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Urinary Arsenic and Cadmium Associations with Findings from Cranial MRI in American Indians: Data from the Strong Heart Study

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Background: Arsenic and cadmium are known cardiovascular toxicants that pose disproportionate risk to rural communities where environmental exposures are high. American Indians have high vascular risk, which may be attributable in part to these exposures.

Objective: We examined urine metal concentrations in association with magnetic resonance imaging findings of vascular brain injury or cerebral atrophy in adult American Indians.

Methods: We measured arsenic and cadmium in American Indian participants from the Strong Heart Study (1989–1991) and evaluated these associations with later (2010–2013) measures of infarct, hemorrhage, white matter hyperintensity (WMH) grade, brain and hippocampal volume, and sulcal and ventricle atrophy using nested multivariate regression analyses.

Results: Among participants with available data ($N = 687$), the median urine arsenic:creatinine ratio was 7.54 μg/g [interquartile range (IQR): 4.90–11.93] and the cadmium:creatinine ratio was 0.96 μg/g (IQR: 0.61–1.51). Median time between metal measurement and brain imaging was 21 y (range: 18–25 y). Statistical models detected significant associations between arsenic and higher burden of WMH [grade increase = 0.014 (95% CI: 0.000, 0.028) per 10% increase in arsenic]; and between cadmium and presence of lacunar infarcts [relative risk (RR) = 1.024 (95% CI: 1.004, 1.045) per 10% increase in cadmium].

Discussion: This population-based cohort of American Indian elders had measured values of urine arsenic and cadmium several times higher than previous population- and clinic-based studies in the United States and Mexico, and comparable values with European industrial workers. Our findings of associations for arsenic and cadmium exposures with vascular brain injury are consistent with established literature. Environmental toxicant accumulation is modifiable; public health policy may benefit from focusing on reductions in environmental metals. https://doi.org/10.1289/EHP6930

Introduction

Arsenic and cadmium are known environmental toxicants. Geographical regions characterized by subsistence or rural economies may have some of the most heavily arsenic- and cadmium-contaminated soil or groundwater, where agriculture (Jayaraj et al. 2016; Walker et al. 2005; Wei et al. 2017; Wolz et al. 2003), mining (Lewis et al. 2017), and industrial contamination (Carey et al. 1980; Fishbein 1981; Pinto and Nelson 1976) combine to result in environmental metal exposures that greatly exceed established safety standards (Harris and Harper 1997). Arsenic concentrations in groundwater are highest in the American Southwest, with residents sometimes exposed to levels 5–10 times the U.S. Environmental Protection Agency (EPA) safety limits of 10 ppb (Welch et al. 2015; U.S. EPA 2001), and in parts of the Great Plains (USGS 2015). Cadmium, which is typically inhaled as airborne particulate matter near industrial sites or from cigarette smoke, or which may be ingested from some foods, including leafy and root vegetables, organ meats, and shellfish, also shows heavy soil contamination throughout the Great Plains (Reeves and Vanderpool 1997; USGS 2015) where lifetime residents may have accumulated more than 25 times the World Health Organization (WHO) threshold for heavy exposure, or 200 $\mu g/m^3$ per year (WHO 2011). Owing to such high environmental exposures, residents of the American Southwest and Great Plains—and especially those residing in close proximity to mining or industrial contamination sites, such as American Indians living on reservations (Lewis et al. 2017)—tend to have higher biochemical profiles of these toxicants, compared with adults of similar age from urban areas in the United States (Navas-Acien et al. 2009; Pang et al. 2016; Tellez-Plaza et al. 2013).

American Indians have a particularly high burden of diseases related to vascular aging (Harwell et al. 2005; Howard et al. 1999; Rosamond et al. 2007; Stansbury et al. 2005; Suchy-Dicey et al. 2017), and both arsenic and cadmium are known to increase cardiovascular or cerebrovascular risk and neurotoxicity, even at low levels of exposure (Carroll et al. 2017; Grandjean and Herz 2015; Moon et al. 2012, 2013; Wang and Du 2013). Whether excess exposure to these environmental toxicants may be responsible for excess risk to the brain among American Indians is yet unclear. It is also undetermined whether any such association would be pathologically associated with cardiovascular comorbidities, such as diabetes, hypertension, or renal insufficiency, or with other toxicants such as alcohol and tobacco. Finally, it is unknown whether different brain structures or disease end points may be affected by different metal exposures. Arsenic is a platelet aggregator and vasoinhibitor, causing endothelial dysfunction and peripheral artery disease, which we hypothesize to result in vascular injury, including infarcts or hemorrhages (Kao et al. 2003; Sharma and Sharma 2013; Zheng et al. 2014). Cadmium may disrupt the endocrine system and trigger oxidative stress, decreasing regenerative capacity of neural tissue (Chow et al. 2008; Wang and Du 2013); hypothetically, long-term outcomes might include atrophy of the cerebral cortex and other brain structures.

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Our analyses are aimed at improving the understanding of the specific, independent associations of these toxic environmental metal exposures with brain magnetic resonance imaging (MRI) end points. Such findings have the potential to identify targeted prevention or treatment opportunities in a heavily exposed, high-risk population, and may also have relevance to other, similarly exposed groups. However, the effect of environmental metal exposures can take many years to accumulate, and their effects may also take many years to become clinically recognizable. To this end, we have used urine assays and brain MRI collected over 25 y of the Strong Heart Study, a longitudinal cohort of older American Indians living in predominantly rural settings across three major geographic regions of the United States, to examine whether arsenic or cadmium exposure assessed in 1989–1991 are associated with measures of vascular disease and cerebral atrophy 20–25 y later and whether any such associations may be independent of or mediated by cardiovascular comorbidities, renal disease, and use of alcohol.

Methods

Setting

Strong Heart Study cohort participants have undergone several waves of data collection from 1989 to 2013, including extensive clinical examinations, blood and urine assays, and brain imaging (Lee et al. 1990; Scheer et al. 2012; Suchy-Dicey et al. 2016, 2017). The original cohort, recruited in 1989–1991, included 4,549 American Indians 35–74 years of age, living in tribal communities in the U.S. Southwest, Northern Plains, and Southern Plains. Arsenic and cadmium levels were measured from urine samples collected during that baseline visit in 3,575 participants. An ancillary, follow-up examination, also known as the Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study, conducted brain MRI and clinical evaluations in 2010–2013 on 1,033 of the original cohort members, representing a follow-up recruitment of 86% of all surviving participants (Suchy-Dicey et al. 2016). All participants provided written, informed consent and all institutional, tribal, and Indian Health Service review boards approved study activities. After CDCAI data collections were completed, one community withdrew consent to use their data ($n = 215$). Of the $N = 818$ participants available for analysis, subsequent exclusions included missing or noninterpretable MRI scans ($n = 29$), missing arsenic or cadmium assay data ($n = 89$), and missing covariate data ($n = 13$), leaving $N = 687$ available for analysis. Some additional numbers were missing for different categories due to, for example, failure in volumetric processing owing to motion artifacts, with the final observation N given in Table 1.

Exposure

Detailed urine collection and assay of arsenic species and cadmium, using anion-exchange high-performance liquid chromatography and inductively coupled plasma mass spectrometry and extensive quality control, have been described in detail (Scheer et al. 2012). The primary arsenic exposure variable was the sum of inorganic arsenic (arsenite + arsenate), methylated methylmalonic acid (MMA), and dimethylacetamide (DMA) arsenic species. Seafood intake in this population is very low, confirmed by low levels of urine arsenobetaine; therefore, the sum of the inorganic and methylated arsenic species is an appropriate measure of arsenic exposure not derived from seafood (Navas-Acien et al. 2011). The limit of detection (LOD) for total inorganic arsenic was 0.1 μg/L and for cadmium, 0.015 μg/L. The number (percentage) of samples with concentrations below LOD was 40 (5.8%) for inorganic arsenic, 5 (0.7%) for MMA, 1 (0.1%) for DMA, 9 (1.3%) for arsenobetaine, and 1 (0.1%) for cadmium. Samples below the LOD were replaced with values obtained by dividing the LOD by the square root of 2. Interassay coefficients of variation for inorganic arsenic, MMA, DMA, and arsenobetaine for an in-house reference urine were 6.0%, 6.5%, 5.9%, and 6.5%, respectively; for cadmium, it was 8.7%. To correct for urinary dilution, arsenic concentrations (in micrograms per liter) were divided by urine creatinine concentrations (in grams per liter), and expressed as micrograms-per-gram arsenic:creatinine ratios. The primary cadmium exposure variable was urine cadmium concentration (in micrograms per liter), divided by creatinine concentration (in grams per liter), expressed as micrograms-per-liter cadmium:creatinine ratios.

Outcome

Methods of MRI acquisition, interpretation, and description have been previously described in detail (Suchy-Dicey et al. 2017). Briefly, participants underwent 1.5 Tesla scans including six sequences (sagittal T1-weighted localizer, co-registered 5-mm axial-T1, 5-mm axial-T2, 5-mm axial-T2* susceptibility weighted in the anterior commissure/posterior commissure plane, 3-mm axial fluid-attenuated inversion recovery, and 1.5-mm sagittal T1-weighted volumetric gradient recall echo). Two independent, blinded neuroradiologists scored images for severity of graded findings (scale 0–9; with 9 being most severe) against standard templates used by the Cardiovascular Health Study; coded the presence, location, and size of lesions; and conducted software processing for volumetric estimations. Graded measures included white matter hyperintensities (WMHs), representing small vessel disease; sulcal widening, representing loss of volume of the cortical gyri; and lateral ventricular enlargement, representing loss of volume in subcortical tissue. Volumetric estimations were done using semiautomated software processing of images for WMHs; whole, left, and right hippocampus, a structure of the limbic system important for the formation of memory; total intracranial gray and white matter brain volume; and whole intracranial space, using the fuzzy lesion extractor technique, FreeSurfer, FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FMRIB Software Library (FSL) 5.0, and the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA1) protocol. Left and right hippocampus were reported separately due to prior research that suggested differential associations with cognition and brain aging (Cholerton et al. 2017). Infarcts were ≥3 mm in diameter; lacunar infarcts were defined as infarcts 3–20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, cerebellar white matter, centrum semiovale, or corona radiata, typically presumed to result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain; and hemorrhages of any size. Quality control for intercoding differences included adjudication until agreement was reached.

Vascular brain injury is the likely pathology underlying MRI findings of brain infarcts, hemorrhages, and WMHs; vascular brain injury and independent degenerative disease processes may both play a role in other MRI findings, including sulcal widening, ventricle enlargement, and hippocampus and total brain volumes. Although clinical context for this population is yet unknown for many of these findings, previous reports in this cohort study have identified more than one-third of American Indians ≥65 years of age as having findings consistent with vascular brain injury and two-thirds as having findings consistent with structural atrophy (Suchy-Dicey et al. 2017), both associated with reduced processing speed (Suchy-Dicey et al. 2020).

Other Variables

Age, sex, study field center (geographic region), education, income, adiposity, smoking, alcohol use, diabetes, hypertension,

Table 1. Medians and interquartile ranges (IQRs) for urine arsenic (inorganic arsenic + DMA + MMA) and cadmium (μg/g creatinine), per selected characteristics, among elderly American Indian participants: the Strong Heart Study.

	N	Urine arsenic (μg/g creatinine) [median (IQR)]	Urine cadmium (μg/g creatinine) [median (IQR)]
Demographic characteristics			
Age (y)			
65–69	237	7.45 (4.97–11.46)	0.90 (0.61–1.32)
70–74	216	7.93 (5.15–12.64)	0.95 (0.61–1.59)
75–79	135	7.63 (4.61–11.78)	1.03 (0.63–1.70)
≥80	99	7.50 (4.12–11.74)	1.08 (0.61–1.62)
Sex			
Male	223	6.56 (4.32–9.74)	0.65 (0.43–0.98)
Female	464	8.38 (5.50–12.95)	1.17 (0.75–1.74)
Study field center			
Northern plains	315	9.15 (6.53–13.72)	1.09 (0.74–1.73)
Southern plains	291	5.47 (3.76–7.47)	0.85 (0.55–1.36)
Southwest	81	13.88 (9.26–20.40)	0.75 (0.54–1.17)
Education			
Did not complete high school	136	7.87 (5.00–12.17)	1.23 (0.82–1.89)
Graduated high school	167	7.22 (4.90–11.20)	0.92 (0.58–1.34)
Attended some college	280	8.18 (5.17–13.10)	0.89 (0.61–1.46)
Graduated college	104	6.63 (4.43–9.81)	0.84 (0.54–1.43)
Annual household income			
<$10,000	211	8.79 (5.60–13.13)	1.17 (0.74–1.74)
$10,000–$20,000	201	7.86 (5.27–12.89)	1.10 (0.68–1.66)
$20,000–$35,000	155	7.40 (4.74–11.62)	0.77 (0.55–1.19)
>$35,000	120	6.36 (4.23–8.95)	0.74 (0.45–1.16)
Health characteristics			
Adiposity			
Normal	103	7.04 (4.32–11.08)	1.08 (0.61–1.81)
Overweight	216	8.24 (5.00–12.79)	1.02 (0.66–1.59)
Obese	367	7.53 (5.07–11.72)	0.90 (0.60–1.40)
Smoking status			
Never smoked	234	7.86 (5.27–12.68)	0.99 (0.65–1.52)
Ever smoked	453	7.48 (4.72–11.72)	0.94 (0.60–1.50)
Alcohol use			
Never	166	8.55 (5.11–12.87)	1.19 (0.68–1.88)
Former drinker	401	7.48 (4.95–12.00)	0.94 (0.61–1.43)
Current drinker	120	7.07 (4.72–11.21)	0.86 (0.56–1.19)
Diabetes			
Diabetes	336	7.65 (5.09–11.96)	0.91 (0.60–1.45)
No diabetes	351	7.43 (4.72–11.93)	1.02 (0.64–1.59)
Hypertension			
Hypertension	555	7.52 (4.85–11.93)	0.93 (0.61–1.46)
No hypertension	132	7.88 (5.14–12.29)	1.01 (0.64–1.71)
Dyslipidemia			
Dyslipidemia	458	7.44 (4.72–11.93)	0.91 (0.56–1.44)
No dyslipidemia	229	7.86 (5.66–12.25)	1.09 (0.69–1.65)
CKD			
CKD	186	7.59 (4.67–11.93)	0.91 (0.61–1.26)
No CKD	501	7.54 (4.95–11.93)	0.98 (0.61–1.60)
Graded outcomes (range 0–9)			
WMH			
Abnormal WMH grade (≥3)	256	7.99 (5.12–13.51)	1.09 (0.66–1.63)
Normal white matter	425	7.40 (4.82–11.11)	0.91 (0.59–1.44)
Sulci			
Abnormal sulcal grade (≥3)	452	7.50 (4.81–11.76)	0.93 (0.61–1.47)
Normal sulci	228	7.61 (5.09–12.26)	1.00 (0.61–1.54)
Ventricles			
Abnormal ventricle grade (≥3)	461	7.56 (4.85–11.95)	0.95 (0.61–1.49)
Normal ventricles	220	7.36 (4.96–11.54)	0.97 (0.61–1.55)
Volumetric outcomes (mL)			
WMH volume (range)			
Low (0.00–3.53)	223	6.82 (4.73–11.46)	0.84 (0.54–1.44)
Middle (3.54–8.18)	222	7.93 (11.72–5.04)	1.00 (0.60–1.40)
High (8.18–45.66)	221	7.93 (5.16–12.68)	1.07 (0.69–1.67)
Hippocampus volume (range)			
Low (0.73–6.26)	223	8.83 (5.16–15.35)	1.04 (0.61–1.65)
Middle (6.26–6.99)	224	7.54 (5.14–10.87)	0.99 (0.66–1.46)
High (6.99–12.74)	210	6.82 (4.58–11.05)	0.86 (0.55–1.31)
Left hippocampus (range)			
Low (0.38–3.01)	221	7.86 (4.90–13.94)	0.99 (0.62–1.65)
Middle (3.01–3.44)	221	7.93 (5.90–12.00)	1.01 (0.67–1.60)
High (3.44–6.51)	216	6.77 (4.43–10.69)	0.86 (0.53–1.25)

Table 1. (*Continued.*)

	N	Urine arsenic (μg/g creatinine) [median (IQR)]	Urine cadmium (μg/g creatinine) [median (IQR)]
Right hippocampus (range)			
Low (0.35–3.22)	225	8.05 (5.18–13.88)	0.91 (0.57–1.51)
Middle (3.22–3.61)	222	7.99 (5.30–11.87)	1.01 (0.65–1.52)
High (3.61–6.22)	211	6.70 (4.49–9.77)	0.96 (0.61–1.47)
Brain volume (range)			
Low (689.58–887.29)	190	7.51 (4.82–13.72)	1.08 (0.63–1.57)
Middle (887.33–975.27)	202	7.65 (5.67–11.71)	0.97 (0.65–1.54)
High (975.42–1,235.36)	189	7.43 (4.74–11.05)	0.83 (0.51–1.29)
Binary outcomes			
Infarcts			
Lacunar infarcts	82	7.61 (6.02–12.34)	1.12 (0.66–1.70)
Non-lacunar infarcts	76	8.38 (4.54–12.78)	0.80 (0.56–1.25)
Both lacunar and non-lacunar infarcts	75	7.62 (4.49–14.32)	1.18 (0.65–1.81)
No infarcts	453	7.52 (4.90–11.40)	0.93 (0.61–1.45)
Hemorrhages			
Hemorrhage	41	8.98 (4.74–15.17)	1.16 (0.64–1.72)
No hemorrhage	642	7.50 (4.90–11.74)	0.95 (0.61–1.46)

Note: CI, confidence interval; CKD, chronic kidney disease; Diff, difference; DMA, dimethylacetamide; MMA, methylmalonic acid; WMH, white matter hyperintensity.

high levels of low-density lipoprotein (LDL), and chronic kidney disease (CKD) were collected and defined as of the time of the MRI visit. Age was calculated based on year of birth and categorized as 65–69, 70–74, 75–79, or ≥80 years of age. Sex (male, female) was self-reported. Study field centers (geographic regions) included the Northern Plains, Southern Plains, and Southwest. Education was self-reported and conceptually categorized as formal education up to 11th grade, high school graduate, any college attendance, and 4-y college graduate (bachelor's degree). Annual household income at the time of study enrollment was self-reported and categorized roughly by quartile as <$10,000, $10,000–$20,000, $20,000–$35,000, and >$35,000. Adiposity was categorized based on body mass index (BMI) as <25, 25–30, or ≥30 kg/m^2. Smoking was self-reported and categorized as a yes or no response to the question, "during your lifetime have you smoked 100 cigarettes or more?" Alcohol use was self-reported and categorized as never having used alcohol, former drinker with no alcohol use within past year, or current drinker or use of alcohol at any time within past year. Diabetes was defined as a measured fasting plasma glucose level of >125 mg/dL or self-reported use of insulin or oral diabetes medications. Hypertension was defined as the measured average of three seated systolic blood pressure measures >139 mmHg, the measured average of three seated diastolic blood pressure measures >89 mmHg, or self-reported use of antihypertensive medications. High LDL was defined as a measured, fasting serum LDL level of >100 mg/dL or use of cholesterol-lowering medications. CKD was defined as a measured, estimated glomerular filtration rate (Modified Diet in Renal Disease equation) of <60 mL/min or a measured urine albumin–creatinine ratio of >30 mg/g.

Statistical Analyses

Regression models included urine arsenic (in micrograms per gram creatinine) or urine cadmium (in micrograms per gram creatinine) as the independent variable and findings from cranial MRI scans as the dependent variable. Creatinine-corrected exposure variables were natural log-transformed to reduce the impact of outliers. Ordinal (WMH, sulcal widening, and ventricle enlargement grades) and continuous (estimated WMH, hippocampus, and brain volume) outcome measures were modeled using linear regression, and coefficients were multiplied by ln (1.10) to estimate the difference in each outcome (on its original scale) with a 10% increase in exposure. Dichotomous outcomes (infarct, lacunar infarct, and hemorrhage) were modeled using Poisson regression and are reported as the relative risk (RR) associated with a 10% increase in exposure.

Regression models were adjusted for *a priori* selected covariates, including both potential confounders and precision variables, defined at the time of the MRI visit, including continuous age, sex, field center, education, income, smoking, alcohol use, and BMI (base model, Model 1). Models for volumetric outcomes (WMH, hippocampus, and brain; in milliliters) were adjusted for total intracranial volume to account for interindividual variation in head size. In addition to the base model, we ran models that were also adjusted for potential causal intermediates, including comorbid conditions [diabetes, hypertension, and elevated LDL (Model 2) and CKD (Model 3)], as well as a fully adjusted model that included the base model covariates and all of the potential intermediates in a single model (Model 4). We also present results stratified by field center and by CKD as of the time of the MRI examination given that it is known that geographic location (Navas-Acien et al. 2009) and CKD status (Zheng et al. 2015) may both influence urine metal levels. To formally assess for consistency of associations across subgroups, we also ran separate interaction models for the exposure with the stratifying feature, and we reported the *p*-values for those product term coefficients. Robust standard errors were used to minimize the effect of inconsistent variance. No correction was applied to adjust significance tests for multiple comparisons because of the high degree of correlation among outcomes and the nonindependence of tests. Statistical significance was assessed based on two-tailed *p*-values of <0.05, as well as by assessing clinical meaningfulness of estimated effect size. All analyses were conducted using Stata (version 14; Stata Corporation).

Results

There was a median of 20.9 y (range: 18.3–24.4 y) between the urine measurement examination and the follow-up brain MRI scan. Measured at the baseline examination (1989–1991), urine arsenic (inorganic arsenic + DMA + MMA, in micrograms per gram creatinine) ranged from 1.71 to 109.07 μg/g, with median = 7.54 [(IQR: 4.90–11.93) μg/g]. Urine cadmium (in micrograms per gram creatinine) ranged from 0.01 to 31.78 μg/g, with a median of 0.96 (IQR: 0.61–1.51) μg/g. At the time of the MRI examination (2010–2013), the mean age of the participants age was >70 y and a majority were female, had at least some college education, and had a household income of <$20,000 per year (Table 1). A majority of participants also had some history of cigarette smoking (66%),

Table 2. Estimated differences and 95% confidence intervals (CIs) in MRI measures of vascular brain injury or atrophy among elderly American Indian participants with a 10% increase in urine arsenic (inorganic arsenic + DMA + MMA) and cadmium (μg/g creatinine): the Strong Heart Study.

		Urine arsenic (μg/g creatinine)			Urine cadmium (μg/g creatinine)		
Outcomes	*N*	Diff	95% CI	*p*-Value	Diff	95% CI	*p*-Value
Graded outcomes (range 0–9)							
WMH grade (model)	681						
1 (base)		0.014	−0.000, 0.028	0.05	0.002	−0.011, 0.015	0.79
2 (+comorbidities)		0.014	−0.000, 0.028	0.05	0.002	−0.011, 0.016	0.74
3 (+CKD)		0.014	−0.000, 0.028	0.05	0.003	−0.011, 0.016	0.70
4 (all)		0.014	0.000, 0.028	0.05	0.003	−0.011, 0.017	0.69
Sulcal widening (model)	680						
1 (base)		0.013	−0.001, 0.027	0.07	−0.003	−0.013, 0.008	0.61
2 (+comorbidities)		0.013	−0.001, 0.026	0.07	−0.001	−0.012, 0.009	0.79
3 (+CKD)		0.013	−0.001, 0.027	0.07	−0.003	−0.013, 0.008	0.63
4 (all)		0.013	−0.001, 0.027	0.07	−0.001	−0.012, 0.009	0.79
Ventricle enlargement (model)	681						
1 (base)		−0.001	−0.018, 0.016	0.90	−0.013	−0.026, 0.001	0.08
2 (+comorbidities)		−0.002	−0.019, 0.015	0.84	−0.009	−0.023, 0.004	0.18
3 (+CKD)		−0.001	−0.018, 0.016	0.90	−0.012	−0.025, 0.002	0.10
4 (all)		−0.001	−0.018, 0.015	0.85	−0.011	−0.023, 0.005	0.21
Volumetric outcomes (mL)							
WMH volume (model)	652						
1 (base)		0.012	−0.087, 0.110	0.82	−0.003	−0.085, 0.080	0.95
2 (+comorbidities)		0.011	−0.088, 0.109	0.83	0.004	−0.080, 0.087	0.93
3 (+CKD)		0.012	−0.087, 0.110	0.81	−0.001	−0.083, 0.081	0.98
4 (all)		0.011	−0.088, 0.109	0.83	0.004	−0.079, 0.875	0.92
Hippocampus volume (model)	657						
1 (base)		−0.012	−0.024, 0.001	0.07	−0.007	−0.017, 0.004	0.20
2 (+comorbidities)		−0.012	−0.024, 0.001	0.07	−0.007	−0.017, 0.003	0.18
3 (+CKD)		−0.012	−0.024, 0.000	0.06	−0.009	−0.018, 0.001	0.09
4 (all)		−0.012	−0.024, 0.000	0.06	−0.009	−0.019, 0.001	0.08
Left hippocampus (model)	658						
1 (base)		−0.006	−0.013, 0.001	0.10	−0.003	−0.009, 0.003	0.33
2 (+comorbidities)		−0.006	−0.013, 0.001	0.11	−0.003	−0.009, 0.003	0.29
3 (+CKD)		−0.006	−0.013, 0.001	0.09	−0.004	−0.010, 0.002	0.18
4 (all)		−0.006	−0.013, 0.001	0.09	−0.004	−0.010, 0.002	0.16
Right hippocampus (model)	658						
1 (base)		−0.005	−0.011, 0.002	0.17	−0.003	−0.008, 0.003	0.33
2 (+comorbidities)		−0.005	−0.011, 0.002	0.17	−0.003	−0.008, 0.003	0.29
3 (+CKD)		−0.005	−0.011, 0.002	0.15	−0.004	−0.009, 0.002	0.17
4 (all)		−0.005	−0.011, 0.002	0.15	−0.004	−0.009, 0.001	0.16
Brain volume (model)	581						
1 (base)		−0.572	−1.222, 0.077	0.08	−0.192	−0.822, 0.439	0.55
2 (+comorbidities)		−0.573	−1.214, 0.068	0.08	−0.287	−0.919, 0.345	0.37
3 (+CKD)		−0.604	−1.256, 0.048	0.07	−0.279	−0.896, 0.338	0.37
4 (all)		−0.600	−1.244, 0.044	0.07	−0.364	−0.984, 0.257	0.25

Note: Estimates from linear regression models showing estimated unit differences in ordinal outcomes (graded outcomes, range 0–9) or continuous outcomes (in mL) for a 10% increase in exposure. Model 1 is adjusted for age, sex, field center, education, income, body mass index, smoking, and alcohol use. Model 2 is adjusted for Model 1 + diabetes, hypertension, and high low-density lipoprotein level. Model 3 is adjusted for Model 1 + chronic kidney disease. Model 4 is adjusted for all factors combined. Models for volumetric outcomes are additionally adjusted for total intracranial volume. Urine metals were measured in 1989–1991, and MRI outcomes were measured in 2010–2013. CKD, chronic kidney disease; Diff, difference; DMA, dimethylacetamide; MMA, methylmalonic acid; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

most were either never (24%) or former (58%) alcohol drinkers, and most had a BMI of either 25–29 (31%) or ≥30 (53%). Approximately one-half had diabetes (49%), two-thirds had high LDL (67%), one-fourth had CKD (27%), and most had hypertension (81%).

Median arsenic levels (Table 1) were higher with lower income, female sex, never drinking, and by field center; the Northern Plains field center had an intermediate arsenic level and the Southwest field center had the highest arsenic level, nearly three times as high as that of the Southern Plains field center. The median cadmium level was higher with older age, lower education, lower income, female sex, never drinking, and by field center; the Northerm Plains field center had the highest cadmium levels. Median arsenic and cadmium levels were higher among participants with abnormal MRI findings, including abnormal WMH grade (grade ≥3), high WMH volume, and low hippocampal volume, as well as the presence of lacunar infarcts (especially for cadmium), cortical infarcts (especially for arsenic), and hemorrhages. Median cadmium levels were higher among participants with low brain volume. The participant characteristic categories provided in Table 1 are mutually exclusive.

Associations between urine metals with WMH grade ($N = 681$), sulcal widening grade ($N = 680$), ventricle enlargement grade ($N = 681$), and WMH ($N = 652$), hippocampus ($N = 657$), and brain volumes ($N = 581$) are presented in Table 2. For urine arsenic, fully adjusted model estimates indicated that WMH grade was 0.014 points higher [95% confidence interval (CI): 0.000, 0.028] and sulcal widening grade was 0.013 points higher (95% CI: −0.001, 0.027) with each 10% increase in exposure, whereas there was no association with ventricle enlargement grade. A 10% increase in urine arsenic was associated with nonsignificant decreases in total brain volume of −0.599 mL (95% CI: −1.244, 0.044) and hippocampal volume of −0.012 mL (95% CI: −0.024, 0.000). A 10% increase in urine cadmium was also associated with nonsignificant decreases in ventricle enlargement grade of –0.011 units (94% CI: –0.023, 0.005) and hippocampus volume of –0.009 (95% CI: –0.019, 0.001), whereas estimates of associations between cadmium and other grade and volume measures were close

Table 3. Estimated relative risks (RRs) and 95% confidence intervals (CIs) for MRI findings of vascular brain injury lesions among elderly American Indian participants with a 10% increase in urine arsenic (inorganic arsenic + DMA + MMA) and cadmium (μg/g creatinine): the Strong Heart Study.

		Urine arsenic (μg/g creatinine)			Urine cadmium (μg/g creatinine)		
Outcomes	*N*	RR	95% CI	*p*-Value	RR	95% CI	*p*-Value
Any infarct (model)	686						
1 (base)		1.009	0.994, 1.025	0.25	1.009	0.994, 1.025	0.24
2 (+comorbidities)		1.009	0.994, 1.025	0.24	1.010	0.994, 1.026	0.22
3 (+CKD)		1.009	0.994, 1.025	0.22	1.011	0.996, 1.027	0.16
4 (all)		1.009	0.994, 1.025	0.22	1.011	0.995, 1.028	0.16
Lacunar infarct (model)	686						
1 (base)		1.010	0.990, 1.029	0.33	1.022	1.002, 1.042	0.03
2 (+comorbidities)		1.011	0.992, 1.030	0.28	1.022	1.002, 1.042	0.03
3 (+CKD)		1.010	0.991, 1.029	0.30	1.025	1.005, 1.045	0.02
4 (all)		1.011	0.992, 1.029	0.26	1.024	1.004, 1.045	0.02
Hemorrhage (model)	683						
1 (base)		1.011	0.963, 1.061	0.67	0.996	0.952, 1.041	0.85
2 (+comorbidities)		1.007	0.958, 1.059	0.77	0.999	0.955, 1.046	0.99
3 (+CKD)		1.011	0.963, 1.061	0.67	0.997	0.952, 1.043	0.89
4 (all)		1.008	0.958, 1.059	0.77	1.001	0.955, 1.049	0.97

Note: Estimates from Poisson regression models showing estimated relative risk in MRI outcomes for a 10% increase in exposure. Model 1 is adjusted for age, sex, field center, education, income, body mass index, smoking, and alcohol use. Model 2 is adjusted for Model 1 + diabetes, hypertension, and high low-density lipoprotein level. Model 3 is adjusted for Model 1 + chronic kidney disease. Model 4 is adjusted for all factors combined. Urine metals were measured in 1989–1991, and MRI outcomes were measured in 2010–2013. CKD, chronic kidney disease; DMA, dimethylacetamide; MMA, methylmalonic acid; MRI, magnetic resonance imaging.

to the null. In general, estimates were similar among models adjusted for different covariates.

Associations between urine metals with binary outcomes of infarct ($N = 686$), lacunar infarct ($N = 686$), and hemorrhage ($N = 683$) are presented in Table 3. Fully adjusted model estimates indicated a 10% increase in urine cadmium was associated with a significantly higher RR of lacunar infarcts [RR = 1.024 (95% CI: 1.004, 1.045)] and was weakly associated with any infarct [RR = 1.011 (95% CI: 0.995, 1.028)] but not associated with MRI evidence of hemorrhage. Urine arsenic was not clearly associated with any of the binary outcomes. Overall, estimates were similar across models adjusted for different covariates.

Models stratified by field center suggested that associations between urine metals and some MRI outcomes may differ by region, although statistical power was limited and inference must be conducted with caution. A 10% increase in urine arsenic may be associated with lower brain volume in the Southern Plains [−1.137 mL (95% CI: −2.154, −0.120)] and Southwest [−1.687 mL (95% CI: −3.208, −0.166)] but little difference in brain volume in the Northern Plains [0.037 mL (95% CI: −0.968, 1.041)] (Table S1). Although a smaller magnitude of difference in brain volume was found, the pattern of results across field centers was similar for urine cadmium. A 10% increase in urine arsenic may also be associated with higher risk of hemorrhage in the Southwest [RR = 1.135 (95% CI: 0.916, 1.407)] compared with that in the Northern [RR = 1.020 (95% CI: 0.948, 1.096)] or Southern Plains [RR = 0.942 (95% CI: 0.847, 1.047)] (Table S2).

The association between urine metals and other MRI outcomes was similar across the three field centers. Models stratified by CKD status (Tables S3 and S4) suggested that a 10% increase in urine cadmium was associated with a smaller hippocampus volume in participants with normal kidney function [–0.022 mL (94% CI: –0.035, –0.010)] and a larger hippocampus volume among participants with CKD [0.020 mL (94% CI: –0.000, 0.040)]. The difference was statistically significant and somewhat more pronounced for the right vs. left hippocampus. The association between urine cadmium and other graded, volumetric, and binary outcomes was similar among participants with and without CKD. Similarly, we observed no differences according to CKD status for the association between urine arsenic and all MRI outcomes. Again, owing to limited sample size, these findings must be interpreted with caution.

A comparison of characteristics for participants included and excluded due to missing MRI scans, metals assays, or covariate data suggested that minor differences may exist based on education and income–with some college education and low income being slightly more likely to have measurements and, therefore, more likely to be included (Table S5). Participants who had available urine metals assays but were excluded on the basis of the absence of other data ($n = 41$) had slightly higher median arsenic levels than participants who were included ($N = 686$).

Discussion

These analyses identified associations between urine biomarkers of toxic environmental metal exposures, measured prospectively in 1989–1990, with findings from brain MRI scans, a common biomarker for vascular brain injury and cerebral atrophy, conducted 25 y later, in 2010–2013. In this study, a higher urine arsenic level was associated with worse WMH grades but not WMH volume; future research may examine whether longitudinal imaging can better capture changes in WMH grade of volume that may be most closely associated with toxicant-related pathology. A higher cadmium exposure was also associated with a higher risk of lacunar infarcts but not with a higher risk of other types of infarcts. Some other associations did not meet statistical significance based on *p*-values alone, such as arsenic with sulcal widening or hippocampal atrophy, but may still have neuropathological effects and should be evaluated with additional research. Subgroup analyses suggested that mediating or modifying features may play a role in these associations, which may also warrant further examination.

High cadmium and/or arsenic exposure have been associated with multiple developmental and degenerative clinical cognitive sequelae in the absence of other explanatory pathologies or significant risk factors, such as advanced age. Prenatal and childhood cadmium exposure in Bangladeshi children, with urine measurements ranging from 0.03 to 2.6 μg/L, have been associated with lower intelligence quotients in boys and poorer social behavior in girls (Gustin et al. 2018); although these measurements were not standardized to urine creatinine to account for urine dilution, the authors reported that exposure ranges are common worldwide. Another study in 600 Mexican children with a mean age of 7 y found that, independent of nutrition and lead levels, urine arsenic levels—which ranged from 78 to 287 μg/g—were associated with poorer performance on tests related to cognitive development and function, including disturbed visual perception, problems with

visuomotor integration, psychomotor speed, attention, speech, and memory (Rosado et al. 2007). A case–control study of 180 children with autism spectrum disorder showed that cases had higher mercury, cadmium, and arsenic, but not lead, levels (Li et al. 2018). A study of children 12–19 years of age using 2005–2008 U.S. National Health and Nutrition Examination Survey (NHANES) data found that, after accounting for the complex survey design, those in the highest quartile of blood lead or urine cadmium exposure were much more likely to have hearing loss (Shargorodsky et al. 2011); in the present study, high risk levels of urine cadmium corresponded to 0.15 μg/g creatinine, which is a similar level of exposure as the lowest ranges of our entire study population (range 0.1–31.8 μg/g creatinine).

Another NHANES 1984–1994 analysis of U.S. adults, 20–59 years of age, with IQR urinary cadmium concentration = 0.19–0.82 μg/L, found that higher urine cadmium was associated with worse performance on cognitive tests for visuomotor speed, attention, perception, learning, and short-term memory, with a per 1-μg/L increase in exposure corresponding to a 1.9% decrease in performance (Ciesielski et al. 2013). This study included adults, so these finding are likely to represent degeneration more than developmental delay; however, the age range is younger than would be expected for those with detectable or symptomatic cognitive impairments from a more common neurodegenerative pathology, such as Alzheimer's disease dementia. Another NHANES data analysis using 2009–2012 surveys focused on the empirical comparison of methods accounting for urinary dilution in order to estimate nationally representative ranges for these urine biomarkers in U.S. adults, with the mean and range of urine arsenic levels reported as 5.7 (1.3–55.6) μg/g creatinine and urine cadmium 0.2 (0.03–2.6) μg/g creatinine (Middleton et al. 2016). Although the NHANES analysis did find that creatinine standardization can overcompensate for urine dilution, with urine osmolality providing a more robust method for adjustment, the specifics of the authors' findings were analyte specific and require replication; furthermore, osmolality data were not available for evaluation in our study population.

Finally, to contrast these population-based analyses in the Americas, a study of European industrial workers with high degree of cadmium exposure were measured with urine cadmium levels ranging from 0.4–38.3 μg/g creatinine (mean 12.6 μg/g creatinine), in comparison with workers with low cadmium exposure who were measured with urine cadmium ranging from 0.1–2.0 μg/g creatinine (mean 0.7 μg/g creatinine) (Viaene et al. 2000). In that study, those with high exposure—age matched to those with low exposure—had worse peripheral neuropathy, autonomic dysfunction, visuomotor speed, reaction time, attention, and concentration compared with those who had low exposure; these effects were independent of age, other neurotoxicants, and renal function. In summary, put into context, our population-based study of American Indian elders had measured values of urine arsenic and/or cadmium levels approximately 10-fold higher than other published studies of U.S. or Mexican children who had documented neurodevelopmental or neurodegenerative clinical findings related to their cadmium or arsenic exposure; multiple times higher than a nationally representative empirical estimate of U.S. adults; and with values consistent with highly exposed European industrial workers who also have documented autonomic, neuropathic, and cognitive complaints that are not explainable by other risk factors or clinical pathologies.

Our findings in sensitivity, stratum-specific analyses (Tables S1 and S2) identified extreme associations among participants from study field centers with the highest arsenic exposure. Arsenic concentrations in groundwater in the American Southwest may expose residents to levels 5–10 times the U.S. EPA limits for acceptable exposure (USGS 2015). Cadmium soil contamination throughout the Great (Northern) Plains may expose residents over a lifetime to more than 25 times the WHO limits for acceptable exposure (WHO 2015). Notably, these differences based on geographic region are an order of magnitude higher than the comparisons of note from this study, suggesting that residents may all be exposed to high levels of risk. Future studies should compare outcomes across larger ranges of metal exposures, to evaluate dose dependence across the range of exposure, and to evaluate whether minimization of exposure can prevent or ameliorate cognitive risk.

This project has some notable strengths and limitations. Urine concentrations taken cross sectionally at baseline may not reflect total body accumulation of metals, capture changes in metal exposures over time, or directly measure total lifetime exposure (Sarkar and Datta 2004). However, despite rapid excretion, exposure to arsenic typically has little variance over decades in many rural communities, where the residents tend to live in a single place, suggesting that urinary excretion of arsenic at one time point may be reflective of exposure levels over much longer periods (Bosch et al. 2016; Levine 2012; Meliker et al. 2007; Navas-Acien et al. 2009). One study of lifetime exposure found that current measures may even tend to underestimate lifetime exposure, given modern efforts to lower arsenic levels in water sources for some regions (Hough et al. 2010). Cadmium, on the other hand, is excreted very slowly with a half-life that is decades long, estimated at 10–35 y (WHO 2015), so urine cadmium concentration is commonly used as a biomarker of long-term exposure in epidemiologic studies (Bosch et al. 2016; Peters et al. 2010; Tellez-Plaza et al. 2012).

Urine dilution is an important source of measurement error in urine biomonitoring; we corrected for urine dilution by dividing by urine creatinine concentrations, as is commonly done in epidemiological studies. We also conducted stratified analyses by CKD status. Urine osmolality data were not available. The long interval between exposure measurement and outcome measurement may have subjected this study population to selection pressures, due to participant dropout and death. Such bias, if present, could result in lower participation from those most strongly affected—such as from stroke, kidney disease, hypertension, or diabetes as detected in a prior analysis of selective survival for this cohort (Suchy-Dicey et al. 2018)—which could limit detectability by increasing bias toward the null hypothesis. For example, the few excluded participants who did have available arsenic data did have slightly higher values for urine arsenic. However, previous reports have detected little evidence of differential survival between participants and nonparticipants in the neurology cohort. In addition, the long lead interval between the measurement of environmental metals and the later MRI examination (median of 21 y) makes it unlikely that the changes in brain structure evident by MRI findings preceded the metal urine exposures. Finally, the present study, as with any observational study, may be subject to unmeasured or residual confounding. However, this study also involved a high-quality, standardized study protocol that systematically obtained and evaluated clinically relevant end points by expert radiological reviewers; highly accurate and precise quantification of metal measures; highly detailed brain imaging, allowing specific evaluation of different MRI findings reflecting vascular brain injury and atrophy; and a focus on a population that is disproportionately affected by environmental metal exposures as well as vascular brain injury and stroke, whose data can be informative for many other populations experiencing similar exposure patterns.

To our knowledge, this population-based study is the first to estimate associations between environmental metal exposures and MRI-based markers of vascular brain injury and cerebral atrophy. These findings suggest that exposure to toxic metals is associated with markers of vascular brain injury and cerebral atrophy as detected by structural imaging. Because environmental metals accumulation in the environment may be modifiable,

reducing exposure to these metals may serve as a guide for cerebrovascular disease reduction or prevention efforts. Future public health and policy studies may examine whether reductions in metal contaminations in the environment, restrictions in water and soil uses in highly affected areas, or early disease identification and treatment efforts may ameliorate the deleterious effects that these toxicants may have.

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