Long-Term Arsenic Exposure and Incidence of Non–Insulin-Dependent Diabetes Mellitus: A Cohort Study in Arseniasis-Hyperendemic Villages in Taiwan

Chin-Hsiao Tseng,[1,2] Tong-Yuan Tai,[1] Choon-Khim Chong,[3] Ching-Ping Tseng,[4] Mei-Shu Lai,[5] Boniface J. Lin,[1] Hung-Yi Chiou,[2] Yu-Mei Hsueh,[2] Kuang-Hung Hsu,[6] and Chien-Jen Chen[7]

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Graduate Institute of Public Health, Taipei Medical College, Taipei, Taiwan; [3]Department of Rehabilitation, Chang Gung Memorial Hospital, and Chong's Physical Medicine and Rehabilitation Clinic, Taipei, Taiwan; [4]School of Medical Technology, Chang Gung University, Taoyuan, Taiwan; [5]Central Bureau of National Health Insurance, Taipei, Taiwan; [6]Department of Health Care Management, Chang Gung University, Taoyuan, Taiwan; [7]Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan

Diabetes prevalence in arseniasis-hyperendemic villages in Taiwan has been reported to be significantly higher than in the general population. The aim of this cohort study was to further evaluate the association between ingested inorganic arsenic and the incidence of non–insulin-dependent diabetes mellitus in these villages. A total of 446 nondiabetic residents in these villages were followed biannually by oral glucose tolerance test. Diabetes is defined as a fasting plasma glucose level ≥ 7.8 mmol/L and/or a 2-hr post-load glucose level ≥ 11.1 mmol/L. During the follow-up period of 1499.5 person-years, 41 cases developed diabetes, showing an overall incidence of 27.4/1,000 person-years. The incidence of diabetes correlated with age, body mass index, and cumulative arsenic exposure. The multivariate-adjusted relative risks were 1.6, 2.3, and 2.1 for age ≥ 55 versus < 55 years, a body mass index ≥ 25 versus < 25 kg/m^2, and a cumulative arsenic exposure ≥ 17 versus < 17 mg/L-years, respectively. The incidence density ratios (95% confidence intervals) between the hyperendemic villages and the two nonendemic 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 findings are consistent with our previous cross-sectional observation that ingested inorganic arsenic is diabetogenic in human beings. *Key words*: diabetes mellitus, incidence, ingested arsenic, oral glucose tolerance test, water pollutant. *Environ Health Perspect* 108:847–851 (2000). [Online 31 July 2000]
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The atherogenic and carcinogenic effects of arsenic have long been observed among individuals exposed to a high level of inorganic arsenic from drinking artesian well water in the villages located at the southwestern coast of Taiwan (*1*).

In our recent study, the prevalence of diabetes mellitus was 2-fold higher in these areas than in Taipei City and the Taiwan area in general (*2*). A dose–response relation between cumulative arsenic exposure (CAE) and the prevalence of diabetes mellitus was also demonstrated after adjustment for multiple risk factors (*2*). Rahman and Axelson (*3*) carried out a small case–control study on Swedish copper smelter workers; using the death records for 1960–1976 from the parish register, they compared three arsenic exposure categories with an unexposed group. They observed an increased risk of dying from diabetes mellitus with increasing arsenic exposure; odds ratios were 2.0, 4.2, and 7.0 ($p = 0.03$ for the trend) for exposure to < 0.5, 0.5, and > 0.5 mg/m^3 arsenic in the air, respectively, as compared to an unexposed control group. In another similar but larger study carried out among art glass workers, the odds ratio of dying from diabetes mellitus was 1.8 [95% confidence interval (CI), 1.1–2.8] for the exposed glass workers as compared to the unexposed ones (*4*). In a community-based survey of diabetes mellitus in Bangladesh, Rahman et al. (*5*) observed a dose–response trend between the prevalence of diabetes mellitus and the arsenic level in drinking water.

Prevalence data provide the information for the generation of hypotheses, but suffer from some drawbacks in evaluating a causal relationship. Because the prevalence of a given disease is a function of its incidence and duration (*6*), an increase of prevalence could be attributable to the increase in disease incidence and/or duration. If long-term arsenic exposure increases the incidence and decreases the survivalship of diabetes mellitus, the dose–response manner between arsenic and diabetes mellitus will be less striking when prevalence is used rather than incidence data. Therefore, it is more appropriate to look further into the association between long-term arsenic exposure and the incidence of diabetes mellitus. In this paper, we describe our study in which we used a biannual 75 g oral glucose tolerance test to follow a cohort of subjects who were free from diabetes mellitus for a period of 4 years.

Materials and Methods

The study area, study subjects, original community-based survey, and estimation of CAE have been previously described in detail (*2*). In brief, the study area included three villages located on the southwestern coast of Taiwan where arseniasis was hyperendemic. Because of the high salinity in the water of shallow wells, residents in these villages used artesian well water for drinking and cooking (*7*). The median arsenic concentration of artesian well water ranged from 0.70 to 0.93 mg/L (*7,8*). A tap water supply system using surface water was implemented in the 1960s, but few people had access to this water until the late 1970s. The standard for arsenic in drinking water set by the U.S. Environmental Protection Agency is 0.05 mg/L (*9*).

In Taiwan, the household registration system is effective and efficient because of the completeness and accuracy of the registration information. To recruit a cohort of residents for a long-term follow-up study on health hazards associated with long-term arsenic exposure, we selected only those residents who lived at least 5 days a week in the study villages. A total of 2,258 residents older than 30 years of age were registered in the study villages, but only 1,571 of them were eligible for the recruitment in our cohort. Most of the other 687 registered residents worked in Chiayi City and its suburban area, returning to the study villages during weekends. All eligible subjects were interviewed at home from September 1988 through June 1989. A standardized personal interview based on a structured questionnaire was carried out by two public health nurses who were well trained in interview techniques and questionnaire details. Information obtained from the interviews included history of high-arsenic artesian well water consumption, residential history, socioeconomic and demographic characteristics,

Address correspondence to C-H. Tseng, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan. Telephone: 886-2-23970800 ext. 7247. Fax: 886-2-23711453. E-mail: ccktsh@ms6.hinet.net

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alcohol intake, cigarette smoking, physical activities, as well as a personal and family history of hypertension and diabetes. A total of 1,081 eligible subjects interviewed between September and December 1988 were invited to participate in a health examination in January and February 1989 on a voluntary basis. No incentives were offered to the subjects. Another 490 eligible subjects who were interviewed after December 1988 were not invited to participate in the examination. A total of 941 residents, including 408 men and 533 women, participated in the community-based health examination from January to February 1989. Among them, 381 (93.4%) men and 510 (95.7%) women agreed to be tested for diabetes mellitus by oral glucose tolerance test. Lai et al. (*2*) analyzed these data and found that the prevalence of diabetes mellitus was significantly associated with CAE. To further clarify the diabetogenic effect of arsenic, we decided to follow the subjects who were not found to be diabetic and whose CAE data were available in the prevalence study for the development of diabetes mellitus. After exclusion of known cases of diabetes mellitus identified during the baseline health examination (86 cases) and residents whose CAE status was unknown (173 cases), a total of 632 subjects were eligible for the evaluation of the association between the incidence of diabetes mellitus and CAE. In 1991 and 1993, 446 of them agreed to participate in the follow-up examination by oral glucose tolerance test.

Some study subjects had moved from one village to another, and the arsenic concentrations were different in the artesian well water of these villages. We derived an index of CAE to reflect the overall exposure to arsenic for each study subject, taking into account both the duration and the arsenic level of artesian well water. This CAE index is the sum of products derived by multiplying the arsenic concentration in well water (in milligrams per liter) by the duration of water consumption (in years) during consecutive periods of residence in different villages. Thus, the CAE is derived by the following formula: $\Sigma(C_i \times D_i)$, where C_i is the median arsenic concentration in the well water of the village where a given study subject lived during period i, and D_i is the duration of drinking well water in the village during period i. We calculated cumulative arsenic exposure only for subjects for whom there was complete information on arsenic exposure from drinking water throughout the subject's lifetime. In other words, the arsenic exposure index of a given subject was classified as unknown if the arsenic concentration of well water in any village where the subject had lived during his or her lifetime was not available. We excluded the subjects with unknown CAEs from the follow-up study of diabetes incidence.

For the determination of fasting plasma glucose, we collected blood samples in the morning after overnight fasting for > 12 hr. We then conducted an oral glucose tolerance test by administering 75 g glucose dissolved in 300 mL water. Post-load blood samples were taken 2 hr after the glucose loading. Plasma glucose levels were determined on-site with a glucose analyzer (LM4 analyzer; Analox Instruments Ltd., London, UK) using a glucose oxidase method. We define diabetes mellitus as a fasting glucose level ≥ 7.8 mmol/L and/or a 2-hr post-load glucose level ≥ 11.1 mmol/L according to the criteria set by the World Health Organization (WHO).

We recorded the follow-up person-time for each individual and calculated diabetes incidence under the assumption that diabetes mellitus is a lifelong disease. We calculated the overall incidence rate of diabetes mellitus in the study population as the total number of incident cases divided by the sum of follow-up person-time in all subjects. The incidence rate in specific subgroups of age, sex, body mass index (BMI), and CAE was calculated as the number of newly diagnosed cases divided by the sum of person-time of individuals in the subgroup. To clarify the effect of arsenic exposure on the incidence of diabetes mellitus adjusting for age, sex, and BMI, we compared the incidences between the lower and higher arsenic exposure groups at different strata of these possible confounders.

For control areas, we used two nonendemic townships for which incidence of non–insulin-dependent diabetes mellitus (NIDDM or Type 2) was recently reported (*10*). We used this published data for ecologic comparison because the two populations (endemic and nonendemic areas) shared many similarities. The study areas are all rural areas in Taiwan. Most of the residents in these areas are engaged in farming, fishery, and salt production. All of the subjects are of the same racial origin (Fukkien Taiwanese) and share similar socioeconomic status, living environments, lifestyles, dietary patterns, medical facilities, and educational levels. The only major differences in environmental exposure among residents in the arseniasis-hyperendemic area appears to be the arsenic level in the drinking water. Moreover, our cohort study shares many similarities in method and analysis with the study of Wang et al. (*10*). Both studies were carried out during similar study periods by using the WHO criteria for diagnosis of diabetes mellitus. The calculation and expression of incidences of diabetes mellitus were similarly based on an incidence density method by calculating the person-years of follow-up of each of the study subject. Moreover, similar confounders such as age, sex, and BMI were all considered in both studies. The values of these variables were also available for making comparisons. To compare our data with those of Wang et al. (*10*), we calculated the age-specific incidences of diabetes mellitus for the arseniasis-hyperendemic villages by categorizing the subjects into age groups similar to those used by Wang et al. (*10*) in the control areas. We also calculated the incidence density ratios between the arseniasis-hyperendemic villages and the control areas.

We used the chi-square test and the Student's *t*-test to compare the differences in the baseline data between the subjects who were followed-up successfully and those who were lost to follow-up in our cohort, between our cohort and the external control cohort by Wang et al. (*10*), and between the incident and nonincident cases in our cohort. We used multivariate analysis by Cox's proportional hazards model to estimate the relative risks of higher arsenic exposure on the incidence of diabetes mellitus after adjustment for the effects of age, sex, and BMI. We calculated the 95% CIs of the relative risks from the corresponding regression coefficients and standard errors.

Results

During a follow-up period of 1499.5 person-years, 41 of 446 subjects developed diabetes mellitus in the arseniasis-hyperendemic villages. The calculated incidence rate was 27.4/1,000 person-years. The follow-up rate was 70.6%. Table 1 shows a comparison of the baseline characteristics between subjects who were followed-up successfully and those who were lost to follow-up in the arseniasis-hyperendemic villages. None of these variables differed significantly between these two groups. In univariate analyses, we found no significant associations with incidence of diabetes mellitus for variables such as sex, cigarette smoking, alcohol consumption, physical activity at work, and family history of diabetes mellitus. However, age and BMI were significantly associated with diabetes incidence.

Table 2 presents the comparison of the baseline characteristics in subjects followed-up

Table 1. Comparison of baseline characteristics between subjects who were followed-up successfully and those who were lost to follow-up in arseniasis-hyperendemic villages.

Variables	Followed-up (n = 446)	Lost (n = 186)
Age (years)	47.4 ± 0.5	47.5 ± 0.9
Sex (% male)	50%	54.3%
Body mass index (kg/m^2)	24.5 ± 0.2	23.9 ± 0.3
CAE	12.1 ± 0.5	13.2 ± 0.8

Values shown are mean ± SE except where indicated. Differences are not significant for any of the variables or on the basis of chi-square test or Student's *t*-test.

successfully between the arseniasis-hyperendemic group and the nonendemic external control group. The BMI was not significantly different between the two groups. However, our arsenic-exposed cohort was younger with an equal number of men and women, and the control group was older and had more women. Because sex was not found to be a significant risk factor for newly developed diabetes mellitus in both our current study and the study by Wang et al. (*10*) and the BMI was similar between the two comparison groups, only age could exert significant confounding effect when the incidence rates in these two groups are compared. We further stratified age into subgroups and compared the age-specific incidence density ratios in each subgroup. The age-specific incidences of diabetes mellitus in the arseniasis-hyperendemic villages and the two nonendemic control townships are shown in Figure 1. The age-specific incidence density ratios (95% CIs) between the hyperendemic villages and 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 subjects living in arseniasis-hyperendemic villages have higher incidence rates of diabetes mellitus than subjects living in nonendemic areas.

The baseline data of the newly diagnosed diabetic and nondiabetic subjects living in arseniasis-hyperendemic villages are shown in Table 3. The distribution of sex was not significantly different between these two groups. However, newly diagnosed diabetic cases had a significantly higher mean age, BMI, and CAE than nondiabetic subjects. We used cutoff points to categorize various continuous variables. We used a BMI cutoff of 25 kg/m^2 because it is generally used to define overweight (*11*). We did not use the definition of obesity (BMI ≥ 30 kg/m^2) because in the Taiwanese population, only a small proportion of diabetic patients met this criterion. We used the age cutoff of 55 years because there was an abrupt increase in the incidence of diabetes mellitus in the age cohort > 55 years of age at the time of recruitment, as shown in Figure 1. We used the CAE cutoff of 17 mg/L-years, the median value of CAE in the newly diagnosed cases, in order to obtain optimal numbers in each subgroup of exposure to assure precise estimates for the relative risks.

Table 4 shows the comparison of the incidence rates of diabetes mellitus between groups of CAE < 17 and ≥ 17 mg/L-years by different strata of age, sex, and BMI. Subjects with a CAE ≥ 17 mg/L-years consistently had a higher incidence rate of diabetes mellitus than those with a CAE < 17 mg/L-years.

Table 5 shows a comparison of the incidence rates and relative risks between different subgroups of age, sex, BMI, and CAE. Age, BMI, and CAE were significantly associated with the development of diabetes. The multivariate-adjusted relative risks (95% CIs) based on the Cox's proportional hazards model were 1.6 (0.8–3.3), 1.1 (0.6–2.1), 2.3 (1.2–4.3), and 2.1 (1.1–4.2), respectively, for groups of old age, male sex, overweight, and high CAE compared with groups of young age, female sex, normal weight, and low CAE. When used as a continuous variable, the CAE was associated with incidence of diabetes mellitus with a relative risk of 1.03 for every 1 mg/L-year of exposure after adjustment for age, sex, and BMI ($p < 0.05$).

Discussion

The results of this study support the association between a long-term arsenic exposure and diabetes mellitus, as found in our previous prevalence study (*2*) and in the studies observed by other investigators (*3–5*). However, this is the first prospective follow-up study that assessed the incidence of diabetes mellitus in the arseniasis-hyperendemic villages by comparing the data to data obtained from two nonendemic control areas (external control) (Figure 1) and by comparing a higher arsenic exposure group to a lower exposure group after adjustment for age, sex, and BMI in the arseniasis-hyperendemic villages (internal control) (Tables 4 and 5). The incidences rose abruptly in the age groups > 55 years among villagers in arseniasis-hyperendemic area (Figure 1). These birth cohorts also have an abrupt increase in the prevalence of peripheral vascular disease assessed with Doppler ultrasonography (*12*). They had higher long-term arsenic exposures than those < 55 years of age. They were exposed to well water for > 30 years, which was deemed to be an induction period for blackfoot disease (BFD) before tap water became commonly accessible. BFD is an endemic peripheral vascular disease confined to the southwestern coast of Taiwan. It is characterized by progressive narrowing of peripheral arteries, especially those involving the lower extremities. Clinically, the patients suffer from coldness, numbness, and intermittent claudication in the lower legs, which may progress to ulceration, gangrene, and spontaneous amputation (*12,13*). Pathologically, BFD is compatible with thromboangiitis obliterans and arteriosclerosis obliterans (*12,13*). The cause of the disease has been ascribed to the drinking of artesian well water containing high arsenic concentrations (*12,13*).

Age and BMI are known risk factors for the development of diabetes mellitus (*10,14*). We also observed this association in the present study. However, the diabetes incidence for the higher arsenic exposure group (CAE ≥ 17 mg/L-years) remained 2 times higher after multivariate adjustment (Table 5). In the comparison between the higher arsenic exposure group (≥ 17 mg/L-years) and the lower exposure group (< 17 mg/L-years) in our cohort, the relative risk for the high exposure group would have been underestimated because a large proportion of the referent group had also been exposed to arsenic. They were not in a group with truly low exposure

Table 2. Comparison of baseline characteristics in subjects who were followed-up successfully between the arseniasis-hyperendemic group and the nonendemic control group.

Variables	Arseniasis-hyperendemic	Nonendemic control	p^a
Age (years)	47.4 ± 0.5	52.3 ± 0.5	< 0.005
Sex (% male)	50%	45.4 %	< 0.005
BMI (kg/m^2)	24.5 ± 0.1	24.2 ± 0.2	NS

NS, not significant. Values shown are mean ± SE except where indicated.
[a]Based on chi-square test or Student's *t*-test.

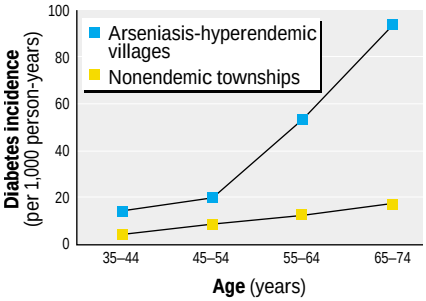

Figure 1. Comparison of age-specific incidence rates (per 1,000 person-years) of diabetes mellitus in arseniasis-hyperendemic villages and in two nonendemic townships in Taiwan.

Table 3. Comparison of baseline characteristics between newly diagnosed diabetic and nondiabetic subjects living in arseniasis-hyperendemic villages in Taiwan.

Variables	Newly diagnosed cases (n = 41)	Noncases (n = 405)	p^a
Sex (% male)	58.5	49.1	NS
Age (% ≥ 55 years)	36.6	18.5	< 0.01
BMI (% ≥ 25 kg/m^2)	58.5	36.3	< 0.01
CAE (% ≥ 17 mg/L-years)	51.2	27.4	< 0.005
Age (years)	52.7 ± 1.6[b]	46.8 ± 0.5	< 0.001
BMI (kg/m^2)	25.8 ± 0.7	24.3 ± 0.2	< 0.05
CAE (mg/L-years)	15.6 ± 1.7	11.8 ± 0.5	< 0.05

NS, not significant.
[a]Based on chi-square test or Student's *t*-test. [b]Mean ± SE.

levels. This can be supported in part by the observation that the age-specific incidence density ratios between the arseniasis-hyperendemic group and the external control group without arsenic exposure had a risk > 2 times higher (Figure 1). According to the continuous data analysis, a CAE difference of 50 mg/L-years will result in a relative risk of 4.4.

We observed NIDDM because all of the study subjects were > 30 years of age. None of them developed diabetic ketoacidosis or required insulin treatment during the period of follow-up. Moreover, all of the subjects were diagnosed by an oral glucose tolerance test without significant clinical symptoms.

There are only a few reports on the incidence of NIDDM. According to the study of Bender et al. (*15*) in Minnesota, the incidence rate of NIDDM in Caucasians is 1.2/1,000 person-years. In Nauruans, the incidence rate is 16.0/1,000 person-years in subjects > 20 years of age (*16*), and in Pima Indians, the incidence rate is 18.5/1,000 person-years for all ages combined and 46/1,000 person-years in subjects > 25 of age (*17*). After standardization to the white population in the United States in 1970, the incidence rates of NIDDM are 1.34/1,000 and 26.5/1,000 person-years for Caucasians and Pima Indians, respectively (*17*). Wang et al. (*10*) followed a cohort for up to 5 years; this cohort, from two townships in Taiwan, was 35–74 years of age and free from diabetes. The crude incidence rates of NIDDM in men and women were 9.8/1,000 and 9.0/1,000 person-years, respectively. After age-standardization to the United States population in 1970, the incidence rate was calculated to be 9.3/1,000 person-years. In our present study carried out in a cohort with arsenic exposure, the incidence of diabetes mellitus standardized to the United States population in 1970 was approximately 2 times higher than that in the nonendemic areas.

The administration of arsenic has been demonstrated to cause hyperglycemia in experimental animals and to affect the functions of insulin receptor and glucose transportation (*18–24*). Arsenic has been found to cause mitochondrial damage, degeneration, and necrosis of β cells in the islets of mice after intraperitoneal injection of arsenite plus hydroxylamine, with a consequence of transient hyperglycemia (*18*). Sulfhydryl groups play important structural and functional roles in both insulin receptors (*25*) and glucose transporters (*26*). Phenylarsine oxide, a trivalent arsenical, forms stable cyclic thioarsenite complexes with vicinal or paired thio groups of cellular proteins. This compound has been shown to inhibit glucose transport in adipocytes stimulated by the insulin mimickers vanadate and hydrogen peroxide (*22*). Phenylarsine oxide has also been shown to inhibit protein internalization, and it exhibits an inhibitory effect on the internalization of insulin receptor complexes in rat hepatocytes (*27*) and CT3-C2 fibroblasts (*28*). Jhun et al. (*29*) demonstrated the existence of a phenylarsine oxide sensitive GLUT4 degradation in rat adipocytes, which might have pathophysiologic significance, giving rise to clinical problems of insulin resistance. Phenylarsine oxide also inhibits the stereospecific uptake of D-glucose in basal and insulin-stimulated rat adipocytes (*19–22*) in a dose–response pattern. Phenylarsine oxide also inhibits insulin binding at a higher concentration and insulin internalization (*19*). Douen and Jones (*19*) suggested that phenylarsine oxide has a direct inhibitory effect on both the receptor system and the transporter system, possibly by reacting with sulfhydryl groups at or near the receptor or transporter sites. This does not exclude the possibility of a reaction with a component of the coupling system between receptor and transporter, as suggested by Frost and Lane (*22*).

Vicinal sulfhydryls also play important roles in the activation of glucose transport by insulin and insulin-like agents in skeletal muscle (*24*). Phenylarsine oxide exhibits an inhibitory effect on insulin-stimulated or hypoxia-stimulated glucose transport in rat skeletal muscle (*24*). Denervation-induced postreceptor resistance of glucose transport to insulin and insulin-like growth factor I also involves primarily a phenylarsine oxide-sensitive pathway in rat skeletal muscle (*23*).

Deficiencies of trace elements such as copper and zinc have been suggested to play some role in the pathogenesis of diabetes mellitus (*30*). On the other hand, administration of cadmium has been shown to cause hyperglycemia (*31*). Arsenic has been reported to interact with these chemicals. Arsenic exposure can lead to a significant increase in renal copper excretion and can potentiate the effects of cadmium when arsenic and cadmium are used together (*32*). Arsenic may also compete with zinc in metal-binding proteins that display vicinal dithiols contained in zinc fingers of DNA binding and repair proteins. This competitive binding causes conformational change and altered biologic function in proteins (*33*). These effects of arsenic may explain some of the possible mechanisms of its diabetogenic effect.

In conclusion, the diabetogenic effect of arsenic in humans has been reported in different ethnic groups via different exposure routes (*2–5*). To the best of our knowledge, this is the first study to evaluate the association

Table 4. Incidence of diabetes mellitus (per 1,000 person-years) in low and high CAE groups in arseniasis-hyperendemic villages in Taiwan.

	CAE (mg/L-years)					
	< 17			≥ 17		
Variable	Total no.	Newly diagnosed cases (*n*)	Incidence rate	Total no.	Newly diagnosed cases (*n*)	Incidence rate
Age (years)						
≥ 55	28	2	21.1	62	13	64.8
< 55	286	18	18.8	70	8	33.3
Sex						
Male	145	11	22.1	78	13	49.2
Female	169	9	16.1	54	8	45.2
BMI (kg/m^2)						
≥ 25	122	11	26.5	49	13	78.1
< 25	192	9	13.8	83	8	28.2

Table 5. Incidence rates (per 1,000 person-years) and relative risks for diabetes mellitus in subgroups of subjects living in arseniasis-hyperendemic villages in Taiwan.

Variable	Total no.	Newly diagnosed DM cases (*n*)	Incidence rate	RR (95% CI)	ARR (95% CI)
Age (years)					
≥ 55	90	15	50.8	2.4 (1.3–4.5)*	1.6 (0.8–3.3)
< 55	356	26	21.6	1.0	1.0
Sex					
Male	223	24	31.5	1.3 (0.7–2.5)	1.1 (0.6–2.1)
Female	223	17	23.1	1.0	1.0
BMI (kg/m^2)					
≥ 25	171	24	42.1	2.3 (1.2–4.3)*	2.3 (1.2–4.3)*
< 25	275	17	18.3	1.0	1.0
CAE (mg/L-years)					
≥ 17	132	21	47.6	2.5 (1.4–4.7)*	2.1 (1.1–4.2)*
< 17	314	20	18.9	1.0	1.0

Abbreviations: DM, diabetes mellitus; RR, relative risk (based on Cox models with each variable singly); ARR, adjusted relative risk (based on Cox model with all variables simultaneously).
* $p < 0.05$.

between high arsenic exposure from drinking water and the development of diabetes mellitus by following the incidence of diabetes in a cohort exposed to arsenic. We also performed an ecologic comparison by comparing the incidences of diabetes mellitus in our cohort and an external control population studied by other investigators (*10*). Our findings support the hypothesis that arsenic is diabetogenic in humans. Although the pathophysiologic mechanisms of arsenic require further investigation, the health hazards of arsenic exposure should be attended and remedial measures should be taken.

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