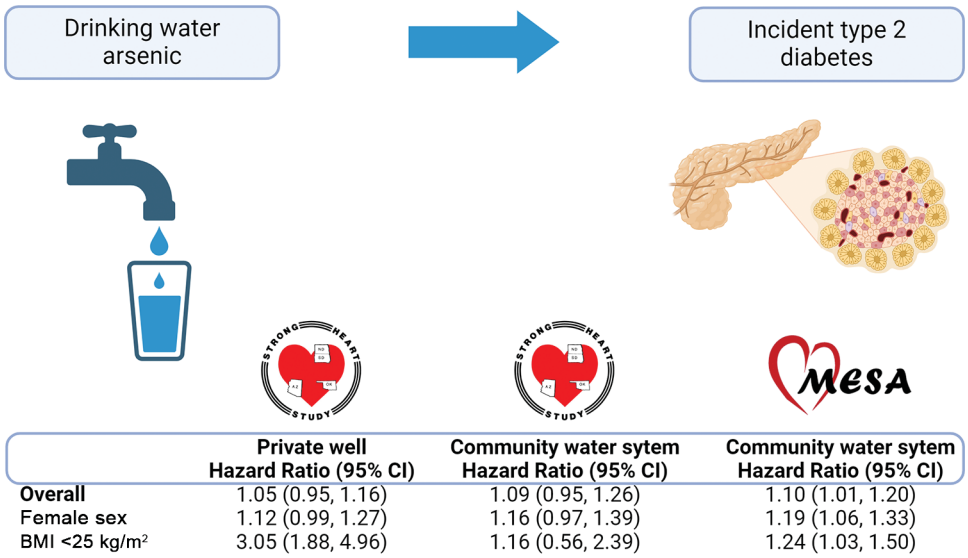
Diabetes Care
American Diabetes Association

Association of Water Arsenic With Incident Diabetes in U.S. Adults: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study

Maya Spaur, Marta Galvez-Fernandez, Qixuan Chen, Melissa A. Lombard, Benjamin C. Bostick, Pam Factor-Litvak, Amanda M. Fretts, Steven J. Shea, Ana Navas-Acien, and Anne E. Nigra

Diabetes Care 2024;47(7):1143–1151 | https://doi.org/10.2337/dc23-2231



	Private well Hazard Ratio (95% CI)	Community water sytem Hazard Ratio (95% CI)	Community water sytem Hazard Ratio (95% CI)
Overall	1.05 (0.95, 1.16)	1.09 (0.95, 1.26)	1.10 (1.01, 1.20)
Female sex	1.12 (0.99, 1.27)	1.16 (0.97, 1.39)	1.19 (1.06, 1.33)
BMI <25 kg/m^2	3.05 (1.88, 4.96)	1.16 (0.56, 2.39)	1.24 (1.03, 1.50)

Association of water arsenic with incident diabetes in the Multi-Ethnic Study of Atherosclerosis and the Strong Family Heart Study. Created with BioRender.com.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Drinking water is an important source of inorganic arsenic exposure. The association between water arsenic and type 2 diabetes (T2D) is understudied.
- **What is the specific question we wanted to answer?**
  We evaluated the association between water arsenic and T2D in the Strong Heart Family Study (SHFS; a cohort of American Indians) and the Multi-Ethnic Study of Atherosclerosis (MESA; a cohort of racially and ethnically diverse, urban/suburban U.S. adults).
- **What did we find?**
  Positive and statistically significant associations were observed in the MESA cohort. Stronger associations were observed among female participants and participants with lower BMI in both the SHFS and MESA cohorts.
- **What are the implications of our findings?**
  Arsenic exposures below current regulatory limits were associated with T2D, underscoring the need to consider T2D as a health outcome for drinking-water arsenic standards.

Association of Water Arsenic With Incident Diabetes in U.S. Adults: The Multi-Ethnic Study of Atherosclerosis and the Strong Heart Study

Maya Spaur,[1] Marta Galvez-Fernandez,[1] Qixuan Chen,[2] Melissa A. Lombard,[3] Benjamin C. Bostick,[4] Pam Factor-Litvak,[5] Amanda M. Fretts,[6] Steven J. Shea,[7] Ana Navas-Acien,[1] and Anne E. Nigra[1]

Diabetes Care 2024;47:1143–1151 | https://doi.org/10.2337/dc23-2231

OBJECTIVE

We examined the association of arsenic in federally regulated community water systems (CWS) and unregulated private wells with type 2 diabetes (T2D) incidence 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 and ethnically diverse urban U.S. communities.

RESEARCH DESIGN AND METHODS

We evaluated 1,791 participants from SHFS and 5,777 participants from MESA who had water arsenic estimates available and were free of T2D at baseline (2001–2003 and 2000–2002, respectively). Participants were followed for incident T2D until 2010 (SHFS cohort) or 2019 (MESA cohort). We used Cox proportional hazards mixed-effects models to account for clustering by family and residential zip code, with adjustment for sex, baseline age, BMI, smoking status, and education.

RESULTS

T2D incidence was 24.4 cases per 1,000 person-years (mean follow-up, 5.6 years) in SHFS and 11.2 per 1,000 person-years (mean follow-up, 14.0 years) in MESA. In a meta-analysis across the SHFS and MESA cohorts, the hazard ratio (95% CI) per doubling in CWS arsenic was 1.10 (1.02, 1.18). The corresponding hazard ratio was 1.09 (0.95, 1.26) in the SHFS group and 1.10 (1.01, 1.20) in the MESA group. The corresponding hazard ratio (95% CI) for arsenic in private wells and incident T2D in SHFS was 1.05 (0.95, 1.16). We observed statistical interaction and larger magnitude hazard ratios for participants with BMI <25 kg/m^2 and female participants.

CONCLUSIONS

Low to moderate water arsenic levels (<10 μg/L) were associated with T2D incidence in the SHFS and MESA cohorts.

In the U.S., drinking water is a source of inorganic arsenic exposure for residents reliant on unregulated contaminated private wells and on some regulated community water systems (CWS) (1,2). Evidence supports inorganic arsenic exposure as a potential risk factor for type 2 diabetes (T2D) (3). Experimentally, inorganic arsenic induces insulin resistance and pancreatic β-cell dysfunction (4,5). Epidemiologically, the association of

[1]*Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY*
[2]*Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY*
[3]*U.S. Geological Survey, New England Water Science Center, Pembroke, NH*
[4]*Lamont-Doherty Earth Observatory of Columbia University, Palisades, NY*
[5]*Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY*
[6]*Department of Epidemiology, University of Washington, Seattle, WA*
[7]*Department of Medicine, Vagelos College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY*

Corresponding author: Maya Spaur, maya.spaur@nih.gov

Received 21 November 2023 and accepted 2 April 2024

This article contains supplementary material online at https://doi.org/10.2337/figshare.25595538.

inorganic arsenic exposure with T2D is consistent and strong at levels ≥50 μg/L in drinking water but inconsistent at lower levels that are more relevant to the general U.S. population (6–9). Epidemiologic studies of arsenic exposure typically rely on urinary biomarkers, which integrate exposure through diet, water, and air. These analyses, however, may be affected by reverse causality because T2D may influence metal excretion in urine, even prior to diagnosis; the analyses could also be affected by the need to account for urine dilution, using urinary creatinine, which could be influenced by impaired renal function due to diabetes (10).

Arsenic occurs naturally in groundwater affecting communities in the Southwest, Northern Plains, Central Midwest, and New England regions, and in the Southwest and Northern Plains in connection with mining contamination, often on or near tribal lands (11). In 2001, the U.S. Environmental Protection Agency (EPA) established the current maximum contaminant level (MCL) for arsenic in CWS at 10 μg/L (12). New Jersey and New Hampshire have established lower, more health-protective MCLs (5 μg/L), and the Netherlands have a guidance of 1 μg/L. In the U.S., racial/ethnic, socioeconomic, and regional inequalities exist in water arsenic exposure and T2D prevalence nationwide, with the highest burden of T2D among American Indians, followed by non-Hispanic Black populations and Hispanic populations (2,13,14). Disproportionately high water-arsenic concentrations affect tribal and Hispanic communities and primarily rural and suburban communities in parts of the Southwest, Central Midwest, and New England (2,15)—communities that are also affected by a high T2D burden.

Investigation of the association between drinking-water arsenic exposures with T2D in the U.S. is lacking, in part, because nationwide estimates of drinking-water arsenic levels were not available previously for epidemiological assessments. Recently, robust nationwide estimates of private-well and public-water arsenic levels have been developed using data from the U.S. Geological Survey and the EPA, respectively (1,2). These drinking-water arsenic estimates have been associated with urinary arsenic biomarkers in the National Health and Nutrition Examination Survey (NHANES), as well as in two prospective cohort studies of cardiovascular disease and its risk factors, the Strong Heart Family Study (SHFS; a study in American Indian communities) and the Multi-Ethnic Study of Atherosclerosis (MESA; a study in racially and ethnically diverse urban and suburban U.S. communities) (16,17). These studies show the validity for use of water arsenic estimates in epidemiological research.

Our objective was to evaluate the prospective association of drinking-water arsenic exposure with incident T2D in the SHFS and MESA cohorts. We also evaluated potential differences in susceptibility to water arsenic–associated T2D by participant subgroups, including BMI and sex, based on prior evidence for effect measure modification by these variables (18,19). Few studies have evaluated the association between drinking-water arsenic exposures and T2D incidence in American Indian and racially/ethnically diverse U.S. populations; in exploratory analyses we also evaluated potential differences by race/ethnicity in the MESA data. Studies on drinking-water arsenic and T2D have generally been conducted at higher levels of exposure than typically found in the U.S. Because diabetes was not considered in the formulation of the current MCL, our findings at levels of water arsenic below current federal standards may support regulatory and prevention efforts to consider T2D as a relevant health outcome for water arsenic exposure in the U.S. Furthermore, few studies have assessed the association using arsenic concentrations measured in drinking water (rather than in urine). Studies using measured water concentrations at low levels are directly relevant for regulatory efforts because public drinking water is directly modifiable by federal action and avoids reverse causality concerns.

RESEARCH DESIGN AND METHODS

Study Populations

The SHFS and MESA are prospective, observational cohort studies investigating cardiovascular disease and its risk factors. Participants in the SHFS are family members of participants enrolled in the Strong Heart Study, which enrolled members in 2001–2003 from American Indian Nations at field centers in Arizona, Oklahoma, North Dakota, and South Dakota (20). MESA is a community-based cohort, and participants were free of clinical cardiovascular disease at baseline (21). Participants were enrolled in 2000–2002 from six urban and suburban centers (Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; Saint Paul, MN; and Winston-Salem, NC), with approximately 38% White, 25% Black, 23% Hispanic/Latino, and 11% Chinese American participants (21).

Among participants in the SHFS (n = 2,919), we excluded participants with T2D at baseline (n = 524) and those for whom the following types of data were missing: baseline exam date (n = 10) or follow-up exams (n = 322); baseline information on education (n = 11); smoking status (n = 4); alcohol intake (n = 3); BMI (n = 9); estimated glomerular filtration rate (n = 11); insulin (n = 26); residential zip code (n = 103); CWS arsenic estimate (n = 474); or private-well arsenic estimate (n = 105), for a final sample size of 1,422 SHFS participants included in CWS analyses and 1,791 SHFS participants included in private-well analyses. SHFS participants without CWS arsenic estimates likely resided in rural areas not served by CWS (17). Among participants in MESA (n = 6,814), we excluded participants with T2D (n = 859) or missing diabetes status (n = 24) at baseline, and for whom the following data were missing: follow-up time (n = 2), baseline information on education (n = 21), insulin (n = 9), residential zip code (n = 40), or CWS arsenic estimate (n = 82), for a total of 5,777 MESA participants included in analyses. Because most MESA participants are likely served by CWS, no private-well analysis was conducted in MESA.

Water Arsenic Assignment

We previously developed and assigned SHFS participants to zip code–level estimates of private-well water arsenic and CWS arsenic levels by baseline residential zip code, and MESA participants to zip code–level estimates of CWS arsenic by baseline residential zip code (17). CWS arsenic estimates represent population-weighted average concentrations (μg/L) from 2006 to 2011. Private-well arsenic estimates represent time-invariant, 90th percentile probabilities of private-well water arsenic >10 μg/L. These methods are described in the Supplementary Material.

T2D Outcome Ascertainment

For SHFS participants, whole blood was collected at each visit after a 12-h fast and immediately stored at not warmer than −70°C (22). Fasting plasma glucose

(FPG) concentrations were then determined through enzymatic methods with reagent kits on a chemistry analyzer (Boehringer Mannheim, Indianapolis, IN), and plasma insulin concentrations were measured by radioimmunoassay (23). T2D was defined as FPG ≥126 mg/dL or self-reported physician diagnosis or self-reported use of insulin or oral diabetes treatment (23). For MESA participants, blood samples were collected at each follow-up visit after a 12-h fast and immediately stored at −80°C (24). Fasting blood glucose (serum) levels were then measured via glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY) (24). T2D was defined as fasting blood glucose ≥126 mg/dL or self-reported physician diagnosis or self-reported use of insulin or hypoglycemic medication (25,26). The HOMA for insulin resistance (HOMA-IR) was calculated from insulin and FPG concentrations according to the following equation (27): insulin (mU/L) × FPG (mg/dL)/405.

Additional Variables

For the SHFS and MESA groups, trained staff administered standardized questionnaires that collected self-reported data on participant sociodemographic characteristics (namely, age, sex, race/ethnicity, site), lifestyle (smoking status, physical activity, alcohol intake, and dietary patterns), and clinical information (20,21). Staff performed a physical exam (measured weight in kilograms was divided by the square of height in meters to calculate BMI); and collected blood and urine samples. Smoking status was defined as never smoking (<100 cigarettes in lifetime), former smoking (≥100 cigarettes in lifetime and not smoking at present), and current smoking (≥100 cigarettes in lifetime and smoking at present). Cigarette pack-years were calculated by multiplying the average number of cigarettes smoked per day by the total years of smoking, divided by 20. Alcohol intake was classified as never (no alcohol consumption in lifetime), former (ever consumed alcohol but no current or recent consumption), and current (20,21). Information on physical activity ascertainment and dietary data are provided in the Supplementary Material.

Statistical Analysis

All data management and statistical analyses were conducted with R software (version 4.1.0). All statistical analyses were conducted at the individual level separately for SHFS and MESA participants. We evaluated descriptive statistics of baseline participant characteristics by incident T2D status and by tertile of drinking-water arsenic levels for the SHFS and MESA cohorts. We evaluated hazard ratios (HRs) of incident T2D per doubling (log2 transformation) of CWS arsenic and private-well arsenic levels, using Cox proportional hazards mixed-effects models. We included random effects for zip code (MESA and SHFS) to account for clustering in water arsenic exposure by residential zip code, and family (SHFS only) to account for the family clustered study design. We used the time of follow-up between study visits as the time metric. Models were progressively adjusted for the following variables: model 1 was adjusted for sex and baseline age, and included random effects for family identifier and zip code. Model 2 further adjusted for baseline educational level (<12 years completed, ≥12 years completed), smoking status (never, current, former), and BMI (kg/m^2).

We performed a random-effects meta-analysis to pool the overall effect estimates across the SHFS and MESA groups using the "metagen" function in the *meta* package in R (28,29). We stratified our analyses by sex and BMI, and assessed models with interaction terms to assess potential heterogeneity in the effect estimates for these subgroups. Because BMI is a powerful risk factor for T2D, we consider BMI to be a likely effect-measure modifier of the water arsenic–T2D association in our conceptual model. In MESA, we also evaluated potential effect-measure modification by race and ethnicity using stratification and interaction to evaluate if there were differential effects of water arsenic on T2D by participant race and ethnicity. Race and ethnicity are social constructs, and such differential effects would be related to social and environmental exposures that are inequitably distributed across racial/ethnic groups that may influence the water arsenic–diabetes association (e.g., inequities in exposure to air pollution or other water contaminants, nutritional status, experiences of racism and discrimination, quality of or access to health care) (2,30). Although individual race/ethnicity is a poor proxy for structural racism, structural racism underlies inequities in these other relevant environmental and social exposures. Adjusting for individual race/ethnicity (treating race/ethnicity as a confounder) may obscure racial disparities in exposures and health outcomes and, in effect, perpetuate them (31).

In secondary analyses, we evaluated the HR of incident T2D across categories of water arsenic instead of using per doubling increases. For private wells, we categorized the 90th percentile probability of private-well arsenic >10 μg/L as ≤0.25 (reference) versus >0.25. For CWS arsenic, we categorized concentrations as ≤1 μg/L (reference) versus >1 μg/L. These categories were based on previous analyses in the MESA and the SHFS that found water arsenic above and below 1 μg/L are meaningful cut points associated with urinary biomarkers (17). Additionally, 1 μg/L is the regulatory standard for the Netherlands and, because it is technically feasible, it represents a potential regulatory target.

We additionally examined associations between CWS and private-well arsenic exposure with prevalent HOMA-IR, as a measure of insulin resistance, at baseline in the SHFS and MESA groups. We used linear mixed-effects models to estimate geometric mean ratios of HOMA-IR per doubling in water arsenic and across water arsenic categories.

Sensitivity Analyses

We further adjusted for dietary quality and physical activity, which are risk factors for T2D, and rice intake, which is a main source of dietary arsenic in Asian and Hispanic populations (32). In the MESA group, we used the ranked physical activity index, measured as poor (none) to ideal (150 min/week of moderate intensity or 75 min/week of vigorous intensity), and diet quality (categorized as poor, intermediate, or ideal) (33). In the SHFS group, we used the categories of poor versus intermediate/ideal for diet and a dichotomous variable for poor versus intermediate or ideal for physical activity (<5,000 vs ≥5,000 steps/day) (34). Adjustment for rice intake did not influence effect estimates (data not shown).

Ethics 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 was cleared by the respective

Tribal Research Review Boards and area Indian Health Service institutional review boards for the SHFS and approved by the Publications and Presentations Committee for MESA.

Data and Resource Availability Statement

Investigators interested in analyzing MESA data can submit a paper proposal for consideration by the Publications and Presentations Committee. The only requirement for an outside investigator is that a MESA investigator be a sponsor. Once a paper proposal has been approved, the lead investigator may request a data set 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 (https://strongheartstudy.org/Research/Study-Data-and-Study-Samples/Study-Data). The statistical code for analysis is available from the corresponding author upon reasonable request.

RESULTS

Participant Characteristics

At baseline, the median age of the participants was 62 years in the MESA and 36 years in the SHFS. Mean follow-up was 14.0 years in the MESA and 5.6 years in the SHFS groups. Participants with versus without incident T2D in the 2 groups were more likely to have higher baseline levels of BMI, fasting glucose and insulin levels, and higher HOMA-IR score (Table 1). Median (interquartile range) CWS arsenic levels were similar by incident T2D status in MESA and slightly higher among SHFS participants with versus without incident T2D. Supplementary Table 1 describes participant characteristics by state and race/ethnicity, and Supplementary Tables S2 and S3 describe participant characteristics by tertile of private-well and CWS arsenic in the MESA and SHFS groups.

In the MESA, the incidence rate of T2D was 11.2 cases per 1,000 person-years (n = 907 T2D cases over 80,918 person-years). In the SHFS, the incidence rate of T2D was 22.2 cases per 1,000 person-years in the CWS arsenic analysis (n = 177 T2D cases over 7,978 person-years) and 24.4 cases per 1,000 person-years in the private-well arsenic analysis (n = 245 T2D cases over 10,035 person-years).

Water Arsenic and Incident T2D

In models fully adjusted for education, smoking status, and BMI, the corresponding HR was 1.10 (95% CI 1.01, 1.20) and 1.09 (0.95, 1.26) per doubling in CWS arsenic concentration in the MESA and the SHFS cohorts, respectively, and 1.05 (95% CI 0.95, 1.16) per doubling of private-well arsenic in the SHFS cohort (Table 2). In a mixed-effects meta-analysis of the adjusted effect estimates of CWS arsenic

Table 1—Participant characteristics by incident diabetes status in the SHFS (n = 1,791) and MESA (n = 5,777) groups

	SHFS*		MESA†	
Characteristic	No incident diabetes	Incident diabetes	No incident diabetes	Incident diabetes
N	1,546	245	4,870	907
Age, median (IQR), years	35.9 (23.1, 46.7)	38.5 (28, 48.6)	62 (53, 70)	59 (52, 67)
Sex, *n* (%)				
Female	922 (60)	142 (58)	2,637 (54)	459 (51)
Male	624 (40)	103 (42)	2,233 (46)	448 (49)
Education, *n* (%), years				
<12	470 (30)	67 (27)	782 (16)	172 (19)
≥12	1,076 (70)	178 (73)	4,088 (84)	735 (81)
Smoking status, *n* (%)				
Never smoker	643 (42)	106 (43)	2,440 (50)	469 (52)
Former smoker	320 (21)	45 (18)	1,799 (37)	317 (35)
Current smoker	583 (38)	94 (38)	631 (13)	121 (13)
Alcohol status, *n* (%)				
Never drank alcohol	180 (12)	28 (11)	941 (19)	191 (21)
Former alcohol drinker	372 (24)	76 (31)	1,091 (22)	204 (23)
Current alcohol drinker	994 (64)	141 (58)	2,819 (58)	510 (56)
BMI, median (IQR), kg/m^2	28.9 (24.9, 33.6)	34.6 (30.1, 39.8)	26.9 (24.0, 30.1)	29.8 (26.8, 34.0)
eGFR, median (IQR), mL/min/1.73 m^2§	118.5 (105.6, 130.7)	118.0 (108.2, 130.7)	76.7 (66.3, 87.5)	80.8 (69.7, 93.3)
Baseline fasting glucose, median (IQR), mg/dL	92 (87, 98)	101 (93, 110)	87 (81, 93)	98 (90, 108)
Insulin, median (IQR)	10.5 (7.2, 16.7)	20.8 (13.3, 31.5)	7.5 (5.7, 10.7)	11.3 (7.9, 15.6)
HOMA-IR, median (IQR)	2.4 (1.6, 3.9)	5.0 (3.4, 8.3)	1.6 (1.2, 2.4)	2.8 (1.9, 3.9)
Water As, median (IQR)‖				
CWS (μg/L)¶	2.66 (1.99, 4.79)	3.10 (1.99, 5.11)	0.35 (0.35, 0.38)	0.35 (0.35, 0.38)
Private well (As probability >10 μg/L)	0.05 (0.04, 0.10)	0.07 (0.04, 0.12)	–	–

As, arsenic; eGFR, estimated glomerular filtration rate; IQR, interquartile range; –, not assigned. *SHFS numbers reflect participants with available private-well As data. †MESA numbers reflect participants with available CWS As data. §eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. ‖Water As estimates were previously developed and published by Spaur et al. (17). ¶CWS As estimates represent population-weighted average concentrations.

Table 2—HR (95% CI) of incident diabetes per doubling in As levels* in CWS and private wells for participants in the MESA (n = 5,777) and SHFS (n = 1,791)

Water source	No. of cases/total	Model 1† HR (95% CI)	Model 1† *P* value§	Model 2‡ HR (95% CI)	Model 2‡ *P* value§
MESA (total person-years = 80,917.6), CWS As (μg/L)					
Overall	907/5,777	1.08 (0.99, 1.18)		1.10 (1.01, 1.20)	
By sex			0.05		0.02
Female	459/3,096	1.16 (1.04, 1.31)		1.19 (1.06, 1.33)	
Male	448/2,681	1.01 (0.89, 1.15)		1.01 (0.89, 1.14)	
By BMI (kg/m^2)			<0.001		<0.001
<25	127/1,767	1.33 (1.10, 1.60)		1.24 (1.03, 1.50)	
25 to <30	339/2,311	1.10 (0.96, 1.25)		1.06 (0.93, 1.22)	
≥30	441/1,699	1.06 (0.94, 1.20)		1.05 (0.93, 1.19)	
SHFS (total person-years = 7,977.9), CWS As (μg/L)					
Overall	177/1,422	1.05 (0.92, 1.20)		1.09 (0.95, 1.26)	
By sex			<0.001		<0.001
Female	102/852	1.11 (0.95, 1.31)		1.16 (0.97, 1.39)	
Male	75/570	0.95 (0.79, 1.14)		0.99 (0.82, 1.20)	
By BMI, kg/m^2			<0.001		0.05
<25	10/349	1.46 (0.29, 7.37)		1.16 (0.56, 2.39)	
25 to <30	35/423	1.01 (0.71, 1.43)		1.05 (0.72, 1.52)	
≥30	132/670	1.09 (0.91, 1.30)		1.09 (0.91, 1.30)	
SHFS (total person-years = 10,035.3), private-well As *Pr* >10 μg/L‖					
Overall	245/1,791	1.12 (1.01, 1.24)		1.05 (0.95, 1.16)	
By sex			0.12		0.06
Female	142/1,064	1.21 (1.07, 1.37)		1.12 (0.99, 1.27)	
Male	103/727	1.06 (0.91, 1.23)		0.95 (0.81, 1.11)	
By BMI, kg/m^2			<0.001		<0.001
<25	16/407	2.93 (1.92, 4.49)		3.05 (1.88, 4.96)	
25 to <30	43/513	0.90 (0.65, 1.24)		0.90 (0.64, 1.25)	
≥30	186/871	1.07 (0.94, 1.21)		1.07 (0.94, 1.21)	

As, arsenic; *Pr*, probability. *Water As estimates were assigned by baseline residential zip code. MESA and SHFS CWS estimates are population-weighted average concentrations (μg/L). SHFS private-well As estimates represent the 90th percentile *Pr* of private-well As >10 μg/L (Spaur et al. [17]; Lombard et al. [1]). †Model 1 included random effects for zip code and family identifier (SHFS only) and was adjusted for sex and age at baseline. Sex-stratified models do not include adjustment for sex. ‡Model 2 = model 1 + adjustment for educational level (<12 years completed, ≥12 years completed), smoking status (never, former, current), and BMI (kg/m^2). BMI-stratified models do not include adjustment for BMI. §*P* value of statistical interaction was obtained using the likelihood ratio test χ^2 test statistic. ‖90th percentile *Pr* of private-well As >10 μg/L.

concentration across the MESA and the SHFS cohorts, the corresponding HR was 1.10 (95% CI 1.02, 1.18; $P = 0.01$).

We observed differences in the association between CWS arsenic and incident diabetes by sex (for interaction, $P \leq 0.05$ for MESA and SHFS participants) (Table 2). In sex-stratified analyses, statistically significant associations were observed between CWS arsenic levels and T2D among female participants but not among male participants. By BMI, the effect estimates were higher among participants with BMI <25 kg/m^2 compared with BMI ≥25 kg/m^2 (for interaction, $P \leq 0.05$ for MESA and for SHFS for both private-well and CWS analyses). By race/ethnicity, in the MESA (Supplementary Table 4), the association was only statistically significant among Chinese American participants (HR 1.18; 95% CI 1.00, 1.41) with no evidence for statistical interaction. In an ad hoc analysis in the MESA among California participants only, the findings were consistent with the main analyses (Supplementary Table 4). Similar results were observed in sensitivity analyses that additionally adjusted for dietary quality and physical activity (Supplementary Table 5).

In fully adjusted analyses comparing CWS arsenic concentrations >1 μg/L with those ≤1 μg/L (reference), the corresponding HRs (95% CI) for the MESA and the SHFS data were 1.34 (1.09, 1.65) and 1.44 (0.86, 2.41), respectively. Comparing the 90th percentile probability of private-well arsenic >0.25 versus ≤0.25 (reference), the HR (95% CI) of incident T2D was 1.44 (0.97, 2.12) among SHFS participants (Table 3).

Water Arsenic and Prevalent HOMA-IR

In the MESA group, a twofold higher CWS arsenic level was associated with higher baseline HOMA-IR (adjusted geometric mean ratio 1.07; 95% CI 1.04, 1.09; Table 4). HOMA-IR was also higher comparing CWS arsenic >1 versus ≤1 μg/L in the MESA group. No corresponding association was observed in the SHFS group for HOMA-IR in adjusted analyses.

CONCLUSIONS

In two multisite cohorts that included rural and urban populations and American Indian, White, Hispanic/Latino, Black, and Chinese American participants, we studied prospective associations between drinking-water arsenic levels with incident T2D. We observed statistically significant associations

Table 3—HR (95% CI) of incident diabetes across categories of As levels† in CWS and private wells for participants in the MESA (*n* = 5,777) and SHFS (*n* = 1,791) cohorts

Water source by study	No. of cases/total	Model 1 HR (95% CI)‡	Model 2 HR (95% CI)§
MESA (total person-years = 80,917.6)			
CWS As, μg/L			
≤1	778/5,092	1.00 (ref)	1.00 (ref)
>1	129/685	1.28 (1.03, 1.60)*	1.34 (1.09, 1.65)**
SHFS (total person-years = 7,977.9)			
CWS As, μg/L			
≤1	21/195	1.00 (ref)	1.00 (ref)
>1	156/1,227	1.35 (0.82, 2.21)	1.44 (0.86, 2.41)
SHFS (total person-years = 10,035.3)			
Private-well As *Pr* >10 μg/L‖			
≤0.25	192/1,605	1.00 (ref)	1.00 (ref)
>0.25	53/186	1.95 (1.36, 2.80)***	1.44 (0.97, 2.12)

As, arsenic; *Pr*, probability; ref, reference. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. †Water arsenic estimates were assigned by baseline residential zip code. MESA and SHFS CWS estimates are population-weighted average concentrations (μg/L). SHFS private-well As estimates represent the 90th percentile *Pr* of private-well As >10 μg/L (Spaur et al. [17], Lombard et al. [1]). ‡Model 1 included random effects for zip code and family identifier (SHFS only) and was adjusted for sex and age at baseline. §Model 2 = model 1 + adjustment for educational level (<12 years completed, ≥12 years completed), smoking status (never, former, current), and BMI (kg/m^2). ‖90th percentile *Pr* of private-well As >10 μg/L.

in the MESA group overall and among female participants and those with lower BMI (<25 kg/m^2). These associations were mostly linear in the SHFS and MESA groups (Supplementary Figs. S1 and S2), especially at water arsenic levels relevant to the majority of participants (<5 μg/L). These findings were generally consistent in the SHFS group, using both public water and private-well arsenic data. We also observed positive associations with T2D incidence at CWS arsenic concentrations >1 μg/L in the MESA group and at >0.25 probability of private-well arsenic >10 μg/L in the SHFS group. These associations were found at low-level arsenic exposures, below current regulatory standards for arsenic in public water systems nationwide.

This study is directly relevant to communities affected by arsenic contamination in drinking water across the U.S., where arsenic exposure is characterized by substantial racial/ethnic, socioeconomic, and regional inequalities (2,35). For private wells, which are unregulated, the significant socioeconomic disparities in private-well testing and treatment may contribute to known exposure disparities (36). Disparities in T2D prevalence by race/ethnicity are also well documented. American Indians experience the highest burden of T2D in the U.S. (13). In the MESA group, we found no significant interaction by race/ethnicity, although the magnitude of the association was stronger among Chinese American participants. Because the SHFS is composed of American Indian participants, we did not stratify by race/ethnicity in the SHFS. To assess whether income (a measure of socioeconomic status) was a potential confounder of the observed

Table 4—GMR (95% CI) of baseline HOMA-IR per doubling and across categories of As levels† in CWS and private wells for participants in the MESA (*n* = 5,777) and SHFS (*n* = 1,791) cohorts

Water source by study	*N*	Model 1 GMR (95% CI)‡	Model 2 GMR (95% CI)§
MESA			
CWS As, μg/L			
Continuous (per doubling μg/L)	5,777	1.06 (1.04, 1.08)***	1.07 (1.04, 1.09)***
≤1	5,092	1.00 (ref)	1.00 (ref)
>1	685	1.15 (1.08, 1.22)***	1.16 (1.10, 1.22)***
SHFS			
CWS As, μg/L			
Continuous (per doubling μg/L)	1,422	1.03 (0.99, 1.07)	1.01 (0.98, 1.04)
≤1	195	1.00 (ref)	1.00 (ref)
>1	1,227	1.06 (0.94, 1.20)	0.99 (0.89, 1.10)
Private-well As, *Pr* >10 μg/L‖			
Continuous (per doubling *Pr* >10 μg/L)	1,791	1.06 (1.02, 1.11)**	1.00 (0.97, 1.03)
≤0.25	1,605	1.00 (ref)	1.00 (ref)
>0.25	186	1.55 (1.34, 1.81)***	1.10 (0.96, 1.26)

As, arsenic; GMR, geometric mean ratio; *Pr*, probability; ref, reference. ***$P < 0.001$, **$P < 0.01$. †Water As estimates were assigned by baseline residential zip code. MESA and SHFS CWS estimates are population-weighted average concentrations (μg/L). SHFS private-well As estimates represent the 90th percentile *Pr* of private-well As >10 μg/L. ‡Model 1 included random effects for zip code and family identifier (SHFS only) and was adjusted for sex and age at baseline. §Model 2 = model 1 + adjustment for educational level (<12 years completed, ≥12 years completed), smoking status (never, former, current), and BMI (kg/m^2). ‖90th percentile *Pr* of private-well As >10 μg/L.

associations, we conducted ad hoc analyses that additionally adjusted for income; results were similar (Supplementary Table 6).

We found consistently stronger associations between water arsenic and incident T2D among participants with a BMI <25 kg/m^2, both in the SHFS (private wells and CWS) and the MESA (CWS). In the SHFS cohort, the CWS arsenic and T2D incidence analysis stratified by BMI category was limited by a small number of T2D cases. It is possible that the strong association between BMI and T2D at higher BMI levels masks any association between water arsenic and T2D at those higher BMI levels. Alternatively, arsenic in drinking water could be a more relevant risk factor for T2D for individuals with lower BMI. In the SHFS cohort (n = 1,838), the association of urinary arsenic (the sum of inorganic and methylated species) with incident T2D was previously found to be stronger among those with lower BMI; the HR (95% CI) was 1.88 (1.03, 3.42), 1.26 (0.87, 1.80), and 1.09 (0.86, 1.39) for participants with BMI <25, 25–29, and ≥ 30 kg/m^2, respectively, although the interaction was not significant (for interaction, P = 0.23) (19). In NHANES 2003–2004, the association between urinary arsenic not derived from seafood and incident diabetes was stronger among participants who were overweight compared with both obese and normal weight people (for interaction, P = 0.11) (18). In the MESA, high seafood intake among the study population, reflected by higher urinary organic arsenic concentrations (generally considered to be nontoxic), complicates the ability to assess associations between urinary inorganic arsenic and T2D (17). Limited evidence in mice has shown significant interaction of inorganic arsenic with body weight and composition, in associations between inorganic arsenic and HOMA-IR (37). These findings support the need to conduct a comprehensive assessment of the role of BMI as a potential modifier of the association between inorganic arsenic exposure and T2D.

The potential association between arsenic and T2D has been historically controversial (6,10). Chronic inorganic arsenic exposure may induce insulin resistance (causing increased production of insulin acutely and glucagon chronically, triggering the release of stored sugars and gluconeogenesis); chronically, this leads to pancreatic β-cell dysfunction, decreased insulin secretion, and T2D (4,5,38). In drinking water, inorganic arsenic has been associated with impaired glucose tolerance in animal studies versus controls and with increased risk of T2D in epidemiologic studies, with conflicting evidence at low-moderate levels (39,40). Urinary arsenic has been cross-sectionally associated with prevalent T2D in U.S. populations such as in the NHANES, and with incident T2D in the SHFS (6,19). These studies relied on urinary arsenic biomarkers, which integrate all exposure sources and do not isolate arsenic exposure in water. In addition, reverse causality, when the disease process can influence the levels of the exposure biomarker of interest, is a limitation of analyses studying the association between urinary metals/metalloids and T2D, especially in cross-sectional studies, because diabetes can increase urinary excretion of metals even during subclinical stages of disease. The use of spot urine samples and the adjustment of urine dilution using urinary creatinine have also been criticisms of studies of urine arsenic and diabetes (10). Given the lack of consensus on the role of inorganic arsenic exposure and T2D risk at low exposure levels, the study of markers of arsenic exposure that are not influenced by urinary dilution or disease status is needed. Using water arsenic as the exposure, rather than urinary biomarkers, avoids these limitations because T2D disease processes cannot influence levels of metals/metalloids in drinking water, the amount of urine dilution related to recent water intake, or other physiopathological issues. Additional adjustment for estimated glomerular filtration rate (a measure of kidney function) did not meaningfully change the effect estimates (Supplementary Table 7). In the San Luis Valley Diabetes Study, in a rural population in Colorado, water arsenic levels estimated using geospatial models of arsenic concentrations in drinking water, were also associated with incident T2D over the follow-up (40). Our study provides additional evidence for the prospective association between low to moderate water arsenic exposures, at levels relevant for U.S. populations, and T2D risk (9).

Our study has several limitations. First, we relied on zip code–level water arsenic estimates and assumed that these were representative of residential exposures. For private wells, however, groundwater arsenic concentrations can vary widely across small spatial distances. For CWS, our approach assumes participants consume public drinking water from within their zip codes, which does account for movement between the home and other places that may be served by other public water systems such as schools, workplaces, and places of worship. Previously, we found that zip code–level factors including water explained approximately 30% and 46% of the variation in urine inorganic arsenic in the MESA and the SHFS, respectively, much higher than previously estimated, indicating that water is a major contributor to total internal dose of inorganic arsenic (17). Because SHFS participants are more likely to live in rural areas than are MESA participants, we expect that nondifferential measurement error in the exposure assessment by rural and urban status could have introduced bias toward the null. We expect any measurement error within the MESA data to be nondifferential, unless the shapefiles of CWS distribution boundaries were more accurate for some states than others; we would expect that nondifferential measurement error by state within the MESA data could introduce bias toward the null. Information on bottled-water use, point-of-use filter use, tap water consumption, and household water source was not available and could not be accounted for in this analysis. An additional limitation is the assumption that CWS arsenic concentrations sampled from 2006 to 2011 reflect public-water arsenic exposures at baseline in the SHFS (2001–2003) and MESA (2000–2002). Although data from the earlier monitoring period (2006–2008) may be assumed to reflect arsenic exposures prior to implementation of the Final Arsenic Rule, more CWS reported monitoring data to the U.S. EPA during the 2009–2011 monitoring period compared with the 2006–2008 period (2). Therefore, we used the 2006–2011 monitoring period to capture the maximum amount of usable data. Similarly, we assumed that private-well arsenic probabilities represent time-invariant estimates; emerging evidence indicates that variations in private-well arsenic concentrations may occur at small time scales (e.g., seasonal), though concentrations have been observed to remain relatively stable over annual and decadal time scales (1). In addition, our study has a relatively short follow-up time. This observational analysis

was potentially limited by residual confounding and measurement error. The modest effect sizes estimated here could plausibly be explained by residual confounding, confounding by other variables (e.g., family history of diabetes, additional domains of socioeconomic status, vulnerability that influence time to diabetes diagnosis), or measurement error of the exposure.

Exposure to low levels of arsenic in unregulated and regulated drinking-water supplies was associated with incident T2D in American Indian communities and diverse urban and suburban communities across the U.S. Despite the limited number of cases available across these two cohorts, our findings were largely consistent (HRs for CWS arsenic levels were 1.10 and 1.09 overall in the MESA and SHFS groups, respectively). T2D was not used quantitatively as a relevant arsenic-related end point when the existing federal water arsenic regulation was enacted (12). Because arsenic in drinking water can be prevented, through regulation and interventions, our findings support that further efforts are needed to assess whether the current MCL for water arsenic in the U.S. is effective and sufficient in reducing arsenic-related risk of T2D and other cardiometabolic diseases.

Acknowledgments. We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at https://www.mesa-nhlbi.org.

Funding. This study was supported by National Institute of Environmental Health Sciences (NIEHS; grants P42ES033719, P30ES009089, R01ES028758, and R01ES032638) and by the National Institutes of Health (NIH) Office of the Director and National Institute of Dental & Craniofacial Research (grant DP5OD031849). Research reported in this publication was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development under grant number P2CHD058486, awarded to the Columbia Population Research Center. M.S. was supported by NIEHS grant F31ES034284.

The Strong Heart Study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, NIH, Department of Health and Human Services, under contract numbers 75N92019D00027, 75N92019D00028, 75N92019D00029, and 75N92019D00030. The study was previously supported by research grants R01HL109315, R01HL109301, R01HL109284, R01HL109282, and R01HL109319 and by cooperative agreements U01HL41642, U01HL41652, U01HL41654, U01HL65520, U01HL65521, R01HL090863, R01ES025216, and R01ES021367.

The MESA was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020-D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

The manuscript was reviewed and approved by the MESA Publications and Presentations Committee. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Indian Health Service but does represent the views of the U.S. Geological Survey. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. government.

Author Contributions. M.S., M.G.-F., Q.C., M.A.L., B.C.B., P.F.-L., S.J.S., A.N.-A., and A.E.N. were involved in the conceptualization and design of the study and interpretation of the results. M.S. wrote the original draft and conducted the statistical analysis and visualization. M.G.-F., M.A.L., A.M.F., and A.E.N. contributed to data preparation, management, and statistical coding. All authors edited, reviewed, and approved the final version of the manuscript. M.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This work was presented in part at the 35th Annual Conference of the International Society for Environmental Epidemiology, Kaohsiung, Taiwan, 17–21 September 2023.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were John B. Buse and Justin B. Echouffo Tcheugui.

References

1. Lombard MA, Bryan MS, Jones DK, et al. Machine learning models of arsenic in private wells throughout the conterminous United States as a tool for exposure assessment in human health studies. Environ Sci Technol 2021;55:5012–5023
2. Nigra AE, Chen Q, Chillrud SN, et al. Inequalities in public water arsenic concentrations in counties and community water systems across the United States, 2006–2011. Environ Health Perspect 2020;128:127001
3. Breathett K, Sims M, Gross M, et al.; American Heart Association Council on Epidemiology and Prevention; Council on Quality of Care and Outcomes Research; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiovascular health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. Circulation 2020;141:e948–e959
4. Chen YW, Yang CY, Huang CF, Hung DZ, Leung YM, Liu SH. Heavy metals, islet function and diabetes development. Islets 2009;1:169–176
5. Kirkley AG, Carmean CM, Ruiz D, et al. Arsenic exposure induces glucose intolerance and alters global energy metabolism. Am J Physiol Regul Integr Comp Physiol 2018;314:R294–R303
6. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Rejoinder: arsenic exposure and prevalence of type 2 diabetes: updated findings from the National Health Nutrition and Examination Survey, 2003-2006. Epidemiology 2009;20:816–820
7. Tseng CH, Tai TY, Chong CK, et al. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. Environ Health Perspect 2000;108:847–851
8. Hendryx M, Luo J, Chojenta C, Byles JE. Exposure to heavy metals from point pollution sources and risk of incident type 2 diabetes among women: a prospective cohort analysis. Int J Environ Health Res 2021;31:453–464
9. Bräuner EV, Nordsborg RB, Andersen ZJ, Tjønneland A, Loft S, Raaschou-Nielsen O. Long-term exposure to low-level arsenic in drinking water and diabetes incidence: a prospective study of the Diet, Cancer and Health cohort. Environ Health Perspect 2014;122:1059–1065
10. Steinmaus C, Yuan Y, Liaw J, Smith AH. On arsenic, diabetes, creatinine, and multiple regression modeling: a response to the commentaries on our reanalysis. Epidemiology 2009;20:e1–e2
11. Lewis J, Hoover J, MacKenzie D. Mining and environmental health disparities in Native American communities. Curr Environ Health Rep 2017;4:130–141
12. U.S. Environmental Protection Agency. Arsenic and clarifications to compliance and new source monitoring rule: a quick reference guide. 2001. Accessed 15 December 2022. Available from https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=300065YM.txt
13. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. Curr Diab Rep 2013;13:814–823
14. Gurka MJ, Filipp SL, DeBoer MD. Geographical variation in the prevalence of obesity, metabolic syndrome, and diabetes among US adults. Nutr Diabetes 2018;8:14
15. Ayotte JD, Medalie L, Qi SL, Backer LC, Nolan BT. Estimating the high-arsenic domestic-well population in the conterminous United States. Environ Sci Technol 2017;51:12443–12454
16. Spaur M, Lombard MA, Ayotte JD, et al. Cross-sectional associations between drinking water arsenic and urinary inorganic arsenic in the United States: NHANES 2003–2014. Environ Res 2023;227:115741
17. Spaur M, Glabonjat RA, Schilling K, et al. 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. J Expo Sci Environ Epidemiol 2024;34:77–89
18. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA 2008;300:814–822
19. Grau-Perez M, Kuo CC, Gribble MO, et al. Association of low-moderate arsenic exposure and arsenic metabolism with incident diabetes

and insulin resistance in the Strong Heart Family Study. Environ Health Perspect 2017;125:127004
20. North KE, Howard BV, Welty TK, et al. Genetic and environmental contributions to cardiovascular disease risk in American Indians: the Strong Heart Family Study. Am J Epidemiol 2003;157:303–314
21. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881
22. Howard BV, Welty TK, Fabsitz RR, et al. Risk factors for coronary heart disease in diabetic and nondiabetic Native Americans. The Strong Heart Study. Diabetes 1992;41(Suppl. 2):4–11
23. Lee ET, Welty TK, Fabsitz R, et al. The Strong Heart Study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol 1990;132:1141–1155
24. Yeboah J, Bertoni AG, Herrington DM, Post WS, Burke GL. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2011; 58:140–146
25. Sobel MH, Sanchez TR, Jones MR, et al. Rice intake, arsenic exposure, and subclinical cardiovascular disease among US adults in MESA. J Am Heart Assoc 2020;9:e015658
26. Kandula NR, Diez-Roux AV, Chan C, et al. Association of acculturation levels and prevalence of diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2008;31: 1621–1628
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412–419
28. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010; 36:1–48
29. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153–160
30. Martinez-Morata I, Bostick BC, Conroy-Ben O, et al. Nationwide geospatial analysis of county racial and ethnic composition and public drinking water arsenic and uranium. Nat Commun 2022; 13:7461
31. Swilley-Martinez ME, Coles SA, Miller VE, et al. "We adjusted for race": now what? A systematic review of utilization and reporting of race in *American Journal of Epidemiology* and *Epidemiology*, 2020-2021. Epidemiol Rev 2023; 45: 15–31
32. Jones MR, Tellez-Plaza M, Vaidya D, et al. Ethnic, geographic and dietary differences in arsenic exposure in the Multi-Ethnic Study of Atherosclerosis (MESA). J Expo Sci Environ Epidemiol 2019;29:310–322
33. Ogunmoroti O, Allen NB, Cushman M, et al. Association between Life's Simple 7 and noncardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2016;5: e003954
34. Fretts AM, Howard BV, McKnight B, et al. Life's Simple 7 and incidence of diabetes among American Indians: the Strong Heart Family Study. Diabetes Care 2014;37:2240–2245
35. Spaur M, Lombard MA, Ayotte JD, et al. Associations between private well water and community water supply arsenic concentrations in the conterminous United States. Sci Total Environ 2021;787:147555
36. Malecki KMC, Schultz AA, Severtson DJ, Anderson HA, VanDerslice JA. Private-well stewardship a