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Arsenic Exposure and Cardiovascular Disease: An Updated Systematic Review

Katherine Moon, MPH[1], **Eliseo Guallar, MD, DrPH**[2,3,4], and **Ana Navas–Acien, MD, PhD**[1,2]

[1]Department of Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

[2]Department of Epidemiology and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

[3]Department of Cardiovascular Epidemiology and Population Genetics, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

[4]Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD

Abstract

In epidemiologic studies, high-chronic arsenic exposure has been associated with cardiovascular disease, despite methodological limitations. At low-moderate arsenic levels, the evidence was inconclusive. Here, we update a previous systematic review (*Am J Epidemiol* 2005;162: 1037–49) examining the association between arsenic exposure and cardiovascular disease. Eighteen studies published since 2005 were combined with 13 studies from the previous review. We calculated pooled relative risks by comparing the highest versus the lowest exposure category across studies. For high exposure (arsenic in drinking water > 50 μg/L), the pooled relative risks (95 % confidence interval) for cardiovascular disease, coronary heart disease, stroke, and peripheral arterial disease were 1.32 (95 % CI: 1.05–1.67), 1.89 (95 % CI: 1.33–2.69), 1.08 (95 % CI: 0.98–1.19), and 2.17 (95 % CI: 1.47–3.20), respectively. At low-moderate arsenic levels, the evidence was inconclusive. Our review strengthens the evidence for a causal association between high-chronic arsenic exposure and clinical cardiovascular endpoints. Additional high quality studies are needed at low-moderate arsenic levels.

Keywords

Arsenic; Cardiovascular disease; Meta-analysis; Systematic review

Introduction

Inorganic arsenic is a naturally occurring toxic metalloid found primarily in drinking water and food [1–3], with an estimated 100 million people worldwide exposed to arsenic at levels exceeding 50 μg/L [4, 5]. In epidemiologic studies, high-chronic arsenic exposure has been linked to cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, and

Corresponding author: Ana Navas–Acien, MD, PhD, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room W7513D, Baltimore, Maryland 21205, Phone: 410-502-4267, Fax: 410-955-1811, anavas@jhsph.edu.
Katherine Moon, MPH, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room W7604, Baltimore, Maryland 21205, Phone: 410-955-5952, kmoon@jhsph.edu
Eliseo Guallar, MD, DrPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 E. Monument Street, Room 2-639, Baltimore, Maryland 21205, Phone: 410-614-0574, Fax: 410-955-0476, eguallar@jhsph.edu

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peripheral arterial disease (PAD) [6, 7]. In particular, arsenic has been established as a cause of blackfoot disease, a form of PAD endemic to areas of Taiwan with extremely high levels of arsenic in drinking water [4, 8, 9]. Experimentally, arsenic exposure can induce atherogenesis and endothelial dysfunction in animal models [10–17]. Proposed mechanisms include up-regulation of inflammatory signals, enhanced oxidative stress, endothelial and smooth muscle cell proliferation, vessel remodeling, and apoptosis [10–12, 16, 17].

In 2005, we summarized the existing evidence on the relationship between arsenic and CVD in a systematic review [6]. We concluded that the evidence supported a role for chronic high-dose arsenic exposure in CVD development, although the magnitude of the association was uncertain, due to study heterogeneity and methodological limitations of the available studies. Few studies had been performed at lower levels of exposure, and the cardiovascular effects of chronic low-dose exposure to arsenic could not be established.

The association of arsenic exposure and CVD is an area of increasing research interest, and several studies have been published since the publication of our systematic review. The purpose of this paper was to update our previous systematic review of arsenic and CVD, and to provide quantitative estimates of the pooled relative risks for CVD associated with arsenic exposure.

Methods

Search Strategy, Study Selection, and Data Abstraction

We searched MEDLINE for epidemiological studies investigating the association between arsenic and CVD with the following free text and Medical Subject Headings (MeSH): “arsenic”, “arsenite”, “arsenate”, “arsenicals”, “arsenic poisoning”, “atherosclerosis”, “carotid artery diseases”, coronary artery disease”, “cardiovascular disease”, “myocardial infarction”, “stroke”, “cerebrovascular disorders”, “peripheral vascular diseases”, “peripheral arterial disease”, “blackfoot disease” and “mortality” (Online Resource 1). We included all studies assessing arsenic exposure either by environmental measures (e.g., water, air), biomarkers (e.g., urine, hair), or indirectly by residence in an arsenic-endemic area. We limited the search to clinical CVD, defined a priori as CHD (including myocardial infarction and ischemic heart disease), stroke (cerebrovascular disease, ischemic and hemorrhagic stroke), and PAD (lower-extremity peripheral arterial disease, diseases of the peripheral arteries, and blackfoot disease), as well as overall CVD. The search period was limited to May 1, 2005 until July 23, 2012 in order to capture articles not included in the previous systematic review [6]. The search had no language restrictions.

Two investigators (K.M. and A.N.A) reviewed all identified abstracts and excluded articles that met any of the following criteria (Online Resource 2): (a) No original research (i.e., reviews, editorials, non-research letters); (b) Non-human study; (c) Case report or case series; (d) No clinical cardiovascular outcomes (e.g., subclinical atherosclerosis); (e) No chronic arsenic exposure levels in general population settings (e.g., occupational exposure, acute arsenic poisoning, arsenic trioxide used as a chemotherapeutical agent, or lewisite). We further excluded two studies for which the date of exposure cessation was unclear [18,19], one study which reported arsenic as a percentage of total particulate composition but not arsenic concentrations [20], one study in which case selection was not independent of exposure status [21], and one study [22] that reported an analysis of CHD prevalence from subjects already included in the previous review, but with a smaller sample size than the previous reference [23]. One study [24] analyzed the same subjects as a study included in the previous review [25], but presented a new analysis on a subset of subjects with urine arsenic measurements, and therefore was considered a new study for the purposes of this review. Any discrepancies were resolved by consensus. A native speaker reviewed the full-

text of any non-English article that could not be included or excluded based on the initial abstract review. An additional manual review of the reference lists from key original research papers and review articles identified no additional studies. We assessed study quality according to the criteria adapted from Longnecker and colleagues [26], consistent with the previous systematic review [6].

Statistical Analysis

Available measures of association (e.g., odds ratios, prevalence ratios, hazard ratios, rate ratios, standardized mortality ratios) and their standard errors or 95 % confidence intervals (CI) were abstracted [8, 27–33] or derived [34–44] using the data reported in the publications [45]. Results presented separately for males and females were combined within each study. For studies with multiple exposure categories, we selected the comparison of the highest to the lowest exposure category. In two studies that reported only mean arsenic levels among cases and non-cases [35, 39, 40], we used the linear discriminant function method [45] to estimate the odds ratios associated with a unit increase in arsenic exposure. For these two studies, and for one study that reported the odds ratio per unit change in arsenic [41], we estimated the odds ratio associated with the difference between the 75^{th} and the 25^{th} percentiles of the arsenic distribution among non-cases, using the mean and standard deviation of arsenic levels reported in non-cases and assuming a standard normal distribution. For two studies that reported adjusted odds ratios and *p*-values but not 95 % confidence intervals, we calculated the 95 % confidence intervals from the adjusted *p*-values [36, 38]. For three cohort studies with external comparisons and multiple exposure categories, we estimated the within-cohort relative risks by comparing the standardized mortality ratios in high and low exposure groups [32•, 43, 44].

For descriptive purposes, we estimated pooled relative risks for CVD, CHD, stroke, and PAD, combining the measures of association from all studies identified in our updated search (Table 1) and in the previous systematic review (eight studies from high arsenic areas in Taiwan and five studies from other countries—Online Resource 3) [6]. Pooled relative risk estimates were calculated assuming an inverse variance-weighted random effects model [46, 47] separately for populations exposed to high arsenic levels (mean arsenic in drinking water > 50 g/L) and for populations exposed to low to moderate levels (mean < 50 g/L). We evaluated heterogeneity between studies using the I^2 statistic, which describes the total variability across all studies due to heterogeneity [48]. For CHD, stroke, and PAD, we also evaluated dose-response trends for each study with three or more exposure categories. Two studies, one found in this updated review [42] and one in the original review [49], could not be included in the pooled analyses, because they did not report enough data to calculate confidence intervals. For studies that presented results for both urine and water arsenic, we used urine arsenic for the pooled analysis and dose-response analysis [8, 25, 28••]. Similarly, for a study that reported results for both urine and hair arsenic, we used urine arsenic [39, 40].

We performed several sensitivity analyses, limiting the pooled analysis to cohort studies with internal comparisons, to cohort studies with external comparisons, to studies assessing arsenic exposure using levels in drinking water, and to studies assessing arsenic exposure using total arsenic levels in urine. Additionally, we tested for influential studies by omitting each study sequentially. Statistical analysis was performed with Stata software Version 12 (StataCorp, College Station, TX, USA) [50] and figures were created using the statistical package R (Version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria) [51].

Results

Study Characteristics

18 studies published since 2005 met the inclusion criteria (Table 1). Twelve studies were conducted in high arsenic exposure areas of Taiwan (5), Bangladesh (3), Chile (1), Inner Mongolia (2) and Pakistan (1), and six studies were conducted in low to moderate arsenic exposure areas in the U.S. (3), Japan (1), Slovakia (1), and Spain (1). Of 12 cohort studies, six used internal comparisons [27, 28••, 29•, 30, 31•, 33] and six used external comparisons [32•, 34, 37, 42–44]. Of the cohort studies with internal comparisons, four were prospective [27, 28••, 29•, 33] and two were retrospective [30, 31•]. The remaining six studies used case control [35, 39, 40] or cross-sectional designs [24, 36, 38, 41].

Most studies assessed arsenic exposure using indirect measures (e.g., living in high arsenic areas) [34, 37, 42, 44] or using environmental measures, such as arsenic in drinking water at the region/county/zip code/municipal/village level [24, 27, 31•, 32•, 36], at the household/individual level [28••, 29•, 30, 33, 38, 41], or in air [43]. Two of the studies measuring arsenic in drinking water calculated an arsenic exposure index accounting for duration of water consumption [24, 27]. Few studies measured biomarkers of arsenic exposure such as urine [24, 28••, 35, 40] or hair [39].

The CVD outcomes and methods of ascertainment also varied across studies. The majority of studies used mortality endpoints [27, 28••, 29•, 30, 32•, 33, 34, 37, 42–44], although several ascertained prevalent cases [24, 35, 36, 38, 41], one study used hospitalizations [31•], and one study identified incident cases [39, 40]. The studies with mortality endpoints used death certificates [27, 32•, 33, 34, 37, 42–44], verbal autopsy and medical records [28••, 30], and verbal autopsy alone [29•]. With respect to studies using prevalent endpoints, CHD was assessed by self-report [41], PAD was assessed with standard clinical criteria [24, 36] or with unspecified methods [35], and the only study assessing prevalent cases of CVD and stroke relied solely on self-report [38]. The only study with incident cases of CHD used standard clinical criteria for case assessment [39, 40].

Overall, most of the studies published since May 2005 did not fulfill important study quality criteria (Online Resource 4). Only nine studies measured arsenic at the individual or household level [24, 28••, 29•, 30, 33, 35, 38–41] and only four studies used objective diagnostic criteria [24, 31•, 36, 39, 40]. Only three studies, one for CHD [39, 40] and two for PAD [24, 36], used standard diagnostic criteria. All but two studies [35, 42] collected information on cardiovascular risk factors in addition to age, and all but five studies [34, 35, 37, 42, 43] adjusted for other cardiovascular risk factors in addition to age and sex. With respect to case control and cross-sectional studies, all but one study [39, 40] were based on prevalent cases, and only one indicated that interviewers were blinded to exposure status [24]. Only two cross-sectional studies indicated their overall response rates of 70 % [24] and 63 % [36].

Studies in High Arsenic Exposure Areas

Arsenic was associated with CVD, CHD and PAD in all studies conducted in high arsenic exposure areas, and it was associated with stroke in six of the seven studies (Table 1). Combining the studies in Table 1 [24, 27, 28••, 29•, 30, 33–40] with the studies from Taiwan summarized in the previous systematic review and in Online Resource 3 [23, 25, 52–58], the pooled relative risk estimates comparing the highest to lowest arsenic exposure categories were 1.32 for CVD (95 % CI: 1.05–1.67; p-heterogeneity = 0.098; I^2 = 43.9 %), 1.89 for CHD (95 % CI: 1.33–2.69; p-heterogeneity = 0.004; I^2 = 70.7 %), 1.08 for stroke (95 % CI: 0.98–1.19; p-heterogeneity = 0.001; I^2 = 74.4 %) and 2.17 for PAD (95 % CI: 1.47–3.20; p-heterogeneity < 0.001; I^2 = 87.7 %) (Table 2, Figure 1, Online Resource 5).

One study was particularly influential for stroke [37]; after omitting it, the pooled relative risk for stroke was 1.12 (95 % CI: 1.04–1.22). The relative risk estimates ranged from 1.22 [37] to 6.62 [40] for CHD (Figure 1), from 0.89 [37] to 2.69 [57] for stroke (Online Resource 5), and from 1.03 [37] to 5.80 [36] for PAD (Online Resource 5).

Among nine studies (four in the updated search and five from the previous review) conducted in high arsenic exposure areas that reported three or more exposure categories, two of three found a consistent dose-response trend for CVD [29•, 30] (data not shown) and all four found a consistent dose-response trend for CHD [23, 28••, 56, 58] (Figure 2). For stroke, three of four studies in high exposure areas [30, 57, 58] found that risk of stroke increased with increasing arsenic levels (Figure 2). For PAD, two of three studies in high exposure areas found a dose-response trend [24, 55] (Figure 2).

Studies in Low to Moderate Arsenic Exposure Areas

Combining the studies conducted in low-moderate arsenic exposure areas in Table 1 [31•, 32•, 41, 43, 44] with the studies summarized in the previous systematic review and in Online Resource 3 [59–62], the pooled relative risks comparing the highest to lowest arsenic exposure categories were: 1.06 for CVD (95 % CI: 0.99–1.14; p-heterogeneity < 0.001; I^2 = 93.4 %), 1.06 for CHD (95 % CI: 0.89–1.26; p-heterogeneity < 0.001; I^2 = 97.3 %), 1.07 for stroke (95 % CI: 0.96–1.20; p-heterogeneity < 0.001; I^2 = 90.9 %) and 1.13 for PAD (95 % CI: 0.77–1.66; p-heterogeneity < 0.001; I^2 = 91.8 %) (Table 2, Figure 1, Online Resource 5), with substantial between-study variability. The relative risk estimates ranged from 0.84 [62] to 1.54 [59] for CHD (Figure 1), from 0.69 [60] to 2.47 [31•] for stroke (Online Resource 5), and from 0.61 [60] to 1.58 [62] for PAD (Online Resource 5).

With respect to dose-response relationships, six studies (three in the updated search and three from the previous review) reported three or more arsenic exposure categories in low-moderate exposure areas. One of three studies found that increasing chronic arsenic exposure was associated with increasing risk of CVD (data not shown) [32•]. For CHD, stroke and PAD, only one study of four [59], one study of six [32•] and one study of two [62], respectively, found a dose-response trend (Figure 2).

Discussion

High Arsenic Exposure

High-chronic exposure to inorganic arsenic from drinking water is a public health problem affecting multiple countries around the world [4, 5, 63]. The recommended safety standard for arsenic in drinking water by the World Health Organization (WHO), the US Environmental Protection Agency (EPA), and the European Union is 10 μg/L. In other countries, such as Bangladesh, the safety standard is 50 μg/L. Arsenic levels well above 50 μg/L affect many populations worldwide, especially in rural areas where groundwater is contaminated with naturally occurring arsenic or with improperly disposed chemicals. Inorganic arsenic is an established carcinogen [1, 3] that may also play a role in the development of respiratory diseases [64], cardiometabolic diseases [65–67], and developmental and reproductive abnormalities [65].

As shown in this systematic review, studies from multiple countries in populations with different ethnic and sociodemographic backgrounds consistently found an association between high-chronic arsenic exposure and CVD. While in our 2005 systematic review evidence for high arsenic areas was limited to studies from Taiwan, in 2012 evidence was also available from Bangladesh, Chile, Inner Mongolia, and Pakistan. The pooled relative risk estimates comparing the highest to lowest arsenic exposure categories were at least moderate for CHD and PAD (1.89 and 2.17, respectively). After excluding an influential

study, the pooled relative risk for stroke was also statistically significant, but still relatively modest.

While the evidence on the association of arsenic and CVD at high exposure levels is compelling, several limitations in the evidence base need to be considered. Most early studies did not adjust for key CVD risk factors, and could not establish the independent role of arsenic. Adjustment for CVD risk factors has substantially improved in recent studies, and most of them adjust for risk factors beyond age and sex. Although six studies adjusted for measures of socioeconomic status, income, or education [28••, 29•, 30, 38–40], socioeconomic status and access to care remain potential confounding factors, given that contaminated water is more common in less affluent and underserved areas. Exposure assessment remains a major limitation. Since 2005, only nine studies measured arsenic at the individual or household level [24, 28••, 29•, 30, 33, 35, 38–41]. Lack of individual-level data may result in measurement error with underestimation of the true effect of arsenic. Environmental measures, however, may also be affected by ecologic biases and information biases that may under or overestimate the associations. Furthermore, assessment of CVD outcomes in most studies of arsenic in high exposure areas was also limited: CVD mortality was ascertained from death certificates or verbal autopsies in most studies. As a consequence, the burden of arsenic-induced CVD may have been substantially underestimated.

The consistency of the associations across different populations, the availability of prospective studies, the clear dose-response relationships, and the decrease in CVD mortality following arsenic reduction [18, 19, 37] all support that the association between high-dose arsenic exposure and CVD is causal. Experimental and mechanistic evidence, including enhanced oxidant signaling and vessel remodeling, provide additional support for a role of high-chronic arsenic exposure in CVD of atherosclerotic origin [10–12, 16, 17]. Overall, we conclude that current evidence is sufficient to infer a causal relationship between high-chronic arsenic exposure and CVD, although future studies with improved exposure and outcome assessment should provide a more complete picture of the burden of arsenic-induced CVD in high exposure areas.

Low and Moderate Arsenic Exposure

Less is known about arsenic-related health effects at arsenic levels in drinking water below the safety standards, which affect most populations worldwide. At those low-moderate arsenic levels in water, moreover, there are other relevant sources of inorganic arsenic including food and ambient air [2, 68]. Indeed, foods such as rice, grains and certain juices are increasingly recognized sources of arsenic for general populations [2, 69, 70].

Some [31•, 32•, 41–44, 49, 62], but not all [60, 61], studies conducted at low-moderate arsenic levels supported an association with increasing CVD risk. The studies were conducted in diverse geographic areas, including Japan, Slovakia, Spain, Hungary, and the United States. All studies published since 2005 reported positive associations, although the magnitude of the associations was relatively modest in most studies, and the pooled relative risks were all small and not statistically significant.

Non-statistically significant associations between low-moderate arsenic exposure and CVD outcomes should be interpreted within the context of the methodological limitations of the studies. Although eight cohort studies were available, only one had internal comparisons [60]. The other seven cohorts were ecological studies that allowed internal comparisons across high and low arsenic exposure categories [32•, 42–44, 49, 62]. Of the 11 studies with low-moderate arsenic exposure, only six adjusted for CVD risk factors beyond age and sex [31•, 32•, 41, 44, 59], and only three studies adjusted for income or education [31•, 32•, 41].

Regarding exposure assessment, only three studies measured arsenic exposure at the individual level (two studies used household drinking water arsenic [41, 59] and one used total urine arsenic without accounting for seafood arsenicals [61]). Outcome assessment was also limited. Mortality was based on death certificates in all cohort studies, and one cohort study of stroke endpoints included stroke hospitalization data to confirm diagnosis [31•]. Prevalent cases of CVD were based on self-report [41, 59], or the ascertainment method was not reported [61]. These limitations in exposure and outcome assessment may severely underestimate the association of low-moderate arsenic exposure with CVD outcomes.

Overall, we conclude that the evidence is insufficient to establish a causal relationship between low to moderate chronic arsenic exposure and clinical CVD. Given the high prevalence of low-moderate arsenic exposure from drinking water, food, and ambient air worldwide, prospective studies with high quality outcomes and arsenic assessment at the individual level are needed.

Occupational Studies

In addition to general populations, occupational studies can also provide useful evidence on the CVD effects of arsenic exposure. In 2005, we systematically reviewed the occupational evidence and concluded that methodological limitations precluded reaching conclusions in favor or against an association [6]. Since then, results from three cohorts of tin and copper workers exposed to inhaled arsenic and CVD mortality endpoints have been published [71–73]. All three studies found a consistently increased risk of stroke mortality among exposed workers compared to external reference populations, but results were inconsistent for CVD and CHD mortality [71–73]. The use of external comparisons, the healthy worker effect, uncertainties in exposure assessment and outcome assessment, and likely exposures to multiple toxicants limit the interpretability of these studies.

Other CVD Endpoints

In addition to clinical cardiovascular outcomes, chronic exposure to arsenic has also been associated with sub-clinical CVD markers and with CVD risk factors. In Southwestern Taiwan, cumulative arsenic exposure was associated with increased prevalence of carotid plaque and with increased intima media thickness [74], and in a small study in Bangladesh, the adjusted odds ratios for carotid intima media thickness > 0.75 mm were 2.1 (95 % CI 0.4–10.5) and 6.0 (95 % CI 0.5–80.7), comparing the highest to the lowest tertiles of well water and urine arsenic concentrations, respectively [75].

Increasing evidence also supports that arsenic may play a role in the development of a number of traditional CVD risk factors, including diabetes [67, 76] and hypertension [66], that could mediate at least in part the cardiovascular effects of arsenic. Arsenic exposure has also been related to markers of endothelial dysfunction and vascular inflammation. In Bangladesh, arsenic exposure was cross-sectionally and prospectively associated with plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) [77, 78].

An important recent development is the identification of an increase in the electrocardiographic QT duration associated with environmental levels of arsenic [79, 80]. Prolongation of the QT interval predisposes to malignant ventricular arrhythmias and is a risk factor for sudden cardiac death [81]. The association between arsenic and QT interval duration has been identified in general population studies from Bangladesh, Taiwan, Inner Mongolia, and the U.S. [79, 80, 82, 83]. In Southwestern Taiwan, chronic exposure to arsenic was associated with QT duration in a dose-dependent manner [84]. Importantly, the association of arsenic exposure with QT duration has also been established in areas of low

arsenic exposure. Indeed, in the Normative Aging Study, an interquartile range increase in toenail arsenic, a biomarker of long-term exposure to arsenic, was associated with a 3.8 millisecond increase in QT interval (95 % CI: 0.82–6.8) and a 2.5 millisecond increase in QTc (heart rate-corrected QT) interval (95 % CI: 0.11–4.9) [79]. No population study has evaluated the association of arsenic with the incidence of arrhythmias or with sudden cardiac death.

Emerging Research Questions

The evaluation of factors that influence individual susceptibility to arsenic-related CVD is an emerging research question. Arsenic methylation patterns [24, 85, 86], genetic polymorphisms [41, 87–89], and cigarette smoking [28••] could modify CVD risk in the presence of arsenic, but a systematic evaluation of these factors is needed. Differences by sex could also be important [90], although the studies that have evaluated sex differences in arsenic-related CVD showed similar patterns in men and women [34, 37, 39, 40, 44, 49, 53, 58, 60, 62].

Recently, epigenetic modifications have been proposed as potential mechanisms to explain health effects related to arsenic exposure [17, 91, 92]. High quality experimental and epidemiologic studies are needed to evaluate the contribution of arsenic exposure to epigenetic modifications such as DNA methylation and histone modifications and their potential mediation to CVD development.

Conclusions

This updated systematic review and meta-analysis strengthens the evidence for a causal association between high-chronic arsenic exposure and CVD, most clearly for CHD and PAD, and less strongly for stroke. At low-moderate arsenic levels, affecting most general populations, the evidence remains inconclusive due to methodological limitations of available studies. Given widespread low-to moderate arsenic exposure and the high burden of CVD worldwide, even a small risk is important. From a public health perspective, urgent measures are needed to protect millions of people worldwide from high-arsenic levels in drinking water. Arsenic mitigation interventions could substantially contribute to reducing CVD burden [18, 19, 37]. At low-moderate arsenic levels, high quality prospective studies including individual-level exposure assessment and standardized CVD outcomes are needed to understand the role of arsenic as a CVD risk factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CI	Confidence Interval
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
PAD	Peripheral Arterial Disease

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Papers of particular interest, published since 2009, have been highlighted as:

• of importance

•• of outstanding importance

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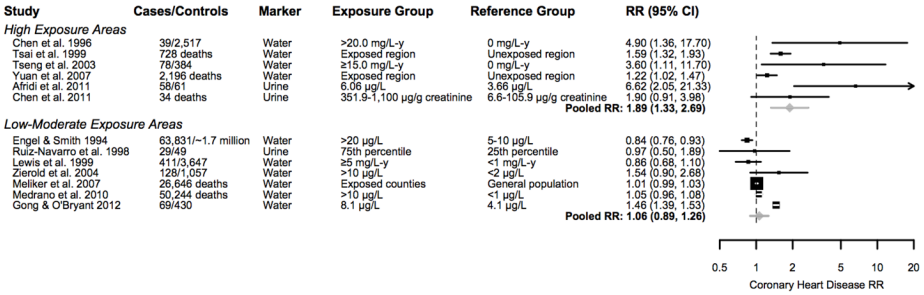

Fig. 1. Relative risks (RR) for coronary heart disease (CHD) comparing the highest to lowest arsenic exposure categories

The area of each black square (individual study) is proportional to the inverse of the variance of the estimated log relative risk. Horizontal lines represent 95 % confidence intervals.

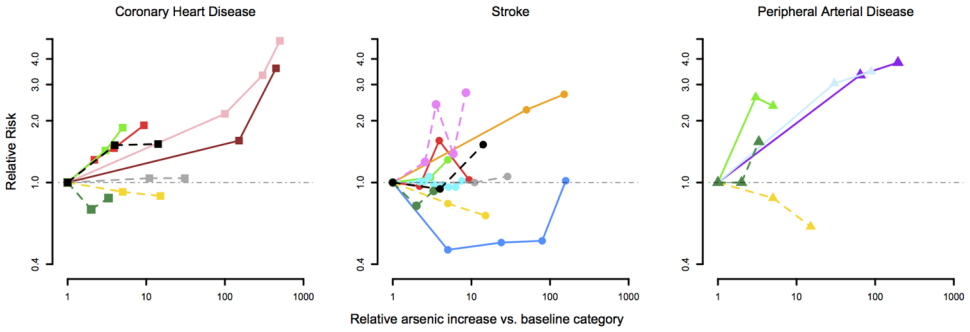

Fig. 2. Dose-response relationship of arsenic exposure and coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD)

Solid lines represent studies conducted in high exposure areas (Taiwan, Bangladesh, Chile, Inner Mongolia, and Pakistan) and dashed lines represent studies conducted in low to moderate exposure areas (U.S., Spain, Slovakia, Hungary, and Japan). Studies of CHD: Chen et al. 2011 [28••] (red); Tseng et al. 2003 [23] (light brown); Chen et al. 1996 [56] (light pink); Wu et al. 1989 [58] (light green); Medrano et al. 2010 [32•] (gray); Zierold et al. 2004 [59] (black); Lewis et al. 1999 [60] (gold); Engel & Smith 1994 [62] (dark green). Studies of stroke: Chen et al. 2011 [28] (red); Wade et al. 2009 [30] (blue); Chiou et al. 1997 [57] (orange); Wu et al. 1989 [58] (light green); Lisabeth et al. 2010 [31•] (pink); Medrano et al. 2010 [32•] (gray); Yoshikawa et al. 2008 [43] (turquoise); Zierold et al. 2004 [59] (black); Lewis et al. 1999 [60] (gold); Engel & Smith 1994 [62] (dark green). Studies of PAD: Tseng et al. 2005 [24] (purple); Wu et al. 1989 [58] (light green); Chen et al. 1988 [55] (light blue); Lewis et al. 1999 [60] (gold); Engel & Smith 1994 [62] (dark green). The reference categories were as follows: Chen et al. 2011 [28••]: 6.6–105.9 μg/g creatinine (urine); Wade et al. 2009 [30]: 0–5 μg/L; Tseng et al. 2005 [24]: 0 CAE (cumulative arsenic exposure) mg/L × year; Tseng et al. 2003 [23]: 0 mg/L-years; Chiou et al. 1997 [57]: <0.1 mg/L - year; Chen et al. 1996 [56]: 0 mg/L - years; Wu et al. 1989 [58]: <0.3 mg/L; Chen et al. 1988 [55]: 0 years; Lisabeth et al. 2010 [31•]: 0.3–4.5 μg/L; Medrano et al. 2010 [32•]: <1 μg/L; Yoshikawa et al. 2008 [43]: <0.77 ng/m^3; Zierold et al. 2004 [59]: <2 μg/L; Lewis et al. 1999 [60]: < 1 mg/L-year; Engel & Smith 1994 [62]: 5–10 μg/L.

Table 1

Studies of arsenic exposure and clinical cardiovascular disease outcomes (18 new studies available after 2005 systematic review)

Study, year	Design	Population	Men (%)	Age Range (yrs)	Arsenic Assessment	Exposed vs. Reference	Endpoint Ascertainment	Outcome (s)	No. of cases/non-cases	Relative Risk	95 % Confidence Interval	Adjustment Factors
Taiwan												
Liao 2012 [27]	CO (Int)	HAA (3 villages in SW Taiwan)	43.3	35–85	CEI from village well water levels	>14.7 vs. <17.4 ppm-y	Death Registry	CVD mortality	10 deaths	1.89	0.50–7.10	Age, sex, cigarette smoking, hypertension, diabetes, abnormal LDH elevation, Framingham CVD risk score, AST
Cheng 2010[a] [34]	CO (Ext)	HAA (SW & NE Taiwan)	56	>35	Village well water levels	HAA vs. general population	Death registry	Stroke mortality	8,867 deaths	1.11	1.07–1.14	Age, sex
Wu 2010 [33]	CO (Int)	HAA (NE Taiwan)	47	≥40	Household well water levels	50–300 vs. ≤50 μg/L	Death registry	CVD mortality	22 deaths	2.07	0.74–5.80	Age, sex, triglyceride, hypertension history, diabetes history, HO-1 genotype, and competing risk of death from malignant neoplasm or other specified causes
Tseng 2005[b] [24]	CS	HAA (3 villages in SW Taiwan)	45	≥30	Urine total arsenic & CEI from village well water	>64.33 μg/L urine vs. 0 mg/L-y CEI	ABI	PAD prevalence	54/425	3.84	0.86–17.25	Age, sex, BMI, alcohol drinking, cholesterol
Horng & Lin 1997[a] [35]	CC	HAA	53	NR	Urine total arsenic	>75th vs. <25th *p* (15.3 μg/L vs. 5.1 μg/L)	Blackfoot disease patients	BFD prevalence	32/32	1.85	1.43–2.40	—
Other high exposure areas (Bangladesh, Chile, Inner Mongolia, and Pakistan)												
Chen 2011 [28••]	CO (Int)	Araihazar, Bangladesh	NR	18–75	Baseline individual well water levels	>80th vs. <20th *p* (mean 266 μg/L vs. mean 3.7 μg/L)	Verbal autopsy, medical records	CVD mortality	106 deaths	1.46	0.96–2.20	Age, sex, education, BMI, smoking status
								CHD mortality	40 deaths	1.94	0.99–3.84	
								Stroke mortality	41 deaths	1.07	0.54–2.12	
					Baseline urine total arsenic levels (μg/g creatinine)	>80th vs. <20th *p* (mean 642 μg/g vs. mean 69 μg/g)		CVD mortality	90 deaths	1.55	1.01–2.37	
								CHD mortality	34 deaths	1.90	0.91–3.98	
								Stroke mortality	35 deaths	1.03	0.53–2.03	
Khan 2010[a] [36]	CS	1 village in Bangladesh	50	≥30	Village drinking water levels	>50 μg/L w/arsenicosis vs. <50 μg/L w/out arsenicosis	ABI	PAD prevalence	19/221	5.8	1.26–26.85	Age, sex, smoking, BMI, diabetes, blood pressure status
Sohel 2009 [29•]	CO (Int)	Matlab, Bangladesh	50	≥15	Household well levels	>300 vs. <10 μg/L	Verbal autopsy	CVD mortality	281 deaths	1.37	1.07–1.77	Age, sex, education, asset score (SES)
Yuan 2007[a] [37]	CO (Ext)	Regions of Chile in 1958–1970 (peak arsenic exposure in Region II)	NR	≥20	Approximate population-weighted drinking water levels	Region II vs. Region V	Death certificate	CVD mortality	6,164 deaths	1.01	0.88–1.17	Age, sex
								CHD mortality	2,196 deaths	1.23	1.00–1.45	
								Stroke mortality	1,624 deaths	0.89	0.78–1.00	
								PAD mortality	790 deaths	1.03	0.84–1.21	
Wade 2009[c] [30]	CO (Int)	Inner Mongolia (1 village)	50	0–>80	Household, shared, or community well levels	>300 vs. <5 μg/L	Verbal autopsy & medical record review	CVD mortality	152 deaths	2.47	0.50–12.18	Age, sex, education, smoking, drinking, and farm work
								Stroke mortality	54 deaths	1.02	0.16–6.71	
Xia 2009[a] [38]	CS	Inner Mongolia (1 village)	50	0 – >80	Household well levels	>300 vs. <5 μg/L	Self-report	CVD prevalence	269/3,038	1.72	0.81–3.67	Age, sex, education, smoking, household income, water source type, alcohol consumption
						Per 50 μg/L increase		Stroke prevalence	127/12,207	1.03	0.93–1.15	

Study, year	Design	Population	Men (%)	Age Range (yrs)	Arsenic Assessment	Exposed vs. Reference	Endpoint Ascertainment	Outcome (s)	No. of cases/non-cases	Relative Risk	95 % Confidence Interval	Adjustment Factors
Afridi 2010, 2011[a,d] [39,40]	CC	Hyderabad, Pakistan	57	45–60	Scalp hair total arsenic levels	75th vs. 25th p (1.28 μg/g vs. 1.14 μg/g)[e]	Coronary angiogram and at least one positive test of MI (stress text or echocardiography)	MI incidence	58/61	3.41	1.67–6.99	Age, SES
					Urine total arsenic levels	75th vs. 25th p (6.06 μg/L vs. 3.66 μg/L)[f]			58/61	6.62	2.05–21.33	
Low to moderate exposure areas (U.S., Spain, Slovakia, Japan)												
Gong & O'Bryant 2012[a] [41]	CS	3 rural counties (Texas, U.S.)	31	40–96	Estimated residential drinking water levels	75th vs. 25th p (8.1 μg/L vs. 4.1 μg/L)	Self-reported physician diagnosis	CHD prevalence	69/430	1.46	1.39–1.53	AS3MT genotype, ethnicity, age, gender, education, smoking, use of antihypertensive meds, alcoholism
Lisabeth 2010[f] [31•]	CO (Int)	27 zip codes in Genesee county (Michigan, U.S.)	50	≥ 45	Population-weighted average zip code drinking water levels	80th vs. 20th p (19–22.3 μg/L vs. 0.3–<4.5 μg/L)	Hospital inpatient database	Ischemic stroke hospitalizations	14,033 admissions	2.74	1.66–4.53	Age, sex, income, race
Medrano 2010 [32•]	CO (Ext)	651 municipalities in Spain	NR	>20	Municipal drinking water levels	>10 vs. < 1 μg/L	Death certificate	CVD mortality	158,419 deaths	1.03	0.98–1.08	Sex, age and the following provincial level variables: income, hospital beds, CV risk factors, dietary factors, and water characteristics
								CHD mortality	50,244 deaths	1.05	0.95–1.08	
								Stroke mortality	42,164 deaths	1.07	0.95–1.09	
Rapant 2009[a] [42]	CO (Ext)	1 region in Slovakia[g]	NR	NR	Mean groundwater levels	Exposed region vs. general population	Death certificate	CVD mortality	NR	1.08	NR	—
Yoshikaw a 2008[a] [43]	CO (Ext)	264 municipalities in Japan	47	NR	5-year average municipal environmental air levels	>90th vs. ≤10th p (≥2.70 ng/m^3 vs. <0.77 ng/m^3)	National health maps	CVD mortality	14,247 deaths	1.03	0.99–1.06	Age, sex
								Stroke mortality	13,596 deaths	1.02	0.98–1.05	
Meliker 2007[a] [44]	CO (Ext)	6 counties (Michigan, U.S.)	NR	≥35	Population-weighted county drinking water levels	6 counties vs. general population	Death certificate	CVD mortality	52,606 deaths	1.13	1.11–1.15	Age, sex, race
								CHD mortality	26,646 deaths	1.01	0.99–1.03	
								Stroke mortality	8,503 deaths	1.19	1.16–1.23	
								PAD mortality	2,549 deaths	1.03	0.97–1.08	

ABI: ankle-brachial blood pressure index; AST: aspartate aminotransferase; BMI: body mass index; CABG: coronary artery bypass graft surgery; CBVD: cerebrovascular disease; CC: case-control; CEI: cumulative exposure index = Σ arsenic levels in drinking water × time of exposure (i: specific village); CI: confidence interval; CO: cohort; CS: cross-sectional; CV: cardiovascular; DAAC: diseases of the arteries, arterioles, and capillaries; ECG: electrocardiogram; Ext.: external comparisons; HAA: High arsenic area; Int.: internal comparisons; LDH: lactate dehydrogenase; MI: myocardial infarction; NR: not reported; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; p: percentile; RR: relative risk; SES: socioeconomic status.

[a] RR and/or 95 % CI derived using the results reported in the original study.

[b] Tseng et al. 2005 [24] presented results from the same subjects as Tseng et al. 1996 [25], which was included in the previous systematic review by Navas–Acien et al. (2005) [6]. However, Tseng et al. 2005 presents a new analysis of PAD prevalence associated with urine total arsenic.

[c] Subset of residents exposed since 1990.

[d] Only including subjects with their first MI.

[e] Weighted average of 75th and 25th percentiles, by number of cases.

[f] The Genesee zip code analysis was selected over results from the entire state of Michigan; Genesee county has the highest levels of exposure and the results were presented in quintiles of exposure.

[g] Spišsko–Gemerské rudohorie Mountains (mean arsenic levels in drinking water: 13 μg/L)

Table 2

Pooled Estimated Relative Risk and 95% CI—All Studies[a]

		Pooled Estimated Relative Risk (95 % CI)			
Exposure Area	**Studies Included**	**CVD**	**CHD**	**Stroke**	**PAD[b]**
High Exposure Areas					
Overall[c]	[23,24,27,28••,29•,30,33–38,40,53–57]	1.32 (1.05–1.67)	1.89 (1.33–2.69)	1.08 (0.98–1.19)[d]	2.17 (1.47–3.20)
Internal comparisons	[27, 28••,29•,30,33,56]	1.46 (1.19–1.80)	2.62 (1.09–6.32)	1.03 (0.55–1.94)	--[e]
External comparisons	[34,37,53]	1.01 (0.88–1.17)	1.39 (1.07–1.80)	1.07 (0.95–1.20)	1.69 (0.62–4.63)
Urine arsenic	[24,28••,35,40,54]	1.55 (1.01–2.37)	3.25 (0.97–10.93)	1.03 (0.53–2.02)	1.86 (1.46–2.37)
Water arsenic	[23,25,27,28••,29•,30,33,36–38,55–57]	1.30 (1.04–1.62)	2.02 (1.33–3.07)	1.16 (0.98–1.37)	3.21 (2.27–4.53)
Low to Moderate Exposure Areas					
Overall	[31•,32•,41,43,44,59–62]	1.06 (0.99–1.14)	1.06 (0.89–1.26)	1.07 (0.96–1.20)	1.13 (0.77–1.66)

CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; PAD: Peripheral arterial disease. RR: relative risk.

[a] Excluding Rapant et al. 2009 [42] and Varsanyi et al. 1991 [49] because they did not report enough data to calculate confidence intervals.

[b] Includes peripheral arterial disease and diseases of the arteries, arterioles, and capillaries.

[c] If a study included results for multiple media, either urine and water arsenic (Chen et al. 2011 [28••] and Tseng et al. 1996 [25]/Tseng et al. 2005 [24]) or urine and hair arsenic (Afridi et al. 2010 [39]; 2011[40]), only the urine result was used in the overall pooled RR.

[d] After removing an influential study, the estimated pooled relative risk for stroke was 1.12 (95 % CI: 1.04, 1.22).

[e] No studies examined for this exposure level, study design, and outcome.