Circulation: Cardiovascular Imaging

EDITORIAL

# Arsenic

## A Metal That Might Break Your Heart

See Article by Pichler et al

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In the past decades, exposure to environmental metal contaminants (eg, arsenic, lead, cadmium, and mercury) through groundwater, food, soil, and ambient air has become a global public health concern.[1] In this regard, arsenic—one of the most abundant environmental metals worldwide—affects >200 million people in >70 countries solely by drinking water route.[2] While a high level of chronic inorganic arsenic (iAs) exposure has previously been linked with a range of neoplastic and non-neoplastic conditions,[2] emerging evidence suggests that low-to-moderate levels of arsenic (eg, level of exposure common in many global regions) might be associated with cardiovascular disease (CVD),[3] its key risk factors (eg, hypertension[4] and diabetes mellitus[2]), and subclinical end points (eg, QT-interval prolongation or subclinical atherosclerosis).[5]

Nevertheless, uncertainties regarding this intriguing link remain. For example, it is unclear (1) what are the relative contributions for various exposure pathways (eg, water, foods, and air), (2) which exact pathophysiological mechanisms lead to arsenic-related adverse CVD consequences, (3) whether arsenic is related directly to cardiac functioning or secondarily through a worse cardiometabolic profile, (4) what is the shape of association with the CVDs for the whole spectrum of arsenic exposure (eg, low versus moderate levels), and (5) if an observational association between low/moderate arsenic levels and CVD is causal.[2] The suggested pathways for environmental arsenic exposure, it's metabolism, key determinants, and potential clinical consequences have been summarized in the Figure.

Briefly, after absorption from the gastrointestinal tract in the blood stream, trivalent and pentavalent iAs ($iAs^{III}$ and $iAs^{V}$) are consecutively methylated by AS3MT (arsenic methyltransferase) in monomethylated (monomethylarsonic acid) and dimethylated (dimethylarsinic acid) compounds.[6] These metabolites may differ in their toxicity dependent on chemical form. For example, higher %monomethylarsonic acid and (however, conversely) lower %dimethylarsinic acid have shown to be associated with adverse CVD outcomes.[7] Numerous potential cardiotoxic effects of arsenic have been suggested, including scarce evidence on altered cardiac geometry.[6,8–10] In animal studies, female mice exposed to drinking water containing 100 ppb sodium arsenite for 22 weeks showed a 43% increment in left ventricular (LV) mass and a relative wall thickness ≥0.45, indicating concentric LV hypertrophy (LVH).[8] Additionally, rats fed on arsenic revealed alterations in LV systolic and end diastolic blood pressure, impaired cardiac contractility, hypertension, and increase in myocyte fibrosis and apoptosis.[6] In human epidemiological studies, Bangladeshi adult arsenicosis patients showed abnormal ECG features indicative of LVH,[9] and Mexican children exposed to elevated arsenic had higher LV mass and lower systolic function in a small cross-sectional study.[10]





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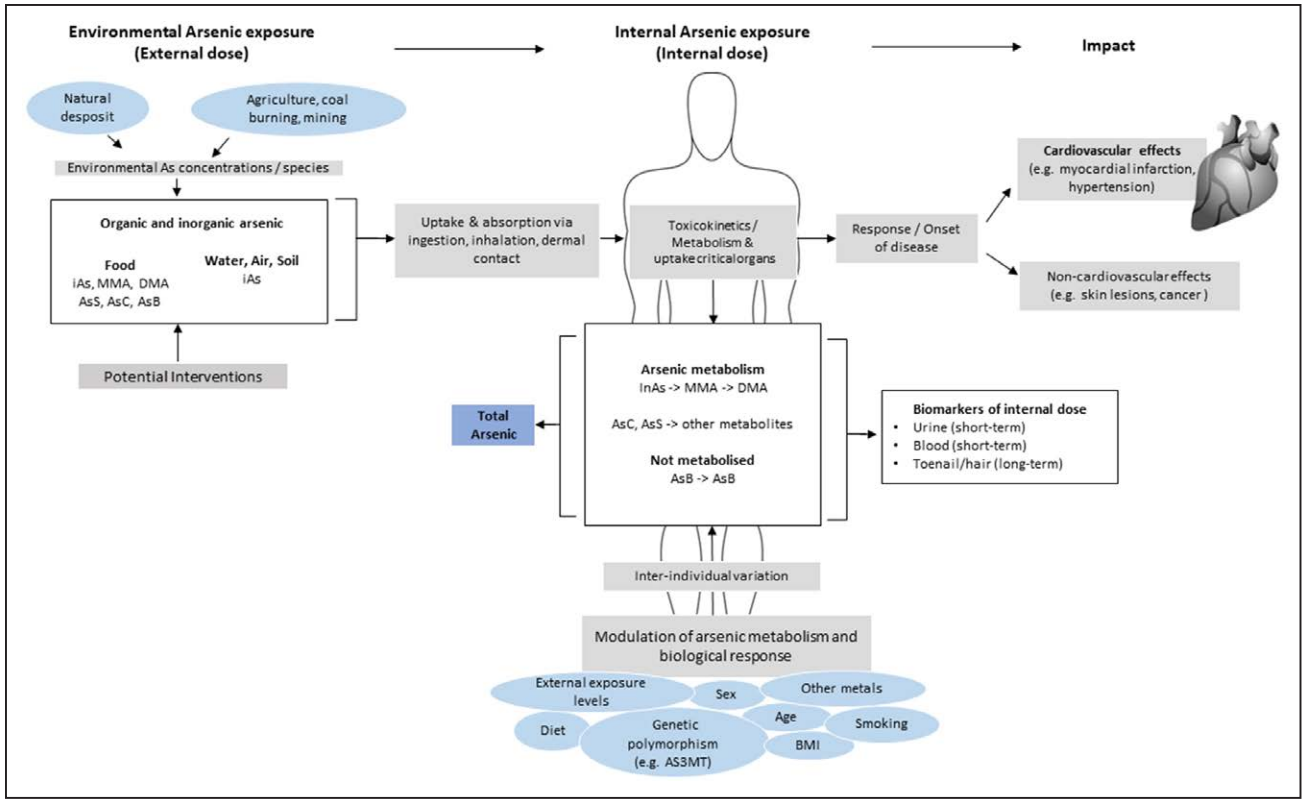


**Figure. Summary of the suggested pathways for environmental arsenic exposure, its metabolism, key determinants, and potential clinical consequences.** AS3MT indicates arsenic methyl transferase; AsB, arsenobetaine; AsC, arsenocholine; AsS, arsenosugars; BMI, body mass index; DMA, dimethylarsinic acid; iAs, inorganic arsenic; and MMA, monomethylarsonic acid.



LVH, LV systolic dysfunction, and LV diastolic dysfunction provide strong prognostic information on clinical CVD outcomes and are considered as effective surrogate markers for these events.[5,11] Moreover, identification of abnormal transthoracic echocardiography measurements, such as LVH, in asymptomatic patients can favorably affect adverse trends through efficient primary and secondary preventative interventions.[12] Despite this, experimental and epidemiological evidence of cardiac anatomic and functional alterations in populations with arsenic exposure is limited and nonexistent in adult human populations.[6,8–10]

In this issue of *Circulation: Cardiovascular Imaging*, Pichler et al[5] present findings from the SHFS (Strong Hearth Family Study), usefully extending the relevant evidence base by analyzing the longitudinal, population-based cohort study (SHS [Strong Heart Study]). The authors evaluate the association of arsenic exposure with LV function and cardiac geometry in American Indian adults (<50 years; n=1337) exposed to low-to-moderate arsenic drinking water levels. The sum of inorganic and methylated urinary arsenic concentrations (ΣAs) was used as the biomarker of internal exposure at baseline. Transthoracic echocardiography was performed to assess various measures of cardiac geometry and function at baseline and follow-up (mean, 5.6 years). The authors reveal that ΣAs was associated with prevalent LVH in all participants with an odds ratio (95% CI) of 1.47 (1.05–2.08) per 2-fold increase in ΣAs. Higher odds were observed among pre-/hypertensive individuals (1.58 [1.04–2.41]). No association was found with incident LVH. Continuous measures of LV geometry and LV functioning (stroke volume and isovolumic relaxation time) were significantly related to ΣAs both cross-sectionally and prospectively. Interestingly, at follow-up, the associations of ΣAs with LV mass index and LV posterior wall thickness were attenuated resulting in a negative annual change.[5]

We commend the authors for this effort and for providing pioneering insights on potential roles of arsenic on LVH, LV systolic dysfunction, and LV diastolic dysfunction in an adult, community-dwelling population. Nevertheless, several (albeit minor) limitations and some unresolved aspects merit careful consideration.

First, although commonly used as biomarker, urinary arsenic reflects recent exposure, generally from the previous day.[13,14] Due to a single measurement of arsenic in this study at baseline, statistical analysis cannot account for changes of arsenic exposure over time nor can a temporal relation (short term and long term) between arsenic exposure and outcome be conclusively established. Additionally, inadequate power of this analysis (eg, <50 incident LVH outcomes), owing to the insufficiently prolonged follow-up of a relatively young cohort

with low CVD burden, may have influenced both prospective arsenic LVH and arsenic metabolite findings. Nonetheless, prior studies in the SHS study showed an intraclass coefficient of 0.64 for repeat measurements of total urinary arsenic between study visits over 10 years, providing some assurance about the urinary arsenic as a measure of usual arsenic exposure. As the authors also accurately pointed out, prevalence of hypertension and CKD, that is, established risk factors for LVH, was low in this population, highlighting the need for further assessments in other populations with higher burden. Further caveats for interpretation arise from reverse causation (in the cross-sectional element) and residual confounding (in the prospective part).[5] Therefore, to reinforce these findings, future research should consider using (1) objective, noninvasive biomarkers of long-term exposure (such as toenail arsenic concentrations), (2) additional repeat measurements of arsenic to account for possible intraindividual and interseasonal variations, and (3) large, sufficiently powered studies with prospective design.

Second, individuals are exposed daily to a mixture of co-occurring environmental metals (eg, arsenic, cadmium, lead, and selenium) that often interrelate in vivo. As a result, cardiotoxic or beneficial effects between metal species may be altered by, for example, changes in bioaccessibility.[15] Exposure to individual metals has been independently associated with CVD risk and LV function in earlier studies. Baseline blood lead concentrations were significantly positively associated with CVD mortality in the National Health and Nutrition Examination Survey while selenium status showed a significant inverse association with CVD risk in a meta-analysis of prospective studies.[16,17] Therefore, possible interactions (eg, synergism, additivity, or antagonism) across multiple co-occuring metal species may confer CVD risk importantly. In this regard, while Pichler et al did include tungsten and uranium in sensitivity analyses, research involving concurrent exposure with other relevant heavy metals in relationship with CVD risk, in general, and cardiac geometry/LV functioning, in particular, is largely missing in the existing literature. This is despite major potential implications on cardiotoxic impact.[15] Such studies (eg, CAPABLE[18] in Bangladesh) are currently underway.

Third, the relative abundance of internal arsenic species reflected in biomarkers varies across individuals. Differences in metabolism and susceptibility to arsenic are reported to be influenced by factors as age, sex, nutrition, and genetic alterations combined with exposure history (Figure).[2,19] Furthermore, in addition to iAs in water, individuals can be exposed arsenic species from a variety of external sources (such as common food items). For instance, arsebobetaine, with a shorter half-life and little toxicity, often occurs in seafoods. Speciation of arsenic metabolites in biomarkers thus needs to be able to separate the contribution of iAs and other arsenic species from a variety of sources. To characterize biological pathways comprehensively and to identify subpopulations susceptible to toxicity, it is important to further elucidate the complex interactions between genes and environmental factors driving arsenic-related CVD.[2] However, as the study by Pichler et al[5] lacked such level of detail, future studies are warranted in these regards. Such detailed work involving evaluation of the external sources will inform targeted interventions and thereby context-specific public health action.

Finally, as the majority of available evidence (including the study by Pichler et al[5]) are based on observational studies, causal evaluation of these intriguing associations will require next-generation, multidimensional studies that can usefully combine genetic, environmental, and clinical evidence collected from the same participants. For example, to evaluate whether any observational associations between arsenic species and CVD are causal, genetic variants known to be associated with arsenic can be used as instrumental variables for Mendelian randomization analyses. By instrumenting arsenic using genetic variants specifically associated with arsenic species, the potential confounding and reverse causation in observational analyses can be avoided. In this regard, variants near the *AS3MT* and *FTCD* genes have previously been reported to be associated with arsenic species.[2,19] Various ongoing efforts (eg, BRAVE [Bangladesh Risk of Acute Vascular Events][20]) should be able to shed further light on the causal relationship between arsenic species and CVD.

In conclusion, while this elegant analysis by Pichler et al[5] helps to clarify the observational associations of iAs with LV geometry and function, it stimulates further complimentary work. Such studies would be essential since CVD remains the single leading cause of adult premature death worldwide, and millions of individuals globally are exposed to arsenic and other metal contaminants.

## ARTICLE INFORMATION

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### Disclosures

Dr Chowdhury is Co-Principal Investigator of a Research Council UK project CAPABLE, which aims to investigate arsenic in relation to cardiovascular disease health in Bangladesh. The other authors report no conflicts.

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