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# Chronic arsenic exposure and risk of carotid artery disease: The Strong Heart Study

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ABSTRACT

*Background:* Inorganic arsenic exposure from naturally contaminated groundwater is related to vascular disease. No prospective studies have evaluated the association between arsenic and carotid atherosclerosis at low-moderate levels. We examined the association of long-term, low-moderate inorganic arsenic exposure with carotid arterial disease.

*Methods:* American Indians, 45–74 years old, in Arizona, Oklahoma, and North and South Dakota had arsenic concentrations (sum of inorganic and methylated species, μg/g urine creatinine) measured from baseline urine samples (1989–1991). Carotid artery ultrasound was performed in 1998–1999. Vascular disease was assessed by the carotid intima media thickness (CIMT), the presence of atherosclerotic plaque in the carotid, and by the number of segments containing plaque (plaque score).

*Results:* 2402 participants (mean age 55.3 years, 63.1% female, mean body mass index 31.0 kg/m$^2$, diabetes 45.7%, hypertension 34.2%) had a median (interquintile range) urine arsenic concentration of 9.2 (5.00, 17.06) μg/g creatinine. The mean CIMT was 0.75 mm. 64.7% had carotid artery plaque (3% with > 50% stenosis). In fully adjusted models comparing participants in the 80th vs. 20th percentile in arsenic concentrations, the mean difference in CIMT was 0.01 (95% confidence interval (95%CI): 0.00, 0.02) mm, the relative risk of plaque presence was 1.04 (95%CI: 0.99, 1.09), and the geometric mean ratio of plaque score was 1.05 (95%CI: 1.01, 1.09).

*Conclusions:* Urine arsenic was positively associated with CIMT and increased plaque score later in life although the association was small. The relationship between urinary arsenic and the presence of plaque was not statistically significant when adjusted for other risk factors. Arsenic exposure may play a role in increasing the severity of carotid vascular disease.

## 1. Introduction

Arsenic is a chemical of major public health concern (World Health Organization, 2015). An established carcinogen, inorganic arsenic is most commonly ingested through drinking naturally contaminated groundwater, although exposure may also occur via food (rice and other grains),

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air pollution, smelting operations, and some occupational settings. In the United States, inorganic arsenic exposure through consumption of naturally contaminated groundwater has been a long-term concern in many rural and suburban communities, especially for those with private water wells (Navas-Acien et al., 2009; Schmidt, 2014).

Increasing evidence supports a role of inorganic arsenic in a broad range of vascular diseases, particularly among populations exposed to levels above the World Health Organization and U.S. Environmental Protection Agency (EPA)'s recommended upper limit in drinking water (10 μg/liter) (Moon et al., 2013; Chen et al., 2011). Arsenic exposure may be a risk factor for vascular disease through its putative role in potentiating atherosclerosis (Wu et al., 2014). A common etiology of stroke is carotid atherosclerosis leading to artery-to-artery thromboembolism into the cerebral circulation. Chronic arsenic exposure has been linked to stroke in other studies (Moon et al., 2013, 2012), but the mechanism has not been well studied. Arsenic may therefore have a subclinical relationship to carotid artery disease that is poorly recognized.

In southwestern Taiwan, a region with historically high arsenic levels, a cross-sectional study found a dose-dependent relationship between the number of years exposed to arsenic-containing well water and a higher degree of carotid atherosclerosis, but not with discrete carotid plaque (Wang et al., 2002). Others have found a relationship with carotid intima media thickness (CIMT) but have used varying definitions of carotid vascular disease (Chen et al., 2013; Li et al., 2009; Huang et al., 2009). Studies at low-moderate levels of arsenic exposure, more similar to those occurring in U.S. populations, are lacking. In large cohort studies in Denmark (Monrad et al., 2017) and Italy (D'Ippoliti et al., 2015) low-moderate levels of arsenic exposure were associated with higher lifetime risk of myocardial infarction and deaths from chronic diseases respectively. We are aware of no prospective studies evaluating the association between arsenic and carotid vascular disease. New data from cohort studies providing individual level arsenic measurements of community dwellers with chronic low-moderate levels of exposure and prospective, long term follow up are needed to measure this potential association.

We aim to examine the prospective association of arsenic exposure with CIMT and atherosclerotic plaque in the Strong Heart Study (SHS) cohort of American Indians from the Southwestern and Central USA. A prior study of carotid artery disease in the SHS found that diabetes and hypertension each statistically significantly increased both the CIMT and carotid plaque score in this cohort (Roman et al. (2012). A separate study found higher levels of low-moderate arsenic exposure in the SHS were related to increased cardiovascular, coronary heart disease, and stroke mortality as well as a higher incidence of each of these conditions (Moon et al., 2013). Given these findings, we hypothesized that inorganic arsenic exposure is a risk factor for subclinical carotid atherosclerosis.

## 2. Methods

### 2.1. Study population

The SHS prospective cohort study of American Indians, begun in the 1980s, in whom vascular diseases were a leading cause of death but little was reported on their vascular risk factors. Targeted enrolment was 1500 participants, ages 45–74 years old, in each of Oklahoma, Arizona, and North and South Dakota (Welty et al., 1995; Lee et al., 1990). Thirteen tribes were included. Cluster sampling was used for participant enrolment in North and South Dakota, whereas all tribal members in the selected communities in Oklahoma and Arizona were invited, either by telephone or letter. Final enrolment in the Strong Heart Study was 4549 participants with a participation rate of 62% (Stoddart et al., 2000). The Indian Health Service, institutional review boards, and the participating tribes approved the study protocol. Each participant provided individuated consent to participate in the Strong Heart Study.

Each participant underwent a structured interview, physical examination, anthropometric measurements, and collection of blood and urine specimens (Welty et al., 1995; Lee et al., 1990). The study observation period began at the date of the participant's baseline study examination (1989–1992) when urinary samples and data to assess vascular risk factors were collected. For the present study, the follow up was until study visit three (1998–1999) when 88% of all surviving cohort participants were re-examined, including carotid ultrasound measurements. We used data from 3974 participants with sufficient urine available for arsenic measurements. We then excluded 1494 participants without available carotid ultrasound data due to death (n = 787), non-participation in the 3rd Strong Heart Study examination (n = 372), and lack of technically adequate carotid imaging (n = 335, including 69 with only a left side measurement and 40 with only a right side measurement). Living subjects who did not undergo carotid ultrasound measurements were not different in terms of baseline risk factors for atherosclerosis compared to those who had the procedure performed (data not shown). After further excluding 78 additional participants due to missing data on other covariates of interest, the final sample size for this study was 2402. Participants in the SHS were followed for vascular events, as defined previously, ending in 2008 (Navas-Acien et al., 2009).

### 2.2. Arsenic measurements

Spot urine arsenic level was measured at the baseline study visit, from one urine sample, and used as a proxy for arsenic exposure and arsenic internal dose. Urine was collected in polypropylene tubes, frozen within 1–2 h of collection, and transported on dry ice to long-term storage at −70 °C at the Penn Medical Laboratory (MedStar Research Institute, Washington DC, USA). Urine arsenic measurements were performed on thawed samples, using up to 1 mL of urine in 2009 (Trace Element Laboratory, Graz University, Austria). Urinary concentrations of inorganic arsenic (arsenite, arsenate), monomethylarsonate (MMA), dimethylarseninate (DMA) and arsenobetaine and other arsenic cations were measured using high-performance liquid chromatography inductively coupled plasma-mass spectrometry (Agilent 1100 HPLC and Agilent 7700x ICP-MS, Agilent Technologies, Waldbronn Germany) (Scheer et al., 2012). The concentration of arsenobetaine - a measure of seafood arsenicals - was very low, confirming that seafood consumption was low in this population (Moon et al., 2013). In a previously reported analysis from a random sample of 380 adults in the Strong Heart Study, the interclass coefficient of combined inorganic and methylated arsenic species was 0.64 (95% confidence interval (CI) 0.60, 0.69), and the average change in urine arsenic concentration between study visits spanning ten years was −0.8 μg/g urine creatinine (Navas-Acien et al., 2009). In general, DMA, MMA, and inorganic arsenic have half-lives of approximately 2, 9, and 38 days respectively (Pomroy et al., 1980; Cullen and Reimer, 1989). To assess inorganic arsenic exposure, the sum of inorganic (arsenite plus arsenate, i.e. iAs) and methylated arsenic species was used, hereafter referred to as "arsenic."

### 2.3. Other risk factors

Smoking was defined as current, past, or never in one's lifetime. Past smoking was defined as having smoked at least 100 cigarettes but not currently smoking. Current smoking includes smoking currently and having smoked at least 100 cigarettes. Current alcohol use was defined as drinking regularly and having 12 alcoholic drinks or more in a lifetime. Past alcohol use was defined as drinking regularly in the past and not drinking alcohol within the previous year. Body mass index was measured in the standard way ($kg/m^2$). The seventh report of the Joint National Committee on Prevention, Detection, and Evaluation, and Treatment of Hypertension definition of hypertension was employed: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or the use of antihypertensive medications to treat blood pressure (The Seventh