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Arsenic Exposure and Cardiovascular Disease: Evidence Needed to Inform the Dose-Response at Low Levels

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Abstract

Purpose of Review Epidemiologic and experimental evidence support that exposure to moderate-to-high arsenic (As) is a cardiovascular disease (CVD) risk factor. Little is known, however, on the cardiovascular effects of low water As exposure (< 10 μg/L) through diet, particularly rice. The goal is to summarize the evidence on As and CVD and the research needs at low levels of exposure.

Recent Findings Studies of populations in Taiwan, Chile, and Bangladesh have consistently shown that high water As (> 100 μg/L) constitutes a CVD risk factor. In experimental studies, chronic inorganic As in drinking water increased atherosclerotic lesions in mice. Cohort studies at low-to-moderate levels of exposure (< 100 μg/L) based on biomarkers or individual water As measures in American Indian from rural communities and in Whites and Hispanics from Colorado found higher risk of CVD incidence and mortality, particularly coronary heart disease (CHD) among those with higher arsenic exposure.

Summary A major limitation of existent dose-response meta-analyses is the limited number of studies in populations exposed to water As at levels < 10 μg/L. Measuring metals, in particular arsenic, in general populations with comprehensive assessment of clinical cardiovascular disease can inform on the cardiovascular role of low-level arsenic and contribute to CVD prevention and control in general populations.

Keywords Arsenic · Cardiovascular disease · Dose-response · Epidemiologic evidence

Introduction

Increasing evidence indicates that metals and metalloids are risk factors for clinical cardiovascular disease (CVD) [1–5]. However, evidence from population-based prospective cohort studies, which are the basis for CVD prevention and control programs in the USA, is lacking. This is particularly true for arsenic (As), for which most of the evidence comes from populations exposed to high water levels internationally (generally > 100 μg/l) [6–9] and to moderate water levels in rural areas in the USA (generally 10–100 μg/l) [10••, 11••]. The significant findings in those international and rural US studies, the relevance of dietary As exposure, and experimental evidence showing increased atherosclerosis even at relatively low levels [12] support the need to investigate the association between As and CVD in populations living in urban settings.

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Prospective cohort studies in general populations with data on subclinical and clinical CVD, wide geographical coverage across US regions, multi-ethnic inclusiveness, and comprehensive characterization of CVD risk factors, covering traditional, environmental, and social risk factors (e.g., air pollution) are needed. Indeed, while low-level As exposure is widespread, very few studies have characterized the potential cardiovascular effects at those low levels.

Methods

In this review, we summarized a large body of literature on the role of arsenic and CVD with a particular focus on the evidence available at low-moderate levels of exposure. We first review the sources of As exposure at low levels and the role of cooking and eating practices across different ethnics groups in general populations. Second, we discuss the evidence on As as a CVD risk factor, the relevant mechanisms, and the shape of the dose-response. Third, we discuss particular challenges when conducting research at low-level As exposure, in particular the challenge of interpreting total As and some As species in the presence of seafood intake and how to address this challenge. Finally, we discuss the research needs for general populations and present an overall conclusion. The manuscripts identified for this review have been compiled over many years by the study investigators through systematic reviews and ongoing systematic searches of the literature using both free text and indexed terms including arsenic, arsenite, arsenate, methylated arsenic species, arsenic poisoning, cardiovascular disease, coronary heart disease, stroke, and other terms.

Sources of Arsenic Exposure in General Populations

Inorganic As (iAs) is a potent [13] toxic and carcinogenic metalloid widespread in the environment. It is found in water, soil, food, and air. Groundwater contaminated with iAs affects populations worldwide, including 5 million people in the USA with water above the EPA standard (10 μg/l) [14]. In populations exposed to water As < 10 μg/l, diet contributes to up to 85% of iAs exposure [15, 16•]. Arsenic enters the food chain from contaminated soil and water, industrial contamination, and past use of As pesticides [16•, 17–19]. Rice is a major source of iAs and dimethylarsinate (DMA) because it accumulates in the grain (Fig. 1) [20–25]. USA-grown rice is particularly high in As. In a US population, consuming ½ cup of cooked rice was estimated to be equivalent to drinking 1 L of water at 10 μg/l [26]. Fruit juice, especially apple, pear, and grape concentrates, can have relatively high iAs levels [16•, 27]. Poultry was a source of iAs and other species before the recent ban of As-based drugs in poultry production (chicken in 2013, turkey in 2015) [28–30, 31•]. Foods that contain lower levels but are consumed in high quantities such as wheat and non-rice cereals can also contribute to exposure [16•]. Seafood is generally low in iAs but contains high levels of arsenobetaine, arsenosugars, and arsenolipids, which have low toxicity but complicate exposure assessment [32–34]. Air pollution can also contribute to iAs exposure, although it has been less studied [35–37]. Given the complexity of exposure sources, epidemiologic studies of low-chronic As exposure must rely on established biomarkers and sensitive methods such as urinary arsenic with low limits of detection.

Cooking and eating preferences differ greatly by racial/ethnic groups and can impact arsenic exposure. It is estimated that rice and rice products contribute to 80.4%, 64.2%, and

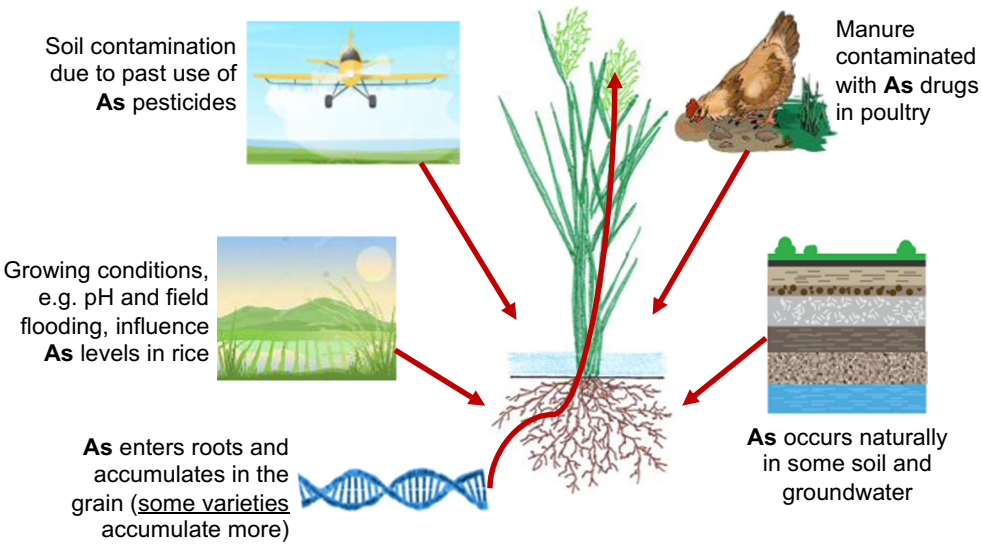

Fig. 1 Sources and reasons of arsenic (As) contamination and accumulation in rice

41.7% of dietary As (excluding seafood) for Asian Americans, non-Mexican-American Hispanics, and non-Hispanic Whites, respectively; while cereals contribute to 1.8%, 9.0%, and 25.0% [27]. Asians also have the highest dietary As exposure (0.11 μg/kg/day) followed by non-Mexican-American Hispanics (0.07), Mexican-Americans (0.06), and non-Hispanic Blacks and Whites (0.05) [38•]. In our pilot in the Multi-Ethnic Study of Atherosclerosis (MESA), Chinese-Americans and Hispanics were disproportionately exposed to As compared to Blacks and Whites. Little is known, however, about the long-term health effects of dietary As and if some racial/ethnic groups are disproportionately affected. Studies with racial/ethnic diversity, for instance MESA, are ideal to assess the long-term cardiovascular effects of low-chronic As exposure, primarily from food.

Evidence on Arsenic as a CVD Risk Factor

Epidemiologic Evidence Studies of populations in Taiwan [8, 39, 40], Chile [6], and Bangladesh [7, 41] have consistently shown that high water As (> 100 μg/l) constitutes a CVD risk factor (Fig. 2). Occupational studies that account for healthy worker effects support this finding [42], as well as experimental studies showing that chronic iAs in drinking water increased lesions covering the aortic intima compared to unexposed mice [12, 43, 44]. Of note, iAs concentrations as low as 10 μg/l increase atherosclerotic lesion in apolipoprotein E knock-out (apoE$^{-/-}$) mice (Fig. 3) [45••]. These data suggest that humans might be susceptible to even lower As concentrations, considering that mice methylate and excrete As at much higher rate than humans [46]. Early epidemiologic CVD research of low-to-moderate As (< 100 μg/l) was limited by ecological designs [47, 48], inconsistent findings [9, 49], or lack of statistical power [7]. In contrast, cohort studies based on biomarkers or individual water As measures in rural American Indian communities from Arizona, Oklahoma, and North and South Dakota (Strong Heart Study [SHS]) [11••] and in White and Hispanic communities from rural Colorado (San Luis Valley Diabetes Study [SLVDS]) [10••] found statistically significant associations with CVD incidence and mortality, particularly coronary heart disease (CHD). In the SHS, the association of As with incident CVD was attenuated after adjustment for hypertension and diabetes, supporting the idea that some of these risk factors may link As and CVD. In experimental and epidemiological studies, As at moderate-to-high levels has also been associated with subclinical outcomes including carotid intima media thickness (CIMT) [50, 51], plaque score [52••], and CVD risk factors such as hypertension [53–55], diabetes [56, 57], and electrocardiographic abnormalities (prolonged QT-interval) [58–60], although the findings are not entirely consistent.

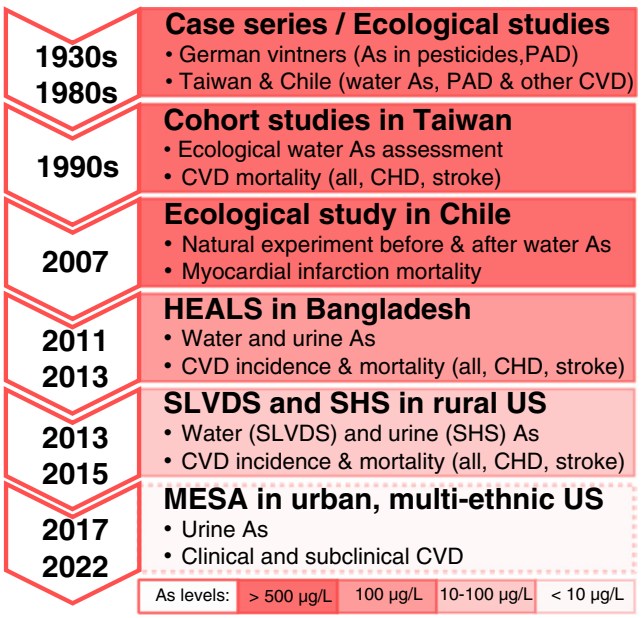

Fig. 2 Highlights of epidemiologic studies on arsenic (As) and cardiovascular disease. The MESA study is ongoing. Abbreviations: HEALS, health effects of arsenic longitudinal study; SLVDS, San Luis Valley Diabetes Study; SHS, strong heart study; MESA, multi-ethnic study of atherosclerosis

Mechanistic Evidence The health effects of As may occur via numerous pathophysiological pathways (Fig. 4), influenced by exposure levels, genetic variants, As metabolism, and nutritional status [58, 61]. Elevated pro-inflammatory cytokines and markers of oxidative stress were detected in plasma, serum, and atherosclerotic lesions of As-treated vs. untreated mice [44]. In mouse models, As interferes with cholesterol homeostasis and functions of macrophage and induces upregulation of inflammatory signaling, enhanced oxidative stress, activation of nuclear factor-κB, and inhibition of NO availability [62–67]. These effects can promote proliferation of endothelial cells and smooth muscle cells, cell adhesion, platelet aggregation, and arterial vasoconstriction [64, 68, 69]. Many of these mechanisms have been evaluated at high levels, although in a recent relatively small study in a population from New Hampshire (n = 415) exposed mostly to water As < 10 μg/L, urinary As was associated with 15-F2t-Isoprostane, a biomarker of oxidative stress [70••]. Neovascularization, angiogenesis, and vessel remodeling have been shown at As levels even below the current water standard [68, 71, 72]. Relatively specific effects of As exposure in animal experiments are cardiac electrophysiology changes, specifically QT prolongation, a risk factor for sudden cardiac death [60, 73, 74]. Prolonged QT-interval is also a common secondary effect of As trioxide, a treatment for promyelocytic leukemia [75–77], consistent with epidemiologic findings [60]. Toxic effects of As may also be

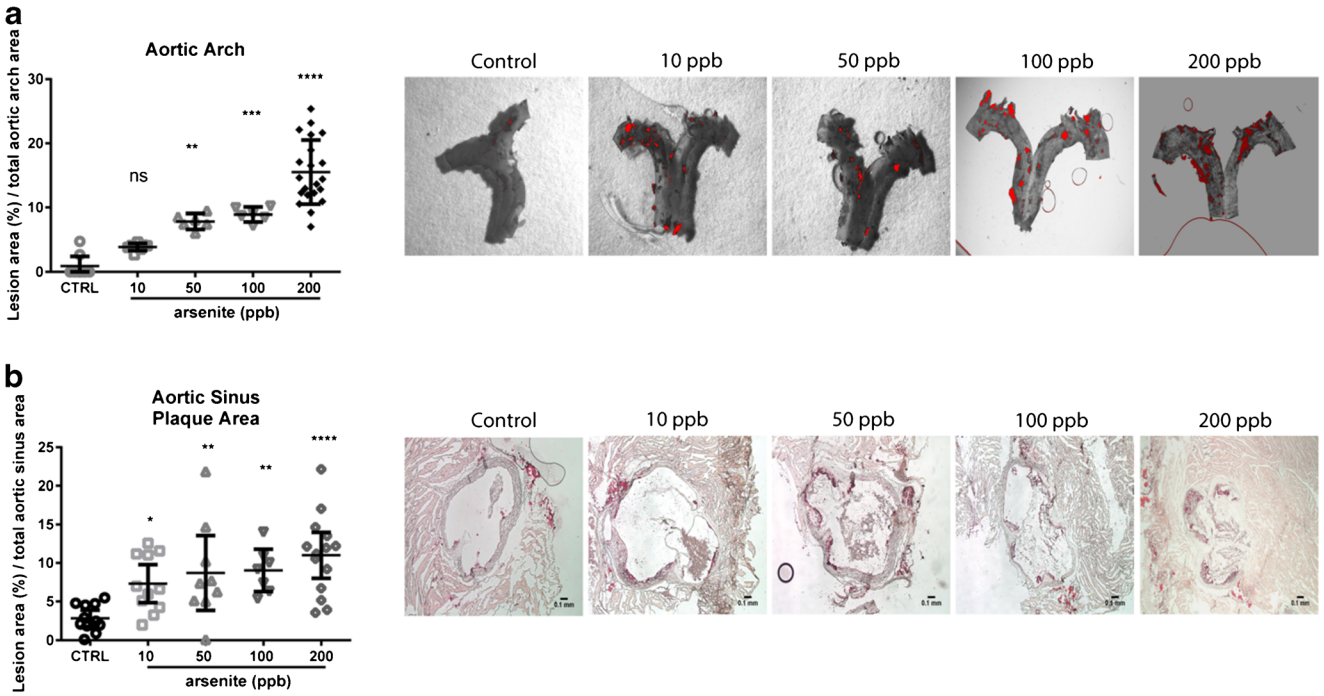

Fig. 3 Low arsenic concentrations increase the size of atherosclerotic plaques dose-dependently. ApoE^{−/−} mice were given tap water or 10–200 ppb arsenic in the drinking water for 13 weeks. Plaque was quantified in the aortic arch (**a**) or aortic sinus (**b**) after oil red O staining and imaging. Statistical significance from control is represented as follows: $*p < .05$; $**p < .01$; $***p < .001$; $****p < .0001$. (Figure reproduced from Makhani K et al., Using the Apolipoprotein E Knock-Out Mouse Model to Define Atherosclerotic Plaque Changes Induced by Low Dose Arsenic Toxicol Sci. 2018;166(1):213–218, with permission from Oxford University Press).

mediated through epigenetic mechanisms, including DNA methylation (DNAm) [78–81]. In addition to experimental studies, human studies with markers of these pathways are available and have been associated with CVD outcomes, providing the opportunity to assess relevant mechanisms of low-chronic As in an epidemiological setting.

Shape of the Dose-Response The shape of the dose-response across low-moderate and high As levels with CVD is uncertain but critical for As risk assessment [82••]. In the SHS, urine As levels > 10 μg/g creatinine (or 10 μg/L in a sensitivity analysis standardized by specific gravity) were associated with higher risk of CVD incidence and mortality [11••]. Below 10 μg/g, however, the shape was inconsistent, showing a potential linear association for incident total CVD and stroke but a possible threshold for incident CHD, although for all outcomes, the confidence intervals were consistent with multiple shapes. In a dose-response meta-analysis of prospective studies of As and CVD, the pooled relative risks (95%CI) for a twofold increase in As levels were 1.11 (1.05, 1.17) (number of studies = 4) and 1.16 (1.07, 1.26) ($n = 6$) for CHD incidence and mortality, respectively [82••]. There was no evidence of non-linearity using flexible splines, although a non-linear dose-response could not be discarded due to low power (Fig. 4). The major limitation of the existing evidence is the lack of data below 10 μg/L in either water or urine. Ongoing measures of arsenic at low levels in the Multi-Ethnic Study of Atherosclerosis (MESA) can help address this gap and inform on the shape of the association with CVD at low chronic As exposure levels.

Important Aspects to Consider when Conducing as Research at Low Levels

Arsenic Exposure Assessment in the Presence of Seafood Measuring As at low levels requires highly sensitive methods. For example, the limit of detection (LOD) for iAs species in NHANES 2003–2010 was 10 times higher [31•] than the current LOD in the Trace Metals Core Laboratory at Columbia University (0.1 μg/L), resulting in a large proportion of the population being undetectable for several of the species (e.g., > 90% had undetectable iAs levels in NHANES [31•]). High sensitivity is thus critical for a successful study at low As levels.

Seafood intake represents another major challenge to assess As exposure in general populations. When seafood intake is low, the sum of iAs, MMA, and DMA in urine reflects As intake from drinking water, other dietary sources like rice and other sources (e.g. air pollution), and is an accepted biomarker of iAs exposure (Fig. 5) [83–85]. Rice may also contain DMA in addition to iAs, which is also excreted through urine. Seafood, including fish, shellfish, and seaweed are important sources of organic arsenicals (arsenobetaine, arsenosugars, and arsenolipids); however, these species have low toxicity

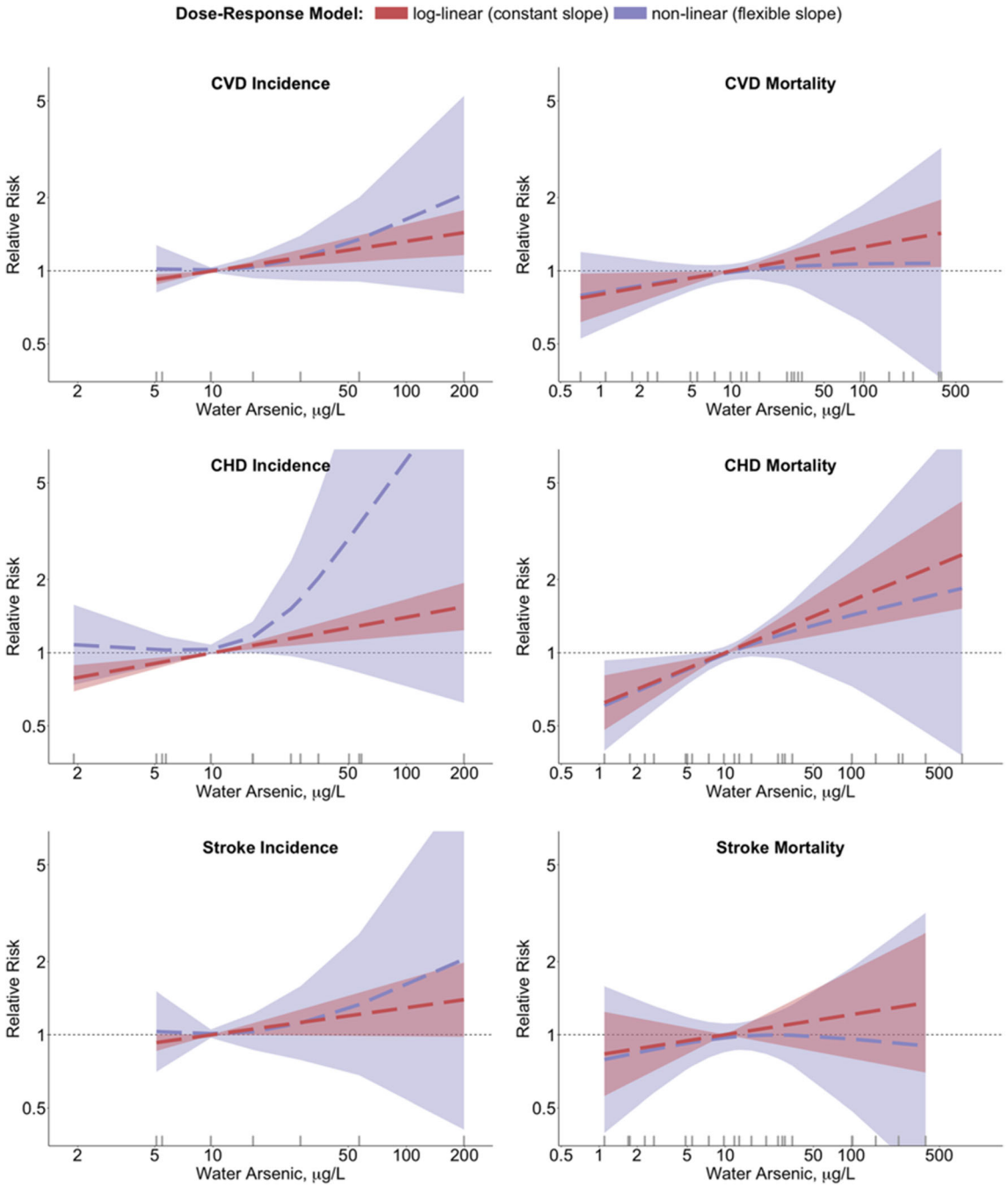

Fig. 4 Dose-response meta-analysis showing pooled log-linear and non-linear relative risks of incident overall cardiovascular disease, coronary heart disease, and stroke in relation to estimated water arsenic. Pooled linear (red) and non-linear (blue) relative risks of CVD endpoints (overall CVD, CHD, and stroke, stratified by studies of incidence and mortality) were estimated for drinking water arsenic concentrations in reference to 10 μg/l. Dashed lines correspond to pooled relative risks, and shaded regions correspond to the 95% confidence intervals of the pooled relative risks. Log-linear associations were estimated from models with log-transformed estimated water arsenic concentrations. Non-linear associations were estimated from models with restricted cubic splines of log-transformed estimated water arsenic concentrations with knots at the 10th, 50th, and 90th percentiles of log-transformed arsenic (exact knot locations vary by model; for CHD incidence, knots were placed at 5.1, 20.5, and 58.7 μg/l). A rug plot along the x-axis provides the median estimated water arsenic concentrations included in each model. (Reproduced from: Moon KA et al. A dose-response meta-analysis of chronic arsenic exposure and incident cardiovascular disease. Int J Epidemiol. 2017;46 (6):1924–1939, with permission from Oxford University Press)

[33, 86–88]. Arsenobetaine (which can be simultaneously measured with iAs, MMA and DMA) is rapidly cleared from the blood stream, excreted unchanged via the kidneys and contributes to total urine As [89–91]. In murine models, iAs, MMA, and DMA, but not arsenobetaine, increased atherosclerotic lesions [92••]. Seaweed, mollusks (e.g., scallops,

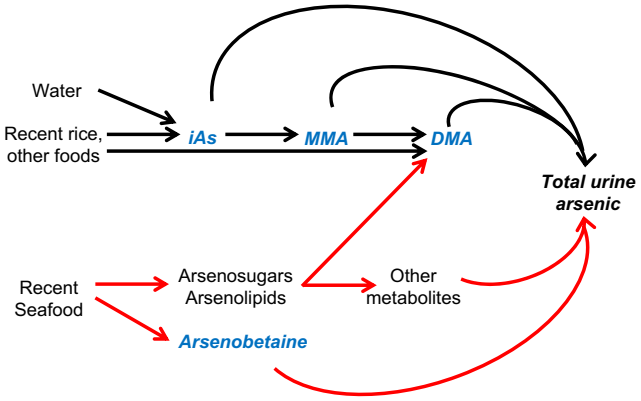

Fig. 5 Arsenic exposure, metabolism, and urine biomarkers. Other sources of arsenic (occupational settings and air pollution) are not shown. Urine arsenic species commonly measured in epidemiologic studies are marked in blue. Red arrows reflect how adjusting for arsenobetaine and extracting model residuals can control the contribution of seafood arsenicals to DMA and total arsenic. (Adapted from Jones MR et al. Estimation of Inorganic Arsenic Exposure in populations with frequent seafood intake: evidence from MESA and NHANES. AJE 2016;184 (8):590–602, with permission from Oxford University Press)

mussels), and fatty fishes are rich in arsenosugars and/or arsenolipids that are metabolized to As species such as DMA and dimethylated thiol As species [29, 30, 32, 33]. Therefore, in populations with moderate-high fish intake, the sum of iAs, MMA, and DMA in urine cannot be used as a biomarker of iAs intake.

To address this important problem, which may explain the scarce number of epidemiologic As studies in general populations, we have developed and validated a method that estimates As exposure not derived from seafood by regressing iAs, MMA, and DMA on arsenobetaine and extracting the arsenobetaine-independent model residuals. The method results and validation have been published [93•]. The residuals reflect As not explained by arsenobetaine and likely by seafood intake. The method of residuals to obtain adjusted estimates has been extensively used in the literature [94–100]. To have As levels that represent concentrations after removing the impact of seafood, we added the mean of the corresponding As species (iAs, MMA, or DMA estimated from participants with low arsenobetaine [< 1 μg/L]) to the residuals, assuming that As not derived from seafood is similar in participants with low and high arsenobetaine [93•]. To validate that estimated biomarkers reflect iAs exposure but not seafood intake, we compared urine As levels by seafood and rice intake data from a FFQ and n-3 fatty acids. Self-reported seafood intake (Table 1), estimated n-3 fatty acids, and measured n-3 fatty acids were positively associated with the original urine As biomarkers but no longer associated with the estimated ones [93•]. The associations with self-reported rice intake, however, remained similar (Table 1). We replicated these findings for DMA in NHANES. These preliminary findings in MESA and the replication in NHANES support that the residual-based method estimates As exposure and metabolism for each participant not due to exposure from seafood, and therefore can be used to investigate the health effects of low-level As in populations with frequent seafood intake.

Understanding Determinants of As Metabolism and their Influence on CVD The toxicity of As depends on its metabolism, a process that is influenced by genetic determinants and relies on folate-dependent one-carbon metabolism (OCM) [101–105]. After exposure to iAs (arsenite and arsenate), As is methylated in the body by As (III) methyltransferase (AS3MT) to mono and dimethylated arsenicals (MMA and DMA) using s-adenosylmethionine (SAM) as the methyl donor [106, 107]. Mice lacking As3MT cannot methylate arsenic [108]. DMA, MMA, and iAs are excreted in the urine, with half-lives ranging from 2 days for DMA to 38 days for iAs [87]. SAM synthesis is dependent on OCM and is inhibited by homocysteine, a sensitive biomarker of OCM nutritional status, collectively reflecting the status of folate and other B vitamins required for OCM [109]. Moreover, nutritional manipulation of OCM has been shown to increase As methylation and to lower blood As concentrations [102, 110]. Other factors that influence As methylation efficiency include age, sex, smoking, and As exposure levels [106, 111–113]. The relative proportions of iAs, MMA, and DMA in urine in respect to their sum (iAs%, MMA%, and DMA%) serve as biomarkers of As metabolism. Patterns of As metabolism in urine that reflect inefficient methylation (e.g., higher MMA% vs. lower DMA%) have been related to higher risk of CVD

Table 1 Geometric mean ratio (95%CI) of urine arsenic levels (sum of iAs, MMA and DMA) by self-reported seafood and rice intake in MESA. (Results adapted from Jones MR et al. Estimation of Inorganic Arsenic Exposure in populations with frequent seafood intake: evidence from MESA and NHANES. AJE 2016;184 (8):590–602. with permission from Oxford University Press)

	By seafood intake			By rice intake		
Seafood/rice intake	*N*	Measured biomarker	Estimated biomarker	*N*	Measured biomarker	Estimated biomarker
≤ 1/month	60	1.00 (ref.)	1.00 (ref.)	42	1.00 (ref.)	1.00 (ref.)
2–4/month	159	1.27 (1.01, 1.59)	0.93 (0.78, 1.16)	105	1.27 (0.98, 1.63)	1.30 (1.04, 1.63)
≥ 2/week	91	1.93 (1.50, 2.48)	1.04 (0.83, 1.30)	162	2.16 (1.70, 2.75)	1.77 (1.43, 2.19)

[114–116]. Deletion of As3MT protects apoE$^{-/-}$ mice from arsenic-induced atherosclerosis [92••]. Candidate gene association studies [117–121], GWAS data from Bangladesh [103], and Metabochip data from the SHS [122] show that variants in *AS3MT* are strong predictors of As metabolic patterns in urine. *AS3MT* genetic variants are also associated with As toxicity [104]. Metabochip data, which provides fine mapping coverage of *AS3MT*, GWAS data, and plasma homocysteine—all available in MESA—will allow for a comprehensive assessment of genetic and nutritional factors that influence As metabolism and interact with As exposure on CVD outcomes.

Research Needs in General Populations

Little is known about the health effects of dietary, geographical, and racial/ethnic disparities in As exposure in the USA. Regarding geographical variability, As in community water systems in L.A. is relatively high compared to other cities (although still < 10 μg/L) (Table 2) [123]. In suburban areas of LA, St. Paul, and Chicago, private wells are also used as a source of drinking water (sometimes > 10 μg/L) [124]. In a pilot study in MESA, participants from LA had higher median As levels compared to other cities for most ethnic groups, supporting that water As in LA contributes to As exposure. Other Western US cities are affected similarly to LA [93•]. Findings from MESA can be relevant for general populations in the USA and other countries.

The extensive existing MESA resources, moreover, can be leveraged for As research, including genomic (GWAS and Metabochip), epigenomic (Illumina 450 K), OCM nutritional status (plasma homocysteine), dietary data (food frequency questionnaire (FFQ)), social and environmental factors (air pollution, geocoding, neighborhood characteristics), CVD risk factors (smoking, blood pressure, glycemia, lipids), and pathophysiological mechanisms (e.g., markers of inflammation, electrocadiographic findings) together with the well-characterized subclinical and clinical outcomes during continuous follow-up. Adding As exposure and metabolism data to MESA will allow us to evaluate a potentially important, modifiable CVD risk factor along with other outcomes relevant for

Table 2 Mean (max) water As levels (μg/L)

	Community water systems	Groundwater (USGS)
Los Angeles	2.6 (8.1)	4.8 (28.0)
New York	< LOD[a]	0.8 (5.6)
Baltimore	< LOD[a]	0.3 (0.7)
St Paul	< LOD[a]	1.7 (10.0)
Winston-Salem	< LOD[a]	0.9 (1.0)
Chicago	0.2 (1.0)	0.3 (5.0)

[a] Below limit of detection (mean and max)

As, including lung and kidney disease, and potentially cancer. The multi-element analytical technique to be used for urine As, moreover, facilitate the assessment of metal mixtures including metals related to CVD such as cadmium [125, 126], nickel, and tungsten [5].

Conclusions

The assessment of metals, in particular arsenic, in high-quality prospective cohort studies of vascular outcomes can provide relevant information for clinical, environmental, nutritional, and occupational CVD prevention programs. This is particularly of high need for arsenic, given the EPA's Integrated Risk Information System (IRIS) ongoing arsenic risk assessment and the lack of data at low levels of exposure. From a clinical perspective, this type of research can impact clinical strategies for CVD risk reduction, including the identification of individuals at risk of As exposure because they use private wells for drinking or rely on As-rich diets (e.g., celiac disease patients, certain racial/ethnic groups). From a risk assessment perspective, the US EPA has so far based the As drinking water standard on quantitative estimates of As cancer effects. An updated risk assessment is ongoing. The 2013 National Research Council committee on iAs recommended that the EPA give priority to the evaluation of CVD [127]. While there is strong evidence at As levels > 10 μg/L, data < 10 μg/L remain insufficient [9, 61, 82••]. These data are critical for informing decisions regarding water As standards, which are currently highly variable: the WHO and the US EPA standard is 10 μg/L while New Jersey's standard is 5 μg/L (the lowest in the USA). In addition, while the need to regulate As in food is agreed upon, the lack of data on health effects of dietary As makes regulation difficult [16•, 128, 129]. All current legislative actions for As in food are non-binding (e.g., As standards in juice and rice baby products are at different legislative stages). Assessing the dose-response relationship between As and CVD at low chronic As exposure, understanding mechanisms, and identifying environmental, genetic, and nutrition susceptibility factors can inform policies to protect the general population as well as susceptible subgroups.

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Compliance with Ethical Standards

Conflict of Interest Koren Mann reports grants from Canadian Institute of Health Research, during the conduct of the study. Ana Navas-Acien,

Tiffany R. Sanchez, and Miranda R. Jones each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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