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Association of low-moderate urine arsenic and QT interval: Cross-sectional and longitudinal evidence from the Strong Heart Study

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Abstract

Epidemiologic studies suggest that chronic exposure to arsenic is related cardiovascular disease (CVD), but the pathophysiological link remains uncertain. We evaluated the association of chronic low-moderate arsenic exposure and arsenic metabolism with baseline difference and annual change in ECG measures (QT interval, JT interval, PR interval, QRS duration, and QT dispersion) using linear mixed models in the Strong Heart Study main cohort (N=1174, median age 55 years) and family study (N=1695 diabetes-free, median age 36 years). At baseline, arsenic exposure was measured as the sum of inorganic and methylated species in urine (As) and arsenic metabolism was measured as the relative percentage of arsenic species. Median As and Bazett heart rate-corrected QT interval (QTc) were 8.6 µg/g creatinine and 424 ms in the main cohort and 4.3 µg/g and 414 ms in the family study, respectively. In the main cohort, a comparison of the highest to lowest As quartile (>14.4 vs. <5.2 µg/g creatinine) was associated with a 5.3 (95% CI: 1.2, 9.5) ms higher mean baseline QTc interval but no difference in annual change in QTc interval. In the family study, a comparison of the highest to lowest quartile (>7.1 vs. <2.9 µg/g creatinine) was associated with a 3.2 (95% CI: 0.6, 5.7) ms higher baseline QTc interval and a 0.6 (95% CI: 0.04, 1.2) ms larger annual increase in QTc interval. Associations with JTc interval were similar but

DISCLOSURES

None.

stronger in magnitude compared to QTc interval. Arsenic exposure was largely not associated with PR interval, QRS duration or QT dispersion. Similar to arsenic exposure, a pattern of lower %MMA and higher %DMA was associated with longer baseline QTc interval in both cohorts and with a larger annual change in QTc interval in the family study. Chronic low-moderate arsenic exposure and arsenic metabolism were associated with prolonged ventricular repolarization.

CAPSULE

Chronic low-moderate arsenic exposure and arsenic metabolism were associated with prolonged ventricular repolarization.

Keywords

Arsenic; QT interval; electrocardiology; ventricular repolarization; cardiovascular disease; longitudinal cohort

INTRODUCTION

The QT interval on an electrocardiogram (ECG) represents the duration of ventricular depolarization and repolarization. Prolonged QT interval has been associated with an increased risk of incident cardiovascular disease (CVD), heart failure, and stroke (Beinart et al., 2014), and a higher risk of fatal CVD events (particularly sudden cardiac death) in both high-risk (Cox et al., 2014) and general populations (Zhang et al., 2011a).

Prolonged QT interval, ventricular tachycardia, and sudden cardiac death are well-known side effects of arsenic trioxide, an inorganic arsenic compound used as a chemotherapeutic agent (Drolet et al., 2004). In experimental studies, arsenic trioxide prolongs the QT interval by disrupting the normal cardiomyocyte action potential, increasing cardiac calcium currents, reducing cardiac potassium channel expression, and inducing cellular calcium overload (Drolet et al., 2004; Ficker et al., 2004; Sun et al., 2006). In population-based epidemiologic studies of chronic arsenic exposure, mainly cross-sectional and at high arsenic levels in drinking water ($>100 \mu\text{g/L}$), higher arsenic exposure was associated with longer QT interval (Ahmad et al., 2006; Chen et al., 2013b; Mordukhovich et al., 2009; Mumford et al., 2007; Wang et al., 2009; Wang et al., 2010; Yildiz et al., 2008).

Hundreds of millions worldwide (Naujokas et al., 2013), including millions of Americans (Ayotte, 2011; Hutson et al., 2004; U.S. Environmental Protection Agency, 2013), are exposed to arsenic in water derived from natural geological deposits (National Research Council, 1999). Food (e.g., rice, grains, and juice) contributes to arsenic exposure in most populations, and dietary sources can make up a large proportion of exposure in populations with low-moderate arsenic levels in drinking water (Navas-Acien and Nachman, 2013). Epidemiologic evidence supports an association between chronic arsenic exposure and a higher risk of incident CVD, particularly coronary heart disease (CHD), in populations exposed to high ($>100 \mu\text{g/L}$) (Chen et al., 2011; Chen et al., 2013a; Soheli et al., 2009) and low-moderate ($<100 \mu\text{g/L}$) arsenic levels in water (Farzan et al., 2015; James et al., 2015; Moon et al., 2013). Low-moderate arsenic exposure was prospectively associated with an

increased risk of CHD and stroke in the Strong Heart Study (SHS), and the association was stronger with fatal events (Moon et al., 2013). The mechanisms explaining that association, however, are uncertain.

In this study, we aimed to estimate the cross-sectional and longitudinal association between chronic low-moderate arsenic exposure and ECG markers of cardiac conduction (QT interval, JT interval, PR interval, QRS duration, and QT dispersion) in the SHS main cohort and ancillary Strong Heart Family Study (SHFS). We also evaluated the cross-sectional and longitudinal association between arsenic metabolism and QT interval. We hypothesized a positive association of arsenic exposure with QT interval, JT interval, and QT dispersion and no association with PR interval and QRS duration based on previous literature (Ahmad et al., 2006; Chen et al., 2013b; Mordukhovich et al., 2009; Mumford et al., 2007; Wang et al., 2009; Wang et al., 2010; Yildiz et al., 2008).

METHODS

Study population

The SHS is a longitudinal study of CVD in American Indian communities in Arizona, Oklahoma, and North and South Dakota (Lee et al., 1990). In the SHS main cohort, 4549 men and women 45 to 74 years old were examined at baseline (1989–91). Surviving participants were examined in 1993–5 and 1998–99 (Visit 2 and 3) (Navas-Acien et al., 2009). In the SHFS, SHS main cohort family members 14 years or older were recruited to participate in a pilot study (1998–99, N=967), a baseline exam in 2001–2003 (Visit 4, N=2871), and a follow-up in 2006–2009 (Visit 5, N=3,232) (North et al., 2003). Details of these SHS cohorts have been described previously (Lee et al., 1990; North et al., 2003). We excluded the data of one community that withdrew their consent to participate in further research in 2016. All participants provided informed consent, and the Indian Health Service institutional review board, the institutional review boards of participating institutions, and the participating tribes approved the study protocol.

We restricted the SHS main cohort analysis to 1174 participants free of prevalent CVD (Lee et al., 1990), not using medications with a risk of QT prolongation (Woosley and Romero, 2015), without conduction disorders, and not missing key baseline variables (eFigure 1). At baseline and Visit 2 of the SHS main cohort, 53% and 28%, respectively, of digital ECG records were missing because of a hard disk crash and data transfer errors in the 1990s (Okin et al., 2000). Participants included in the final analytic sample (N=1174) were largely similar to participants who were excluded because of missing data (eTable 1).

In the SHFS, urine arsenic was measured in participants without diabetes at baseline who were re-examined at Visit 5 and who had enough stored urine for a study of environmental and genetic risk factors of incident diabetes. For this study, the SHFS analysis was further restricted to 1695 participants not using medications that could prolong the QT interval (Woosley and Romero, 2015), without conduction disorders, and not missing key baseline variables (eFigure 2).

Urine arsenic (Inorganic arsenic and methylated metabolites)

The analytical and quality control methods for urine arsenic measurements have been described (Scheer et al., 2012). We used measured arsenic species, including those that directly reflect inorganic arsenic exposure (arsenite, arsenate, monomethylarsenate (MMA), and dimethylarsenate (DMA)), and the generally nontoxic seafood arsenic species (e.g., arsenobetaine) (National Research Council, 1999). The Trace Element Laboratory of the University of Graz (Austria) measured arsenic species in urine using high-performance liquid chromatography coupled to inductively coupled plasma mass spectrometry (Agilent 1100 and 7700×, Agilent Technologies).

In the SHS main cohort, the inter-assay coefficients of variation (CV) using an in-house reference urine for inorganic arsenic, MMA, DMA, and arsenobetaine were 6.0%, 6.5%, 5.9%, and 6.5%, respectively (Scheer et al., 2012). In the SHFS, the CV ranged from 5.4 to 14.4% for inorganic arsenic, 4.8 to 8.6% for MMA, and 5.5 to 8.1% for DMA. 5.2%, 0.8%, and 0.03% of samples were below the LOD (0.1 µg/L) for inorganic arsenic, MMA, and DMA, respectively. We imputed concentrations below the LOD as the LOD divided by the square root of two.

We used the sum of inorganic (arsenite and arsenate) and methylated (MMA and DMA) arsenic species (ΣAs) as a proxy for chronic arsenic exposure. The relative percentages of arsenic species over their sum in urine was used as a measure of arsenic metabolism (%iAs, %MMA, and %DMA). To account for variability in spot urine dilution, we divided urine arsenic concentrations by urine creatinine concentrations (µg/g creatinine). We also conducted sensitivity analyses to correct for urine dilution by adjusting for urine creatinine concentrations in regression models or by adjusting urine arsenic concentrations by specific gravity. The latter was conducted only in the subset of participants without diabetes or albuminuria. The results of these sensitivity analyses were consistent with the main analysis (not shown).

Electrocardiographic markers

A standard digital 12-lead electrocardiogram was performed using MAC-PC or MAC-12 digital ECG systems (GE-Marquette Medical Systems) in the morning of each exam (Okin et al., 2001). QT interval was automatically measured from median complexes using interactive software (QT-Guard, GE-Marquette Medical Systems). QT dispersion was calculated from the difference between the maximum and the minimum QT interval across all leads. QT interval and QT dispersion measurements in the SHS main cohort baseline exam were validated by an investigator (PMO) unaware of clinical data (Okin et al., 2000). JT interval, an alternative measure of ventricular repolarization in the presence of ventricular conduction disorders (Rautaharju et al., 2009), was calculated by subtracting the QRS duration from the QT interval.

For the main analysis, we used the Bazett method to correct the QT interval for residual correlation with heart rate (QTc-B) because it is the clinical standard and most commonly used method (Bazett, 1997), despite a known bias at fast and slow heart rates (Luo et al., 2004). In sensitivity analyses, we corrected for heart rate using two alternative formulas: a

linear regression function of QT interval on age, sex, and RR interval (QTc-LR) (Zhang et al., 2011b) recommended by American Heart Association guidelines (Rautaharju et al., 2009), and the Hodges formula (QTc-H) (Hodges et al., 1983). Prolonged QTc was defined as a QTc interval greater than or equal to 450 ms in men, and greater than or equal to 460 ms in women (Rautaharju et al., 2009).

Other variables

Administered by trained staff and following a standardized protocol, each SHS study visit consisted of a questionnaire (sociodemographics, smoking status, alcohol use, medication use, medical history), clinical exam (height, weight, systolic and diastolic blood pressure), and collection of fasting blood and spot urine sample collection (Lee et al., 1990; North et al., 2003). After at least a 12-hour overnight fast, blood and urine samples were collected in the morning. Methods to measure blood pressure, lipids, fasting glucose, 75-g oral glucose tolerance, hemoglobin A1c, albumin, and creatinine have been described previously (Lee et al., 1990; North et al., 2003). We defined hypertension as systolic/diastolic blood pressure 140/90 mm Hg or antihypertensive medication use (Alderman, 1993). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation (Friedewald et al., 1972) if triglycerides were less than 400 mg/dL. In the main cohort, missing values were replaced with measured LDL cholesterol using the beta-quantification procedure. We defined albuminuria as a urine albumin to creatinine ratio (ACR) of 30 mg/g or greater (National Kidney Foundation, 2002). We estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (Shara et al., 2012). We defined diabetes as a fasting glucose 126 mg/dL, two-hour plasma glucose 200 mg/dL, hemoglobin A1c 6.5%, or self-reported use of insulin or an oral hypoglycemic agent (American Diabetes Association, 2012).

Statistical analysis

In descriptive analyses, we examined participant characteristics and ECG outcomes overall and by quartiles of baseline urine arsenic in each cohort. We evaluated the association between baseline urine arsenic concentrations and repeated measures of QT interval, PR interval, and QRS duration separately in the SHS main cohort (Visits 1, 2, and 3) and in the family study (Visit 3 pilot/4 and Visit 5). For QT dispersion, which was only measured in the SHS main cohort baseline exam, we examined the cross-sectional association with baseline urine arsenic using a linear regression with similar modeling strategies as described below.

We jointly analyzed both the cross-sectional association between baseline arsenic exposure and baseline ECG outcomes and the relationship between baseline arsenic and the annual change in ECG outcomes using a linear mixed model. Using QTc interval as an example, with subjects indexed by i and time in years from baseline exam until follow-up exam indexed by j :

$$E[QTc\ interval_{ij}] = \beta_0 + \beta_1 \left(\sum As\ quartile\ 2_i \right) + \beta_2 \left(\sum As\ quartile\ 3_i \right) + \beta_3 \left(\sum As\ quartile\ 4_i \right) + \beta_4 \left(years_{ij} \right) + \beta_5 \left(years_{ij} \right) \left(\sum As\ quartile\ 2_i \right) + \beta_6 \left(years_{ij} \right) \left(\sum As\ quartile\ 3_i \right) + \beta_7 \left(years_{ij} \right) \left(\sum As\ quartile\ 4_i \right) + \beta\ Z_{i0} + \mu_{0i} + \mu_{1i} \left(years_{ij} \right) + \epsilon_{ij}$$

Years_{ij} represents the time in years from baseline exam until follow-up exam j for subject i . β_0 represents the mean baseline QTc interval arsenic [As]. β_1 , β_2 , and β_3 represent the mean difference in baseline QTc interval comparing the 2nd, 3rd, and 4th quartiles of arsenic to the 1st quartile (i.e., the cross-sectional association). β_4 represents the annual change from baseline in mean QTc interval for participants in the reference group (1st quartile of arsenic [As]). β_5 , β_6 , and β_7 represent the difference in the annual increase in QTc interval comparing the 2nd, 3rd, and 4th quartiles of arsenic, respectively, to the 1st quartile (i.e., the longitudinal association). βZ_{i0} is a vector of coefficients of potential confounders measured at baseline. The random intercept (μ_{0i}) and random slope (μ_{1i}) account for the within-subject correlation across time. Additional random effects for family in the SHFS did not improve model fit or resulted in unstable model estimates and were not included in final models.

We modeled arsenic exposure as quartiles, log-transformed continuous (per doubling), and restricted cubic splines of log-transformed urine arsenic concentrations (knots at the 10th, 50th, and 90th percentiles). We used a Wald test of the non-linear coefficient to assess statistical evidence of a non-linear association. We selected the best fitting models by likelihood ratio tests and a comparison of the Akaike Information Criteria (AIC) using restricted maximum likelihood, and final models were fit with maximum likelihood. We tested for an interaction between baseline arsenic and time by a Wald test of the interaction between arsenic (quartiles or continuous) and time (years from baseline until follow-up).

We progressively adjusted for confounding using a priori knowledge of potential confounders. An initial model adjusted for age, education, smoking, and alcohol use. We progressively added body mass index, LDL cholesterol, hypertension, and study center. In final models, we adjusted the associations for age, education (no, some, or finished high school), smoking (never, former, current), alcohol use (never, former, current), body mass index (BMI) (kg/m²), LDL cholesterol (mg/dL), hypertension (yes/no), eGFR (mL/min/1.73 m²), and study center (Arizona, Oklahoma, North and South Dakota). Albuminuria and diabetes could be confounders or mediators of an association between arsenic and ECG markers. In a sensitivity analysis, we further adjusted for albuminuria (yes/no), diabetes (yes/no), and a measure of diabetes control (hemoglobin A1c, %) in the SHS main cohort, and for fasting glucose (mg/dL) and albuminuria (yes/no) in SHFS participants without diabetes. While hypertension could also be a mediator of the association between arsenic and cardiovascular disease, in preliminary analyses urine arsenic was not associated with blood pressure or hypertension (results not shown). In a planned subgroup analysis, we examined effect modification by sex using a three-way interaction model with arsenic, time, and sex. ECG markers vary by sex (Rautaharju et al., 2009) and a previous study found a cross-sectional association limited to women (Chen et al., 2013b). We also examined effect modification by age in a post-hoc analysis stratified by the median baseline age in each cohort.

We further examined the association between the measures of arsenic metabolism (%iAs, %MMA, and %DMA) and QTc-B interval in linear mixed models comparable to the main analysis. The association with each arsenic metabolism species was modeled per a 5%-point increase using two models: a conventional model, where each arsenic species is evaluated in separate models, and a leave-one-out model. Leave-one-out models have previously been

used to evaluate arsenic metabolism (Kuo et al., 2015; Spratlen et al., 2018). In a model with %MMA and %iAs, for example, the %MMA coefficient can be interpreted as the association of increasing %MMA while decreasing %DMA, and the %iAs coefficient can be interpreted as the association of increasing %iAs while decreasing %DMA. Mixed models of arsenic metabolism included the same random effects as the main analysis (random intercept and slope) and adjusted for arsenic exposure (log-transformed As and log-transformed As*[years from baseline]) in addition to the main analysis potential confounders. Statistical analyses were conducted using Stata (StataCorp, Version 14) and R (Version 3.4.3).

RESULTS

Baseline participant characteristics

SHS main cohort participants were older than SHFS participants without diabetes (median age 55 vs. 36 years). The median (interquartile range, IQR) of urine arsenic (As) was 8.6 (5.2, 14.4) µg/g creatinine in the SHS main cohort compared to 4.3 (2.9, 7.1) µg/g creatinine in the SHFS (Table 1). The medians (IQR) of QTc-B interval were 424 (411, 442) ms and 414 (405, 427) ms in the main SHS cohort and the SHFS, respectively. The prevalence of prolonged QTc-B in men and women, respectively, was 11% and 13% in the SHS main cohort and 2% and 4% in the SHFS. For the SHS main cohort and SHFS, respectively, we present selected participant characteristics by quartiles of urine arsenic in Table 2 and eTable 2 and by quartiles of QTc-B interval in Table 3 and eTable 3.

QT interval and JT interval

In the SHS main cohort, participants in the highest quartile of baseline urine arsenic (>14.4 µg/g creatinine) had 5.3 (95% CI: 1.2, 9.5) ms longer mean QTc-B interval, after adjustment for age, sex, education, smoking, alcohol drinking, BMI, LDL cholesterol, hypertension, eGFR, and study center, when compared to the lowest quartile (<5.2 µg/g creatinine) (Table 4). There was no evidence of a longitudinal association between baseline urine arsenic and annual change in QTc-B interval in the SHS main cohort (p-interaction with time=0.93 with arsenic quartiles; p-interaction with time=0.73 with log-transformed continuous arsenic). In a corresponding analysis in the SHFS participants without diabetes, a comparison of the highest to lowest quartile of baseline urine arsenic (>7.1 vs. <2.9 µg/g creatinine) was associated with a 3.2 (95% CI: 0.6, 5.7) ms longer baseline QTc-B interval and a 0.6 (95% CI: 0.04, 1.2) ms greater annual increase in QTc-B interval (Table 4). Per doubling of baseline arsenic, the adjusted annual increase in QTc-B interval was 0.2 (95% CI: 0.01, 0.4) ms (p-interaction with time=0.037).

Using a flexible spline model, the cross-sectional associations between log-transformed baseline urine arsenic and QTc-B interval were approximately linear for both the SHS and SHFS (Figure 1). For both cohorts, the cross-sectional and longitudinal associations between urine arsenic and QTc-B remained similar after adjustment for diabetes, hemoglobin A1c or fasting glucose, and albuminuria (results not shown). Alternative methods to correct for the association between QTc interval and heart rate produced associations that were consistent but attenuated in magnitude compared to the associations with QTc-B interval (QTc-LR and

QTc-H, eTable 4). Associations between baseline urine arsenic and JTc-B interval, a measure of repolarization duration only, were similar but stronger in magnitude compared to the associations between arsenic and QTc-B interval, which also includes the duration of ventricular depolarization (eTable 4).

There was some qualitative evidence for a stronger cross-sectional association in men in the SHS main cohort and in women in the SHFS (eTable 5). In the SHFS, the longitudinal association between baseline arsenic and annual change in QTc-B interval was evident only in men (p-value for interaction with sex=0.006). In a post-hoc analysis to examine the effect of differences in baseline age between cohorts, we found that the association with annual change in QTc-B interval was strongest in the younger SHFS participants (median age 23 years) (eTable 6). For older SHFS participants (median age 46 years) and younger SHS participants (median age 49 years), the cross-sectional and longitudinal associations with QT interval were comparable across cohorts. In older SHS participants (median age 62 years), the cross-sectional association was still present but the difference in annual change was negative, although non-significant.

PR interval, QRS duration, and QT dispersion

We observed no associations between baseline arsenic exposure and PR interval in the SHS main cohort or among SHFS participants without diabetes (eTable 4). In the SHS main cohort, there was no cross-sectional association between arsenic and baseline QRS duration, but a doubling of arsenic was associated with a small annual increase (0.1 ms, 95% CI: 0.01, 0.2) in QRS duration (p-interaction with time=0.029) (eTable 5). In SHFS participants, there was no cross-sectional or longitudinal association between arsenic and QRS duration (eTable 5). There was no cross-sectional association between arsenic and QT dispersion in the SHS main cohort (eTable 5).

Arsenic metabolism and QT interval

At baseline in the SHS main cohort and among SHFS participants without diabetes, adjusted conventional models indicated that a 5% increase in %MMA was associated with shorter mean QTc-B interval (main cohort: -1.8 ms [95% CI: -3.1, -0.5]; family study: -1.0 ms [-2.0, -0.1]), while higher %DMA was associated with longer mean QTc-B interval (main cohort: 0.9 ms [95% CI: 0.1, 1.7]; family study: 0.2 ms [-0.3, 0.7]) (eTable 8). In the SHFS participants without diabetes, a 5% increase in %MMA was associated with a smaller annual change in QTc-B interval (-0.3 ms [95% CI: -0.5, -0.1]) and a 5% increase in %DMA was associated with a larger annual change in QTc-B interval (0.1 ms [95% CI: 0.03, 0.2]). In adjusted leave-one-out models, the cross-sectional and longitudinal associations between %MMA and QTc-B interval were similar regardless of whether the increase in %MMA was due to a decrease in %iAs or %DMA (eTable 8). Further, the leave-one-out model associations between higher %DMA and QTc-B interval were positive only when the increase in %DMA was due to a decrease in %MMA.

DISCUSSION

In this study, we evaluated the cross-sectional and longitudinal associations between chronic low-moderate arsenic exposure and arsenic metabolism and ECG markers of combined conduction and repolarization (QTc interval), repolarization (JTc interval), cardiac conduction (PR interval and QRS duration), and heterogeneity of conduction and repolarization (QT dispersion) in the SHS. We identified a cross-sectional association between baseline arsenic exposure and QTc interval and JTc interval, and suggestive evidence for an association between higher arsenic exposure and a larger annual increase in QTc interval and JTc interval among SHFS participants without diabetes. We also observed an association between arsenic metabolism and QTc interval. Similar to the association with arsenic exposure, lower %MMA and higher %DMA was associated with longer QTc interval at baseline and with a larger annual increase in QTc interval in the SHFS participants without diabetes. These findings add weight to the epidemiological, clinical, and toxicological evidence that low-moderate arsenic exposure ($<100 \mu\text{g/L}$ in water) may lead to changes in ventricular repolarization. This is the first study to evaluate a longitudinal association between chronic arsenic exposure and annual change in ECG markers.

Previous epidemiologic studies evaluating the association between chronic arsenic exposure and QT interval have largely been cross-sectional and most are conducted in populations with high arsenic levels in water ($>100 \mu\text{g/L}$), much higher than is common in the US (Ahmad et al., 2006; Chen et al., 2013b; Mumford et al., 2007; Wang et al., 2009; Wang et al., 2010; Yildiz et al., 2008). In a population exposed to high levels of arsenic in water (mean $95 \mu\text{g/L}$) in Bangladesh, higher water and urine arsenic concentrations were associated with higher odds of prolonged QTc-B interval only in women (Chen et al., 2013b). In a previous study of low-moderate arsenic exposure in water ($<100 \mu\text{g/L}$) and QTc interval, an interquartile range difference in toenail arsenic (a marker of chronic exposure to arsenic) was cross-sectionally associated with a 2.5 (95% CI: 0.11, 4.9) ms longer QTc-B interval in older men in Boston (Mordukhovich et al., 2009). These previous studies that suggested sex-specific associations were limited to baseline QT interval. In this study, stratified analyses found suggestive qualitative differences in both cross-sectional and longitudinal associations by sex, but these differences were inconsistent across the SHS main cohort and family study. Overall, our results suggest that arsenic exposure is associated with QTc interval in both men and women. In contrast to our findings, two previous studies did find an association between arsenic exposure and QT dispersion, but these studies were conducted in populations exposed to higher levels of arsenic exposure, which may not be generalizable, and relied on ecological exposure assessment (Wang et al., 2010; Yildiz et al., 2008). Further, the clinical implications of QT dispersion for CVD risk are uncertain (Rautaharju et al., 2009). Coherent with a previous study (Chen et al., 2013b), we observed no consistent associations with PR interval or QRS interval.

No previous studies have examined the association between markers of arsenic metabolism and ECG outcomes. Individuals with lower %MMA and higher %DMA in urine, which in our study was associated with longer baseline QTc interval and with larger annual change in QTc interval, are considered to be more efficient metabolizers of arsenic, and thus hypothesized to be at lower risk of toxicity. However, the link between arsenic metabolism

profiles and disease risk is not yet clear. In general, higher %MMA and lower %DMA have been most often associated with arsenic-related cancer and cardiovascular outcomes, whereas lower %MMA and higher %DMA have been associated with diabetes-related outcomes (Kuo et al., 2017). Some studies have suggested that the higher risk of diabetes and metabolic-related outcomes with lower %MMA and higher %DMA could be related to the more toxic trivalent species (Del Razo et al., 2011; Kuo et al., 2015; Mendez et al., 2016); however, we cannot differentiate between trivalent and pentavalent species in urine.

Chronic arsenic exposure may affect ventricular myocytes similarly to arsenic trioxide, the arsenic chemotherapeutic drug. Arsenic trioxide prolongs the QT interval by disrupting potassium channel gene expression (*hERG* and *KCNJ2*), increasing calcium currents, and producing intracellular calcium overload (Drolet et al., 2004; Ficker et al., 2004; Shan et al., 2013; Sun et al., 2006). Arsenic may cause cardiotoxicity via DNA alteration, reactive oxygen species generation, and apoptosis (Alamolhodaei et al., 2015) but the molecular mechanisms underlying these functional changes have not been completely elucidated. Recent experimental studies with co-exposure to antioxidants have demonstrated a key role for oxidative stress pathways (Sun et al., 2016; Zhang et al., 2013).

Prolonged QT interval is connected to sudden cardiac death through arrhythmia and ventricular fibrillation (Beinart et al., 2014). The underlying mechanism for the association between longer QT interval and incident CVD endpoints is not known but may include increased catecholamine levels, parasympathetic stimulation, and autonomic imbalance (Beinart et al., 2014). Smaller differences in QT interval, and not just prolonged QT interval beyond a threshold, have been associated with an increased risk of mortality and incident CVD (Beinart et al., 2014; Zhang et al., 2011a). In healthy individuals, a recent study found that each 10 ms increase in QTc interval was associated with a 12% increased risk of incident CVD (Beinart et al. 2014). Future studies should evaluate whether QT interval partially mediates the association between chronic arsenic exposure and CVD, especially events such as sudden cardiac death and fatal CHD. If arsenic-related CVD is mediated through QT interval, ECGs could potentially be used as a population-level screening or intervention tool in arsenic-exposed populations to reduce the massive economic, social, and public health burden of CVD.

This study had several strengths compared to previous studies. We used a high-quality measurement method for inorganic and methylated arsenic species in urine. At low-moderate levels of water arsenic, accounting for arsenic derived from food and water is essential. The low seafood intake of the SHS population makes it likely that arsenic species represent inorganic arsenic in the SHS (Navas-Acien et al., 2011). Although dividing urine metal concentrations by urine creatinine can lead to bias (Nermell et al., 2008), we found similar results in models adjusting for urine creatinine and dividing arsenic concentrations by specific gravity. The SHS conducted high quality measurements of ECG markers and key CVD risk factors, and standardized procedures across the main cohort and SHFS facilitate cross-cohort comparisons. Previous studies of chronic arsenic exposure and QTc interval have used only the Bazett correction method. Different heart rate correction methods can produce discordant QTc values outside the range of normal heart rate, but studies of the association between QT interval and CVD events have generally found consistent

associations (Nilsson et al., 2006). The reason for the stronger association between arsenic and QTc interval with the Bazett correction compared to other methods is not clear, but residual confounding is possible.

Our study also had limitations. Water arsenic measurements were not available, and we used a single baseline measurement of urine arsenic as a proxy for long-term exposure. However, concentrations of urine arsenic in a subset of main cohort participants were relatively stable over a 10-year period (Moon et al., 2013) and participants are likely to have resided in their communities for many years. The reason for the difference in urine arsenic concentrations between the two SHS cohorts is not clear, but some of the communities may have received interventions to reduce arsenic in drinking water. Except for the ECG data losses at baseline and Visit 2 in the main cohort, the SHS had few losses to follow-up and low prevalence of missing data. We do not believe that the missing data is likely to result in substantial selection bias, although we cannot rule it out. The data losses were accidental, and the baseline characteristics of participants without ECG were similar to participants with ECG on most sociodemographic and CVD risk factors. The association between arsenic exposure and annual change in QTc interval only in the family study could be related to the younger age of family study participants but may also be related to other disparities in arsenic exposure levels, diabetes, and CVD risk factors. We identified a cross-sectional association with QTc interval at baseline in both SHS cohorts despite these differences. ECGs were conducted in all study participants in the morning, minimizing potential bias due to the diurnal variability (Molnar et al., 1996). Residual confounding by sociodemographic factors is possible, although our results were robust to adjustment for education and study site. Finally, given the multiple comparisons, our results should be interpreted with caution.

In conclusion, we found positive associations between baseline chronic arsenic exposure, as measured by urine arsenic, and baseline QTc interval and JTc interval, and suggestive evidence for a longitudinal association between baseline arsenic and a higher annual increase in QTs interval and JTc interval. We also identified a positive association between arsenic metabolism, particularly lower %MMA, and QTc interval. This study adds to the confluence of evidence from clinical, toxicological, and epidemiologic studies suggesting that arsenic can cause changes in ventricular repolarization in men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Difference in baseline QTc-B interval by restricted cubic splines of log-transformed baseline urine arsenic in Strong Heart Study main cohort participants and Strong Heart Family Study participants without diabetes

Solid lines are the adjusted mean differences in baseline QTc-B interval by baseline urine arsenic concentrations, in relation to the 10th percentile of urine arsenic (3.5 in the main cohort, and 2.2 $\mu\text{g/g}$ creatinine in the family study). Shaded areas represent the 95% confidence intervals of the adjusted mean differences. Mean differences were estimated from a linear mixed model with fixed effects for restricted cubic splines of log-transformed arsenic (knots at the 10th, 50th, and 90th percentiles), time (years from baseline), interactions between arsenic terms and time, and baseline age (years), sex, education (no, some, or finished high school), smoking (never, former, current), alcohol drinking (never, former, current), body mass index (kg/m^2), low density lipoprotein (LDL) cholesterol (mg/dL), hypertension (yes/no), estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2), and study center (Arizona, Oklahoma, North and South Dakota), and random effects for subject and time (years from baseline).

Table 1.

Baseline characteristics of the Strong Heart Study main cohort participants and Strong Heart Family Study participants without diabetes

	Strong Heart Study main cohort (Visit 1) N=1174	Strong Heart Family Study without diabetes (Visit 3 pilot/Visit 4) N=1695	p-value
Follow-up time, years	7.2 (4.1, 7.9)	5.3 (4.7, 6.7)	<0.001
Age, years	55 (49, 62)	36 (24, 47)	<0.001
Female, %	694 (59%)	1018 (60%)	0.61
Finished high school, %	700 (60%)	1190 (70%)	<0.001
Current smoker, %	458 (39%)	650 (38%)	0.72
Current drinker, %	518 (44%)	1068 (63%)	<0.001
BMI, kg/m ²	29 (26, 33)	30 (26, 35)	0.21
SBP, mg/dL	124 (112, 137)	119 (110, 130)	<0.001
Hypertension, %	419 (36%)	373 (22%)	<0.001
Diabetes, %	514 (44%)	N/A *	
LDL cholesterol, mg/dL	121 (99, 145)	99 (80, 119)	<0.001
Hemoglobin A1c, %	5.4 (4.8, 7.2)	N/A (a)	
Fasting glucose, mg/dL	110 (98, 154)	93 (87, 100)	<0.001
eGFR, mL/min/1.73 m ²	99 (89, 106)	119 (107, 131)	<0.001
Albuminuria, %	294 (25%)	144 (8%)	<0.001
Urine ΣAs, µg/g creatinine	8.6 (5.2, 14.4)	4.3 (2.9, 7.1)	<0.001
%iAs	7.9 (5.6, 11.0)	10.2 (7.0, 14.2)	<0.001
%MMA	14.8 (11.2, 18.5)	14.5 (11.2, 18.1)	0.33
%DMA	77.0 (70.8, 82.1)	74.4 (67.7, 80.6)	<0.001
Urine creatinine, mg/dL	1.2 (0.8, 1.7)	1.4 (0.9, 2.1)	<0.001
Heart rate, bpm	66 (60, 74)	62 (57, 69)	<0.001
QTc-B interval, ms	424 (411, 442)	414 (405, 427)	<0.001
JTc-B interval, ms	332 (318, 351)	324 (312, 338)	<0.001
PR Interval, ms	160 (148, 172)	156 (144, 170)	<0.001
QRS duration, ms	92 (84, 100)	92 (84, 98)	0.002
QT dispersion, ms	17 (12, 25)	N/A *	
Prolonged QTc-B interval, % [†]	133 (11%)	54 (3%)	<0.001

ΣAs, sum of inorganic and methylated arsenic species; LDL, Low-density lipoprotein; BMI, Body mass index; SBP, Systolic blood pressure; eGFR, estimated glomerular filtration rate; ms, milliseconds; N/A, Not available; QTc-B interval, QT interval corrected for heart rate with Bazett formula; JTc-B interval, JT interval corrected for heart rate with Bazett formula; SHFS, Strong Heart Family Study; bpm, beats per minute. iAs, inorganic arsenic; MMA, monomethylarsenate; DMA, dimethylarsenate

Values are median (interquartile range) or N (%). P-values are from a nonparametric Kruskal-Wallis test of equality of populations for continuous variables and a chi-square test of independent proportions for categorical variables

* Urine arsenic was only measured among participants without diabetes at baseline in the SHFS. QT dispersion measurements were not available in the SHFS. Hemoglobin A1c was only measured in a small subset of participants in the SHFS.

[†] Prolonged QTc = QTc > 450 ms in men and > 460 ms in women.

Table 2.

Baseline characteristics by urine arsenic quartiles in Strong Heart Study main cohort participants

	Quartiles of urine ΣAs (μg/g creatinine)				p-value
	Q1 N=294	Q2 N=296	Q3 N=291	Q4 N=293	
Mean (SD)	3.7 (0.9)	6.8 (1.0)	11.3 (1.6)	25.1 (16.4)	
Median (IQR)	3.8 (3.1, 4.5)	6.8 (5.9, 7.6)	11.4 (9.8, 12.8)	20.2 (16.3, 27.2)	
Range	1.7, 5.2	5.2, 8.6	8.7, 14.4	14.4, 179.9	
Age, years	54 (48, 62)	55 (49, 62)	54 (49, 61)	56 (50, 63)	0.06
Female, %	143 (49%)	180 (61%)	174 (60%)	197 (67%)	<0.001
Finished high school	200 (68%)	189 (64%)	169 (58%)	142 (48%)	<0.001
Current smoker, %	111 (38%)	111 (38%)	127 (44%)	109 (37%)	0.32
Current drinker, %	108 (37%)	120 (41%)	146 (50%)	144 (49%)	0.001
BMI, mg/kg ²	29 (26, 34)	30 (27, 34)	29 (26, 34)	28 (25, 33)	0.018
SBP, mg/dL	126 (116, 136)	126 (111, 138)	120 (111, 135)	121 (111, 138)	0.020
Hypertension, %	112 (38%)	116 (39%)	93 (32%)	98 (33%)	0.193
Diabetes, %	112 (38%)	120 (41%)	117 (40%)	165 (56%)	<0.001
Hemoglobin A1c, %	5.3 (4.9, 6.2)	5.4 (4.9, 6.4)	5.2 (4.7, 6.9)	5.7 (4.8, 9.7)	0.001
FPG, mg/dL	109 (98, 133)	108 (97, 142)	107 (97, 143)	124 (100, 243)	<0.001
LDL cholesterol, mg/dL	126 (100, 148)	125 (101, 146)	123 (104, 147)	114 (94, 137)	0.001
eGFR, mL/min/1.73 m ²	98 (86, 104)	99 (88, 106)	100 (89, 106)	100 (92, 108)	0.002
Albuminuria, %	53 (18%)	65 (22%)	60 (21%)	116 (40%)	<0.001
QTc-B interval, ms	420 (408, 434)	421 (409, 440)	424 (412, 445)	431 (416, 446)	<0.001
JTc-B interval, ms	326 (313, 342)	330 (316, 349)	333 (320, 353)	339 (325, 358)	<0.001
PR interval, ms	164 (148, 176)	160 (148, 176)	160 (144, 176)	158 (144, 170)	0.029
QRS duration, ms	92 (88, 100)	92 (88, 100)	92 (84, 100)	92 (84, 100)	0.004
QT dispersion, ms	15 (10, 24)	16 (11, 27)	18 (12, 25)	18 (12, 25)	0.025

As, sum of inorganic and methylated arsenic species; LDL, Low-density lipoprotein; BMI, Body mass index; SBP, Systolic blood pressure; eGFR, estimated glomerular filtration rate; ms, milliseconds; QTc-B interval, QT interval corrected for heart rate with Bazett formula; JTc-B interval, JT interval corrected for heart rate with Bazett formula.

Values are median (interquartile range) or N (%). P-values are from a nonparametric Kruskal-Wallis test of equality of populations for continuous variables and a chi-square test of independent proportions for categorical variables.

Table 3. Baseline participant characteristics by quartiles of QTc-B interval in the Strong Heart Study main cohort

	Quartiles of QTc-B interval (N=1174)				p-value
	Q1 N=308	Q2 N=304	Q3 N=273	Q4 N=289	
Median (IQR)	405 (401, 408)	418 (415, 421)	432 (428, 437)	455 (448, 467)	
Age, years	52 (48, 60)	54 (49, 62)	55 (49, 63)	57 (50, 64)	<0.001
Finished high school, %	203 (66%)	190 (62%)	164 (60%)	143 (49%)	<0.001
Current smoker, %	126 (41%)	125 (41%)	108 (40%)	99 (34%)	0.28
Current drinker, %	143 (46%)	135 (44%)	129 (47%)	111 (38%)	0.134
BMI, mg/kg ²	29 (26, 32)	29 (26, 34)	29 (26, 33)	30 (26, 34)	0.52
SBP, mg/dL	121 (111, 131)	125 (112, 138)	123 (113, 135)	127 (113, 142)	0.004
Hypertension, %	89 (29%)	118 (39%)	93 (34%)	119 (41%)	0.009
Diabetes, %	110 (36%)	120 (39%)	114 (42%)	170 (59%)	<0.001
Hemoglobin A1c, %	5.3 (4.8, 6.3)	5.3 (4.8, 6.6)	5.4 (4.8, 6.6)	5.7 (5.0, 9.1)	0.002
FPG, mg/dL	107 (98, 134)	107 (97, 146)	110 (98, 152)	122 (100, 219)	<0.001
LDL cholesterol, mg/dL	126 (103, 148)	123 (104, 146)	114 (95, 144)	119 (95, 141)	<0.001
eGFR, mL/min/1.73 m ²	99 (90, 106)	100 (90, 106)	99 (88, 107)	97 (85, 105)	0.094
Albuminuria, %	55 (18%)	62 (20%)	66 (24%)	111 (38%)	<0.001

LDL, Low-density lipoprotein; BMI, Body mass index; SBP, Systolic blood pressure; eGFR, estimated glomerular filtration rate; ms, milliseconds; N/A, Not available; FPG, Fasting plasma glucose; IQR, interquartile range.

Values are median (interquartile range) or N (%). P-values are from a nonparametric Kruskal-Wallis test of equality of populations for continuous variables and a chi-square test of independent proportions for categorical variables.

Table 4.

Baseline difference and annual change in QTc-B interval associated with baseline urine arsenic exposure (As, $\mu\text{g/g}$ creatinine) in Strong Heart Study main cohort participants and Strong Heart Family Study participants without diabetes

Urine ΣAs , $\mu\text{g/g}$ creatinine	Strong Heart Study (SHS) main cohort			Strong Heart Family Study (SHFS) without diabetes		
	N	Baseline difference (ms)	Annual change (ms)	N	Baseline difference (ms)	Annual change (ms)
Q1: 1.7 – 5.2 (3.8) *	294	0.0 (Reference)	0.0 (Reference)	426	0.0 (Reference)	0.0 (Reference)
Q2: 5.2 – 8.6 (6.8) *	296	0.4 (–3.2, 4.0)	0.2 (–0.5, 0.8)	422	0.3 (–2.1, 2.8)	0.2 (–0.4, 0.8)
Q3: 8.7 – 14.4 (11.4) *	291	3.0 (–0.8, 6.9)	–0.03 (–0.6, 0.6)	424	0.03 (–2.4, 2.5)	0.2 (–0.4, 0.8)
Q4: 14.4 – 179.9 (20.2) *	293	5.3 (1.2, 9.5)	0.03 (–0.6, 0.7)	423	3.2 (0.6, 5.7)	0.6 (0.04, 1.2)
Per doubling	1174	1.8 (0.4, 3.2)	–0.04 (–0.3, 0.2)	1695	0.9 (–0.1, 1.9)	0.2 (0.01, 0.4)
p-interaction: time x ΣAs quartiles/continuous $\dagger$			0.93 / 0.73			0.20 / 0.037
p-interaction: time x ΣAs quartiles/continuous $\dagger$						

As, Sum of inorganic and methylated arsenic metabolites (MMA and DMA); QTc-B interval, QT interval corrected for heart rate with the Bazett formula.

* For each quartile: Minimum - maximum (median) of ΣAs . The 25th, 50th, and 75th percentiles of arsenic in the main cohort were 5.23, 8.64, 14.38 $\mu\text{g/g}$ creatinine, respectively; in the family study: 2.89, 4.33, 7.06 $\mu\text{g/g}$ creatinine, respectively.

$\dagger$ P-value from a Wald test of the interaction between arsenic terms (either quartiles or log-transformed continuous) x time (years from baseline).

All models adjusted for age (years), sex, education (no, some, or finished high school), smoking (never, former, current), alcohol drinking (never, former, current), BMI (kg/m^2), LDL cholesterol (mg/dL), hypertension (yes/no), eGFR (mL/min/1.73 m^2), and study center (Arizona, Oklahoma, North and South Dakota).