs while As estimates were available for 36,406 CWSs.[24, 30] Missing CWS records are mostly related to missing data for entire states that were not relevant for the current study (e.g. Colorado, Delaware, Georgia, and Mississippi). Similarly, private well U measurements in the National Uranium Resource Evaluation Hydrogeochemical and Stream Sediment Reconnaissance were denser in MESA relevant areas versus SHFS areas. Further

studies that generate additional measurements should improve U estimates in both CWSs and private wells, and be able to evaluate if improved, higher resolution water U estimates are more strongly associated with urine U in the SHFS. At the same time, we cannot discount the possibility that airborne and dust exposures to U might be more relevant in rural areas and Native American lands, in particular near abandoned mines.[27]

### 4.1 Limitations

We assigned drinking water exposures to participants based on baseline residential zip code and could not integrate information about non-residential addresses relevant for water (e.g., workplace, schools). Residential history and self-reported drinking water source (e.g., community system, private well, bottled water) were also not available. We assigned zip-code level water As and U levels, which assumes spatially heterogeneous water concentrations that are representative of exposures within that area. However, both water systems and cohort participants are distributed with population density, minimizing this potential difference.

Our study was additionally limited by a temporal discrepancy between water and urine As and U estimates. While urine biomarkers were collected from 2001–2003 (SHFS) and from 2000–2002, 2010–2011 (MESA), assigned CWS As and U concentrations represent the 2006–2011 (As) and 2000–2011 (U) time periods. In the Strong Heart Study, urine As concentrations are known to be stable over time.[69] Prior evidence supports that CWS U concentrations were stable from 2000–2011,[30] and CWS As concentrations were stable during the relevant SHFS time period (2001–2003).[24, 70] To assess whether findings for MESA were impacted by changes in CWS As concentrations, we conducted ad hoc analyses assigning MESA participants to period specific CWS As concentrations. The association between CWS As and urinary As remained similar across time periods. Private well As and U estimates are largely considered relatively stable over time; previous studies have shown that As in groundwater is relatively stable across long time periods, but some variability can occur seasonally.[71, 72]

We used concentrations of U collected in water sources from 1975–1980 through the NURE program as a proxy for private well U estimates. The NURE data were collected for other purposes than studies such as this one and were not randomized; biases in sample locations (and the corresponding lack of sample locations in areas where many SHFS participants resided) could result in bias or uncertainty in our assignment of U exposure from private wells. We are not aware that NURE data have been validated against other private well or groundwater monitoring programs in published studies. However, to date these were the best publicly available data to approximate U concentrations in well water.

Despite likely measurement error attributed to zip-code level water As and U assignment,we found that zip-code level water As and U contribute significantly to urinary As and U levels in models that also included random effects for zip code identifier and participant (MESA, with repeat measurements for a subset) or family identifier (SHFS). We suspect that zip-code level variation in urine As is primarily due to shared drinking water sources and similar total drinking water exposures, rather than any additional As sources that cluster at the zip-code level. Although we were unable to robustly characterize exposure measurement error

due to assigning water estimates at the zip-code level versus other levels of aggregation in our current analysis, future studies with robust individual-level drinking water measurements available should comprehensively characterize the likely exposure measurement error in zip-code level water As and U estimates. A limitation of the current work is our zip code level estimates for North Dakota and South Dakota (SHFS) and Maryland and New York (MESA) were not assigned using CWS distribution boundary shapefiles, as shapefiles were not publicly accessible for those states. While we were unable to evaluate alternative methods of exposure assignment for participants in these states, in sensitivity analyses restricted to participants in all other states, we did not observe a significant difference in our results for either the SHFS or MESA (effect estimate 95% CIs overlapped). This is a limitation of the current available data nationwide, and future studies of water As and U epidemiology may benefit from federal policies that support states to publish these shapefiles. For states that published CWS distribution boundaries, we assessed within-zip code variability in CWS As and U concentrations and in the number of CWSs serving a ZCTA. To comply with confidentiality requirements, we are only able to provide this for all ZCTAs within the states that publish CWS distribution boundaries, not just the areas that SHFS and MESA participants lived in. Across all ZCTAs in these states, the mean (range) of the number of CWSs serving a ZCTA (with population >0) was 2.3 (1, 22). The mean (median) of the standard deviation of CWS As and U concentrations within a given ZCTA were 1.17 (0.48) and 2.59 (1.27), respectively, indicating low variability in As and U concentrations within a given ZCTA.

We were unable to estimate the daily As dose from private well water for SHFS participants because we could not convert probabilities to a concentration used for computation of the average daily dose. However, previous studies have shown that water As exposures from CWSs and private wells are similar in areas of the country where aquifers serving private wells and public supplies are similar, particularly in the Southwest and Central Midwest.[23] Our estimates of average daily dose of CWS As may therefore be relevant to private well users.

Our imputation of urine As and U samples below the LOD as the LOD divided by the square root of two is an additional potential limitation of this study. Though this method is the standard approach used by the CDC in describing environmental biomarkers and concentrations, it may be less reliable than alternative approaches of imputation, such as the use of maximum likelihood estimation techniques. Future studies may benefit from the use of alternative methods.[73]

Our findings suggest that interventions for water supplies – even for public water users – can have a major impact on reducing As and U exposures. These exposures are linked to numerous adverse health outcomes, even at levels of As exposure common in MESA, SHFS, and the general US population, and the maximum contaminant level goals are zero for both elements.[60, 74] For this reason, additional regulatory efforts and interventions to reduce both public water and private well As and U can have major public health benefits by reducing total exposure.

### 4.2 Conclusions

Water from unregulated private wells and regulated CWSs is a major contributor to estimated internal dose of As and U in both the SHFS and MESA populations. Additional water interventions, regulations, and policies can have a major impact on reducing total inorganic As and U exposures.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability Statement:

Investigators interested in analyzing MESA data can submit a manuscript proposal for consideration by the Publications and Presentations (P&P) Committee. The only requirement on an outside investigator is that a MESA investigator be a sponsor. Once a manuscript proposal has been approved, the lead investigator may request a dataset from the Coordinating Center.

Investigators interested in analyzing SHS data can apply to use the data according to established protocol for SHS Resource and Data Sharing, including community approval through formal application (strongheart.ouhsc.edu/datarequest.html).

The statistical code for analysis is available upon reasonable request, please contact Maya Spaur at mss2284@cumc.columbia.edu.

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74. New Jersey Department of Environmental Protection. Policy Directive 2003–06, Subject: Drinking Water Standard for Arsenic, 2003.

**Impact statement:**

We found that water from unregulated private wells and regulated CWSs is a major contributor to urinary As and U (an estimated measure of internal dose) in both rural, American Indian populations and urban, racially/ethnically diverse populations nationwide, even at levels below the current regulatory standard. Our findings indicate that additional drinking water interventions, regulations, and policies can have a major impact on reducing total exposures to As and U, which are linked to adverse health effects even at low levels.

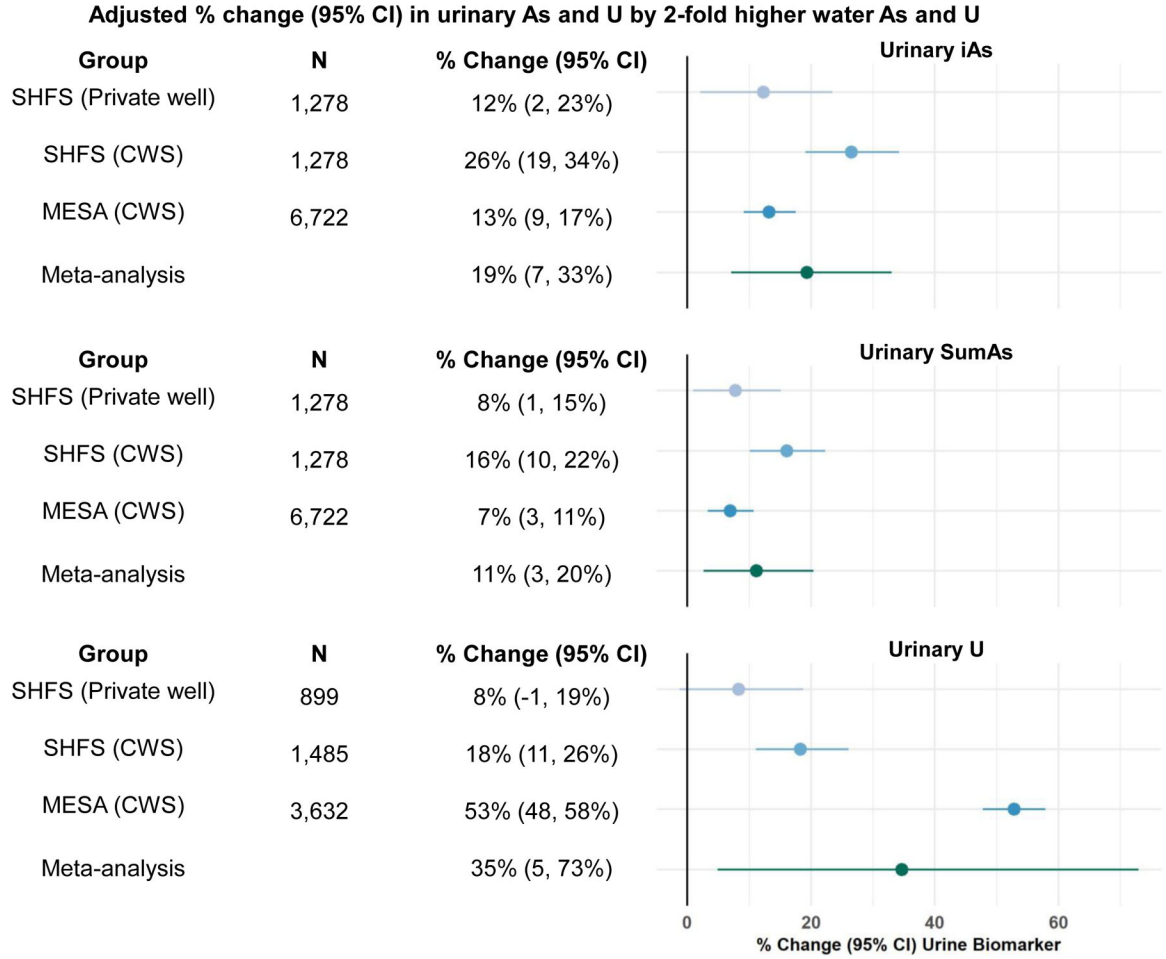


**Figure 1. Percent change (95% confidence intervals, CIs) in urinary arsenic (As) or uranium (U) by 2-fold higher water As[1,2] or U[3,4] in the Strong Heart Family Study (SHFS) and the Multi-Ethnic Study of Atherosclerosis (MESA).**

Estimates represent the adjusted percent change in urinary As per log μg/L increase in community water system (CWS) As, CWS U, or private well U, or the 25% increase in the probability of 90$^{th}$ percentile private well water As > 10 μg/L. % change was calculated as (Geometric mean ratio −1) * 100%. Lines represent 95% CIs. iAs = inorganic As (arsenite and arsenate). SumAs =sum of iAs, monomethyl arsonate, and dimethylarsinate.

[1]Arsenic model for SHFS includes random effects for zip code identifier and family identifier, and adjustment for natural log transformed creatinine, natural log transformed arsenobetaine, sex, age, smoking status, pack years, BMI, and natural log transformed dietary intake (g) of rice, organ meat, processed meat, and fish.

[2]Arsenic model for MESA includes random effects for zip code identifier and participant identifier, and adjustment for natural log transformed creatinine, natural log transformed arsenobetaine, sex, age, smoking status, pack years, body mass index (BMI), number of weekly servings of rice, and natural log transformed dietary intake (g) of red meat, and fish.

[3]Uranium model for SHFS includes random effects for zip code identifier and family identifier, and adjustment for natural log transformed creatinine, sex, age, smoking status, pack years, BMI, and natural log transformed dietary intake (g) of organ meat.

[4]Uranium model for MESA includes random effects for zip code identifier and participant identifier, and adjustment for natural log transformed creatinine, sex, age, smoking status, pack years, BMI, and natural log transformed dietary intake (g) of red meat.

**Table 1.**

**Descriptive characteristics of participants in the Strong Heart Family Study (SHFS) included in arsenic (As) analyses.**

Participants had urinary As biomarker and private well and community water system (CWS) As data available. Urine As concentrations measured below than the limit of detection (LOD, 0.01 μg/L for iAs, MMA, DMA, and arsenobetaine) were replaced by the LOD / sqrt(2).

| | Arsenic analyses | | | |
|---|---|---|---|---|
| | **Overall** | **Tertile 1 CWS As 0.33 – 2.00 μg/L** | **Tertile 2 CWS As >2.00 – 4.50 μg/L** | **Tertile 3 CWS As >4.50 – 13.10 μg/L** |
| **N (%)** | 1,278 | 459 (35.9%) | 473 (37.0%) | 346 (27.1%) |
| **Urinary As (μg/L)** [1] | | | | |
| Inorganic As (iAs, arsenite and arsenate) | 0.47 (0.25, 0.84) | 0.37 (0.17, 0.62) | 0.49 (0.28, 0.82) | 0.67 (0.33, 1.22) |
| Monomethyl arsonate (MMA) | 0.75 (0.44, 1.22) | 0.63 (0.39, 0.99) | 0.76 (0.45, 1.15) | 0.99 (0.55, 1.70) |
| Dimethylarsinate (DMA) | 3.92 (2.43, 6.27) | 3.21 (2.08, 4.96) | 3.88 (2.47, 5.85) | 5.52 (3.06, 8.58) |
| SumAs (iAs + MMA + DMA) | 5.32 (3.29, 8.53) | 4.25 (2.82, 6.64) | 5.33 (3.32, 7.95) | 7.33 (4.27, 11.04) |
| **Urinary arsenobetaine (μg/L)** [1,2] | 0.50 (0.32, 1.05) | 0.50 (0.32, 1.16) | 0.52 (0.33, 1.02) | 0.50 (0.31, 0.97) |
| **Urinary creatinine (mg/dL)** [1] | 1.44 (0.88, 2.06) | 1.43 (0.86, 2.07) | 1.53 (0.93, 2.12) | 1.34 (0.82, 2.00) |
| **Private well As (*Pr* >10 μg/L)** [3] | 0.09 (0.02, 0.96) | 0.06 (0.03, 0.14) | 0.09 (0.03, 0.96) | 0.13 (0.03, 0.96) |
| **CWS As (2006–11 μg/L)** [1] | 3.10 (1.99, 4.79) | 1.26 (0.48, 1.99) | 3.90 (2.16, 4.49) | 5.92 (5.21, 5.92) |
| **Average daily dose CWS As (mg/kgBW-day)** [1] | 2.10e-5 (1.23e-5, 3.60e-5) | 9.95e-6 (3.48e-6, 1.40e-5) | 2.54e-5 (1.72e-5, 3.25e-5) | 4.34e-5 (3.54e-5, 5.49e-5) |
| **Age (years), Mean (SD)** | 38.4 (15.8) | 38.7 (15.8) | 37.6 (15.7) | 39.0 (15.7) |
| **Sex, N (%)** | | | | |
| Female | 775 (60.6%) | 278 (60.6%) | 287 (60.7%) | 210 (60.7%) |
| Male | 503 (39.4%) | 181 (39.4%) | 186 (39.3%) | 136 (39.3%) |
| **Annual Household Income ($), N (%)** | | | | |
| < 15k | 386 (30.2%) | 121 (26.4%) | 162 (34.2%) | 103 (29.8%) |
| 15 - <35k | 393 (30.8%) | 132 (28.8%) | 147 (31.1%) | 114 (32.9%) |
| 35 - <50k | 111 (8.7%) | 52 (11.3%) | 32 (6.8%) | 27 (7.8%) |
| > 50k | 113 (8.8%) | 59 (12.9%) | 31 (6.6%) | 23 (6.6%) |
| NA | 275 (21.5%) | 95 (20.7%) | 101 (21.4%) | 79 (22.8%) |
| **Education, N (%)** | | | | |
| < High School | 323 (25.3%) | 107 (23.3%) | 115 (24.3%) | 101 (29.2%) |

| | Arsenic analyses | | | |
|---|---|---|---|---|
| | **Overall** | **Tertile 1 CWS As 0.33 – 2.00 µg/L** | **Tertile 2 CWS As >2.00 – 4.50 µg/L** | **Tertile 3 CWS As >4.50 – 13.10 µg/L** |
| High School or equivalent | 580 (45.4%) | 214 (46.6%) | 223 (47.1%) | 143 (41.3%) |
| > High School | 368 (28.8%) | 137 (29.8%) | 132 (27.9%) | 99 (28.6%) |
| NA | 7 (0.5%) | 1 (0.2%) | 3 (0.6%) | 3 (0.9%) |
| **Smoking status, N (%)** | | | | |
| Never | 533 (41.7%) | 202 (44.0%) | 191 (40.4%) | 140 (40.5%) |
| Former | 270 (21.1%) | 93 (20.3%) | 98 (20.7%) | 79 (22.8%) |
| Current | 475 (37.2%) | 164 (35.7%) | 184 (38.9%) | 127 (36.7%) |
| **Pack years, Mean (SD)** | 6.1 (12.8) | 6.4 (13.8) | 5.6 (11.3) | 6.3 (13.6) |
| **Body mass index, Mean (SD)** | 30.34 (6.81) | 30.28 (6.64) | 30.23 (6.88) | 30.56 (6.93) |
| **Dietary servings (g/day), Mean (SD)** [4] | | | | |
| Fish | 11.6 (27.7) | 11.8 (29.4) | 12.3 (28.6) | 10.4 (23.8) |
| Rice | 17.5 (32.9) | 17.4 (33.5) | 18.4 (34.3) | 16.4 (29.9) |
| Organ meat | 6.1 (25.3) | 5.3 (21.4) | 6.0 (21.3) | 7.2 (33.9) |
| Processed meat | 37.0 (45.9) | 33.9 (45.8) | 38.7 (48.3) | 38.6 (42.7) |

[1] Values are median ($25^{th}$, $75^{th}$ percentile).

[2] Arsenobetaine + other neutral and cationic As species.

[3] Values are mean (minimum, maximum).

[4] Collected during self-reported food frequency questionnaire.

**Table 2.**

**Descriptive characteristics of the Multi-Ethnic Study of Atherosclerosis (MESA) included in arsenic (As) analyses.**

Community water system estimates reflect population weighted averages. All descriptive characteristics for As analyses represent participants with As biomarker and community water system (CWS) As data available. Urine As estimates < LOD (0.04 μg/L for iAs, 0.03 μg/L for MMA, DMA, and arsenobetaine) were replaced by the LOD / sqrt(2).

| | Arsenic analyses | | | |
|---|---|---|---|---|
| | **Overall** | **Tertile 1 CWS As 0.35–0.35 μg/L** | **Tertile 2 CWS As >0.35 – 0.38 μg/L** | **Tertile 3 CWS As >0.38 – 5.86 μg/L** |
| **N (%)** | 6,722 | 4,087 (60.8%) | 1,386 (20.6%) | 1,249 (18.6%) |
| **Urinary As (μg/L)** [1] | | | | |
| Inorganic As (iAs, arsenite and arsenate) | 0.33 (0.17, 0.60) | 0.27 (0.14, 0.47) | 0.36 (0.20, 0.67) | 0.56 (0.34, 0.90) |
| Monomethyl arsonate (MMA) | 0.57 (0.30, 1.03) | 0.46 (0.25, 0.82) | 0.62 (0.35, 1.15) | 0.96 (0.57, 1.52) |
| Dimethylarsinate (DMA) | 5.30 (2.74, 10.71) | 4.33 (2.19, 8.51) | 6.38 (3.12, 12.65) | 8.57 (4.85, 15.39) |
| SumAs (iAs + MMA + DMA) | 6.32 (3.34, 12.48) | 5.18 (2.66, 9.81) | 7.45 (3.83, 14.18) | 10.20 (5.95, 17.93) |
| **Urinary arsenobetaine (μg/L)** [1,2] | 4.87 (1.12, 17.25) | 3.85 (0.91, 14.46) | 7.03 (1.78, 21.28) | 6.23 (1.42, 21.11) |
| **Urinary creatinine (g/L)** [1] | 1.05 (0.59, 1.57) | 1.03 (0.55, 1.56) | 0.99 (0.56, 1.53) | 1.15 (0.75, 1.66) |
| **CWS As (2006–11 μg/L)** [1] | 0.35 (0.35, 0.38) | 0.35 (0.35, 0.35) | 0.38 (0.37, 0.38) | 1.58 (0.79, 2.47) |
| **Average daily dose CWS As (mg/kgBW-day)** [1] | 2.97e-6 (2.39e-6, 3.85e-6) | 2.67e-6 (2.23e-6, 3.15e-6) | 3.13e-6 (2.52e-6, 3.69e-6) | 1.31e-5 (6.93e-6, 1.96e-5) |
| **Age (Years), Mean (SD)** | 62.0 (10.2) | 61.8 (10.1) | 62.2 (10.2) | 62.6 (10.5) |
| **Sex, N (%)** | | | | |
| Female | 3541 (52.7%) | 2177 (53.3%) | 726 (52.4%) | 638 (51.1%) |
| Male | 3181 (47.3%) | 1910 (46.7%) | 660 (47.6%) | 611 (48.9%) |
| **Race/ethnicity, N (%)** | | | | |
| Non-Hispanic White | 2698 (40.1%) | 1957 (47.9%) | 614 (44.3%) | 127 (10.2%) |
| Non-Hispanic Black | 1726 (25.7%) | 1266 (31.0%) | 317 (22.9%) | 422 (33.8%) |
| Hispanic | 1421 (21.1%) | 810 (19.8%) | 54 (3.9%) | 143 (11.4%) |
| Chinese American | 877 (13.0%) | 54 (1.3%) | 401 (28.9%) | 557 (44.6%) |
| **Annual Household Income ($), N (%)** | | | | |
| < 12,000 | 719 (10.7%) | 364 (8.9%) | 135 (9.7%) | 220 (17.6%) |
| 12 - <50,000 | 3125 (46.5%) | 1932 (47.3%) | 451 (32.5%) | 742 (59.4%) |

| | Arsenic analyses | | | |
|---|---|---|---|---|
| | **Overall** | **Tertile 1 CWS As 0.35–0.35 μg/L** | **Tertile 2 CWS As >0.35 – 0.38 μg/L** | **Tertile 3 CWS As >0.38 – 5.86 μg/L** |
| 50 - <75,000 | 1117 (16.6%) | 792 (19.4%) | 211 (15.2%) | 114 (9.1%) |
| > 75,000 | 1532 (22.8%) | 819 (20.0%) | 561 (40.5%) | 152 (12.2%) |
| NA | 229 (3.4%) | 180 (4.4%) | 28 (2.0%) | 21 (1.7%) |
| **Education, N (%)** [3] | | | | |
| < High School | 1197 (17.8%) | 610 (14.9%) | 136 (9.8%) | 451 (36.1%) |
| High School or GED | 1173 (17.5%) | 824 (20.2%) | 115 (8.3%) | 234 (18.7%) |
| Some college, technical school degree or associate degree | 1868 (27.8%) | 1232 (30.1%) | 344 (24.8%) | 292 (23.4%) |
| Bachelor’s degree or above | 2483 (36.9%) | 1420 (34.7%) | 791 (57.1%) | 272 (21.8%) |
| **Smoking status, N(%)** | | | | |
| Never | 3464 (51.5%) | 1961 (48.0%) | 722 (52.1%) | 781 (62.5%) |
| Former | 2446 (36.4%) | 1576 (38.6%) | 519 (37.4%) | 351 (28.1%) |
| Current | 812 (12.1%) | 550 (13.5%) | 145 (10.5%) | 117 (9.4%) |
| **Pack years, Mean (SD)** | 11.1 (20.6) | 12.3 (21.4) | 11.4 (22.3) | 6.6 (14.7) |
| **Body mass index, Mean (SD)** | 28.15 (5.36) | 28.93 (5.36) | 26.58 (5.05) | 27.35 (5.18) |
| **Number of weekly servings of rice** | | | | |
| <1 | 2723 (40.5%) | 2029 (49.6%) | 473 (34.1%) | 221 (17.7%) |
| 1–6 | 3146 (46.8%) | 1888 (46.2%) | 638 (46.0%) | 620 (49.6%) |
| >6 (1+ serving per day) | 853 (12.7%) | 170 (4.2%) | 275 (19.8%) | 408 (32.7%) |
| **Dietary servings (g/week), Mean (SD)** [4] | | | | |
| Fish | 0.31 (0.34) | 0.29 (0.33) | 0.38 (0.37) | 0.30 (0.35) |
| Red meat | 0.37 (0.37) | 0.35 (0.35) | 0.40 (0.38) | 0.42 (0.44) |

[1] Values are median ($25^{th}$, $75^{th}$ percentile).

[2] Arsenobetaine + other neutral and cationic As species.

[3] Education was missing for 1 participant in tertile 1.

[4] Collected during self-reported food frequency questionnaire.

**Table 3.**

**Unadjusted geometric means (GMs) (95% confidence intervals) and fully adjusted geometric mean ratios (GMRs) (95% confidence intervals) of urinary arsenic (As) and uranium (U) across categories of community water system (CWS, μg/L) As and U in the Strong Heart Family Study (SHFS) and the Multi-Ethnic Study of Atherosclerosis (MESA).**

Urine iAs = inorganic arsenic, arsenite and arsenate (μg/L). Urine sumAs = sum of iAs, monomethyl arsonate (MMA), and dimethylarsinate (DMA) (μg/L). Urine U = uranium (μg/L).

| | | Urine iAs[1] | | Urine sumAs[1] | |
|---|---|---|---|---|---|
| **SHFS** | **N** | **GM** | **GMR** | **GM** | **GMR** |
| ≤ 1 μg As/L water | 170 | 0.24 (0.21, 0.27) | 1.00 (ref) | 3.39 (3.04, 3.77) | 1.00 (ref) |
| > 1–5 μg As/L water | 827 | 0.43 (0.40, 0.45) | 1.50 (1.22, 1.85) | 5.02 (4.79, 5.27) | 1.22 (1.02, 1.46) |
| > 5 μg As/L water | 281 | 0.65 (0.57, 0.74) | 2.56 (1.98, 3.30) | 7.40 (6.74, 8.14) | 1.88 (1.51, 2.34) |
| P-trend[2] | 1,278 | -- | <0.001 | -- | <0.001 |
| **MESA** | **N** | **GM** | **GMR** | **GM** | **GMR** |
| ≤ 1 μg As/L water | 5,850 | 0.27 (0.27, 0.28) | 1.00 (ref) | 5.93 (5.77–6.08) | 1.00 (ref) |
| > 1 μg As/L water | 872 | 0.56 (0.53, 0.59) | 1.32 (1.20, 1.46) | 10.65 (10.07, 11.27) | 1.18 (1.08, 1.28) |
| P-trend[2] | 6,722 | -- | <0.001 | -- | <0.001 |

| | | Urine U [3] | |
|---|---|---|---|
| **SHFS** | **N** | **GM** | **GMR** |
| ≤ 1 μg U/L water | 1,094 | 0.027 (0.025, 0.029) | 1.00 (ref) |
| > 1–10 μg U/L water | 153 | 0.030 (0.025, 0.035) | 1.21 (0.95, 1.52) |
| > 10 μg U/L water | 238 | 0.111 (0.096, 0.129) | 3.53 (2.51, 4.96) |
| P-trend[2] | 1,485 | -- | <0.001 |
| **MESA** | **N** | **GM** | **GMR** |
| ≤ 1 μg U/L water | 1,054 | 0.004 (0.004, 0.005) | 1.00 (ref) |
| > 1–5 μg U/L water | 1,643 | 0.005 (0.005, 0.006) | 2.17 (1.81, 2.62) |
| > 5 μg U/L water | 935 | 0.023 (0.022, 0.024) | 5.05 (4.23, 6.02) |

| | | Urine iAs[1] | | Urine sumAs[1] | |
|---|---|---|---|---|---|
| **SHFS** | **N** | **GM** | **GMR** | **GM** | **GMR** |
| P-trend[2] | 3,632 | -- | | <0.001 | |

[1]Model for SHFS includes random effects for zip code identifier and family identifier, and adjustment for natural log transformed creatinine, natural log transformed arsenobetaine, sex, age, body mass index (BMI), smoking status, pack years (the number of cigarettes smoked per day multiplied by the number of years smoking), and natural log transformed dietary intake (g) of rice, organ meat, processed meat, and fish. Model for MESA includes random effects for zip code identifier and participant identifier, and adjustment for natural log transformed creatinine, natural log transformed arsenobetaine, sex, age, BMI, smoking status, pack years, number of weekly servings of rice, and natural log transformed dietary intake (g) of red meat, and fish.

[2]Statistical significance evaluated using the Mantel test for trend.

[3]Model for SHFS includes random effects for zip code identifier and family identifier, and adjustment for natural log transformed creatinine, sex, age, BMI, smoking status, pack years, and natural log transformed dietary intake (g) of organ meat. Model for MESA includes random effects for zip code identifier and participant identifier, and adjustment for natural log transformed creatinine, age, BMI, smoking status, pack years, natural log transformed creatinine, and natural log transformed dietary intake (g) of red meat.

**Table 4.**

**Conditional $R^2$ of linear mixed-effects model analyses of urinary arsenic and uranium in the Strong Heart Family Study (SHFS) and the Multi-Ethnic Study of Atherosclerosis (MESA).**

Urine iAs = inorganic arsenic, arsenite and arsenate (μg/g creatinine, cr). Urine sumAs = sum of iAs, monomethyl arsonate (MMA), and dimethylarsinate (DMA) (μg/g cr). Urine U = uranium (μg/g cr). CWS = community water system.

| Biomarker (As) | Water As + random effects[1] | + urine arsenobetaine[3] | + age, sex, BMI, smoking status, pack years, and dietary As (fish, rice, meat)[4] | + SHFS additional dietary As (grains, non-alc beer)[5] |
|---|---|---|---|---|
| **iAs** | | | | |
| MESA – CWS | 0.46 | 0.46 | 0.45 | |
| SHFS – CWS | 0.31 | 0.32 | 0.34 | 0.34 |
| SHFS – Private well | 0.36 | 0.37 | 0.39 | 0.39 |
| **SumAs** | | | | |
| MESA – CWS | 0.54 | 0.60 | 0.61 | |
| SHFS – CWS | 0.43 | 0.48 | 0.50 | 0.50 |
| SHFS – Private well | 0.46 | 0.51 | 0.53 | 0.53 |
| **Biomarker (U)** | **Water U + random effects** [6] | | **+ age, sex, BMI, smoking status, pack years, and dietary U (meat)** [8] | **+ SHFS additional dietary U (root vegetables)** [9] |
| MESA – CWS | 0.60 | | 0.60 | |
| SHFS – CWS | 0.22 | | 0.23 | 0.23 |
| SHFS – Private well | 0.17 | | 0.19 | 0.19 |

[1] Crude As model includes random effects for zip code identifier and family identifier (SHFS) or participant identifier (MESA).

[2] Crude As model + adjustment for natural log transformed arsenobetaine.

[4] Additional adjustment for sex, age, body mass index (BMI), smoking status, pack years (the number of cigarettes smoked per day multiplied by the number of years smoking), and dietary As (MESA = number of weekly servings of rice, and natural log transformed dietary intake (g) of red meat, and fish; SHFS = natural log transformed dietary intake (g) of rice, organ meat, processed meat, and fish).

[5] Additional adjustment for natural log transformed dietary intake (g) of grains and non-alcoholic beer.

[6] Crude As model includes random effects for zip code identifier and family identifier (SHFS) or participant identifier (MESA).

[8] Additional adjustment for sex, age, BMI, smoking status, pack years, natural log transformed creatinine, and natural log transformed dietary intake (g) of red meat (MESA) or organ meat (SHFS).

[9] Additional adjustment for natural log transformed dietary intake (g) of root vegetables and sweet potatoes.