

## A review of the epidemiologic literature on the role of environmental arsenic exposure and cardiovascular diseases

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### Abstract

Cardiovascular disease is the leading cause of mortality worldwide. Arsenic is a ubiquitous metalloid in the crust of the earth. Chronic arsenic poisoning is becoming an emerging epidemic in Asia. Epidemiological studies have shown that chronic arsenic poisoning through ingestion of arsenic-contaminated water is associated with various cardiovascular diseases in dose–response relationships. These cardiovascular disorders include carotid atherosclerosis detected by ultrasonography, impaired microcirculation, prolonged QT interval and increased QT dispersion in electrocardiography, and clinical outcomes such as hypertension, blackfoot disease (a unique peripheral vascular disease endemic in southwestern Taiwan), coronary artery disease and cerebral infarction. Chronic arsenic poisoning is an independent risk factor for cardiovascular disease. The adverse cardiovascular effects of long-term arsenic exposure may be persistent and/or irreversible. Arsenic-induced cardiovascular diseases in human population may result from the interaction among genetic, environment and nutritional factors. The major adverse cardiovascular effect of chronic arsenic poisoning has been established qualitatively and quantitatively in the high arsenic exposure areas, but the low-dose effect of arsenic on cardiovascular diseases remains to be explored. Cardiovascular death is the major cause of mortality worldwide, and a small increased risk may imply a large quantity of excess mortality.

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### Introduction

Arsenic is a ubiquitous metalloid in the crust of the earth, and human exposure to inorganic arsenic is mainly through ingestion of drinking water contaminated with naturally occurring arsenic (World Health Organization, 1981). Chronic arsenic poisoning is becoming an emerging epidemic in Asia, and over 100 million people are exposed

to underground water with high concentration of arsenic (Chen et al., 1999). The magnitude of this arsenic catastrophe has projected to be the largest in history of environmental disaster that will be more serious than those at Chernobyl, Ukraine in 1986 and Bhopal, India in 1984 (Smith et al., 2000). In the United States, over 350,000 people are exposed to water contaminated with arsenic greater than 50 µg/L and over 2.5 million to water with arsenic greater than 25 µg/L (Nordstrom, 2002). Long-term exposure to ingested arsenic has been documented to induce various cancers and cardiovascular diseases (Chen et al., 1988a, 1988b). The maximum contamination level for arsenic in drinking water has been lowered from 50 to 10 ppb by the

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US Environmental Protection Agency (Smith et al., 2002). However, there remain debates on the scientific basis of this new regulatory standard and its adequacy for protection of public health.

Previous studies have reported the pleiotropism of arsenic-induced health effects including hypertension, diabetes mellitus, carotid atherosclerosis, impaired microcirculation, peripheral artery disease, coronary heart disease, stroke and various cancers is dose–response relationships. This review will focus on the cardiovascular effects (atherosclerosis, QT prolongation and dispersion, peripheral vascular disease, ischemic heart disease and cerebrovascular disease) and a look at gene–environment–nutrient interactions.

### Studies in general populations

Epidemiological studies conducted in Taiwan have demonstrated that long-term exposure to arsenic is associated with various subclinical and clinical outcomes of cardiovascular system including carotid atherosclerosis, peripheral vascular disease (PVD), ischemic heart disease (IHD), and cerebrovascular disease (CVD) showing a dose–response relationship. Increased risk of impaired microcirculation has also been observed in residents in the arseniasis-endemic area in southwestern Taiwan. In general populations, arsenic exposure occurs mainly through drinking water, whereas in occupational populations, exposure is mainly via inhalation. In studies of Taiwan, the range of relative risks of peripheral vascular disease (PVD), ischemic heart disease (IHD) and stroke were 1.7–4.3 (median, 2.4), 1.6–4.9 (median, 3.6) and 1.2–2.7 (median 1.9) respectively (Navas-Acien et al., 2005). However, studies conducted outside of Taiwan, the range of relative risks of PVD, IHD and stroke were 0.6–1.6 (median, 1.1), 0.8–1.5 (median, 0.9) and 0.7–1.5 (median, 0.9), respectively.

The strength of the studies conducted in Taiwan include internal comparisons within the studies, control for potential confounding by several traditional risk factors, accurate diagnosis of the cardiovascular endpoints, and a high participation (>70%) among the non-cases. Significant dose–response relationships were found between the drinking water arsenic level in Taiwan and various outcomes including carotid atherosclerosis, PVD, IHD and CVD. These risk trends are consistent irrespective of study design (e.g., case–control, cross-sectional and cohort studies). Limitations of the Taiwan studies include: group rather than individual measures of drinking water arsenic; lack of biomarkers to confirm arsenic exposure; and the underestimation of confounders such as contaminated food and cooking water. The exposure to very high arsenic levels may also limit the applicability of the findings in southwestern Taiwan to other populations, especially those with lower levels of arsenic exposure. The limitations of studies conducted in other countries include: the uncertain comparability of exposure, socioeconomic status, and access to health care among the groups studied; the use of prevalent rather than incident cases in cross-sectional or case–control

studies; and the inaccuracy of diagnosis of the cardiovascular endpoints.

### Arsenic and subclinical disorders in cardiovascular system

Long-term exposure to arsenic has been documented to be associated with several subclinical disorders in the circulatory system as shown in Table 1. Both carotid atherosclerosis detected by duplex ultrasonography and abnormal QT wave detected by electrocardiogram are associated with chronic arsenic poisoning in a dose–response relationship.

#### *Arsenic and carotid atherosclerosis*

A cross-sectional survey on the association between ingested arsenic via drinking water and carotid atherosclerosis assessed by duplex ultrasonography has been conducted in the arseniasis-endemic area in southwestern Taiwan (Wang et al., 2002). A total of 199 male and 264 female adult residents were recruited, and the severity and extent of atherosclerosis in extra-cranial carotid arteries were assessed by plaque and maximum stenosis. Three indices of long-term exposure to ingested arsenic including the duration of consuming artesian well water, the average arsenic concentration in consumed artesian water, and the cumulative arsenic exposure were all significantly associated with the prevalence of carotid atherosclerosis in a dose–response relationship. The gradient effect remained significant after controlling for traditional risk factors such as age, gender, hypertension, diabetes mellitus, cigarette smoking, alcohol consumption, waist-to-hip ratio, and serum levels of total cholesterol and low-density lipoprotein cholesterol. The multivariate-adjusted odds ratio (95% confidence interval) was 3.1 (1.3–7.4) and 1.8 (0.8–3.8) for those who had a cumulative arsenic exposure of  $\geq 20$  and 0.1–19.9 ppm-years, respectively, compared with those without exposure to arsenic from drinking artesian well water as the reference group. The dose–response relationship and the biological plausibility for the association indicate that chronic arsenic poisoning is an independent risk factor for atherosclerosis (Wang et al., 2002).

The pathology of blackfoot disease had been extensively studied in 63 amputated extremities from 51 patients from southwestern Taiwan. The pathology of blackfoot disease is compatible with two distinct types: arteriosclerosis obliterans and thromboangiitis obliterans (Yeh and How, 1963). In three autopsy cases of blackfoot disease, the typical pathological finding is the generalized atherosclerosis involving large, medium-size, and small arteries. Notably, in an autopsy case of a 24-year-old woman with thromboangiitis obliterans, severe atherosclerosis of coronary and other medium-size arteries was observed. Similarly, an autopsy finding on children with chronic arsenic poisoning in Antofagasta, Chile had shown systemic arterial intimal thickening in small and medium-size arteries involving the heart, gastrointestinal tract, liver, skin, and pancreas (Rosenberg, 1974). Therefore, accelerated arteriosclerosis can occur under chronic arsenic poisoning in the absence

Table 1  
Epidemiological studies on association between long-term arsenic exposure and subclinical cardiovascular outcomes in general populations

Author, year	Study design	Study population	Cardiovascular lesions	Arsenic exposure	Relative risk (95% confidence interval)	Factors adjusted
Wang et al. (2002)	Cross-sectional survey	463 residents in the arseniasis-endemic area in southwestern Taiwan	Carotid atherosclerosis (plaque or IMT $\geq$ 1 mm) by duplex ultrasonography	Unexposed 0.1–19.9 ppm-years >20.0 ppm-years	1.0 (referent) 1.8 (0.8–3.8) 3.5 (1.3–7.4)	Age, gender, hypertension, diabetes, cigarette smoking, alcohol consumption, waist-to-hip ratio, serum levels of cholesterol and low-density lipoprotein cholesterol
Wang (2003)	Cross-sectional survey	630 residents in the arseniasis-endemic area in southwestern Taiwan	QTc interval prolongation by electrocardiograms Increased QT dispersion by electrocardiograms	Unexposed 0.1–19.9 ppm-years >20 ppm-years Unexposed 0.1–19.9 ppm-years >20.0 ppm-years	1.0 (referent) 2.3 (1.0–5.3) 7.6 (3.1–18.5) 1.0 (referent) 2.3 (1.1–4.7) 4.4 (2.0–9.6)	Age, gender, hypertension, diabetes, cigarette smoking, alcohol consumption, waist-to-hip ratio, serum levels of cholesterol and triglycerides

of traditional coronary risk factors. Long-term exposure to arsenic may be sufficient to induce the process of arteriosclerosis in human. Carotid atherosclerosis is a novel biomarker for chronic arsenic poisoning. It strongly suggests that chronic arsenic poisoning may also lead to generalized atherosclerosis.

#### *Arsenic and QT prolongation and QT dispersion*

The association between ingested arsenic and electrocardiographic abnormality has recently been studied (Wang, 2003). A total of 280 male and 350 female adults from the southwestern area of endemic arseniasis in Taiwan were studied. Both heart rate-corrected QT (QTc) and QT dispersion (QTD) were measured by a computerized program. Three indices of chronic arsenic poisoning including the duration of consuming artesian well water, the average arsenic level, and the cumulative arsenic exposure were all significantly associated with QTc prolongation and increased QTD showing dose–response relationships ( $p < 0.001$ ). After adjustment for age, gender, hypertension, diabetes, cigarette smoking, alcohol consumption, body mass index, and serum levels of total cholesterol and triglycerides, the multivariate-adjusted odds ratio (95% confidence interval) of increased QTc prolongation was 7.6 (3.1–18.5) and 2.3 (1.0–5.3) for those who had a cumulative arsenic exposure  $\geq$  20 and 0–19.9 ppm-years, respectively, compared with those without exposure to arsenic as the reference group. The corresponding figures for increased QTD were 4.4 (2.0–9.6) and 2.3 (1.1–4.7), respectively.

#### **Clinical manifestations in cardiovascular system**

##### *Arsenic and PVD*

Table 2 shows the findings of several studies on the association between long-term arsenic exposure and PVD risk. Historically, ingested inorganic arsenic has been documented to cause blackfoot disease, a unique endemic peripheral vascular disease in southwestern Taiwan (Tseng, 1977). Clinically, the

disease begins with coldness and/or numbness of lower extremities, progresses over years to intermittent claudication, and ends with dry gangrene and spontaneous amputation of distal parts of affected extremities. Sporadic cases of blackfoot disease were first identified in southwestern Taiwan in the early 20th century, and the peak incidence was noted between 1956 and 1960. The prevalence of blackfoot disease per 1000 residents ranged from 6.51 to 18.85 in different endemic villages. Tseng (1977) reported the first dose–response relationship between ingested arsenic and prevalence of blackfoot disease. The prevalence of blackfoot disease among residents consuming well water containing an arsenic level of  $< 0.30$ , 0.30–0.59, and  $\geq 0.60$  ppm, respectively, was 0.5%, 1.3% and 1.4% for the age group of 20–39 years; 1.1%, 3.2% and 4.7% for the age group of 40–59 years; as well as 2.0% 3.2% and 6.1% for age group of 60 or more years.

A 30-year follow-up study had shown that 68% of the 1300 clinical patients of blackfoot disease underwent spontaneous or operative amputation, and the re-amputation rate was 23.3% (Tseng, 1989). The case fatality rate of blackfoot disease was 66.5%, and 44% of the deaths was due to cardiovascular diseases (Tseng, 1989). Switching to a surface water supply system in the arsenic-exposure area of southwestern Taiwan has resulted in a gradual decline of blackfoot disease incidence. In a case–control study on multiple risk factors for blackfoot disease, a dose–response relationship was found between the duration of consuming high arsenic artesian well water and the risk of blackfoot disease (Chen et al., 1988b). The multivariate-adjusted odds ratios were 3.0 and 3.5 for those who consumed high-arsenic artesian well water for a duration of 1–29 and  $\geq 30$  years, respectively, compared with those without arsenic exposure after adjustment for dietary factors, family history of blackfoot disease, and arsenic-induced skin lesions.

An increased mortality from PVD mortality was reported in an ecological study conducted in arseniasis-endemic areas in southwestern Taiwan (Wu et al., 1989). Its age-adjusted mortality increased in a dose–response relationship with increasing median levels of arsenic in artesian well water. The age-adjusted mortality from PVD per 100,000 persons for the

Table 2  
Epidemiological studies on association between long-term arsenic exposure and peripheral vascular disease in general populations

Author, year	Study design	Study population	Peripheral vascular disease diagnosis	Arsenic exposure	Mortality or relative risk (95% CI)	Factors adjusted
Chen et al. (1988b)	Cross-sectional survey	241 blackfoot disease patients and 759 age–gender–residence-matched controls in arseniasis-endemic areas in southwestern Taiwan	Blackfoot disease by clinical evaluation	Unexposed 1–29 years >30 years	BFD prevalence 1.0 (referent) 3.0 (not available) 3.5 (not available)	Age, gender, diet, family history of blackfoot disease, education, arsenic-induced skin lesions
Lin and Yang (1988)	Case–control study	20 blackfoot disease patients and 20 controls in arseniasis-endemic areas in southwestern Taiwan	Blackfoot disease by clinical evaluation	Urinary arsenic 25th percentile 75th percentile	BFD prevalence 1.0 (referent) 1.7 (0.8–3.5)	Age, gender
Wu et al. (1989)	Ecological study	Residents in 42 villages of arseniasis-endemic areas in southwestern Taiwan	Underlying cause (ICD 440–448) in death certificates	<0.30 ppm 0.30–0.59 ppm ≥0.60 ppm	PVD mortality (per 100,000) Males      Females 22.5      18.2 57.8      48.0 60.4      35.8	Age
Engel and Smith (1994)	Cohort study	30 counties in United States	Underlying cause (ICD 440–448) in death certificates	5–10 ppb 10–20 ppb >20 ppb	Standardized mortality ratio Males      Females 1.1 (1.1–1.2)      1.1 (1.1–1.2) 1.1 (1.0–1.1)      1.1 (1.0–1.2) 1.6 (1.5–1.8)      1.9 (1.7–2.1)	Age, gender
Tseng et al. (1996)	Cross-sectional survey	69 arsenic-exposed and 513 unexposed residents in a rseniasis-endemic areas in southwestern Taiwan	Peripheral vascular disease defined by ratio of ankle/ brachial systolic blood pressure <0.9	Unexposed 0.1–19.9 ppm-years >20.0 ppm-years	PVD prevalence 1.0 (referent) 2.8 (0.8–9.1) 4.3 (1.3–14.5)	Age, gender, hypertension, diabetes, cigarette smoking, body mass index, serum levels of cholesterol and triglycerides
Tsai et al. (1999)	Ecological study	Populations in arseniasis-endemic and non-endemic areas in southwestern Taiwan	Underlying cause (ICD 440–448) in death certificates	Unexposed Exposed	PVD mortality Males      Females 1.0 (referent)      1.0 (referent) 3.6 (2.9–4.3)      2.3 (1.8–2.9)	Age
Lewis et al. (1999)	Cohort study	Mormons of Millard County, Utah, United States	Underlying cause in death certificates (diseases of arteries and capillaries)	<1 ppm-years 1–5 ppm-years ≥5 ppm-years All exposure groups	Standardized mortality ratio Males      Females 1.0      1.3 1.0      0.8 0.8      0.6 0.9 (0.6–1.4)      0.9 (0.5–1.3)	Age and gender
Wang and Chang (2001)	Case–control study	31 blackfoot disease patients and 30 controls in arseniasis-endemic areas southwestern Taiwan	Blackfoot disease by clinical evaluation	Arterial tissue arsenic 25th percentile 75th percentile	BFD prevalence 1.0 (referent) 2.4 (2.0–2.9)	Crude

arsenic level of  $<0.30$ ,  $0.30$ – $0.59$ , and  $\geq 0.6$  ppm was 22.5, 57.8 and 60.4, respectively, for males ( $P$  for trend  $<0.01$ ) and 18.2, 48.0 and 35.8, respectively, for females ( $P$  for trend  $<0.05$ ). There was no individual measurement of arsenic exposure in this ecological study.

A cross-sectional study was conducted to detect the dose–response relationship between PVD and chronic arsenic poisoning among residents in the arseniasis-endemic areas in southwestern Taiwan, in which a total of 263 adult male and 319 female residents were studied (Tseng et al., 1996). Using Doppler ultrasound measurements of systolic pressure on bilateral ankle and brachial arteries, the researchers established the diagnosis of the PVD based on the ankle–brachial index (the ratio between ankle and brachial systolic pressure)  $<0.9$  on either side. There was a dose–response relationship between PVD prevalence and cumulative arsenic exposure after adjustment for age, gender, body mass index, cigarette smoking, and serum levels of total cholesterol and triglycerides. The multivariate-adjusted odds ratio (95% confidence interval) of developing PVD was 4.28 (1.26–14.54) and 2.77 (0.84–9.14), respectively, for those who had cumulative arsenic exposures of  $\geq 20$  and  $0.1$ – $19.9$  ppm-years compared with those without the exposure as the reference group. This study used a more objective and sensitive tool to identify PVD as well as an individual measure of arsenic exposure.

In an ecological study conducted in the arseniasis-endemic areas in southwestern Taiwan, mortality from PVD during 1971–1994 was compared with those of general populations in southwestern and entire Taiwan (Tsai et al., 1999). There was a significantly increased age-adjusted mortality from PVD with a standardized mortality ratio (95% confidence interval) of 3.56 (2.91–4.30) for males and 2.30 (1.78–2.93) for females compared with residents in non-endemic areas of southwestern Taiwan. In the analysis of standardized mortality ratio of PVD among residents in the arseniasis-endemic areas in southwestern Taiwan from 1971 to 2003, a gradual decline in PVD mortality was observed after cessation of consumption of high-arsenic artesian well water (Yang, 2006).

An increased prevalence of peripheral vascular disease has also been documented among inhabitants with long-term exposure to drinking water contaminated with high level of arsenic in Chile and Mexico (World Health Organization, 1981; National Research Council, 1999).

Impaired peripheral microcirculation of the toe was observed in clinically normal subjects with a past history of long-term arsenic exposure in southwestern Taiwan (Tseng et al., 1995). The microcirculatory assessment also revealed the insufficiency of capillary blood flow and permeability in clinical normal skin of patients with chronic arsenic poisoning (Yu et al., 2002). A vasospastic disorder of peripheral arteries, Raynaud's disease, has been reported to be associated with long-term environmental exposure to arsenic (Lagerkvist et al., 1988).

In a case–control study on urinary arsenic level and blackfoot disease, 20 patients affected with blackfoot disease and 20 unaffected controls were recruited (Lin and Yang, 1988). The urinary arsenic level was higher in patients than controls

showing an age–sex-adjusted odds ratio (95% confidence interval) of 1.7 (0.8–3.5) for those with a urinary arsenic level in 75th and higher percentiles compared with those with a level in the 25th and lower percentiles as the reference. As urinary arsenic level is a short-term biomarker of arsenic exposure, the causal temporality between arsenic exposure and blackfoot disease in this study remained to be elucidated. The small sample size is another limitation of this study. In another case–control study on arsenic in arterial tissues and risk of blackfoot disease, 31 patients and 30 unaffected controls were examined (Wang et al., 2001). Blackfoot disease patients had higher arsenic contents in arterial tissues than unaffected controls. The crude odds ratio (95% confidence interval) was 2.4 (2.0–2.9) for those with arsenic contents in arterial tissue in the 75th and higher percentiles compared with those with contents in the 25th and lower percentiles as the reference. The causal temporality issue and small sample size may limit the interpretation of the findings.

#### *Arsenic and IHD*

Table 3 illustrates several studies on the association between long-term arsenic exposure and risk of IHD. The dose–response relationship between IHD mortality and long-term arsenic exposure was further examined in a report on an ecological study and a cohort study (Chen et al., 1996). In the analysis of IHD mortality in 60 villages of the arseniasis-endemic areas in southwestern Taiwan, the cumulative IHD mortality from birth to age 79 were 3.4%, 3.5%, 4.7% and 6.6%, respectively, for residents who lived in villages with the median arsenic levels of artesian well water at  $<0.1$ ,  $0.1$ – $0.34$ ,  $0.35$ – $0.59$  and  $\geq 0.6$  ppm. In the follow-up of a cohort of 263 patients affected with blackfoot disease and 2293 unaffected community controls for an average period of 5 years, a biological gradient of IHD mortality with increasing cumulative arsenic exposure was observed. After adjustment for age, gender, cigarette smoking, body mass index, hypertension, diabetes, and serum levels of cholesterol and triglycerides, the relative risk (95% confidence interval) was 2.5 (0.5–11.4), 4.0 (1.0–15.6) and 6.5 (1.9–22.2), respectively, for those who had a cumulative arsenic exposure of  $0.1$ – $9.9$ ,  $10.0$ – $19.9$  and  $\geq 20.0$  ppm-years compared with those without arsenic exposure. Blackfoot disease patients had a significantly higher IHD mortality than unaffected residents, showing a multivariate-adjusted relative risk (95% confidence interval) of 2.5 (1.1–5.4).

In a case–control study carried out in the arseniasis-endemic villages in southwestern Taiwan, a significant association with IHD risk was observed for the duration of consuming high arsenic artesian well water, but not for the cumulative arsenic exposure (Hsueh et al., 1998). The diagnoses of IHD in 74 cases and 193 unaffected controls were based on both resting electrocardiograms and structured questionnaires on major cardiovascular diseases. The multivariate-adjusted odds ratio (95% confidence interval) was 2.5 (0.9–6.8) and 3.4 (1.1–10.6), respectively, for those who consumed high-arsenic artesian well water for 13–29 and  $\geq 30$  years compared with those without arsenic exposure.

Table 3  
Epidemiological studies on association between long-term arsenic exposure and ischemic heart disease in general populations

Author, year	Study design	Study population	Ischemic heart disease diagnosis	Arsenic exposure	Mortality or relative risk (95% CI)		Factors adjusted
Engel and Smith (1994)	Cohort study	30 counties in United States	Underlying cause (ICD 410–414) in death certificates	5–10 ppb 10–20 ppb >20 ppb	Standardized mortality ratio Males 1.0 (1.0–1.0) 0.7 (0.7–0.7) 0.8 (0.8–0.9)	Females 0.9 (0.9–1.0) 0.7 (0.7–0.7) 0.8 (0.8–0.9)	Age, gender
Chen et al. (1996)	Ecological study	Residents in 60 villages of arseniasis-endemic areas in southwestern Taiwan	Underlying cause (ICD 410–414) in death certificates	<0.10 ppm 0.10–0.34 ppm 0.35–0.59 ppm ≥0.60 ppm	Cumulative mortality (79 years old) 3.4% 3.5% 4.7% 6.6%		Age, gender, cigarette smoking, body mass index, hypertension, diabetes, serum levels of cholesterol and triglycerides
Chen et al. (1996)	Cohort study	263 blackfoot disease patients and 2293 unaffected residents in arseniasis-endemic areas in southwestern Taiwan	Underlying cause (ICD 410–414) in death certificates	Unexposed 0.1–9.9 ppm-years 10–19.9 ppm-years ≥20 ppm-years	1.0 (referent) 2.5 (0.5–11.4) 4.0 (1.0–15.6) 6.5 (1.9–22.2)		Age, gender, cigarette smoking, body mass index, hypertension, diabetes, serum levels of cholesterol and triglycerides
Hsueh et al. (1998)	Case–control study	74 ischemic heart disease patients and 193 controls from arseniasis-endemic areas in southwestern Taiwan	Cardiovascular questionnaire and electrocardiograms	<13 years 13–29 years ≥30 years	1.0 (referent) 2.5 (0.9–6.8) 3.4 (1.1–10.6)		Age, gender, cigarette smoking, body mass index, hypertension, diabetes, serum levels of cholesterol and high-density lipoprotein cholesterol
Tsai et al. (1999)	Ecological study	Populations in arseniasis-endemic and non-endemic areas in southwestern Taiwan	Underlying cause (ICD 410–414) in death certificates	Unexposed Exposed	Males 1.0 (referent) 1.8 (1.6–1.9)	Females 1.0 (referent) 1.4 (1.3–1.6)	Age
Tseng et al. (2003)	Cross-sectional survey	462 residents in arseniasis-endemic areas in southwestern Taiwan	Cardiovascular questionnaire and electrocardiograms	Unexposed 0.1–14.9 ppm-years ≥15.0 ppm-years	1.0 (referent) 1.6 (0.5–5.4) 3.6 (1.1–11.7)		Age, gender, cigarette smoking, body mass index, hypertension, diabetes, serum levels of lipids
Zierold et al. (2004)	Cross-sectional survey	1185 residents with private wells in Wisconsin, USA	Self-reported heart attack	<2 ppb 2–10 ppb >10 ppb	1.0 (referent) 1.3 (0.7–2.5) 2.1 (1.1–4.3)		Age, gender, cigarette smoking, body mass index

An ecological study conducted in the arseniasis-endemic areas in southwestern Taiwan, mortality from IHD during 1971–1994 was compared with those of general populations in southwestern and entire Taiwan (Tsai et al., 1999). There was a significantly increased age-adjusted mortality from IHD with a standardized mortality ratio (95% confidence interval) of 1.75 (1.59–1.92) for males and 1.44 (1.27–1.61) for females compared with residents in non-endemic areas of southwestern Taiwan. IHD mortality in the arseniasis-endemic areas of southwestern Taiwan was found to decline gradually for approximately 17 to 20 years after the implementation of tap water system and the cessation of consumption of high-arsenic artesian well water (Chang et al., 2004).

The dose–response relationship between the prevalence of IHD and long-term arsenic exposure has been reported in a study in the arseniasis-endemic areas of southwestern Taiwan (Tseng et al., 2003). The diagnosis of IHD was based on Minnesota codes of probable and possible coronary heart disease on resting electrocardiograms. The multivariate-adjusted IHD prevalence odds ratio (95% confidence interval) was 1.6 (0.5–5.3) and 3.6 (1.1–11.7), respectively, for those who had cumulative arsenic exposures of 0.1–14.9 and >15.0 ppm-years compared with those without arsenic exposure.

In a community-based cross-sectional study on 1185 residents in Wisconsin, the arsenic concentration in private well water samples ranged from undetectable to 2389 ppb with a median of 2 ppb (Zierold et al., 2004). Questionnaire interview was used to obtain the information on self-reported chronic diseases. After adjustment for age, sex, cigarette smoking and body mass index, the prevalence odds ratio (95% confidence interval) of heart attack was 2.1 (1.1–4.3) for arsenic exposure level of >10 ppb compared with the level <2 ppb as the reference group. The accuracy of IHD diagnosis remained to be verified.

#### *Arsenic and CVD*

Table 4 shows the findings of several studies on the association between long-term exposure to arsenic and risk of CVD. An excess in CVD mortality was observed among residents who consumed artesian well water with an arsenic level  $\geq 0.60$  ppm in the arseniasis-endemic areas in southwestern Taiwan (Wu et al., 1989). The age-adjusted mortality rates per 100,000 for arsenic level in well water of <0.30, 0.30–0.59 and  $\geq 0.60$  ppm were 137.8, 145.4 and 175.7, respectively, for males and 92.4, 98.1 and 120.7, respectively, for females. However, the increasing mortality trend by arsenic level was not statistically significant.

A dose–response relationship between prevalence of CVD and ingested arsenic was reported in northeastern Taiwan (Chiou et al., 1997). A total of 8102 men and women from 3901 households were recruited. The clinical endpoint of CVD was identified through home-visit personal interview based on structured questionnaire on major cardiovascular diseases, and further ascertained through review of hospital records and computed tomography. There were 139 patients affected with CVD including 95 (68%) cerebral infarction, 22 (16%)

cerebral hemorrhage, and 22 (16%) undetermined types. A significant dose–response relationship was observed between arsenic level in well water and prevalence of CVD after adjustment for age, gender, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption. The biological gradient was more prominent for cerebral infarction, showing multivariate-adjusted odds ratios (95% confidence interval) of 1.0 (reference group), 3.4 (1.6–7.3), 4.5 (2.0–9.9) and 6.9 (2.9–16.4), respectively, for those who consumed well with arsenic level of 0, 0.1–50.0, 50.1–299.9 and >300 ppb (Chiou et al., 1997).

An ecological study conducted in the arseniasis-endemic areas in southwestern Taiwan, mortality from CVD during 1971–1994 was compared with those of general populations in southwestern and entire Taiwan (Tsai et al., 1999). There was a significantly increased age-adjusted mortality from CVD with a standardized mortality ratio (95% confidence interval) of 1.14 (1.08–1.21) for males and 1.24 (1.18–1.31) for females compared with residents in non-endemic areas of southwestern Taiwan.

In a community-based cross-sectional study on 1185 residents in Wisconsin, the arsenic concentration in private well water samples ranged from undetectable to 2389 ppb with a median of 2 ppb (Zierold et al., 2004). Questionnaire interview was used to obtain the information on self-reported chronic diseases. After adjustment for age, sex, cigarette smoking and body mass index, the prevalence odds ratio (95% confidence interval) was 1.5 (0.6–4.1) for arsenic exposure level of >10 ppb compared with the level <2 ppb as the reference group. The accuracy of CVD diagnosis remained to be verified.

#### *Arsenic and combined vascular diseases*

Table 5 illustrates the findings of three studies on the association between arsenic exposure and risk of combined vascular diseases. An increased mortality from all vascular diseases combined was also found in an ecological study in arseniasis-endemic areas in southwestern Taiwan (Wu et al., 1989). The age-adjusted mortality rates for all vascular diseases combined (ICD 8th; 401–448) and cardiovascular diseases combined (ICD 8th; 410–411, 420–429) increased with increasing arsenic level in artesian well water for males and females in a dose–response relationship.

In a community-based study on mortality of 4058 residents in Millard County, Utah, where the arsenic concentration in drinking water ranging from 3.5 to 620 ppb, a significantly increased mortality was observed for hypertensive cardiovascular disease and other heart diseases (Lewis et al., 1999). The standardized mortality ratio (95% confidence interval) for hypertensive cardiovascular disease was 2.20 (1.36–3.36) for males and 1.73 (1.11–2.58) for females; and the standardized mortality ratio (95% confidence interval) for all other heart disease was 0.94 (0.71–1.22) for males and 1.43 (1.11–1.80) for females 1.4 (1.1–1.8).

In the previously mentioned study in Wisconsin, a dose–response relationship was observed between arsenic level in well water and prevalence of self-reported circulatory problems

Table 4  
Epidemiological studies on association between long-term arsenic exposure and cerebrovascular disease in general populations

Author, year	Study design	Study population	Cerebrovascular disease diagnosis	Arsenic exposure	Mortality or relative risk (95% CI)		Factors adjusted
Wu et al. (1989)	Ecological study	Residents in 42 villages of arseniasis-endemic areas in southwestern Taiwan	Underlying cause (ICD 430–438) in death certificates	<0.3.0 ppm 0.30–0.59 ppm ≥0.6 ppm	Mortality (per 100,000)		Age
					Males	Females	
					137.8	92.4	
Engel and Smith (1994)	Cohort study	30 counties in United States	Underlying cause (ICD 430–438) in death certificates	5–10 ppb 10–20 ppb >20 ppb	Standardized mortality ratio		Age, gender
					Males	Females	
					1.1 (1.1–1.1)	1.1 (1.1–1.1)	
Chiou et al. (1997)	Cross-sectional survey	8102 residents in northeastern Taiwan	Self-reported disease confirmed by hospital medical records including computed tomography	Unexposed 0.1–50.0 ppb 50.1–299.9 ppb ≥300.0 ppb	Cerebral infarction		Age, gender, cigarette smoking, alcohol consumption, hypertension, diabetes
					1.0 (referent)		
					3.4 (1.6–7.3)		
Lewis et al. (1999)	Cohort study	Mormons of Millard County, Utah, United States	Underlying cause in death certificates	<1 ppm-years 1–5 ppm-years ≥5 ppm-years All exposure groups	Standardized mortality ratio		Age, gender
					Males	Females	
					1.0	1.0	
Tsai et al. (1999)	Ecological study	Populations in arseniasis-endemic and non-endemic areas in southwestern Taiwan	Underlying cause (ICD 430–438) in death certificates	Unexposed Exposed	Males		Age
					1.0 (referent)	1.0 (referent)	
					1.14 (1.08–1.21)	1.24 (1.18–1.31)	
Zierold et al. (2004)	Cross-sectional survey	1185 residents with private wells in Wisconsin, USA	Self-reported stroke	<2 ppb 2–10 ppb >10 ppb	1.0 (referent) 0.9 (0.6–2.1) 1.5 (0.6–4.1)	Age, gender, cigarette smoking, body mass index	

(Zierold et al., 2004). After adjustment for age, sex, cigarette smoking and body mass index, the prevalence odds ratio (95% confidence interval) was 1.3 (0.6–2.9) and 2.6 (1.2–6.0), respectively, for arsenic exposure level of 2–10 and >10 ppb compared with the level <2 ppb as the reference group. The accuracy of diagnosis for circulatory problem remained to be verified.

### Studies in occupational populations

Although epidemiological studies conducted in general populations strongly support chronic arsenic exposure as a risk factor for atherosclerosis and various cardiovascular diseases, the studies of occupational populations are inconclusive (National Research Council, 1999, 2001; Navas-Acien et al., 2005). Methodological limitations are common in the occupational studies, and most results are based on external comparisons. In many studies, there are uncertainties in exposure quantification and outcome ascertainment (e.g., misclassification bias) and a lack of information about exposure to other metals and traditional occupational risk factors (e.g., possible confounding). The healthy worker effect may also lead to underestimate or invalidate the risk assessment of cardiovascular disease. A study conducted in United States has shown that after adjustment for healthy worker effect, the association between arsenic and IHD became stronger and the increasing trend was statistically significant (Hertz-Picciotto et al., 2000).

### Persistence and irreversibility of cardiovascular effects by arsenic

Due to the implementation of public surface water supply system in 1970s, residents in the southwestern endemic area of Taiwan had stopped consumption of high-arsenic artesian well water long before their participation in the above-mentioned studies (Chen et al., 1996; Tseng et al., 1996; Wang et al., 2002). Although the consumption of high-arsenic well water stopped, the studies conducted in southwestern Taiwan have shown that all the adverse cardiovascular effects including PVD, IHD, CVD, carotid atherosclerosis, QT abnormalities, and impaired microcirculation were associated with previous arsenic exposure in a dose–response relationship. This suggests that ingested arsenic may induce irreversible and/or persistent adverse cardiovascular effects in the arsenic-exposed subjects.

### Gene–environment–nutrient interactions

Despite of the significant biological gradient of cardiovascular hazards with increasing long-term arsenic exposure, only a small proportion of arsenic-exposed subjects develop arsenic-induced cardiovascular diseases. It is known that both genetic and acquired susceptibility may modify the risk of arsenic-induced cardiovascular diseases (Hsueh et al., 1998; Wang, 2003; Chen et al., 2005). In a case–control study in arseniasis-hyperendemic villages of southwestern Taiwan,

serum samples of 74 IHD patients and 193 matched healthy controls were tested for serum levels of micronutrients (Hsueh et al., 1998). A significant reverse dose–response relationship with arsenic-induced IHD was found for serum levels of  $\alpha$ - and  $\beta$ -carotene, but not for serum levels of retinol, lycopene, and  $\alpha$ -tocopherol, after adjustment for age, gender, body mass index, hypertension, and the ratio between serum total cholesterol and high-density lipoprotein cholesterol.

In a study on 605 residents in northeastern Taiwan, the prevalence of carotid atherosclerosis was significantly associated with the genetic polymorphism of glutathione *S*-transferase (GST) P1 and p53, but not with GST M1 and T1 (Chiou et al., 2001; Wang et al., in press). The high arsenic exposure group with one or two variant genotypes of GSTP1 and p53 had an increased risk of carotid atherosclerosis showing an odds ratio of 2.8 and 6.1, respectively, compared with those with wild types.

In another study including 26 male and 38 female adult residents from the arsenic-exposed area in northeastern Taiwan, the blood level of arsenic was positively associated with plasma level of reactive oxidants and negatively with antioxidant capability (Wu et al., 2001). In a study on gene expression of human genes by using cDNA microarray hybridization of mRNA isolated from cultured lymphocytes of 24 residents in the arsenic-exposed area in northeastern Taiwan, 62 of 708 transcripts were found to have significant differences in gene expression among three groups with different blood levels of arsenic (Wu et al., 2003). Several cytokines and growth factors involving inflammation were up-regulated in persons with an increased arsenic exposure. The oxidant/antioxidants and inflammatory process may involve in the arsenic-induced atherosclerosis.

The biomarkers of early biological effects of ingested inorganic arsenic may include blood levels of reactive oxidants and anti-oxidant capacity, inflammatory molecules, as well as cytogenetic changes. Biomarkers of susceptibility to arsenic-induced health hazards included genetic polymorphisms of enzymes involved in xenobiotic metabolism, DNA repair, and oxidative stress, as well as serum level of carotenoids (Chen et al., 2005). Arsenic-induced cardiovascular diseases may result from the interactions among genetic, environmental and nutritional factors through toxicological mechanisms including genomic instability and oxidative stress.

### Conclusions

Because cardiovascular death is the major cause of mortality worldwide, small increased risks, such as those observed with arsenic exposure may result in significant excess mortality. Experiences and studies from Taiwan have documented that long-term arsenic exposure is a dominant and independent risk factor for cardiovascular diseases. The emerging epidemic of chronic arsenic poisoning could become a significant public health issue in the future. Implementation of surface-water supply system in the arsenic-exposure area of southwestern Taiwan has resulted in declining incidence of blackfoot disease and IHD

Table 5  
Epidemiological studies on association between long-term arsenic exposure and combined cardiovascular diseases in general populations

Author, year	Study design	Study population	Endpoints and ascertainment	Arsenic exposure	Mortality or relative risk (95% CI)	Factors adjusted	
Wu et al. (1989)	Ecological study	Residents in 42 villages of arseniasis-endemic areas in southwestern Taiwan	Underlying cause in death certificates All vascular diseases (ICD 401–448)	<0.30 ppm 0.30–0.59 ppm ≥0.6 ppm	Mortality (per 100,000)		Age
					Males	Females	
					364.1	277.5	
					421.5	370.8	
					572.7	386.4	
					125.9	91.1	
Lewis et al. (1999)	Cohort study	Mormons of Millard County, Utah, United States	Underlying cause in death certificates Hypertensive heart disease	<1 ppm-years 1–5 ppm-years ≥5 ppm-years All exposure groups	Standardized mortality ratio		Age, gender
					Males	Females	
					2.4	1.7	
					1.9	2.3	
					2.3	1.3	
					2.2	1.7	
Zierold et al. (2004)	Cross-sectional survey	1185 residents with private wells in Wisconsin, United States	Self-reported circulatory problems	<2 ppb 2–10 ppb >10 ppb	Standardized mortality ratio		Age, gender, cigarette smoking, body mass index
					Males	Females	
					1.1	2.3	
					1.0	1.4	
					0.7	0.7	
					0.9	1.4	

mortality. For the mitigation of arsenic-related environmental catastrophe, the supply of drinking water with low level of arsenic is extremely important.

The major adverse cardiovascular effect of chronic arsenic poisoning has been established qualitatively and quantitatively in the high arsenic exposure areas, but the low-dose effect of arsenic on cardiovascular diseases remains to be explored. Large-scale prospective studies on general populations using appropriate biomarkers or clinical endpoints are recommended.

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