Review

Arsenic Exposure and Cardiovascular Disease: A Systematic Review of the Epidemiologic Evidence

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Arsenic exposure is a likely cause of blackfoot disease and a potential risk factor for atherosclerosis. The authors performed a systematic review of the epidemiologic evidence on the association between arsenic and cardiovascular outcomes. The search period was January 1966 through April 2005. Thirteen studies conducted in general populations (eight in high-arsenic areas in Taiwan, five in other countries) and 16 studies conducted in occupational populations were identified. Exposure was assessed ecologically in most studies. In Taiwan, relative risks comparing the highest arsenic exposure category with the lowest ranged from 1.59 to 4.90 for coronary disease, from 1.19 to 2.69 for stroke, and from 1.66 to 4.28 for peripheral arterial disease. In other general populations, relative risks ranged from 0.84 to 1.54 for coronary disease, from 0.69 to 1.53 for stroke, and from 0.61 to 1.58 for peripheral arterial disease. In occupational populations, relative risks ranged from 0.40 to 2.14 for coronary disease mortality and from 0.30 to 1.33 for stroke mortality. Methodologic limitations, however, limited interpretation of the moderate-to-strong associations between high arsenic exposure and cardiovascular outcomes in Taiwan. In other populations or in occupational settings, the evidence was inconclusive. Because of the high prevalence of arsenic exposure, carefully performed studies of arsenic and cardiovascular outcomes should be a research priority.

arsenic; arteriosclerosis; cardiovascular diseases; review [publication type]

Abbreviation: CI, confidence interval.

INTRODUCTION

Cardiovascular disease is the leading cause of mortality worldwide (1). Atherosclerosis is the most common pathologic process underlying cardiovascular disease, and it often manifests clinically as coronary disease, stroke, or peripheral arterial disease. Environmental toxicants have been suggested to play a role in atherogenesis (2). In particular, long-term exposure to arsenic, a documented poison and carcinogen, has been implicated as a risk factor for cardiovascular disease (3, 4).

Arsenic is likely to cause blackfoot disease, a severe form of peripheral arterial disease in southwestern Taiwan that is characterized by thromboangiitis obliterans, severe arteriosclerosis, and high arsenic levels in the arterial wall (3, 5–7). While epidemiologic studies conducted in Taiwan support a role for high chronic arsenic exposure in atherosclerosis (8, 9), data on other populations are scarce and results are

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inconclusive (8, 9). Because of the limited quantity and quality of the epidemiologic evidence, the US Environmental Protection Agency considered cardiovascular outcomes only qualitatively in risk analyses to establish the maximum contaminant level of arsenic in drinking water (10). To our knowledge, no systematic reviews or meta-analyses have summarized the evidence on the relation between arsenic and cardiovascular disease.

Our objective was to perform a systematic review and a meta-analysis of the epidemiologic evidence on the association of arsenic with cardiovascular disease. Because of the substantial heterogeneity in and methodologic limitations of the available evidence, we present a qualitative systematic review without quantitative pooling of study results.

METHODS

Search strategy and study selection

We searched MEDLINE and TOXNET for epidemiologic studies investigating the relation of arsenic with cardiovascular disease by using free text and the following Medical Subject Headings: arsenic, arsenite, arsenate, arsenicals, atherosclerosis, cardiovascular disease, myocardial infarction, stroke, peripheral vascular disease, peripheral arterial disease, and mortality. The search period was January 1966 through April 2005. There were no language restrictions. In addition, we manually reviewed the reference lists from relevant original research and review articles, as well as the investigators’ files.

We aimed to identify all studies assessing the relation between arsenic exposure determined using environmental measures (drinking water or airborne arsenic levels), biomarkers, or indirect measures (job titles or living in arseniasis-endemic areas) and clinical cardiovascular disease outcomes (including coronary disease, stroke, and peripheral arterial disease). Our exclusion criteria were: 1) publications containing no original research (reviews, editorials, nonresearch letters); 2) studies not carried out in humans (experimental studies); 3) case reports and case series; 4) studies lacking a clinical cardiovascular outcome (e.g., a study of subclinical atherosclerosis (11)); and 5) studies lacking data on arsenic exposure during adulthood (e.g., persons who had lived within 4 km of a smelter during childhood (12)) or studies of arsenic compounds for which human exposure is uncommon (e.g., lewisite (13)). Four case-control studies were excluded because cases and controls were selected on the basis of prior history of arsenic exposure (14–17). We also excluded a cohort of patients who had taken Fowler’s solution (potassium arsenite) between 1945 and 1969 in Lancashire, England (18).

When several papers had been published on the same population, the publication with the longest follow-up period was selected; when follow-up periods were equivalent, we...
selected the study with the largest number of cases, the study using internal comparisons, or the most recent publication. Figure 1 summarizes the study selection process.

In nonoccupational populations, arsenic exposure occurs mainly through drinking water, while in occupational settings, exposure usually occurs via inhalation. In addition to differences in the route of exposure, occupational studies usually also differ methodologically from nonoccupational studies. For this reason, we separated the analyses of studies conducted in general populations from those of studies conducted in occupational cohorts.

Data abstraction

Two investigators independently abstracted data from the articles that met the selection criteria. They resolved discrepancies by consensus. The following fatal and nonfatal cardiovascular outcomes were defined a priori: coronary disease (myocardial infarction and ischemic heart disease); stroke (cerebrovascular disease, ischemic and hemorrhagic stroke); and peripheral arterial disease (lower-extremity peripheral arterial disease, diseases of peripheral arteries, and blackfoot disease). We also included five occupational studies (19–23) and one general population study (24) that reported only total cardiovascular disease mortality.

To assess study quality, we adapted the criteria used by Longnecker et al. (25) for observational studies (figure 2).

Statistical analysis

Measures of association (odds ratios, prevalence ratios, standardized mortality ratios, relative risks, relative hazards, comparisons of means) and their standard errors were abstracted or were derived using data reported in the publications (26). Adjustment did not substantially modify the conclusions of individual studies. In the studies by Lin and Yang (27) and Ruiz-Navarro et al. (28), we used the linear discriminant function method to estimate relative risks from mean arsenic levels in cases and noncases (26). In the studies by Varsanyi et al. (24), Engel and Smith (29), Lewis et al. (30), and Xuan et al. (31), we estimated the within-cohort relative risks by comparing standardized mortality ratios in the highest category of exposure with those in the lowest.

Because drinking water arsenic levels were much higher in studies carried out in Taiwan than in other studies, we present data from Taiwan separately from data from other countries. For descriptive purposes, we report the range of relative risk estimates and the unweighted median values. For studies carried out in general populations (5, 14, 29, 30, 32–37) or occupational populations (38, 39) with published results for at least three exposure categories, we graphically present the dose-response trend in relative terms. A dose-response meta-analysis was considered inappropriate because of the heterogeneity in and methodologic limitations of the available studies.
<table>
<thead>
<tr>
<th>Location and study (authors, year, and ref. no.)</th>
<th>Design</th>
<th>Population</th>
<th>% men</th>
<th>Age range (years)</th>
<th>Arsenic assessment</th>
<th>Comparison (exposed vs. reference)</th>
<th>Endpoint ascertainment</th>
<th>Outcome(s) studied</th>
<th>No. of cases</th>
<th>No. of noncases</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Factors adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lin and Yang, 1988 (27)</td>
<td>Case-control</td>
<td>HAA*</td>
<td>NR*</td>
<td>NR</td>
<td>Urine (hydride AAS*)</td>
<td>75th percentile vs. 25th percentile</td>
<td>NR</td>
<td>BFD* prevalence</td>
<td>20</td>
<td>20</td>
<td>1.66</td>
<td>0.78, 3.51</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Chen et al., 1988 (36)</td>
<td>Case-control</td>
<td>HAA</td>
<td>49</td>
<td>&lt;50–60</td>
<td>Years of well-water consumption</td>
<td>≥30 years vs. 0 years</td>
<td>Clinical examination</td>
<td>BFD prevalence</td>
<td>241</td>
<td>759</td>
<td>3.47</td>
<td>2.20, 5.48</td>
<td>Age, sex, diet, family history of BFD</td>
</tr>
<tr>
<td>Tseng et al., 1996 (5)</td>
<td>Cross-sectional</td>
<td>HAA</td>
<td>45</td>
<td>Mean = 53</td>
<td>CEI*, from village drinking water</td>
<td>≥20 mg/liter-year vs. 0 mg/liter-year</td>
<td>Ankle-brachial blood pressure index</td>
<td>PAD* prevalence</td>
<td>69</td>
<td>513</td>
<td>4.28</td>
<td>1.26, 14.5</td>
<td>Age, sex, smoking, BMI, lipids, hypertension, DM*</td>
</tr>
<tr>
<td>Chen et al., 1996 (32)</td>
<td>Cohort (internal comparisons)</td>
<td>HAA</td>
<td>52</td>
<td>40–70</td>
<td>CEI from village drinking water</td>
<td>≥20 mg/liter-year vs. 0 mg/liter-year</td>
<td>Death certificate</td>
<td>CHD* mortality</td>
<td>39</td>
<td>2,517</td>
<td>4.90</td>
<td>1.36, 17.7</td>
<td>Age, sex, smoking, BFD, BMI, lipids, hypertension, DM</td>
</tr>
<tr>
<td>Chiu et al., 1997 (34)</td>
<td>Cross-sectional</td>
<td>HAA</td>
<td>50</td>
<td>40–70</td>
<td>CEI from village drinking water</td>
<td>≥5 mg/liter-year vs. &lt;0.1 mg/liter-year</td>
<td>Self-report + medical records</td>
<td>Stroke prevalence</td>
<td>139</td>
<td>7,963</td>
<td>2.69</td>
<td>1.35, 5.38</td>
<td>Age, sex, smoking, alcohol, hypertension, DM</td>
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<tr>
<td>Wu et al., 1989 (35); Tsai et al., 1999 (40)</td>
<td>Cohort (external comparisons)</td>
<td>HAA</td>
<td>35</td>
<td>All ages</td>
<td>Village drinking water level</td>
<td>HAA vs. general population</td>
<td>Death certificate</td>
<td>CHD mortality</td>
<td>728</td>
<td>deaths</td>
<td>1.59</td>
<td>1.32, 1.93</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Wang and Chang, 2001 (6)</td>
<td>Case-control</td>
<td>HAA</td>
<td>67</td>
<td>Mean = 63</td>
<td>Arterial tissue (AAS)</td>
<td>75th percentile vs. 25th percentile</td>
<td>Surgery</td>
<td>BFD prevalence</td>
<td>31</td>
<td>30</td>
<td>2.40</td>
<td>2.00, 2.89</td>
<td>(Crude)</td>
</tr>
<tr>
<td>Tseng et al., 2003 (33)</td>
<td>Cross-sectional</td>
<td>HAA</td>
<td>44</td>
<td>30–60</td>
<td>CEI from village drinking water</td>
<td>≥15 mg/liter-year vs. 0 mg/liter-year</td>
<td>Electrocardiogram</td>
<td>CHD prevalence</td>
<td>78</td>
<td>384</td>
<td>3.60</td>
<td>1.11, 11.7</td>
<td>Age, sex, smoking, BMI, lipids, hypertension, DM</td>
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<tr>
<td>Other countries</td>
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<tr>
<td>Varsanyi et al., 1991 (24)</td>
<td>Cohort (external comparisons)</td>
<td>12 villages (Hungary)</td>
<td>49</td>
<td>All ages</td>
<td>Village drinking water level</td>
<td>&gt;50 μg/liter vs. &lt;40 μg/liter</td>
<td>Death certificate</td>
<td>Cardiovascular disease mortality</td>
<td>NR</td>
<td>NR</td>
<td>Men: 1.19</td>
<td>Women: 0.82</td>
<td>Age</td>
</tr>
<tr>
<td>Engel and Smith, 1994 (29)</td>
<td>Cohort (external comparisons)</td>
<td>30 counties (United States)</td>
<td>43</td>
<td>0–65</td>
<td>County drinking water level</td>
<td>&gt;20 μg/liter vs. 5–10 μg/liter</td>
<td>Death certificate</td>
<td>CHD mortality</td>
<td>63,831</td>
<td>~1.7 million</td>
<td>0.84</td>
<td>0.76, 0.93</td>
<td>Age, sex</td>
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</tbody>
</table>

**Note:** NR = Not reported.
STUDIES IN GENERAL POPULATIONS

Study characteristics

Thirteen studies conducted in general populations (figure 1 and table 1) met our inclusion criteria. Eight studies were from Taiwan, three were from the United States, one was from Hungary, and one was from Spain. Of the cohort studies, two studies used internal comparisons (30, 32) and three used external comparisons (24, 29, 40). The remaining studies used cross-sectional (5, 33, 34, 37) or case-control (6, 27, 28, 36) designs. Studies ascertaining coronary disease used death certificates (29, 30, 32, 40), electrocardiographic criteria (33), and self-reported bypass surgery, angina, or heart attack (37). In one study, the diagnostic criteria for myocardial infarction were not specified (28). Studies ascertaining stroke used death certificates (29, 30, 40), self-reported stroke followed by review of medical records (34), or self-reported stroke exclusively (37). Studies ascertaining peripheral arterial disease used criteria for blackfoot disease (6, 27, 36), death certificates (29, 30, 40), or the ankle-brachial blood pressure index (5). One study ascertained total cardiovascular disease mortality (24).

Arsenic exposure was assigned on the basis of drinking water levels in most general population studies. Four studies from Taiwan (5, 32–34) and one study from the United States (30) created a cumulative arsenic exposure index (mg/liter-year) by multiplying the number of years of living in a specific village/area by the average arsenic level in drinking water in that village/area (usually measured at a single point in time). Other studies conducted in Taiwan assigned exposure on the basis of residence in an area with high arsenic levels in water (40) or number of years of drinking artesian well water (36). Three studies used village (24), county (29), or individual (37) drinking water arsenic levels. Only three studies used biomarkers of exposure: Two of them measured total urinary arsenic (27, 28) and the third measured arsenic in arterial tissue (6).

Quality assessment

Most of the 13 general population studies failed to fulfill important quality criteria (figure 2). Only four studies carried out in general populations assessed arsenic exposure at the individual level, and only three studies used biomarkers. Thus, arsenic exposure in most of these studies was based on geographic or other grouped or ecologic measurements. Furthermore, only two studies used standard criteria to diagnose cardiovascular disease, and only six studies had information on established cardiovascular disease risk factors.

For cohort studies, losses to follow-up were clearly independent of exposure in only two studies, and in no study was the intensity of the search for disease clearly independent of exposure status. For case-control and cross-sectional studies, data were collected in a similar manner in all study participants, with interviewers blinded to the case or exposure status of the participants in only three studies. Because of the lack of objective criteria, in only two studies was it possible to be certain that noncases would have been classified as cases if they had developed the disease. Finally,
none of the case-control studies were based on incident cases of disease.

Relative risk estimates

The relative risk estimates comparing the highest category of exposure with the lowest in each individual study for different cardiovascular outcomes are shown in table 1. Relative risks were higher in studies conducted in Taiwan than in studies conducted in other countries. In Taiwan, relative risks ranged from 1.59 to 4.90 (median, 3.60) for coronary disease, from 1.19 to 2.69 (median, 1.94) for stroke, and from 1.66 to 4.28 (median, 2.40) for peripheral arterial disease. In studies conducted outside of Taiwan, the ranges of relative risk estimates for coronary disease, stroke, and peripheral arterial disease were 0.84–1.54 (median, 0.92), 0.69–1.53 (median, 0.91), and 0.61–1.58 (median, 1.10), respectively.

Figure 3 presents the relative risk estimates for studies reporting results for three or more categories of arsenic exposure. The risks of coronary disease, stroke, and peripheral arterial disease generally increased with increasing exposure in studies from Taiwan (32–35). Risk trends in studies from the United States were inconsistent.

STUDIES IN OCCUPATIONAL POPULATIONS

Study characteristics

Sixteen studies carried out in occupational populations (figure 1 and table 2) met our inclusion criteria. The studies were conducted in copper smelters in the United States (39, 41), Japan (42), and Sweden (38); in mines and refineries in Japan (43), China (31), France (20), and the United Kingdom (44); in a power plant in the Czech Republic (23); in pesticide/insecticide industries in the United States (22, 45, 46); in a factory handling inorganic arsenic in the United Kingdom (19); and in the glass industry in Sweden (21) and Italy (47). In the mine/refinery study carried out in Japan (43), residents were also included because of evidence that arsenic contamination of soil, ambient air, and water had existed for at least 28 years. Similarly, the study by Nakadaaira et al. (48) included mostly residents living close to a dye factory that had contaminated drinking water for 5 years (1954–1959) with arsenic levels of 3,000 μg/liter (48).

All occupational studies reported only mortality data. The studies used death certificates to identify coronary and stroke deaths (11 studies), peripheral arterial disease deaths (one study), and overall cardiovascular disease mortality (five studies). Most occupational studies used external comparisons to derive standardized mortality ratios; the exceptions were one proportional mortality study (19), one case-control study (21), and four cohort studies with internal comparisons (31, 38, 39, 45). Exposure was ascertained mostly on the basis of job titles. Two studies assigned exposure on the basis of receipt of compensation for arsenic poisoning (43) and residence in a village with water contaminated by an industrial source (48). Several studies measured arsenic in urine or air to confirm exposure, but this information was not linked to cardiovascular outcomes (20, 22, 41, 45, 46). Only three studies created a cumulative exposure index (mg/m³-year) for each worker (31, 38, 39). Arsenic trioxide was the main chemical form of arsenic exposure in at least three studies (39, 41, 43), and it was also mentioned among other arsenicals in a fourth study (46).

Quality assessment

The occupational studies did not fulfill most of the prespecified quality criteria (figure 2). With the exception of four studies (31, 38, 39, 49), the reported effect estimates were based on age-adjusted standardized mortality ratios.
Relative risk estimates

Findings in the occupational studies were heterogeneous, with increased, decreased, and null relative risks (table 2). The relative risk estimates ranged from 0.40 to 2.14 (median, 0.83) for coronary disease and from 0.30 to 1.33 (median, 0.76) for stroke. Studies in the three copper smelters with a large number of cases (38, 39, 41) showed an increased relative risk for coronary disease, although the confidence intervals overlapped the null value. The study by Hertz-Picciotto et al. (39) also reported mortality data for peripheral arterial disease. The crude relative risk of peripheral arterial disease mortality for workers exposed to ≥20 mg/m³-year compared with workers exposed to less than 2 mg/m³-year was 3.46 (95 percent confidence interval (CI): 0.77, 15.5) (39).

The dose-response relation for coronary disease by cumulative airborne arsenic exposure was available in two studies (38, 39) (figure 4). Coronary disease mortality tended to increase with increasing cumulative exposure to arsenic, particularly after adjustment for the healthy worker survivor effect in the study by Hertz-Picciotto et al. (39). No clear trends were observed for stroke.

One study controlled for the healthy worker survivor effect by introducing a 20-year lag and adjusting for employment status in each year of follow-up (39). The relative risk of coronary disease mortality comparing copper smelter workers with ambient air cumulative exposure of ≥20 mg/m³-year with those with exposure of less than 0.75 mg/m³-year was 1.3 (95 percent CI: 0.87, 2.1) before adjustment for the healthy worker survivor effect and 1.5 (95 percent CI: 0.95, 2.5) after adjustment. After adjustment, the trend of increasing coronary disease mortality risk with increasing arsenic exposure was statistically significant (p trend = 0.003; figure 4). The corresponding relative risks for stroke mortality were 0.45 (95 percent CI: 0.18, 1.1) before adjustment and 0.67 (95 percent CI: 0.23, 1.9) after adjustment, with no consistent trend with increasing arsenic exposure.

DISCUSSION

Summary of findings

This systematic review revealed common limitations in the epidemiologic literature on arsenic and cardiovascular outcomes, including the use of indirect indicators of exposure rather than direct measurements, the uncertain comparability between exposed and unexposed participants, and the use of nonstandardized outcome definitions. These limitations added uncertainty to the association of high chronic arsenic exposure in drinking water with peripheral arterial disease and other cardiovascular outcomes identified in Taiwan. Moreover, in populations outside of Taiwan or in occupational populations, the epidemiologic evidence on the association between low-to-moderate arsenic concentrations and cardiovascular outcomes was inconclusive because of methodologic limitations.

General population studies

Taiwan. The association between arsenic in drinking water in southwestern Taiwan and blackfoot disease is probably causal (3, 7). This association is most evident at very high cumulative doses of arsenic, typically above 10 mg/liter-year (equivalent, for instance, to continuous exposure to 500 μg/liter of arsenic in drinking water for 20 years). A causal role of arsenic in peripheral arterial disease and angiitis is also supported by early reports from outside of Taiwan. From the 1930s to the 1950s, peripheral arterial disease and amputations were described among German vintners exposed to inorganic arsenic through the application of arsenical pesticides and intake of arsenic-contaminated wine (3, 49–52), including pathology reports of a combination of endangiitis and atheromatosis (52). In addition, long-term arsenic inhalation in occupational settings was associated with the Raynaud phenomenon (53, 54), an intermittent form of vasculitis characterized by digital paleness and low finger blood pressure on cooling that also occurs in thromboangiitis obliterans. Similarly, persons exposed to high levels of arsenic in drinking water (up to 1,790 μg/liter) in Inner Mongolia, China, showed an improved vascular response to cold stress 13 months after an intervention providing lower-arsenic drinking water (37 μg/liter).

To our knowledge, the pathologic characteristics of coronary disease and stroke associated with high arsenic exposure in southwestern Taiwan have not been described in the accessible literature. In Antofagasta, Chile, researchers who conducted histopathologic studies of children and young adults exposed to high levels of arsenic in drinking water (~600 μg/liter (55)) described fibrous intimal thickening of small and medium-sized arteries (56–58). Some of these children had electrocardiographic signs of myocardial infarction before death (57). In Taiwan, a dose-response pattern has also been reported associating arsenic exposure with carotid plaques and intima-media thickness, which are subclinical markers of atherosclerosis (11).

While high arsenic exposure in Taiwan may relate to cardiovascular disease, the magnitude of the associations is uncertain. The use of average drinking water levels and the lack of individual measures of arsenic make it possible to systematically underestimate exposure due to other sources in these areas, such as contaminated food and cooking water (8). In addition, other methodologic limitations may have a substantial impact on the magnitude of the associations. Because arsenic exposure was assessed at the village level, this ecologic association could be related to unmeasured confounders.

Other factors may limit the generalizability of the Taiwan findings even to high-arsenic areas. Exposure to high arsenic levels in drinking water in Taiwan occurred over a long period of time. Moreover, there may be differences in arsenic species to which populations were exposed (59), in other exposures (7, 59), in socioeconomic development, or in dietary deficiencies (such as carotenoids, selenium, or zinc.
<table>
<thead>
<tr>
<th>Study (authors, year, and ref. no.)</th>
<th>Country</th>
<th>Design (type of comparison)</th>
<th>Occupational population</th>
<th>% men</th>
<th>Age range (years)</th>
<th>Arsenic assessment (compound(s))</th>
<th>Comparison (exposed vs. reference)</th>
<th>Mortality outcome(s) studied</th>
<th>No. of cases</th>
<th>Duration of follow-up (years)</th>
<th>Age-adjusted relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradford Hill and Faning, 1948 (19)</td>
<td>United Kingdom</td>
<td>Proportional mortality</td>
<td>Factory with inorganic arsenic</td>
<td>100</td>
<td>&gt;20 at death</td>
<td>Job title (inorganic arsenic)</td>
<td>Workers vs. other workers</td>
<td>CVD*</td>
<td>393</td>
<td>33</td>
<td>0.73</td>
<td>0.45, 1.19†</td>
</tr>
<tr>
<td>Tokudome and Kuratsune, 1976 (42)</td>
<td>Japan</td>
<td>Cohort (external)</td>
<td>Copper smelter, Oita</td>
<td>100</td>
<td>42–76 at death</td>
<td>Job title (NS*)</td>
<td>Workers vs. general population</td>
<td>CHD*</td>
<td>7</td>
<td>22</td>
<td>0.47</td>
<td>0.22, 0.99</td>
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<tr>
<td>Mabuchi et al., 1980 (46)</td>
<td>United States</td>
<td>Cohort (external)</td>
<td>Pesticide manufacturer, Maryland</td>
<td>75</td>
<td>&lt;20–40 at time of hiring</td>
<td>Job title (lead arsenate, arsenic trioxide, sodium arsenite)</td>
<td>Workers vs. general population</td>
<td>CHD</td>
<td>76</td>
<td>31</td>
<td>0.90</td>
<td>0.72, 1.13</td>
</tr>
<tr>
<td>Bencko et al., 1980 (23)</td>
<td>Czech Republic</td>
<td>Proportional mortality</td>
<td>Coal-burning power plant</td>
<td>100</td>
<td>30–80 at death</td>
<td>Job title (NS)</td>
<td>Workers vs. other workers</td>
<td>CVD</td>
<td>101</td>
<td>18</td>
<td>0.88</td>
<td>0.58, 1.33†</td>
</tr>
<tr>
<td>Wingren and Axelson, 1987 (21)</td>
<td>Sweden</td>
<td>Case-control</td>
<td>Glass industry area</td>
<td>100</td>
<td>45–75 at death</td>
<td>Job title (NS)</td>
<td>Workers vs. general population</td>
<td>CVD</td>
<td>2,029</td>
<td>32</td>
<td>1.20</td>
<td>1.10, 1.40</td>
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<tr>
<td>Sobel et al., 1988 (22)</td>
<td>United States</td>
<td>Cohort (external)</td>
<td>Insecticide manufacturer, Michigan</td>
<td>100</td>
<td>NR*</td>
<td>Job title (lead arsenate, calcium arsenate, magnesium arsenate, copper acetarsenite)</td>
<td>Workers vs. general population</td>
<td>CVD</td>
<td>96</td>
<td>8</td>
<td>0.80</td>
<td>0.65, 0.98</td>
</tr>
<tr>
<td>Jarup et al., 1989 (38)</td>
<td>Sweden</td>
<td>Cohort (internal)</td>
<td>Copper smelter, Ronskar</td>
<td>100</td>
<td>&lt;20–&gt;80 at death</td>
<td>CEI*, † (µg/m³-year) with air monitoring and employee work history (NS)</td>
<td>CHD &gt; 100 mg/m³-year vs. &lt;0.25 mg/m³-year</td>
<td>CHD</td>
<td>437</td>
<td>39</td>
<td>1.12</td>
<td>0.64</td>
</tr>
<tr>
<td>Tsuda et al., 1990 (43)</td>
<td>Japan</td>
<td>Cohort (external)</td>
<td>Mine/refinery, Toruku (workers/residents)</td>
<td>50</td>
<td>Mean = 61</td>
<td>Compensated for arsenic poisoning (arsenic trioxide)</td>
<td>Workers vs. general population</td>
<td>CHD</td>
<td>7</td>
<td>17</td>
<td>2.14</td>
<td>0.77</td>
</tr>
<tr>
<td>Xuan et al., 1993 (31)</td>
<td>China</td>
<td>Cohort (internal)</td>
<td>Tin mine</td>
<td>86</td>
<td>Mean = 19 at time of hiring</td>
<td>CEI (mg/m³-year) with air monitoring (NS)</td>
<td>CHD &gt; 75th percentile vs. &lt;25th percentile</td>
<td>Stroke</td>
<td>8</td>
<td>0.40</td>
<td>0.30</td>
<td>0.17, 0.92</td>
</tr>
<tr>
<td>Simonato et al., 1994 (20)</td>
<td>France</td>
<td>Cohort (external)</td>
<td>Gold mine/ refinery</td>
<td>100</td>
<td>NR</td>
<td>Job title (NS)</td>
<td>Workers vs. general population</td>
<td>CVD</td>
<td>43</td>
<td>32</td>
<td>0.54</td>
<td>0.39, 0.73</td>
</tr>
<tr>
<td>Tollestrup et al., 1995 (45)</td>
<td>United States</td>
<td>Cohort (internal)</td>
<td>Orchard workers</td>
<td>66</td>
<td>8–55 at time of hiring</td>
<td>Job title (lead arsenate)</td>
<td>Workers vs. general population</td>
<td>CHD</td>
<td>45</td>
<td>1.27</td>
<td>0.82</td>
<td>0.72, 2.23</td>
</tr>
</tbody>
</table>

* CVD = cardiovascular disease, CHD = coronary heart disease, Stroke |
† Estimates limited to arsenic exposure; other arsenic exposure not considered.
Possible mechanisms for arsenic-related cardiovascular disease

The possibility that arsenic causes cardiovascular disease is supported by several biologic mechanisms. Arsenic can increase the production of reactive oxygen species like (27, 60) that may interact with arsenic. Differences among populations in the prevalence of functional polymorphisms in genes related to arsenic metabolism may also play a role (61–65).

Other countries. The cardiovascular effects of low chronic arsenic exposure are unknown. Studies from Taiwan are inadequate to address this question, because few subjects were exposed to low or intermediate levels in drinking water. Furthermore, studies from other populations with likely lower exposures, including the United States, are scarce and inconclusive (24, 28–30, 37).

Important common limitations include the uncertain comparability of exposure groups in terms of cardiovascular disease risk factors, socioeconomic development, and access to care; the use of cross-sectional or case-control designs based on prevalent cases; the lack of individual exposure assessment; and the lack of standardized criteria for diagnosing cardiovascular endpoints. The inconsistent associations between arsenic and cardiovascular outcomes in these studies cannot be interpreted as evidence of a lack of effect of arsenic. Because of the methodologic limitations of these studies, it is possible that even a substantial effect could have been undetected. High-quality prospective studies evaluating the association between long-term arsenic exposure and cardiovascular endpoints in populations with a varied range of exposures should be a public health research priority.
hydrogen peroxide (68, 69), hydroxyl radicals (70), and others (68). Lipid peroxidation increased significantly after 6 months of arsenic feeding in mice (71). Persons exposed to high arsenic in drinking water in Inner Mongolia had higher levels of lipid peroxides (72), and in Taiwanese subjects, blood arsenic was positively correlated with levels of superoxide radicals (73). The production of reactive oxygen species has been implicated as the initial step in arsenic-induced endothelial cell proliferation (68) and apoptosis (69, 74), two mechanisms proposed for arsenic-related atherosclerosis (73).

Arsenic may also induce alterations in nitric oxide metabolism and endothelial function (75, 76). Persons exposed to high-arsenic drinking water in Inner Mongolia had decreased serum and urine concentrations of nitric oxide metabolites (75, 76), and this association was reversed after an intervention provided lower-arsenic drinking water (76). In Mexican children from Región Lagunera, urinary arsenic levels were inversely associated with nitric oxide production in activated monocytes (77). In human endothelial cells, arsenite at concentrations of 1–25 μM inhibited endothelial nitric oxide synthase activity (78, 79), resulting in decreased cell growth. At concentrations below 1 μM, however, arsenite up-regulated the expression of constitutive nitric oxide synthase 3, and this mechanism was proposed as a possible explanation for arsenic-induced cell growth and angiogenesis (79).

In addition, inorganic arsenic up-regulates inflammatory signals (80, 81), releases tumor necrosis factor α from mononuclear cells (81), and stimulates cyclooxygenase-2 expression (82). An inflammatory component was also reported in studies exposing apolipoprotein E-deficient mice to arsenic in drinking water at 10,000–20,000 μg/liter for 18–24 weeks (83, 84). At these very high doses, arsenic accumulated in vessel walls, and plaques covering the intima were increased in size in comparison with unexposed mice (83, 84). Arsenic-treated mice had higher serum levels of leukotriene E₄ and prostacyclin (prostaglandin I₂) (84), and in vitro, arsenic induced the expression of genes coding inflammatory mediators, including interleukin-8 (83).

Arsenic may also induce atherosclerosis by enhancing arterial thrombosis and platelet aggregation (85, 86). Finally, arsenic exposure has been related to diabetes (87–89) and hypertension (90, 91), but these studies have often had significant methodologic limitations, and their findings have been inconsistent (37, 41).

While experimental studies suggest potential mechanisms for arsenic atherogenicity, their relevance to low or moderate arsenic exposures is uncertain, because these experimental studies were typically performed using high arsenic concentrations. Experimental studies using lower concentrations of arsenic are needed to identify mechanistic pathways for arsenic-induced atherosclerosis.

Quality of the evidence and limitations

Limitations in the assessment of exposure (often performed in an ecologic manner) and cardiovascular outcomes, the cross-sectional or retrospective nature of many studies, and the lack of adjustment for potential confounders, among other methodologic limitations, make it impossible to establish firm conclusions regarding the effects of arsenic on cardiovascular outcomes at concentrations lower than those observed in Taiwan. Similar methodologic limitations make it difficult to quantify the magnitude of the association in Taiwan. Unfortunately, the evidence on the association between arsenic and cardiovascular outcomes that is available from other areas with high arsenic levels in drinking water (in Chile, Argentina, Mexico, Bangladesh, and Inner Mongolia) is limited to uncontrolled case reports on cardiovascular endpoints (56, 58, 92), even though there are case-control studies of arsenic and cancer from these areas (93, 94). The lack of epidemiologic reports from these populations could be related to publication bias, but it could also reflect a lack of investigation.
Conclusion

The evidence from Taiwan is consistent with a role for high arsenic exposure in atherosclerosis, although the magnitude of the association is uncertain because of the methodologic limitations of the available studies. These cardiovascular effects, together with cancer, developmental and reproductive effects, and skin lesions, provide strong support for widespread efforts to reduce arsenic exposure (8). The cardiovascular effects of chronic low-dose exposure to arsenic are unknown, and current epidemiologic studies are inadequate to answer this question. It is becoming increasingly evident, however, that low-level chronic exposure to environmental pollutants may have important cardiovascular effects (2, 95–99), and it is plausible that low-level arsenic exposure also increases cardiovascular risk. Since low or moderate arsenic exposure is widely prevalent, even a small effect of arsenic on cardiovascular risk is potentially important. Carefully planned prospective studies in populations exposed to a wide range of arsenic levels, using individual biomarkers of arsenic exposure and standardized information on cardiovascular disease risk factors and outcomes, is a public health research priority.

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REFERENCES


