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ORIGINAL RESEARCH

Relationship Between Urinary Uranium and Cardiac Geometry and Left Ventricular Function

The Strong Heart Study

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ABSTRACT

BACKGROUND Uranium is a potentially cardiotoxic, nonessential element commonly found in drinking water throughout the United States.

OBJECTIVES The purpose of this study was to evaluate if urinary uranium concentrations were associated with measures of cardiac geometry and function among American Indian young adults from the Strong Heart Family Study.

METHODS Urinary uranium was measured among 1,332 participants free of diabetes, cardiovascular disease, and <50 years of age at baseline (2001-2003). Transthoracic echocardiography and blood pressure were assessed at baseline and at a follow-up visit (2006-2009). We estimated adjusted mean differences in cardiac geometry and function measures at baseline and follow-up using linear mixed-effect models with a random intercept and slope over time.

RESULTS Median (interquartile range) uranium was 0.029 (0.045) μg/g creatinine. In fully adjusted cross-sectional models, a log-doubling of urinary uranium was positively associated with left ventricular (LV) mass index (mean difference: 0.49 g/m^2, 95% CI: 0.07-0.92 g/m^2), left atrial systolic diameter (0.01 cm/m^2, 0.01-0.02 cm/m^2), and stroke volume (0.66 mL, 0.25-1.08 mL) at baseline. Prospectively, uranium was associated with increases in left atrial diameter (0.01 cm/m^2, 0.01-0.02 cm/m^2), pulse pressure (0.28 mm Hg, 0.05-0.52 mm Hg), and incident LV hypertrophy (odds ratio: 1.25, 95% confidence interval: 1.06, 1.48).

CONCLUSIONS Urinary uranium levels were adversely associated with measures of cardiac geometry and LV function among American Indian adults, including increases in pulse pressure and LV hypertrophy. These findings support the need to determine the potential long-term subclinical and clinical cardiovascular effects of chronic uranium exposure, and the need for future strategies to reduce exposure. (JACC Adv. 2024;3:101408) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

ICP-MS = Inductively coupled plasma-mass spectrometry

LOD = limit of detection

LV = left ventricular

NHANES = National Health and Nutrition Examination Survey

SBP = systolic blood pressure

U.S. = United States

Uranium contamination of soil and water is an understudied global health concern,[1,2] with regional differences in uranium concentrations stemming from both geogenic and anthropogenic sources.[2-4] Throughout the United States (U.S.), uranium is widespread in drinking water and detectable in over 50% of public water systems.[5] Drinking uranium-contaminated water is reflected in urine, a biomarker capturing total internal dose.[6] However, the health effects associated with the chemical toxicity of uranium remain understudied, especially for chronic uranium exposure at lower levels relevant to U.S. populations.

An increasing body of literature emphasizes environmental metal exposures as risk factors for cardiovascular disease (CVD).[7-9] Findings from the Strong Heart Study (SHS), a prospective cohort of CVD and its risk factors among American Indian communities, revealed associations of chronic, low-to-moderate levels of arsenic and cadmium with increased CVD risk.[10,11] Uranium, however, remains an understudied metal potentially associated with CVD.[12-14] In the U.S., many Indigenous communities are affected by chronic uranium exposure, related in part to active and abandoned uranium mines, dust inhalation, and the contamination of groundwater and drinking water sources.[15,16] SHS participants have significantly higher urinary uranium levels compared to the general U.S. population and other U.S. cohorts.[17-19]

Despite evidence supporting associations of acute and chronic uranium exposures with nephrotoxicity, neurotoxicity, reproductive toxicity, hepatoxicity, and bone toxicity, research is limited for cardiovascular outcomes.[1,20] Findings within the general U.S. population are sparse, with 1 study reporting a trend of increasing CVD risk with higher levels of uranium.[14] Echocardiographic measures of cardiac geometry and left ventricular (LV) function are useful for capturing risk, subclinical disease, and progression to clinical CVD outcomes. These subclinical echocardiographic measures are available in the SHS, and prior work has identified that arsenic is associated with changes in cardiac geometry and LV function in the SHS.[21] However, it remains important to investigate how uranium influences these metrics and the CVD trajectory.

Our primary objective was to evaluate if uranium exposure, as measured in urine, was associated cross-sectionally and longitudinally with echocardiographic measures of cardiac geometry, LV function, and LV hypertrophy in the SHFS (Strong Heart Family Study), a family-based extension of the original SHS. We hypothesized that higher urinary uranium levels would be associated with metrics of altered geometry and impaired LV function, reflecting increased risk of subclinical CVD.

METHODS

STUDY SAMPLE. The data underlying this article can be shared with external investigators following procedures established by the SHS but not in an unrestricted manner due to limitations in the consent forms and in the agreements between the SHS tribal communities and the SHS investigators.

The SHS is a prospective cohort of CVD in American Indian adults from tribes and communities in Arizona, Oklahoma, North Dakota, and South Dakota. All adults 45 to 74 years of age at baseline were invited to participate in the Phase 1 baseline examination (1989-1991)[22,23] (participation rate 62%[24]). A total of 4,549 adults were recruited; 1,032 participants from 1 community were subsequently excluded from further research by tribal request. The SHFS was derived from original SHS families and initiated with a pilot study during SHS Phase 3 (1997-1999). Families were eligible if they had at least 5 living family members, of which 3 were original SHS participants. Additional SHS cohort family members 15 years of age and older were enrolled during the first SHFS-only visit at Phase 4 (2001-2003) and were re-evaluated at Phase 5 (2006-2009). All SHS protocols were approved by institutional review boards, participating tribes, and the respective area Indian Health Service institutional review board. All participants provided informed

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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consent. This analysis used the STROBE cohort reporting guidelines.[25]

In the current analysis, SHFS participants with urinary uranium measures and echocardiographic measures at baseline were eligible for inclusion (n = 2,919). Analyses were restricted to participants <50 years of age who were free of clinically evident CVD and diabetes mellitus at baseline (n = 1,752). We excluded 293 participants missing urine uranium measures and 92 participants missing echocardiographic measures at baseline, as well as 19 participants missing data on cofounders of interest. Nine participants with outlier levels of measured echocardiographic measures (values ≥2*percentile 99th) and 7 participants with outlier levels of urinary uranium (values ≥3*percentile 99th) were further excluded, resulting in a final sample of 1,332 participants for this analysis.

URINARY URANIUM MEASUREMENTS. Participants provided a morning spot urine sample at Phase 4 and samples were stored at −80 °C at MedStar Health Research Institute, the central SHS biorepository and laboratory. Urine uranium was assayed at the Trace Metals Laboratory at the University of Graz, Austria using inductively coupled plasma-mass spectrometry (Agilent 7,700x inductively coupled plasma-mass spectrometry; Agilent Technologies).[26] The limit of detection for uranium was 0.008 μg/L. Values < limit of detection (17.9%) were replaced with the limit of detection divided by the square root of 2, consistent with prior SHS metal research.[21] Albumin, creatinine, specific gravity, and other metals, including the sum of inorganic and methylated arsenic species, were measured as described.[26] Urine uranium values were divided by urine creatinine to account for urine dilution and expressed as μg/g creatinine. Other laboratory details and extensive quality control/quality assurance have been published.[26]

ECHOCARDIOGRAPHIC MEASURES OF CARDIAC GEOMETRY AND FUNCTION. Participants underwent transthoracic echocardiograms with phased-array echocardiographs with M-mode, 2-dimensional and Doppler capabilities[21] during Phase 4 and 5 study visits, according to standardized and previously described methods.[27] Echocardiograms were performed by trained sonographers and reviewed by 2 readers, with approximately 97% of echocardiograms finally interpreted by a single highly experienced investigator, as recommended by the American Society of Echocardiography.[28] At least 10 consecutive beats of 2-dimensional and M-mode recordings of cardiac geometry parameters were recorded in the parasternal acoustic window at or just below the tips of the mitral leaflets in both long and short-axis views. Left atrium diameter was measured at end-systole. We used the following parameters of cardiac geometry at the end of diastole: LV internal diameter, interventricular septum, LV posterior wall thickness, and relative wall thickness. LV mass was calculated by a necropsy-validated formula and normalized for body surface area.[29,30] LV mass/body surface area ratio was used to define LV hypertrophy (>115 g/m^2 in men and >95 g/m^2 in women).

Ejection fraction (calculated from LV linear dimensions[31]), and stroke volume, derived from the Doppler method,[32] were used to assess LV systolic function. Cardiac diastolic function was evaluated by Doppler interrogation. We used the following parameters of cardiac diastolic function: transmitral early (E) and late (A) filling velocities (measured at the annular level), and early peak rapid filling velocity to peak atrial filling velocity (measured as the E/A ratio).

SOCIODEMOGRAPHIC AND CLINICAL VARIABLES. Centrally trained SHS examiners collected information from a standardized interview, physical examination, medication review, and biospecimen collection at each study visit.[22] Sociodemographic and lifestyle information was collected from standardized questionnaires, including age, sex, and smoking status (never/former/current).

Systolic and diastolic blood pressure (mm Hg) were measured by auscultation, as previously described.[22,33] Brachial pulse pressure was defined as the difference between systolic and diastolic blood pressure. We defined hypertension status as systolic blood pressure (SBP) ≥140 mm Hg, or diastolic blood pressure (DBP) ≥90 mm Hg, or use of antihypertensive drugs. We defined prehypertension status as SBP≥120 mm Hg, or DBP≥80 mm Hg, or use of antihypertensive drugs. Normal pressure was defined as SBP<120 mm Hg and DBP<80 mm Hg and no use of antihypertensive drugs. We calculated estimated glomerular filtration rate (eGFR) using age, sex, and urinary creatinine (mg/dL) via the 2009 Chronic Kidney Disease-Epidemiology Collaboration formula.[34] We defined dyslipidemia as total cholesterol ≥200 mg/dL, low-density-lipoprotein cholesterol ≥130 mg/dL, high-density-lipoprotein cholesterol ≤40 mg/dL, total triglycerides ≥150 mg/dL, or reported use of lipid-lowering medication. Impaired fasting glucose was defined as fasting blood glucose ≥100 mg/dL and <126 mg/dL; normal fasting glucose was defined as fasting blood glucose <100 mg/dL. Hypertension treatment was defined as taking any

antihypertensive drugs and having a recorded history or diagnosis of hypertension.

STATISTICAL ANALYSIS. All analyses were conducted in R, version 4.1.1. The distribution of urinary uranium concentrations was skewed and modeled in the log-scale (Supplemental Figure 1). We first compared baseline (Phase 4) participant characteristics and baseline echocardiographic measures overall and stratified by quartiles of urine uranium, adjusted for creatinine. We then calculated the Pearson correlation coefficients between urinary uranium concentrations and metrics of cardiac geometry and function.

We used generalized estimating equations for binary measures and linear mixed-effects models for continuous measures to evaluate the association between baseline uranium and baseline and follow-up outcome measures. Our primary outcomes were continuous measures of cardiac geometry and LV function, as well as prevalent and incident LV hypertrophy. We first evaluated the prevalence OR (95% CI) of LV hypertrophy and LV diastolic dysfunction at baseline and at follow-up per log-doubling of urine uranium using the "gee" package in R. We further stratified these analyses by prehypertension status to determine effects according to blood pressure, as this has been shown to be relevant for these metrics in the SHS.[21] These models estimate an OR at a particular time (Phase 4 or Phase 5) and cluster on family identifier. We evaluated the adjusted mean difference at baseline, annual mean change, and mean difference at 5 years of follow-up in metrics of cardiac geometry and function per log-doubling of urine uranium using linear mixed-effect models. These models were performed using the "nlme" package in R and included a random intercept and random slope over time for each participant. Models were further stratified by hypertension status. A sensitivity analysis was performed with a random effect for participant identifier nested within family identifier to account for family clustering. An additional sensitivity analysis investigating binary measures was performed accounting for repeated measures.

All model adjustment variables were measured at Phase 4 (baseline). Model 1 was adjusted for age (continuous) and sex. Model 2 was further adjusted for smoking status (never/former/current), body mass index (continuous), study center, eGFR (continuous), fasting glucose (continuous), dyslipidemia (yes/no), and the sum of inorganic and methylated arsenic (continuous), as arsenic has been shown to influence cardiac geometry and LV function.[21] Model 3 (the main model of interest) was further adjusted for baseline hypertension treatment (yes/no) and systolic blood pressure (continuous). To explore potential effect measure modification, we stratified analyses of the association of urinary uranium with measures of cardiac geometry and function by sex, age group (≤/> median age of 30.4 years) and urinary arsenic concentrations (≤/> median concentration of 4.23 μg/L), and we corrected P values for interaction by the number of groups ($P = 0.05/3$ groups $= 0.0167$). To determine the impact of high arsenic and high uranium on cardiac geometry and function metrics, urine uranium and urine arsenic concentrations were both categorized into tertiles. These tertiles were then summed to create a uranium/arsenic tertile score (ranging from 1 to 6), and the relationships with cardiac geometry and functioning metrics were investigated for participants in the highest uranium + arsenic tertile score compared to participants in the lowest uranium + arsenic tertile score.

We used flexible natural cubic spline models to evaluate potential nonlinearity between urinary uranium and cardiac geometry and functioning metrics. We included knots at the 10th, 50th and 90th percentiles of the urine uranium distributions and set the reference to the 10th percentile.

RESULTS

PARTICIPANT CHARACTERISTICS. The mean age of participants was 30.8 ± 10.4 years and 39.3% were male. The mean follow-up period for participants across the 2 study visits was 5.6 ± 1.2 years. The median of urine uranium at baseline was 0.029 (25th, 75th percentile: 0.013, 0.058) μg/g creatinine. Participants with higher urine uranium levels were more likely to be current smokers, and to have higher fasting glucose, eGFR and urine arsenic levels (**Table 1**). Urine uranium was also higher among participants with higher left atrium diameter, LV internal diameter, and stroke volume. In correlation analyses, urine uranium was positively associated with all measures of cardiac geometry, except relative wall thickness (Supplemental Figure 2), and with the measures of cardiac function of stroke volume, E-velocity, and A-velocity (Supplemental Figure 3).

URINE URANIUM AND LV GEOMETRY. There were 61 participants (4.6%) with LVH at baseline and 58 participants (4.6%) with LVH at follow-up. The fully adjusted OR for LVH for a log-doubling of urine uranium was 1.09 (95% CI: 0.91-1.31) at baseline and 1.25 (95% CI: 1.06-1.48) at follow-up for all participants (**Table 2**). The corresponding association at baseline was similar and remained nonsignificant for

TABLE 1 Participant Characteristics, Cardiac Geometry, and Cardiac Function Measures at Baseline by Urinary Uranium

	Overall (0.001-1.61) (N = 1,332, 100%)	Quartile 1 (≤0.013) (n = 333, 25%)	Quartile 2 (0.013-0.029) (n = 333, 25%)	Quartile 3 (0.029-0.058) (n = 333, 25%)	Quartile 4 (>0.058) (n = 333, 25%)	*P* Value
Participant characteristics						
Female	809 (60.7)	209 (62.8)	204 (61.3)	197 (59.2)	199 (59.8)	0.779
Age (y)	30.7 ± 10.4	31.4 ± 10.2	30 ± 10.2	30.9 ± 10.8	30.8 ± 10.3	0.742
Smoking						
Never	561 (42.1)	162 (48.7)	147 (44.2)	132 (39.7)	119 (35.7)	0.023
Former	246 (18.5)	53 (15.9)	59 (17.8)	71 (21.3)	63 (18.9)	
Current	525 (39.4)	118 (35.4)	126 (38.0)	130 (39.0)	151 (45.4)	
BMI (kg/m^2)	30.2 ± 7.4	30.4 ± 7	30.2 ± 7.1	30.6 ± 7.8	29.8 ± 7.4	0.439
Hypertension	192 (14.4)	52 (15.6)	44 (13.2)	48 (14.4)	48 (14.4)	0.854
Prehypertension	662 (49.7)	166 (49.8)	171 (51.4)	170 (51.1)	155 (46.5)	0.586
Fasting glucose	92 ± 9.4	92.2 ± 9	90.8 ± 8.6	91.7 ± 9.9	93.4 ± 9.8	0.04
Prediabetes	20 (8.6)	9 (8.3)	2 (5.1)	3 (7.9)	6 (12.5)	0.668
Dyslipidemia	682 (51.2)	170 (51.1)	162 (48.6)	181 (54.4)	169 (50.8)	0.527
eGFR (mL/min/1.73 m^2)	123.4 ± 15.7	121.1 ± 16.7	122.9 ± 14.2	125.6 ± 15.2	124.1 ± 16.3	0.002
Sum of inorganic and methylated arsenic μg/L	5.7 ± 5.3	4.3 ± 3.0	4.7 ± 4.1	6.1 ± 5.4	7.8 ± 7.0	<0.001
Cardiac geometry						
LV mass index (g/m^2)	76.6 ± 14.3	75.5 ± 14.7	76.2 ± 13.6	76.6 ± 13.9	78.2 ± 14.7	0.013
Left atrium diameter (cm/m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	<0.001
LV internal diameter (cm/m^2)	4.6 ± 0.4	4.6 ± 0.4	4.6 ± 0.4	4.6 ± 0.5	4.7 ± 0.5	0.005
Interventricular septum (cm)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.105
LV posterior wall thickness (cm) (2-D module)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.008
Relative wall thickness	0.3 ± 0.04	0.3 ± 0.04	0.3 ± 0.04	0.3 ± 0.04	0.3 ± 0.04	0.960
Cardiac function						
Stroke volume (mL)	81.9 ± 14.4	79.8 ± 14.5	82.2 ± 14.9	83 ± 14.1	82.4 ± 14	0.016
Ejection fraction (%)	60 ± 5	60 ± 4.8	60.2 ± 4.9	60.2 ± 5.2	59.7 ± 5.1	0.481
Midwall shortening	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.556
E-velocity (cm/s)	69.7 ± 14.1	68.6 ± 14.6	70.8 ± 14.5	68.7 ± 13.8	70.6 ± 13.2	0.250
A-velocity (cm/s)	51.7 ± 11.8	51.1 ± 12.1	50.8 ± 11.6	52.5 ± 11.3	52.3 ± 11.9	0.071
E/A ratio	1.4 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.517
IVRT isovolumic relaxation time (ms)	76 ± 10.6	77.6 ± 10.4	76.6 ± 11.3	75.2 ± 10.6	74.4 ± 10	<0.001
Systolic blood pressure (mm Hg)	117.7 ± 13.2	118 ± 13.7	117.6 ± 12.5	117.9 ± 13.9	117.3 ± 12.8	0.582
Diastolic blood pressure (mm Hg)	75.3 ± 11	75.7 ± 11.3	74.6 ± 11.3	75.4 ± 11	75.5 ± 10.6	0.972
Pulse pressure (mm Hg)	42.4 ± 10.2	42.3 ± 10.1	43 ± 10.1	42.5 ± 10.9	41.8 ± 9.7	0.453

Values are n (%) or mean ± SD. Urinary uranium was creatinine adjusted.

participants with and without prehypertension/hypertension but was markedly stronger at follow-up for participants with prehypertension/hypertension (OR: 1.37, 95% CI: 1.16-1.63).

In linear mixed-effect models, the adjusted mean difference at baseline and follow-up for a 2-fold higher baseline urinary uranium was, respectively, 0.49 (95% CI: 0.07-0.92) and 0.30 (95% CI: −0.12 to 0.71) g/m^2 for LV mass index, 0.01 (95% CI: 0.01-0.02) and 0.01 (95% CI: 0.01-0.02) cm/m^2 for left atrial systolic diameter, and 0.02 (95% CI: 0.01-0.02) and 0.01 (95% CI: 0.00-0.02) cm/m^2 for LV internal diameter (**Table 3**). These relationships were consistent by prehypertension/hypertension status, although relationships only remained statistically significant at baseline for left atrial systolic diameter (**Table 4**). Flexible spline models supported the linear relationship of urine uranium with LV mass and left atrium systolic diameter, particularly at baseline, while relationships with LV internal diameter increased and then plateaued (**Figure 1**, **Central Illustration**). Relationships of urinary uranium with interventricular septum thickness, LV posterior wall thickness, and relative wall thickness were null (**Table 3**, Supplemental Table 3, and Supplemental Figure 4). A sensitivity analysis additionally including a random effect for family identifiers yielded similar results (data not shown). The sensitivity analysis investigating LVH and accounting for repeated measures were attenuated overall, but still stronger in the prehypertension subset (Supplemental Table 6).

TABLE 2 OR (95% CI) for Left Ventricular Hypertrophy at Baseline (2001-2003) and at Follow-Up (2006-2009) per a Log-Doubling of Urinary Uranium, According to Hypertension Status at Baseline

	Baseline (Visit 4)			Follow-Up (Visit 5)		
		Prevalence OR (95% CI)			Prevalence OR (95% CI)	
LV Hypertrophy (LVMI)	Cases/Noncases	Model 1	Model 2	Cases/Noncases	Model 1	Model 2
All participants	61/1,271	1.10 (0.91-1.32)	1.09 (0.91-1.31)	28/1,159	1.14 (0.96-1.36)	1.25 (1.06-1.48)
Prehypertension/hypertension	42/620	1.16 (0.91-1.47)	1.11 (0.89-1.37)	23/553	1.24 (1.04-1.48)	1.37 (1.16-1.63)
Normal blood pressure	19/651	1.16 (0.91-1.47)	1.11 (0.89-1.37)	5/606	0.88 (0.54-1.46)	0.84 (0.47-1.53)

Urinary uranium was creatinine adjusted and $\log_2$-transformed. Models specified are generalized estimating equations accounting for family structure, where Model 1 was adjusted for sex and age and Model 2 was additionally adjusted for smoking, body mass index, dyslipidemia, estimated glomerular filtration rate, study center, fasting glucose, urinary arsenic, systolic blood pressure, and hypertension treatment.

CI = confidence interval; LV = left ventricular; LVMI = LV mass index; OR = odds ratio.

Effect modification models for cardiac geometry outcomes were largely consistent across subgroups defined by age, sex, and urine arsenic levels (Supplemental Table 1).

Comparing the highest to lowest uranium/arsenic score groups, significant associations were observed at baseline and follow-up, respectively, for LV mass index (mean difference: 5.23 g/m^2, 95% CI: 2.66-7.81 g/m^2; mean difference: 4.55 g/m^2, 95% CI: 2.06-7.05 g/m^2), left atrium diameter (0.08 cm/m^2, 0.04-0.11 cm/m^2; 0.08 cm/m^2, 0.05-0.12 cm/m^2), LV internal diameter (0.08 cm/m^2, 0.02-0.13 cm/m^2; 0.11 cm, 0.05-0.17 cm/m^2), and LV posterior wall thickness (0.05 cm, 0.03-0.07 cm; 0.02 cm, 0.01-0.04 cm) (Supplemental Figure 6).

URINE URANIUM AND LV FUNCTION. There were 502 participants (60.5%) with LV diastolic dysfunction at baseline and 121 (18.8%) at follow-up. Uranium was not associated with LV diastolic dysfunction (OR: 0.98 [95% CI: 0.91-1.06] at baseline and 0.98 [95% CI: 0.86, 1.11] at follow-up comparing a log-doubling of urine uranium) (Supplemental Table 2). In linear mixed-effect models, the adjusted mean difference (95%) at baseline and follow-up comparing a 2-fold higher baseline urine uranium was, respectively, 0.66 (0.25, 1.08) and 0.29 (−0.10, 0.69) mL for stroke volume and 0.13 (−0.13, 0.39) and 0.28 (0.05, 0.52) mm Hg for pulse pressure (**Table 3**), and these associations remained consistent by prehypertension/hypertension status, although not always statistically

TABLE 3 Adjusted Mean Difference (95% CI) of Left Ventricular Measurements per a Log-Doubling of Urinary Uranium at Baseline, Annual Change, and at 5 Years of Follow-Up. Mean (95% CI) of Annual Change During Follow-Up for the Same Comparison

	Mean Difference Baseline	Annual Change	Mean Difference Follow-Up
Cardiac geometry			
LV mass index, g/m^2	0.49 (0.07-0.92)	−0.04 (−0.09 to 0.01)	0.30 (−0.12 to 0.71)
Left atrium systolic diameter, cm/m^2	0.01 (0.01-0.02)	−0.00 (−0.00 to 0.00)	0.01 (0.01-0.02)
LV internal diameter, cm/m^2	0.02 (0.01-0.02)	−0.00 (−0.00 to 0.00)	0.01 (0.00-0.02)
Interventricular septum, cm	0.00 (−0.00 to 0.01)	−0.00 (−0.00 to 0.00)	−0.00 (−0.01 to −0.00)
LV posterior wall thickness, cm	0.00 (−0.00 to 0.01)	−0.00 (−0.00 to 0.00)	0.00 (−0.00 to 0.00)
Cardiac function			
Stroke volume, mL	0.66 (0.25-1.08)	−0.07 (−0.16 to 0.02)	0.29 (−0.10 to 0.69)
Ejection fraction, %	−0.04 (−0.20 to 0.11)	−0.01 (−0.03 to 0.02)	−0.07 (−0.22 to 0.07)
Heart rate, beats/min	−0.18 (−0.51 to 0.15)	0.02 (−0.04 to 0.09)	−0.07 (−0.38 to 0.24)
Mitral E-velocity, cm/s	0.20 (−0.21 to 0.61)	−0.07 (−0.17 to 0.02)	−0.17 (−0.53 to 0.19)
Mitral A-velocity, cm/s	0.22 (−0.12 to 0.56)	−0.06 (−0.14 to 0.02)	−0.10 (−0.40 to 0.20)
E/A ratio	−0.00 (−0.01 to 0.01)	0.00 (−0.00 to 0.00)	−0.00 (−0.01 to 0.01)
Deceleration time, ms	−0.43 (−1.53 to 0.68)	0.20 (−0.09 to 0.49)	0.56 (−0.43 to 1.55)
Isovolumic relaxation time, ms	−0.55 (−0.86 to −0.23)	0.11 (0.03-0.19)	0.01 (−0.27 to 0.29)
Pulse pressure (mm Hg)	0.13 (−0.13 to 0.39)	0.03 (−0.04 to 0.10)	0.28 (0.05-0.52)

Models were adjusted for sex, age, smoking, body mass index, dyslipidemia, eGFR, study center, fasting glucose, urinary arsenic, blood pressure and hypertension treatment (yes/no). Uranium was corrected by urine creatinine and further $\log_2$-transformed. Mixed effect models included a random intercept and slope over time for participant.

CI = confidence interval; LV = left ventricular.

TABLE 4 Adjusted Mean Difference (95% CI) of Left Ventricular Measurements per a Log-Doubling of Urinary Uranium by Blood Pressure Status at Baseline and at Follow-up. Mean (95% CI) of Annual Change During Follow-Up for the Same Comparison

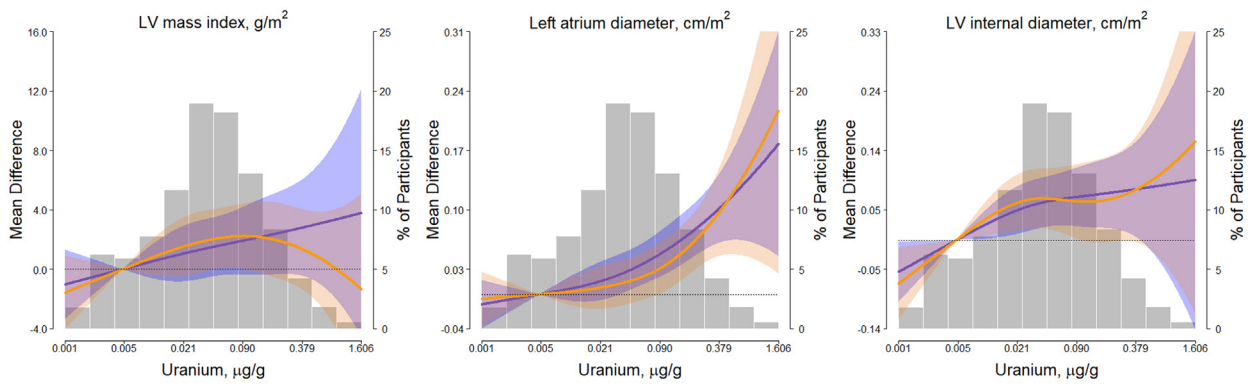
	Prehypertension/Hypertension			Normal Blood Pressure		
	Mean Difference Baseline	Annual Change	Mean Difference Follow-Up	Mean Difference Baseline	Annual Change	Mean Difference Follow-Up
Cardiac geometry						
LV mass index, g/m^2	0.49 (−0.16 to 1.14)	−0.03 (−0.11 to 0.05)	0.34 (−0.29 to 0.97)	0.44 (−0.13 to 1.01)	−0.04 (−0.11 to 0.03)	0.23 (−0.32 to 0.77)
Left atrium systolic diameter, cm/m^2	0.01 (0.01-0.02)	0.00 (−0.00 to 0.00)	0.02 (0.01-0.02)	0.01 (0.00-0.02)	−0.00 (−0.00 to 0.00)	0.01 (−0.00 to 0.01)
LV internal diameter, cm/m^2	0.01 (0.00-0.03)	0.00 (−0.00 to 0.00)	0.02 (0.00-0.03)	0.01 (0.00-0.03)	−0.00 (−0.00 to 0.00)	0.01 (−0.00 to 0.02)
Cardiac function						
Stroke volume, mL	0.82 (0.18-1.46)	−0.09 (−0.23 to 0.04)	0.35 (−0.25 to 0.96)	0.49 (−0.05 to 1.03)	−0.05 (−0.18 to 0.07)	0.22 (−0.29 to 0.73)
Pulse pressure (mm Hg)	0.25 (−0.16 to 0.66)	0.05 (−0.06 to 0.16)	0.49 (0.12-0.86)	0.01 (−0.29 to 0.31)	0.01 (−0.08 to 0.09)	0.05 (−0.22 to 0.32)

Models were adjusted for sex, age, smoking, body mass index, dyslipidemia, eGFR, study center, fasting glucose, urinary arsenic, blood pressure and hypertension treatment (yes/no). Models assessing blood pressure did not adjust for blood pressure. Uranium was corrected by urine creatinine and further $\log_2$-transformed. Mixed-effect models included a random intercept and slope over time for participant.
CI = confidence interval; LV = left ventricular.

significant (Table 4). Urinary uranium was not significantly associated with ejection fraction, mitral E-velocity, mitral A-velocity, E/A ratio, or the remaining measures of cardiac function at baseline or follow-up (Table 3, Figure 2, Supplemental Figure 5, Supplemental Tables 3 and 4).

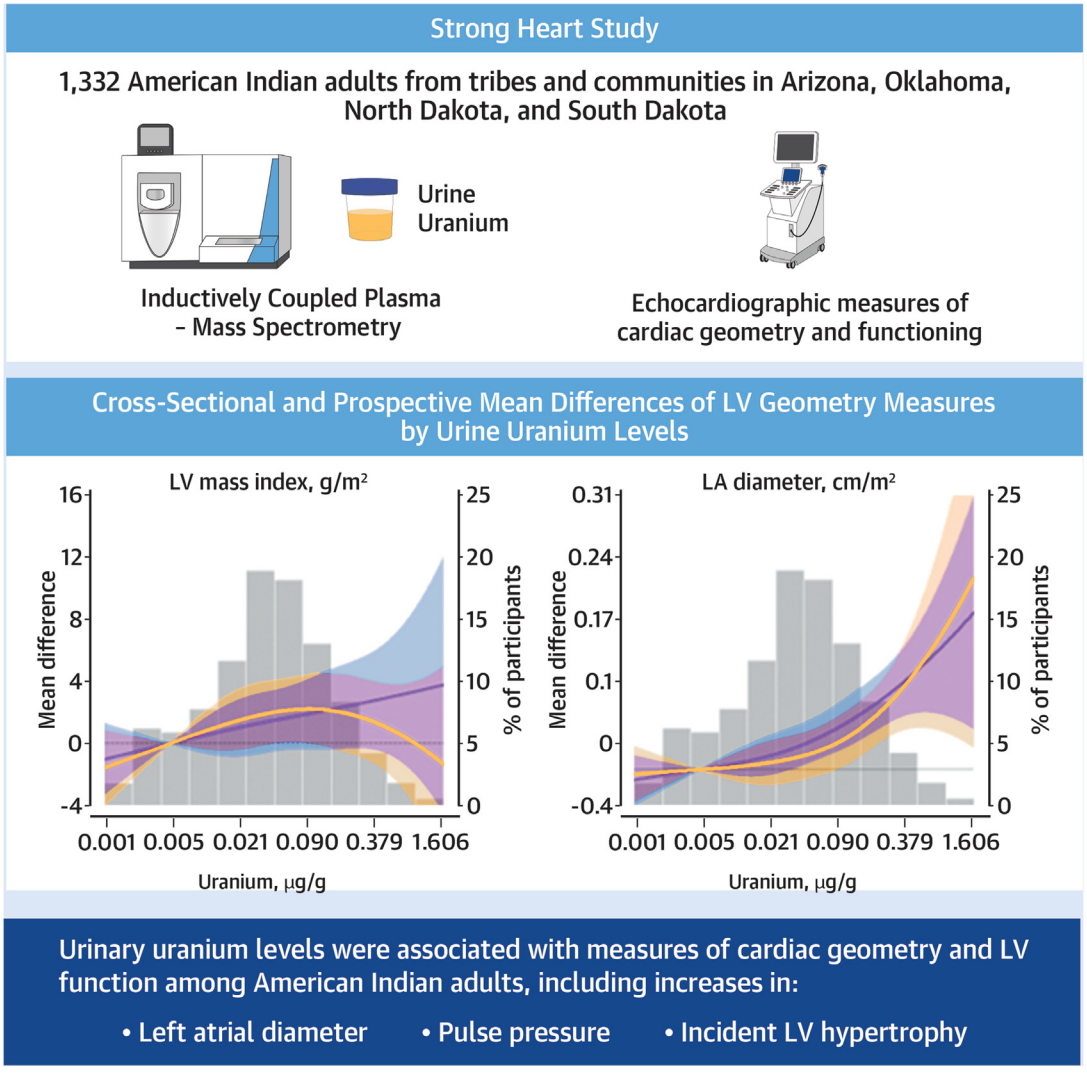
Effect modification models for cardiac functional outcomes were consistent by subgroups except for DBP and pulse pressure by sex and DBP by age (Supplemental Table 1). A log-doubling of urinary uranium was associated with lower DBP levels in males both at baseline (mean difference: −0.54 mm Hg, 95% CI: −0.99 to −0.10 mm Hg) and follow-up (mean difference: −0.59 mm Hg, 95% CI: −1.00 to −0.19 mm Hg) but not among females either at baseline (0.01 mm Hg, 95% CI: −0.31 to 0.33 mm Hg) or follow-up (0.02 mm Hg, 95% CI: −0.27 to 0.31 mm Hg). A significant interaction by sex was observed for pulse pressure (P value for interaction = 0.003), with positive increases in pulse pressure in males at baseline (mean difference 0.39 mm Hg, 95% CI: −0.10 to 0.87) and follow-up (0.60 mm Hg, 95% CI: 0.18-1.02) and no association among females. A significant interaction was also observed according to age (P value for interaction = 0.01), with a log-doubling of urinary uranium being associated with lower DBP levels in participants <30.4 years both at baseline (mean difference: −0.61 mm Hg, 95% CI: −1.03 to −0.19 mm Hg) and follow-up (mean difference: −0.74 mm Hg, 95% CI: −1.12 to −0.35 mm Hg), while the association was positive although not

FIGURE 1 Cross-Sectional and Prospective Adjusted Mean Differences of LV Geometry Measures by Urine Uranium Levels



Adjusted mean differences of selected left ventricular geometry measures based on restricted cubic splines for log-transformed uranium distribution with knots at 10th (reference), 50th, and 90th percentiles. Blue represents associations at baseline, and orange represents associations at follow-up. Models were adjusted for sex, age, study center, smoking (never, former, current), body mass index (kg/m^2), sum of inorganic and methylated arsenic (µg/g creatinine), dyslipidemia (no/yes), fasting glucose level (continuous), estimated glomerular filtration rate (mL/min/1.73 m^2), systolic blood pressure (continuous), and hypertension treatment (no/yes). Histograms represent the distribution of uranium.

CENTRAL ILLUSTRATION **Relationship of Urinary Uranium With Cardiac Geometry and Left Ventricular Function: The Strong Heart Study**



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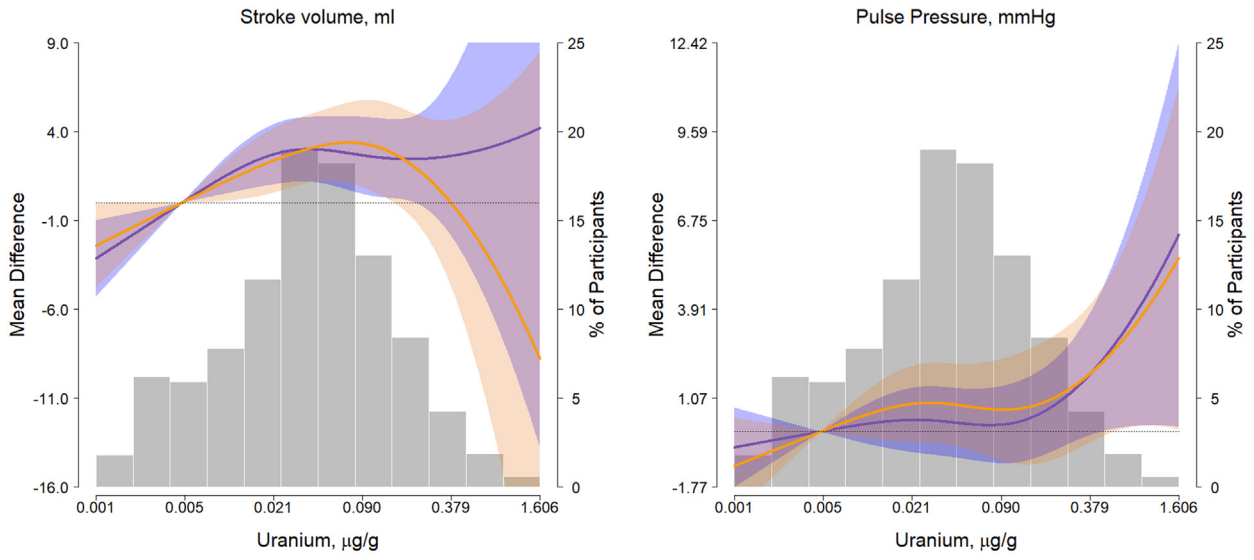
significant for participants >30.4 years both at baseline (mean difference: 0.05 mm Hg, 95% CI: −0.27 to 0.38 mm Hg) and follow-up (0.19 mm Hg, 95% CI: −0.11 to 0.48 mm Hg).

Participants in the highest uranium + arsenic tertile compared to those in the lowest tertile, showed higher LV mass index at baseline (mean difference 5.23 g/m^2, 95% CI: 2.66-7.81 g/m^2) and follow-up (4.55 g/m^2, 95% CI: 2.06-7.05 g/m^2), higher stroke volume at baseline (mean difference: 5.08 mL, 95% CI: 2.57-7.58 mL) and follow-up (2.49 mL, 95% CI: 0.12-4.85 mL). The corresponding associations were inverse with isovolumic relaxation time at baseline (mean difference: −2.55 milliseconds, 95% CI: −4.44 to −0.66 milliseconds) but null as the follow-up. The associations tended to be positive with SBP at baseline and follow-up, and inverse with DPB, which was significant at follow-up (mean difference: −1.52 mm Hg, 95% CI: −2.96 to −0.08 mm Hg) (Supplemental Figure 6).

DISCUSSION

In this study evaluating the impact of individually-estimated uranium exposure on measures of LV geometry and function in an epidemiological cohort,

FIGURE 2 **Cross-Sectional and Prospective Adjusted Mean Differences of Selected Left Ventricular Function Measures by Urine Uranium Levels**



Adjusted mean differences of selected left ventricular function measures and pulse pressure based on restricted cubic splines for log-transformed uranium distribution with knots at 10th (reference), 50th, and 90th percentiles. Blue represents associations at baseline, and orange represents associations at follow-up. Models were adjusted for sex, age, study center, smoking (never, former, current), body mass index (kg/m^2), sum of inorganic and methylated arsenic (µg/g creatinine), dyslipidemia (no/yes), fasting glucose level (continuous), estimated glomerular filtration rate (mL/min/1.73 m^2), systolic blood pressure (continuous), and hypertension treatment (no/yes). Histograms represent the distribution of uranium.

urine uranium was positively associated with increases in LV mass, left atrium systolic diameter, and LV internal diameter at baseline and over follow-up, both in participants without and with prehypertension/hypertension, as well with LV hypertrophy at follow-up, primarily driven by participants with prehypertension and hypertension. Urine uranium was positively associated with increases in stroke volume at baseline and with pulse pressure at follow-up, notably among the prehypertensive/hypertensive subgroup, but not significantly associated with other measures of systolic or diastolic function.

Our findings contribute novel evidence from an epidemiologic cohort of young American Indian adults. The current literature on uranium and CVD mainly stems from occupational settings,[1,13] with limited evidence relating CVD with chronic environmental uranium exposure in the general population. One study using NHANES 2007 to 2008 data has linked higher uranium exposure to increased risk of congestive heart failure (OR: 5.20, 95% CI: 1.52-17.80).[14] Drinking uranium-contaminated water was associated with increases in SBP and DPB in Finland,[12] exposure to uranium mining on Navajo Nation Land was associated with hypertension,[35] and higher urine uranium levels were associated with incident hypertension in the SHFS. An additional study of Ohio residents proximate to a uranium processing center reported that females with higher exposure had elevated SBP, but not DBP or hypertension, compared to those with lower exposure.[36]

In the present analysis, we report an increase in pulse pressure at follow-up, underscored by a decrease in diastolic blood pressure. A widened pulse pressure is considered a risk factor for CVD incidence and mortality.[37,38] Higher pulse pressure indicates structural changes in the arterial wall that result in increased arterial stiffness.[39] Associations between uranium and LVH and left atrium diameter may reflect diastolic dysfunction, as increased LVMi results in elevated filling pressures, as expressed by an increase in left atrium size. We do not report associations with E-velocity or A-velocity, but several different E/A patterns are observed in diastolic dysfunction.[40] Our finding that uranium was significantly associated with LVH, LV internal diameter, as well as pulse pressure, especially among those with prehypertension or hypertension, suggests not only the relevance of uranium for subclinical disease but

also the differing impact among those whose cardiovascular systems are already compensating to elevated blood pressure.

Our findings integrate into prior research in the SHS, which identified that increased pulse pressure was associated with an increased risk of cardiovascular mortality and increases in LV mass.[41] Prior findings from the SHFS have also identified that urinary arsenic was related to an increase in LV wall thickness, LV hypertrophy, stroke volume, and ejection fraction.[21] Although arsenic and uranium are correlated, and likely share common sources,[5] in the present analysis we adjusted for urinary arsenic, supporting that the findings with LVH and pulse pressure were specific to uranium.

Uranium is an established nephrotoxicant.[20] Studies have identified that uranium can dysregulate calcium[42] and iron homeostasis,[43] induce oxidative stress,[44] and modulate levels of proteins in the kidneys, including increased albuminuria.[45] Experimental and observational studies support uranium-related kidney damage.[12,46,47] In general, uranium is proposed to induce toxicity through oxidative stress and inflammation,[1] although the underlying toxicologic mechanism are understudied in comparison to other metals.

This study is not without limitations. While the SHS has a high prevalence and incidence of diabetes, prediabetes, CVD and CVD risk factors, analyses were restricted to study participants <50 years of age, and free of CVD at baseline and of diabetes mellitus at baseline. Additionally, statistical models accounted for other CVD risk factors, including smoking status, body mass index, and eGFR. This analysis should be investigated in a larger sample size and in different populations. Urinary uranium was only available at baseline, while echocardiographic measures were available at baseline and follow-up. Cross-sectional associations at baseline could thus reflect potential reverse causation. Urine, however, is a useful biomarker of long-term exposure and accumulation when exposures are constant,[6] and we provide prospective and annual change associations. Transthoracic echocardiography was performed at the follow-up visit in 2006 to 2009. Having a longer follow-period would provide more information to study the long-term effects of chronic uranium exposure. Our study has further strengths, including the large number of young adults with uranium, cardiac geometry, and cardiac function measures available, the high-quality outcome assessment performed in the SHS, and data concern relevant confounders.

CONCLUSIONS

In a sample of young American Indian adults, urine uranium levels measured in 2001 to 2003 were related to LV hypertrophy and pulse pressure, as well as distinct measures of cardiac geometry and LV function assessed in 2006 to 2009, potentially reflecting the early cardiovascular impact of uranium exposure. These findings highlight the potential long-term clinical and subclinical cardiovascular effects of chronic uranium exposure, the need to replicate findings in additional populations, and support for strategies to reduce uranium exposure.

AVAILABILITY OF DATA AND MATERIAL. The data were collected, analyzed, and reported under agreements made with the sovereign tribal nations that have partnered in this research, which precludes commonly accepted modes of data sharing. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Strong Heart Study Coordinating Center at https://strongheartstudy.org/. Requests will be reviewed by tribal research partners before data may be released. This policy is consistent with the NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this study of American Indian adults in the SHS, we provide further evidence of contaminant metals as risk factors for cardiovascular disease and support the need for interventions to reduce exposure.

TRANSLATIONAL OUTLOOK: Uranium measured in urine was related to distinct changes in cardiac geometry, pulse pressure, and LV hypertrophy. Future efforts are warranted to assess the relationship of uranium with subclinical measures and clinical outcomes to reduce cardiovascular disease.

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KEY WORDS **American Indian populations, cardiac geometry, left ventricular function, uranium**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**