



Low-level inorganic arsenic exposure and neuropsychological functioning in American Indian elders



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ABSTRACT

Background: Inorganic arsenic at high and prolonged doses is highly neurotoxic. Few studies have evaluated whether long-term, low-level arsenic exposure is associated with neuropsychological functioning in adults.

Objectives: To investigate the association between long-term, low-level inorganic arsenic exposure and neuropsychological functioning among American Indians aged 64–95.

Methods: We assessed 928 participants in the Strong Heart Study by using data on arsenic species in urine samples collected at baseline (1989–1991) and results of standardized tests of global cognition, executive functioning, verbal learning and memory, fine motor functioning, and speed of mental processing administered during comprehensive follow-up evaluations in 2009–2013. We calculated the difference in neuropsychological functioning for a 10% increase in urinary arsenic with adjustment for sex, age, education, and study site.

Results: The sum of inorganic and methylated arsenic species (Σ As) in urine was associated with limited fine motor functioning and processing speed. A 10% increase in Σ As was associated with a .10 (95% CI $-.20, -.01$) decrease on the Finger Tapping Test for the dominant hand and a .13 decrease (95% CI $-.21, -.04$) for the non-dominant hand. Similarly, a 10% increase in Σ As was associated with a .15 (95% CI $-.29, .00$) decrease on the Wechsler Adult Intelligence Scale–Fourth Edition Coding Subtest. Σ As was not associated with other neuropsychological functions.

Conclusions: Findings indicate an adverse association between increased urinary arsenic fine motor functioning and processing speed, but not with other neuropsychological functioning, among elderly American Indians.

1. Introduction

Inorganic arsenic is a naturally occurring element that is toxic to virtually all life forms in high or prolonged doses. Acute, high-level exposure to inorganic arsenic has been shown to cause severe neuropsychological impairment in humans (Bolla-Wilson and Bleecker, 1987). More recent work has confirmed the adverse effects of high-level arsenic exposure on neurological and cognitive functioning in both humans and rodents, the biological mechanisms of which include altered neurological signaling, synaptic plasticity, and behavioral deficits (Tyler and Allan, 2014). Moderate to high levels of exposure through drinking water levels of $> 50 \mu\text{g/L}$ can increase risk of cancer (Smith et al., 2002), low birth weight (Hopenhayn et al., 2003), and cardiovascular disease (Moon et al., 2012). Although less

studied, long-term, low-level inorganic arsenic exposure—e.g., through drinking water levels of $10\text{--}20 \mu\text{g/L}$ over 15 years—is associated with elevated mortality rates for circulatory disease (Meliker et al., 2007; Medrano et al., 2010), and with neuropsychological impairment (Gong et al., 2011; O'Bryant et al., 2011; Tyler and Allan, 2014).

Some rural and minority populations in the United States (US) might be at increased risk for negative health outcomes associated with such long-term, low-level exposure. The current US Environmental Protection Agency (EPA) standard for arsenic levels in drinking water is $10 \mu\text{g/L}$, revised in 2001 from $50 \mu\text{g/L}$ (DHHS 2007). In the western US, rocks and soil are more likely to contain moderate to high levels of naturally occurring inorganic arsenic than in other regions of the country (Welch et al., 2000). Arsenic leaches from the soil into groundwater (Peters et al., 1996), so that arsenic concentrations in

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water from rural wells can be at or above federal standards in several US regions (Navas-Acien et al., 2009). Most rural American Indian communities are located in the western US, and many rely heavily on well water for daily consumption. These communities therefore experience a relatively high risk of long-term, low-level arsenic exposure.

The Strong Heart Study (SHS) was the largest epidemiologic study ever conducted with American Indian communities. From 1989 to 1999, SHS researchers collected longitudinal data on risk factors, incidence, prevalence, and mortality associated with cardiovascular disease in a cohort drawn from 13 American Indian tribes and communities in the western US (Arizona, Oklahoma, North Dakota, and South Dakota) (Lee et al., 1990; Navas-Acien et al., 2009). Recent studies using data on this unique cohort have associated long-term, low to moderate inorganic arsenic exposure with elevations in mortality due to cancer (García-Esquinas et al., 2013), prevalence of diabetes and albuminuria (Gribble et al., 2012; Zheng et al., 2013), and incidence of cardiovascular disease (Moon et al., 2013). However, no studies have investigated this cohort to determine the relationship between chronic, low to moderate arsenic exposure and neuropsychological outcomes.

We combined data from the SHS and an ancillary study, the Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study (Suchy-Dickey et al., 2016), to examine the association of urinary arsenic concentrations measured at baseline (1989–1991) in 928 American Indian adults aged 45–74 years with neuropsychological functioning measured 20 years later. We investigated how this association might differ according to demographic characteristics including age, education, and sex.

2. Methods

2.1. Study setting and sample

The SHS collected data in three phases (Phase I: 1989–1991, Phase II: 1993–1994, Phase III: 1998–1999). During Phase I, 4549 tribal members aged 45–74 years were enrolled and examined: 1500 in the American Southwest, 1527 in the Central Plains, and 1522 in the Northern Plains. Among eligible community members, participation rates were 72% at the Southwest center, 62% at the Central Plains center, and 55% at the Northern Plains center. Trained local staff collected data on participants' medical history; family history of related illness; diet, alcohol and tobacco consumption; physical activity; and socioeconomic status. Objective measurements included body fat, waist circumference, body mass index (BMI), blood pressure, blood tests relevant to diabetes and cardiovascular disease, and urinary creatinine and albumin (see Lee et al., 1990 for a full discussion of methods). In 2009, urinary arsenic concentrations were measured in 3973 Phase I participants who had stored urine samples available and whose demographic information was complete (Moon et al., 2013).

From 2009 to 2013, the CDCAI study, designated as the “Strong Heart Stroke Study” by participating communities and field centers, collected data pertinent to vascular and structural brain disease from surviving SHS participants. The study goals were to examine the prevalence of and risk factors for brain disease among American Indian adults aged 64–95 years. Trained local staff successfully contacted 1664 (85%) of 1956 surviving participants from all three study sites. More than half of those contacted (1033; 62%) were eligible and agreed to participate in the new study. Among 631 participants who did not participate, 201 (32%) did not meet eligibility criteria (see below), 169 (27%) refused, and 261 (41%) became deceased or unable to attend the study visit because of physical limitations between the beginning of recruitment and the start of data collection (Fig. 1). Exclusion criteria included prior surgery for a cerebral aneurysm; an internal metal or electrical device such as a pacemaker, metal prosthesis, or cochlear implant; weight ≥ 158 kg; and inability to complete study procedures. Study procedures included magnetic resonance imaging (MRI) of the brain and completion of a neuropsychological battery measuring general cognitive functioning, speed of mental processing, phonemic verbal fluency, immediate and delayed verbal memory, and fine motor functioning (see Suchy-Dickey et al., 2016 for a full discussion of methods). The sample for the current analysis consisted of 928 participants in the CDCAI study whose urinary arsenic levels were measured in 1989–1991.

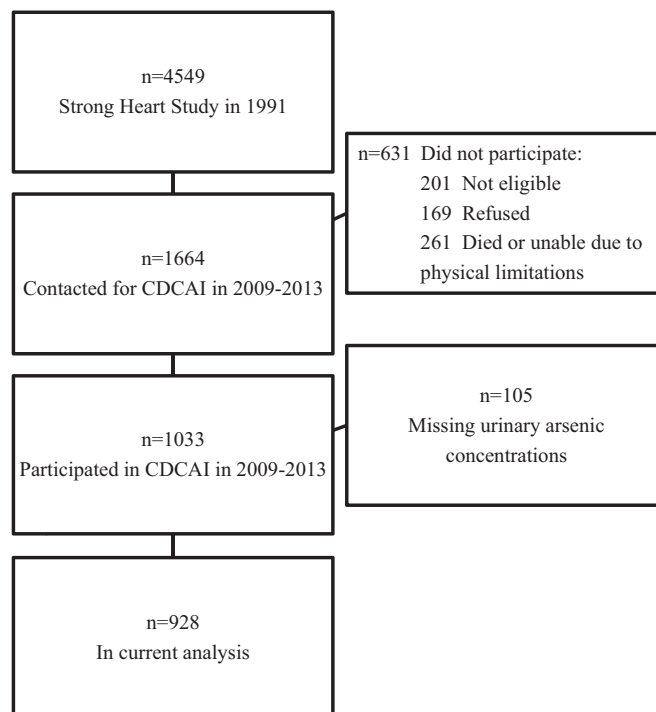


Fig. 1. Sample selection flow-chart.

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2.2. Urinary arsenic concentration

Arsenic exposure is commonly assessed by measuring inorganic and methylated arsenic species in urine. Methylated arsenic species refer to monomethylarsonate (MMA) and dimethylarsinate (DMA). During Phase I of the SHS, spot urine samples were collected by using polypropylene tubes, then frozen within two hours, shipped on dry ice to the Penn Medical Laboratory (Hyattsville, Maryland) and the MedStar Health Research Institute (Washington, D.C.), and stored at -80 °C. In 2009, concentrations of arsenic species (inorganic arsenic, MMA, DMA, arsenobetaine, and other arsenic cations) were measured by the Trace Element Laboratory in Graz, Austria, by using inductively coupled plasma mass spectrometry (ICPMS) and high-performance liquid chromatography (Scheer et al., 2012). Urinary cadmium was also measured using ICPMS. The detection limit for all arsenic species was $.1$ $\mu\text{g/L}$. Values for samples that fell below this limit were replaced with $[\text{limit of detection}/\sqrt{2}]$ or $.07$ $\mu\text{g/L}$. Urine samples with arsenic species below the limit of detection included 5.3% for inorganic arsenic, .7% for MMA, and $<.1\%$ for DMA. For urine cadmium, .1% were below the detection limit. At the time of collection, a blinded quality control analysis of 47 duplicate urine aliquots stored in different vials found an intraclass correlation coefficient of .99 for total arsenic concentrations and arsenic species (Gribble et al., 2012). The inter-assay coefficient of variation based on an in-house urine sample analyzed in each analytical run, together with the study samples, was 4.4% for total arsenic, 6.0% for inorganic arsenic, 6.5% for MMA, 5.9% for DMA, and 6.5% for arsenobetaine and other cations (Scheer et al., 2012). Our analysis focused on inorganic and methylated arsenic as a biomarker of inorganic arsenic exposure. Organic arsenic species from seafood were low in the SHS population, as seafood intake is rare in the study communities (Navas-Acien et al., 2009). Prior research with the SHS sample demonstrated long-term constancy in urinary arsenic concentrations and excretory patterns (intra-class correla-

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