Arsenic and diabetes and hypertension in human populations: A review

Chien-Jen Chen ^{*}, Shu-Li Wang, Jeng-Min Chiou, Chin-Hsiao Tseng, Hung-Yi Chiou,
Yu-Mei Hsueh, Shu-Yuan Chen, Meei-Maan Wu, Mei-Shu Lai

Genomics Research Center, Academia Sinica, 128 Academia Road Section 2, Nankang, Taipei 11529, Taiwan
Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Miaoli, Taiwan
Institute of Statistical Science, Academia Sinica, Taipei, Taiwan
Department of Internal Medicine, National Taiwan University, Taipei, Taiwan
School of Public Health, Taipei Medical University, Taipei, Taiwan
Department of Public Health, Tzu-Chi University, Hualien, Taiwan
Graduate Institute of Preventive Medicine, National Taiwan University, Taipei, Taiwan

Received 20 September 2006; revised 27 December 2006; accepted 28 December 2006

Available online 8 January 2007

Abstract

Long-term exposure to ingested arsenic from drinking water has been well documented to be associated with an increased risk of diabetes mellitus and hypertension in a dose-response relationship among residents of arseniasis-endemic areas in southwestern Taiwan and Bangladesh. An increased risk of self-reported hypertension but not diabetes was reported in a community-based study of residents who consumed drinking water with a low level of arsenic. Increased glycosylated hemoglobin level and systolic blood pressure were observed in workers occupationally exposed to arsenic. Inconsistent findings of arsenic and diabetes in occupational studies may result from the healthy worker effect and the variation in exposure measurement, age composition, number of patients, accuracy in diagnosis and classification of underlying causes of death, competing causes of death, and method to detect diabetes. The dose-response relationship and toxicological mechanisms of arsenic-induced diabetes and hypertension need further elucidation.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Arsenic; Diabetes mellitus; Hypertension; Human populations; Dose-response relationship

Introduction

Inorganic arsenic has been recognized as a human poison since ancient times. The arsenic-related human toxicity is systemic involving a number of organ systems. Acute, subacute and chronic toxic effects of inorganic arsenic exposed through inhalation and ingestion have been reviewed periodically (World Health Organization, 1981, 2001; US Public Health Service, 1989; Chen et al., 1997a, 1997b; National Research Council, 1999, 2001; International Agency for Research on Cancer, 2004). Ingested arsenic has been well documented to be associated with the development of peripheral vascular disease (Tseng, 1977; Chen et al., 1988;

Tseng et al., 1995), ischemic heart disease (Chen et al., 1996) and cerebrovascular accidents (Chiou et al., 1997) in a dose-response relationship in the endemic areas of arseniasis in southwestern Taiwan. A biological gradient in prevalence of carotid atherosclerosis with increasing exposure to ingested arsenic has also been observed in the same arseniasis-endemic area (Wang et al., 2002). Both diabetes mellitus and hypertension are important risk predictors of atherosclerotic diseases. Several epidemiological studies have been carried out to examine the association between long-term arsenic exposure and the development of diabetes mellitus and hypertension. These include community-based and hospital-based studies in both high and low arsenic exposure areas, as well as occupational studies of arsenic exposures from various sources. This review article will compare the findings, advantages and limitations of these studies. Recommendations on future studies will also be made.

^{*} Corresponding author. Fax: +886 2 2737 7668.

E-mail address: cjchen@ha.mc.ntu.edu.tw (C.-J. Chen).

Arsenic exposure and diabetes mellitus

Most community-based studies carried out in areas of high arsenic exposure in Taiwan have found a significantly increased morbidity and mortality of diabetes mellitus in the arsenic exposed area compared with the unexposed area (Lai et al., 1994; Tsai et al., 1999; Tseng et al., 2000; Wang et al., 2003). A dose–response relationship has also been observed between arsenic exposure and diabetes mellitus prevalence in community-based studies in high arsenic exposure areas in Taiwan (Lai et al., 1994) and Bangladesh (Rahman et al., 1998; Rahman et al., 1999a), but not in several occupational studies on workers with high arsenic exposure. While no significant association between arsenic exposure and diabetes mellitus was observed in community-based studies in areas of low arsenic exposure in the USA (Lewis et al., 1999; Zierold et al., 2004), occupational exposure to arsenic was associated significantly with an increased level of glycosylated hemoglobin in Denmark.

Community-based studies in high arsenic exposure areas

Table 1 shows several epidemiological studies of the association between long-term arsenic exposure and risk of diabetes mellitus. In a community-based cross-sectional survey

carried out in the arseniasis-endemic area in southwestern Taiwan, a total of 891 residents gave their informed consent to participate in 1989 (Lai et al., 1994). They were personally interviewed according to a structured questionnaire to obtain information on socio-demographical characteristics, life style variables (including habits of cigarette smoking and alcohol consumption), residential and water consumption history, personal and family history of major diseases with their treatments, as well as physical activity and sunlight exposure at work. An oral glucose tolerance test was carried out for each study participant who was not currently receiving regular treatments with insulin or sulfonylurea agents. The status of diabetes mellitus was defined by positive findings in an oral glucose tolerance test or the regular use of sulfonylurea agents or insulin. As residents living in a given village shared only few public wells, their exposure to arsenic from consuming well water was estimated from the median arsenic level in water of these shared wells. In other words, the cumulative arsenic exposure of each participant was derived by the median arsenic concentration (mg/L) in water of wells in each residential village and the duration (years) of drinking well water when the participant lived in the village.

The prevalence of diabetes mellitus was first compared with those reported from studies using the same method to define

Table 1
Epidemiological studies on the association between long term arsenic exposure and risk of diabetes mellitus

Author, year	Study design	Study population	Diabetes diagnosis	Arsenic exposure	Prevalence/ Incidence*	Odds ratio (95% CI)	Adjustment variables
Lai et al., 1994	Cross-sectional	891 residents in arseniasis-endemic area in southwestern Taiwan	OGTT and currently treated diabetes	Unexposed <15.0 ppm-years ≥15.0 ppm-years	0.9% 7.0% 14.4%	1.0 (reference) 6.6 (0.9–51.0) 10.1 (1.3–79.9)	Age, sex, physical activity, body mass index
Tseng et al., 2000	Cohort follow-up	446 non-diabetic residents in arseniasis-endemic area in southwestern Taiwan	OGTT	<17.0 ppm-years ≥17.0 ppm-years	1.9%* 4.8%*	1.0 (reference) 2.1 (1.1–4.2)	Age, sex, body mass index
Wang et al., 2003	Cross-sectional	66,667 residents in southwestern arseniasis-endemic area and 639,667 residents in non-endemic area in Taiwan	Currently treated diabetes reimbursed by National Health Insurance	Unexposed Exposed	3.5% 7.5%	1.00 (reference) 2.69 (1.65–2.73)	Age, sex
Rahman et al., 1998	Cross-sectional	163 arsenic exposed and 854 unexposed residents in Bangladesh	Self-reported symptoms, glucosuria test, confirmed by OGTT	Unexposed <0.5 ppm 0.5–1.0 ppm >1.0 ppm	2.9% 9.0% 11.8% 21.4%	1.0 (reference) 2.6 (1.2–5.7) 3.9 (1.8–8.2) 8.8 (2.7–28.4)	Age, sex
Rahman et al., 1999a,b	Cross-sectional	1481 arsenic exposed and 114 unexposed residents in Bangladesh	Glucosuria test	Unexposed <1.0 ppm-years 1.0–5.0 ppm-years 5.1–10.0 ppm-years >10.0 ppm-years	12.3% 7.1% 16.3% 18.3% 25.1%	1.0 (reference) 0.8 (0.3–1.9) 1.7 (0.9–2.9) 2.1 (1.0–4.0) 2.9 (1.6–5.2)	Age, sex
Zierold et al., 2004	Cross sectional	1185 residents in Wisconsin, USA	Self reported disease	<2 ppb 2–10 ppb >10 ppb	– – –	1.0 (reference) 1.4 (0.8–2.3) 1.0 (0.5–2.2)	Age, sex, body mass index, smoking status
Jensen and Hansen, 1998	Cross-sectional case–control study	34 arsenic-exposed workers and 25 unexposed controls in Denmark	Glycosylated hemoglobin	Unexposed Exposed	Mean±S.D. (Kruskal–Wallis test)	4.4±1.1% 5.7±0.5% (<i>P</i> <0.001)	Two groups matched on age and smoking status

diabetes status in unexposed areas in Taipei City and Taiwan Province. Residents in the arseniasis-endemic area had a twofold increase in age–sex-adjusted prevalence of diabetes mellitus (10.9% among 891 residents) compared with residents in two non-endemic areas (5.2% among 2206 residents in Taipei City, and 5.8% among 11,478 residents in Taiwan Province). Among residents in the endemic area, there was a dose–response relation between cumulative arsenic exposure and prevalence of diabetes mellitus (Lai et al., 1994). The biological gradient remained significant after adjustment for age, sex, body mass index, and physical activity level at work by a multiple logistic regression analysis, with an adjusted odds ratio (95% confidence interval) of 6.6 (0.9–51.0) and 10.1 (1.3–77.9), respectively, for those who had a cumulative arsenic exposure of 0.1–15.0 and >15.0 mg/L-years compared with those who were unexposed. The 95% confidence intervals were wide due to the low prevalence of diabetes, small number of study subjects, and adjustment for many risk factors.

Among 632 non-diabetic participants recruited in the above-mentioned survey in 1989, a total of 446 (71%) were followed biannually with an oral glucose tolerance test (Tseng et al., 2000). During the follow-up period of 1499.5 person-years, 41 cases developed diabetes mellitus showing an incidence of 27.4 per 1000 person-years, which was higher than that in two non-endemic townships in Taiwan. The incidence ratios (95% confidence interval) between the arseniasis-endemic villages and the two non-endemic control townships were 3.6 (3.5–3.6), 2.3 (1.1–4.9), 4.3 (2.4–7.7), and 5.5 (2.2–13.5), respectively, for the age groups of 35–44, 45–54, 55–64, and 65–74 years. The drop in incidence ratios at ages of 45–54 years might be due to the low prevalence of diabetes and small number of study subjects. Among the cohort members in the endemic area, there was a significant association between incidence of diabetes mellitus and arsenic exposure from consuming high-arsenic well water. As there were few cases of newly developed diabetes, the cumulative arsenic exposure was dichotomized using 17 mg/L-years as the cutoff point. After adjustment for age, sex and body mass index, the adjusted incidence ratio (95% confidence interval) was 2.1 (1.1–4.2) for a cumulative arsenic exposure ≥ 17 mg/L-years compared with the reference group of <17 mg/L-years.

In a secondary data analysis of National Health Insurance Database for 1999–2000, the prevalence of diabetes mellitus and related vascular diseases by age and sex were compared between 66,667 residents aged 25 years or older in the arseniasis-endemic area in southwestern Taiwan and 639,667 residents randomly sampled from the non-endemic areas in Taiwan (Wang et al., 2003). The status of diabetes and vascular diseases was ascertained through disease diagnosis and treatment prescription included in the reimbursement claims of clinics and hospitals. The prevalence of diabetes mellitus (95% confidence interval) adjusted for age and gender to the general population in Taiwan was 7.5% (7.4–7.7%) in the arseniasis-endemic areas and 3.5% (3.5–3.6%) in the non-endemic areas, showing an adjusted prevalence odds ratio (95% confidence interval) of 2.69 (2.65–2.73). Among both diabetics and non-diabetics, a higher prevalence of microvascular and

macrovascular diseases was observed in arseniasis-endemic area than in the non-endemic areas. Age–gender-adjusted prevalence of microvascular diseases (including renal diseases, neurological disorders and retinopathy) in endemic and non-endemic areas was 20.0% and 6.0%, respectively, for diabetics; and 8.6% and 1.0%, respectively, for non-diabetics. The corresponding prevalence of macrovascular diseases (including ischemic heart diseases, cerebrovascular diseases and peripheral vascular diseases) was 25.3% and 13.7% for diabetics, and 12.3% and 5.5% for non-diabetics.

In order to analyze the association between the arsenic concentration in well water and the prevalence of microvascular disease for residents in the arseniasis-endemic area in southwestern Taiwan, an analysis was carried out based on a subgroup of 28,499 residents in villages where arsenic in well water was available (Chiou et al., 2005). The arsenic concentration in artesian well water in the villages of the study area was used as an index of ingested arsenic exposure. The prevalence of microvascular diseases increased significantly with increasing arsenic exposure, especially at higher levels, and the relationship was stronger in diabetics than in non-diabetic subjects. The age–sex-adjusted prevalence (95% CI) of microvascular diseases was 7.51% (7.50–7.51%), 6.59% (6.59–6.60%), 8.02% (8.02–8.03%) and 11.82% (11.81–11.83%), respectively, for arsenic level of <0.1, 0.1–0.29, 0.3–0.59 and ≥ 0.6 mg/L in non-diabetic subjects. For diabetic patients, the corresponding prevalence (95% CI) was 16.41% (16.37–16.45%), 15.85% (15.8–15.9%), 21.69% (21.6–21.8%), and 28.31% (28.2–28.4%). The patterns of increasing disease prevalence with arsenic exposure were similar for neurological disease and renal disease (Chiou et al., 2005).

Mortality from diabetes mellitus from 1971 to 1994 was compared among residents in the arseniasis-endemic and non-endemic areas in southwestern Taiwan and the entire general population in Taiwan (Tsai et al., 1999). The standardized mortality ratio (95% confidence interval) in the arseniasis-endemic area using the southwestern non-endemic area as the reference was 1.35 (1.16–1.55) for males and 1.55 (1.39–1.72) for females. Using the general population in Taiwan as the reference, the standardized mortality ratio (95% confidence interval) in the arseniasis-endemic area was 1.14 (0.98–1.31) for males and 1.23 (1.11–1.37) for females. The secular trend of standardized mortality ratio of diabetes mellitus in the arseniasis-endemic area from 1970 to 2000 was examined in another study (Chu et al., 2006). A decreasing trend was observed from 1978 to 2000 for males and from 1976 to 2000 for females. Several limitations of these mortality studies need consideration. The impact of competing cause of death, the variation in coding and classification of underlying cause of death, the comparability between study and control areas, and the discrepancy in detection and treatment of diabetes mellitus might bias the findings. As most diabetics may die from ischemic heart disease and stroke, their diabetes status might not be coded as an underlying cause of death. As arsenic may induce several lethal cancers and diabetes is less lethal if detected and managed early, mortality of diabetes might not correctly reflect its incidence. As the arseniasis-endemic area is

a rural area, it may not be appropriate to use the entire population in both urban and rural areas of Taiwan as the standard population to derive the standardized mortality ratio. Based on these limitations, the findings of the mortality studies should be interpreted carefully.

A dose–response relationship between prevalence of diabetes mellitus and arsenic in drinking water was reported in two cross-sectional surveys in Bangladesh (Rahman et al., 1998, 1999a). In a study of 163 patients affected with keratosis and 854 unexposed individuals, the status of diabetes was determined sequentially by questionnaire interview on history of symptoms and previously diagnosed diabetes, screening of urine samples for glucosuria, and confirmation by oral glucose tolerance test (Rahman et al., 1998). The time-weighted average exposure to arsenic was based on measurements of arsenic concentrations in drinking water and duration of consuming the well water. Despite of the inadequacy in the diagnosis of diabetes mellitus, there was a significant dose–response relationship between arsenic exposure and prevalence of diabetes mellitus ($P < 0.001$ for trend). The age–sex-adjusted prevalence odds ratio (95% confidence interval) was 2.6 (1.2–5.7), 3.9 (1.8–8.2) and 8.8 (2.7–28.4), respectively, for arsenic exposure level of <0.5 , $0.5–1.0$, and >1.0 ppm compared with the unexposed.

In another study of 1481 arsenic-exposed and 114 unexposed residents in Bangladesh, the arsenic exposure was estimated based on the history of consuming well water and current arsenic concentration of the well water (Rahman et al., 1999a,b). The status of diabetes mellitus was indicated by glucosuria identified by a urine test using glucometric strips. There was a significant dose–response relationship between cumulative arsenic exposure and diabetes mellitus ($P < 0.001$). The age–sex-adjusted odds ratio (95% confidence interval) for cumulative arsenic exposures of <1.0 , $1.0–5.0$, $5.1–10.0$, >10.0 ppm-years, respectively, was 0.4 (0.1–1.0), 0.9 (0.5–1.7), 1.2 (0.6–2.2) and 1.7 (1.0–2.9) compared with the unexposed as the reference group among residents without skin lesions including hyperpigmentation, keratosis and hypopigmentation. The corresponding figures for residents with skin lesions were 0.8 (0.3–1.9), 1.7 (0.9–2.9), 2.1 (1.0–4.0) and 2.9 (1.6–5.2), respectively.

Community-based studies in low arsenic exposure areas

In a community-based cross-sectional study investigated arsenic exposure and self-report of nine chronic diseases in Wisconsin in 2000–2002 (Zierold et al., 2004), a total of 1185 residents from 19 townships participated in the study. The water samples from their private wells water were tested for arsenic concentration, which ranged from undetectable to 2389 ppb with a median of 2 ppb. An interview questionnaire was used to obtain the information on self-reported chronic diseases, lifetime residential history, usual drinking water consumption, use of water-treatment systems, and family health status. The mean age ($\pm$ standard deviation) was 62 years (± 12 years) with a mean period of drinking well water ($\pm$ standard deviation) of 30 years (± 10 years). After adjustment for age, sex, cigarette smoking and body mass index, the prevalence odds ratio (95%

confidence interval) was 1.35 (0.78–2.33) and 1.02 (0.49–2.15), respectively, for arsenic exposure level of 2–10 and >10 ppb compared with the level <2 ppb as the reference group. The authors did not give any explanation why the prevalence odds ratio was lower in the high exposure group compared to the low exposure group. It was questionable whether the information on diabetes status based on questionnaire interview was accurate.

Another community-based study on the associations between arsenic exposure from drinking water and mortality from various diseases was carried out in Millard County, Utah (Lewis et al., 1999). Median drinking water arsenic concentration for selected study towns ranged from 14 to 166 ppb with the minimum and maximum arsenic concentration of 3.5 and 620 ppb, respectively. Cohort members were assembled using historical documents of the Church of Jesus Christ of Latter-day Saints (Mormons). There were a total of 4058 residents with 2203 deaths included in the data analysis. The underlying cause of death listed in death certificates was coded using the ICD-9 classification and analyzed. The general population in Utah was used as the standard population to derive the expected number of deaths from various causes. Standard mortality ratios with 95% confidence intervals were derived using the observed and expected numbers of death for various causes. No significant increase in mortality from diabetes mellitus was observed showing standardized mortality ratio (95% confidence interval) of 78 (48–122) for males and 123 (86–171) for females. However, there was an increased mortality from arteriosclerosis and hypertensive heart disease for both males and females and from all other heart disease for females. As most study subjects were Mormons who had personal lifestyle including prohibition of tobacco use and alcohol consumption, the standardized mortality ratios of most major diseases including cancers and ischemic heart disease were significantly lower than the general population in Utah. The small number of deaths from diabetes also resulted in less precise estimation of the standardized mortality ratio. The interpretation of the findings has to take all these limitations into consideration.

Occupational studies based on death certificates

There were inconsistent findings on the association between arsenic exposure and diabetes mellitus in several occupational studies (Mabuchi et al., 1980; Enterline and Marsh, 1982; Lagerkvist and Zetterlund, 1994; Rahman and Axelson, 1995; Rahman et al., 1996; Bartoli et al., 1998; Lubin et al., 2000; Tollestrup et al., 2003). Four studies showed an increased morbidity and mortality of diabetes mellitus in arsenic-exposed workers compared with the general population or unexposed workers (Lagerkvist and Zetterlund, 1994; Rahman and Axelson, 1995; Rahman et al., 1996; Tollestrup et al., 2003), another four studies showed a decreased mortality of diabetes mellitus among arsenic-exposed workers than the general population (Mabuchi et al., 1980; Enterline and Marsh, 1982; Bartoli et al., 1998; Lubin et al., 2000). Neither increased nor decreased risk was statistically significant. These occupational studies had following limitations: the bias of healthy worker

effect, the low case fatality rate of diabetes mellitus, the competing of various causes of death induced by arsenic, the accuracy in coding and classification of underlying cause of death, the poor estimation of occupational arsenic exposure, small number of deaths from diabetes mellitus, and the inadequacy in control of confounding factors.

Occupational study based on biomarkers

In a study of 40 workers occupationally exposed to arsenic and 34 unexposed references in Denmark, the blood concentration of glycosylated hemoglobin was tested as a biomarker of diabetes mellitus (Jensen and Hansen, 1998). The median arsenic concentration in urine samples was 22.3 and 12.0 nmol arsenic/nmol of creatinine, respectively, for arsenic-exposed workers and unexposed reference group ($P < 0.001$). The blood level of glycosylated hemoglobin was significantly ($P < 0.001$) higher in arsenic-exposed workers (mean $\pm$ standard deviation = $5.7 \pm 1.1\%$) than the unexposed reference group ($4.4 \pm 0.5\%$). There was also a significant association between blood glycosylated hemoglobin level and urinary arsenic level among arsenic-exposed workers ($P = 0.034$). For every 1 nmol increase of arsenic/nmol of creatinine in urine, the blood glycosylated hemoglobin increased 0.0078%.

Arsenic exposure and hypertension

Three community-based studies carried out in areas of high and low arsenic exposure found a dose–response relationship between arsenic exposure and hypertension risk in Taiwan (Chen et al., 1995), Bangladesh (Rahman et al., 1999a,b) and Wisconsin, USA (Zierold et al., 2004) as shown in Table 2. An occupational study showed significantly higher systolic blood pressures in arsenic-exposed workers than unexposed

controls in Denmark. They are discussed in the following sections.

Community-based studies in high arsenic exposure areas

A cross-sectional study in southwestern Taiwan reported an increased prevalence of hypertension among residents in the arseniasis-endemic area than those in non-endemic area, as well as a dose–response relationship between ingested inorganic arsenic and prevalence of hypertension (Chen et al., 1995). The status of hypertension in 898 residents was defined by a systolic blood pressure ≥ 160 mm Hg, a diastolic blood pressure ≥ 95 mm Hg, or a history of hypertension regularly treated with antihypertensive drugs. The age–sex-adjusted prevalence (95% confidence interval) was 23.2% (19.3–27.1%) in the arseniasis-endemic area and 14.4% (12.9–15.9%) in non-endemic areas. The findings were similar to those reported in two previous studies carried out in 1963 (Tseng, 1980; Tsai et al., 1966). In this study, the duration of artesian well water consumption, the average arsenic concentration in drinking water, and the cumulative arsenic exposure were all significantly associated with hypertension prevalence in a dose–response relationship. The increasing hypertension prevalence across the cumulative arsenic exposure remained significant after adjustment for age, sex, diabetes mellitus status, proteinuria, body mass index, and serum triglycerides level. The adjusted odds ratio (95% confidence interval) was 0.8 (0.2–3.2), 2.3 (0.8–6.8), 3.4 (1.2–9.2), 3.8 (1.4–10.3) and 2.9 (1.1–7.3), respectively, for those who had a cumulative arsenic exposure of 0.1–6.3, 6.4–10.8, 10.9–14.7, 14.8–18.5, and > 18.5 ppm-years compared with those who were unexposed.

In the above-mentioned mortality study in southwestern Taiwan (Tsai et al., 1999), the standardized mortality ratio (95% confidence interval) of hypertension for residents in the

Table 2
Epidemiological studies on the association between long-term arsenic exposure and risk of hypertension

Author, year	Study design	Study population	Hypertension diagnosis	Arsenic exposure	Prevalence	Odds ratio (95% CI)	Adjustment variables
Chen et al., 1995	Cross-sectional	898 residents in arseniasis-endemic area in southwestern Taiwan	SBP ≥ 160 mm Hg/ DBP ≥ 95 mm Hg/ Currently treated hypertension	Unexposed 0.1–6.3 ppm-years 6.4–10.8 ppm-years 10.9–14.7 ppm-years 14.8–18.5 ppm-years >18.5 ppm-years	5.0% 4.9% 12.8% 22.1% 26.5% 29.2%	1.0 (reference) 0.8 (0.2–3.2) 2.3 (0.8–6.8) 3.4 (1.2–9.2) 3.8 (1.4–10.3) 2.9 (1.1–7.3)	Age, sex, body mass index, diabetes, proteinuria, fasting serum triglycerides level
Rahman et al., 1999a,b	Cross-sectional	1481 arsenic-exposed and 114 unexposed residents in Bangladesh	SBP ≥ 140 mm Hg/ DBP ≥ 90 mm Hg/	Unexposed <1.0 ppm-years 1.0–5.0 ppm-years 5.1–10.0 ppm-years >10.0 ppm-years	7.9% 9.7% 12.0% 14.3% 22.9%	1.0 (reference) 0.8 (0.3–1.7) 1.5 (0.7–2.9) 2.2 (1.1–4.4) 3.0 (1.5–5.8)	Age, sex, body mass index
Zierold et al., 2004	Cross-sectional	1185 residents in Wisconsin	Self-reported disease	<2 ppb 2–10 ppb >10 ppb	– – –	1.0 (reference) 1.2 (0.8–1.6) 1.7 (1.1–2.5)	Age, sex, body mass index
Jensen and Hansen, 1998	Cross-sectional case–control	34 arsenic-exposed workers and 25 unexposed controls in Denmark	Digital blood pressure equipment	Unexposed Exposed	Mean±S.D. of systolic blood pressure 119.9±11.9 mm Hg 127.5±14.4 mm Hg (P=0.023, Kruskal–Wallis test)	Two groups matched on age and smoking status	

arseniasis-endemic area was 0.73 (0.62–0.85) for males and 1.20 (1.06–1.37) for females compared with residents in southwestern non-endemic area as the reference group. The corresponding figures using the general population in Taiwan as the reference group were 0.71 (0.61–0.83) and 1.02 (0.89–1.15), respectively. The impact of competing cause of death, the variation in coding and classification of underlying cause of death, the comparability between study and control areas, and the discrepancy in detection and treatment of hypertension might bias the findings. As most hypertensives may die from ischemic heart disease and stroke, their hypertension status might not be coded as an underlying cause of death. As arsenic may induce several lethal cancers and hypertension is less lethal if detected and managed early, mortality of hypertension might not correctly reflect its incidence. As the arseniasis-endemic area is a rural area, it may not be appropriate to use the entire population in both urban and rural areas of Taiwan as the standard population to derive the standardized mortality ratio. Based on these limitations, the findings of the mortality studies should be interpreted carefully.

Another study on 1481 residents in Bangladesh also found a dose–response relationship between ingested arsenic and hypertension prevalence (Rahman et al., 1999b). The status of hypertension was defined as a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg. Cumulative arsenic exposure was estimated from the history of consuming well water and the current arsenic concentration in well water. After adjustment for age, sex, and body mass index, the odds ratio (95% confidence interval) was 0.8 (0.3–1.7), 1.5 (0.7–2.9), 2.2 (1.1–4.4) and 3.0 (1.5–5.8), respectively, for cumulative arsenic exposure of <1.0, 1.0–5.0, 5.1–10.0 and >10.0 ppm-years compared with the unexposed as the reference group. The dose–response relationship was statistically significant ($P < 0.001$).

Community-based studies in low arsenic exposure areas

In the above-mentioned study in Wisconsin (Zierold et al., 2004), a significant dose–response relationship between arsenic concentration in private well water and self-reported hypertension was observed. After adjustment for age, sex and body mass index, the prevalence odds ratio (95% confidence interval) was 1.2 (0.8–1.6) and 1.7 (1.1–2.5), respectively, for arsenic exposure level of 2–10 and >10 ppb compared with the level <2 ppb as the reference group.

Occupational studies based on biomarkers

In the above-mentioned occupational study in Denmark (Jensen and Hansen, 1998), the arsenic-exposed workers had higher systolic and diastolic blood pressure than the unexposed reference group. The difference in systolic blood pressure was statistically significant ($P = 0.023$), but not the difference in diastolic blood pressure. The mean $\pm$ standard deviation of systolic blood pressure were 119.9 ± 11.9 mm Hg in the unexposed reference group and 127.5 ± 14.4 mm Hg in the

arsenic-exposed workers. The mean diastolic blood pressure was 77.9 mm Hg in the arsenic-exposed workers and 74.7 mm Hg in the unexposed reference group.

Conclusions and recommendations for future research

It is concluded that an increased prevalence of diabetes mellitus and hypertension has consistently observed among residents in the high arsenic exposure areas in Taiwan and Bangladesh, showing a dose–response relationship with arsenic level in drinking water. Inconsistent findings have been reported from occupational studies and community-based studies in low arsenic exposure areas, which might be biased by the inaccurate measurement of arsenic exposure and health outcome, inadequate number of study subjects, and limited control of confounding factors.

The low dose effect of arsenic on diabetes and hypertension needs further validation from cohort follow-up studies in populations with environmental or occupational exposure to arsenic. Future studies should have following characteristics: 1) an accurate diagnosis of diabetes mellitus using the fasting plasma glucose test; 2) a precise estimation of total arsenic burden from dietary, environmental and occupational sources during the entire exposure period; 3) a large sample size to ensure an adequate statistical power of the study; 4) an extended duration of follow-up long enough to allow the development of the chronic diseases; 5) an extensive use of biomarkers to assess integral arsenic exposure over time, arsenic methylation capability, and genetic susceptibility to arseniasis (Chen et al., 2005); 6) a comprehensive control of possible confounding variables; and 7) an intensive analysis of interaction between age, quantity and duration of exposure, and other risk factors for the chronic diseases under investigation.

In summary, high concentration of arsenic in drinking water is an important risk factor to induce diabetes mellitus and hypertension. The low dose effect and toxicological mechanism need further investigations.

References

- Bartoli, D., Battista, G., De Santis, M., Iaia, T.E., Orsi, D., Tarchi, M., Pirastu, R., Valiani, M., 1998. Cohort study of art glass workers in Tuscany, Italy: mortality from non-malignant diseases. *Occup. Med. (Lond.)* 48, 441–445.
- Chen, C.J., Wu, M.M., Lee, S.S., Wang, J.D., Cheng, S.H., Wu, H.Y., 1988. Atherogenicity and carcinogenicity of high-arsenic artesian well water: multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 8, 452–460.
- Chen, C.J., Hsueh, Y.M., Lai, M.S., Shyu, M.P., Chen, S.Y., Wu, M.M., Tai, T.Y., 1995. Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension* 25, 53–60.
- Chen, C.J., Chiou, H.Y., Chiang, M.H., Lin, L.J., Tai, Y.T., 1996. Dose–response relationship between ischemic heart disease mortality and long-term arsenic exposure. *Arterioscler. Thromb. Vasc. Biol.* 16, 504–510.
- Chen, C.J., Chiou, H.Y., Huang, W.I., Chen, S.Y., Hsueh, Y.M., Tseng, C.H., Lin, L.J., Shyu, M.P., Lai, M.S., 1997a. Systemic noncarcinogenic effects and developmental toxicity of inorganic arsenic. In: Abernathy, C.O., Calderon, R.L., Chappell, W.R. (Eds.), *Arsenic: Exposure and Health Effects*. Chapman and Hall, London, pp. 124–134.

- Chen, C.J., Hsueh, Y.M., Chiou, H.Y., Hsu, Y.H., Chen, S.Y., Horng, S.F., Liaw, K.F., Wu, M.M., 1997b. Human carcinogenicity of inorganic arsenic. In: Abernathy, C.O., Calderon, R.L., Chappell, W.R. (Eds.), *Arsenic: Exposure and Health Effects*. Chapman and Hall, London, pp. 232–242.
- Chen, C.J., Hsu, L.I., Wang, C.H., Shih, W.L., Hsu, Y.H., Tseng, M.P., Lin, Y.C., Chou, W.L., Chen, C.Y., Lee, C.Y., Wang, L.H., Cheng, Y.C., Chen, C.L., Chen, S.Y., Wang, Y.H., Hsueh, Y.M., Chiou, H.Y., Wu, M.M., 2005. Biomarkers of exposure, effect and susceptibility of arsenic-induced human hazards in Taiwan. *Toxicol. Appl. Pharmacol.* 206, 198–206.
- Chiou, H.Y., Huang, W.I., Su, C.L., Chang, S.F., Hsu, Y.H., Chen, C.J., 1997. Dose–response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke* 28, 1717–1723.
- Chiou, J.M., Wang, S.L., Chen, C.J., Deng, C.R., Lin, W., Tai, T.Y., 2005. Arsenic ingestion and increased microvascular disease risk: observations from the southwestern arseniasis-endemic area in Taiwan. In: *J. Epidemiol.* 35, 936–943.
- Chu, H.F., Chang, C.C., Tsai, S.S., Yang, C.Y., 2006. Does arsenic exposure increases the risk for diabetes mellitus? *Occup. Environ. Med.* 48, 63–67.
- Enterline, P.E., Marsh, G.M., 1982. Cancer among workers exposed to arsenic and other substances in a copper smelter. *Am. J. Epidemiol.* 116, 895–911.
- International Agency for Research on Cancer, 2004. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Some Drinking-Water Disinfectants and Contaminants, Including Arsenic*, Vol. 84. International Agency for Research on Cancer, Lyon.
- Jensen, G.E., Hansen, M.L., 1998. Occupational arsenic exposure and glycosylated hemoglobin. *Analyst* 123, 77–80.
- Lagerkvist, B.J., Zetterlund, B., 1994. Assessment of exposure to arsenic among smelter workers: a five-year follow-up. *Am. J. Ind. Med.* 25, 477–488.
- Lai, M.S., Hsueh, Y.M., Chen, C.J., Shyu, M.P., Chen, S.Y., Kuo, T.L., Wu, M.M., Tai, T.Y., 1994. Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am. J. Epidemiol.* 139, 484–492.
- Lewis, D.R., Southwick, J.W., Ouellet-Hellstrom, R., Recnch, J., Calderon, R.L., 1999. Drinking water arsenic in Utah: a cohort mortality study. *Environ. Health Perspect.* 107, 359–365.
- Lubin, J.H., Pottner, L.M., Stone, B.J., Fraumeni Jr., J.F., 2000. Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. *Am. J. Epidemiol.* 151, 554–565.
- Mabuchi, K., Lilienfeld, A.M., Snell, L.M., 1980. Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev. Med.* 9, 51–77.
- National Research Council, 1999. *Arsenic in Drinking Water*. National Academy Press, Washington DC.
- National Research Council, 2001. *Arsenic in Drinking Water: 2001 Update*. National Academy Press, Washington DC.
- Rahman, M., Axelson, O., 1995. Diabetes mellitus and arsenic exposure: a second look at case–control data from a Swedish copper smelter. *Occup. Environ. Med.* 52, 773–774.
- Rahman, M., Wingren, G., Axelson, O., 1996. Diabetes mellitus among Swedish art glass workers—An effect of arsenic exposure? *Scand. J. Work Environ. Health* 22, 146–149.
- Rahman, M., Tondel, M., Ahmad, S.A., Axelson, O., 1998. Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am. J. Epidemiol.* 148, 198–203.
- Rahman, M., Tondel, M., Chowdhury, I.A., Axelson, O., 1999a. Relations between exposure to arsenic, skin lesions, and glucosuria. *Occup. Environ. Med.* 56, 277–281.
- Rahman, M., Tondel, M., Ahmad, S.A., Chowdhury, I.A., Faruquee, M.H., Axelson, O., 1999b. Hypertension and arsenic exposure in Bangladesh. *Hypertension* 33, 74–78.
- Tollestrup, K., Frost, F.J., Harter, L.C., McMillan, G.P., 2003. Mortality among children residing near the American Smelting and refining Company (ASARCO) cooper smelter in Ruston, Washington. *Arch. Environ. Health* 58, 683–691.
- Tsai, H.C., Yen, T.S., Wang, L.T., Cheng, J.T., Tseng, W.P., Chen, C.M., 1966. An epidemiologic study of the cardiovascular diseases among inhabitants of a fishing village in Taiwan. Report 1: Blood pressure and hypertension. *J. Formos. Med. Assoc.* 65, 249–258.
- Tsai, S.M., Wang, T.N., Ko, Y.C., 1999. Mortality for certain diseases in areas with high levels of arsenic in drinking water. *Arch. Environ. Health* 54, 186–193.
- Tseng, W.P., 1977. Effects and dose–response relationships of skin cancer and blackfoot disease with arsenic. *Environ. Health Perspect.* 19, 109–119.
- Tseng, W.P., 1980. Outcome of untreated hypertensives in an agricultural population: a 15-year follow-up study. *J. Formos. Med. Assoc.* 314, 488–500.
- Tseng, C.H., Chong, C.C., Chen, C.J., Tai, T.Y., 1995. Dose–response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis* 120, 125–133.
- Tseng, C.H., Tai, T.Y., Chong, C.K., Tseng, C.P., Lai, M.S., Lin, B.J., Chiou, H.Y., Hsueh, Y.M., Hsu, K.H., Chen, C.J., 2000. Long-term arsenic exposure and incidence of non insulin dependent diabetes mellitus: a cohort study in arseniasis hyperendemic villages in Taiwan. *Environ. Health Perspect.* 108, 847–851.
- US Public Health Service, 1989. *Toxicological Profile for Arsenic*. US Public Health Service, Washington, DC.
- Wang, C.H., Jeng, J.S., Yip, P.K., Chen, C.L., Hsu, L.I., Hsueh, Y.M., Chiou, H.Y., Wu, M.M., Chen, C.J., 2002. Biological gradient between long term arsenic exposure and carotid atherosclerosis. *Circulation* 105, 1804–1809.
- Wang, S.L., Chiou, J.M., Chen, C.J., Wu, T.N., Chang, L.W., 2003. Prevalence of diabetes mellitus and its vascular complications in southwestern arseniasis endemic and non endemic areas in Taiwan. *Environ. Health Perspect.* 111, 155–159.
- World Health Organization, 1981. *Arsenic. Environmental Health Criteria*, vol. 18. World Health Organization, Geneva.
- World Health Organization, 2001. *Arsenic and Arsenic Compounds*, 2nd ed. *Environmental Health Criteria*, vol. 224. World Health Organization, Geneva.
- Zierold, K.M., Knobeloch, L., Anderson, H., 2004. Prevalence of chronic diseases in adults exposed to arsenic contaminated drinking water. *Am. J. Public Health* 94, 1936–1937.