Hypertension Incidence after Tap-Water Implementation: A 13-Year Follow-up Study in the Arseniasis-Endemic Area of Southwestern Taiwan

Shu-Li Wang[1,2], Wan-Fen Li[1], Chien-Jen Chen[3,4], Yeou-Lih Huang[5], Jen-Wen Chen[1], Kuang-Hsi Chang[1], Lih-Yu Tsai[6], Kai-Ming Chou[7]

[1]Division of Environmental Health & Occupational Medicine, National Health Research Institutes, Miaoli, Taiwan; [2] The Department of Public Health, Chung Shan Medical University, Taichung, Taiwan; [3]Genomics Research Center, Academia Sinica, Taipei, Taiwan; [4]Graduate Institute of Epidemiology, National Taiwan University, Taipei, Taiwan; [5]Faculty of Biomedical Laboratory Science, Kaohsiung Medical University, Kaohsiung, Taiwan, [6]Department of Clinical Laboratories, Kaohsiung Medical University, Kaohsiung, Taiwan; [7]Department of Public Health, School of Medicine, Taipei Medical University, Taipei, Taiwan.

Corresponding Author:

Dr Shu-Li Wang, Division of Environmental Health and Occupational Medicine, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan, ROC.

E-Mail: slwang@nhri.org.tw; slwang.tw@gmail.com. Skyp: slwang.tw

Tel.: +886-37-246-166 ext. 36509. Fax: +886-37-587-406.

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Abstract

The risk of disease from previous inorganic arsenic exposure, even after a significant reduction of ingestion, is a global public health concern. The authors first assessed the incidence of hypertension two to three decades after high arsenic exposure and examined its relationship to previous arsenic ingestion, later arsenic exposure, and conventional risk factors. Before 1970, local residents of an arseniasis-endemic area of southwestern Taiwan drank artesian well water. After 1970, the tap water supply system gradually began to cover these areas, replacing the well water as the primary water source. The study began in 1990 and consisted of 490 non-hypertensive residents over 30 years of age from this area of southwestern Taiwan. A total of 138 subjects were lost to follow-up. Of the remaining 352 subjects, 110 developed hypertension. The 7th Joint National Committee criterion was adopted for the definition of hypertension at both the baseline and the 2002/03 follow-up. Arsenic concentrations in the artesian well water consumed by the local residents during the 1960s and urinary arsenic levels measured in 2002/03 were both utilized to determine exposure risk. The incidence of hypertension appeared not to be significantly associated with previous exposure to arsenic. The incidence increased 2.32 fold (95% CI: 0.97–5.55, p=0.058) in those subjects with As(V) ≥2.67μg/g creatinine (the upper tertile) after adjustments for age, gender, BMI, cigarette smoking, and education. Diastolic blood pressure was shown to increase with an increased cumulative arsenic ingestion from drinking water (beta=0.27,

p<0.001). The slightly increased risk of hypertension might have resulted from a moderately increased inorganic arsenic exposure above background. This study indicated that monitoring of arsenic exposure and related incidence of cardiovascular disease is necessary in arsenic exposure areas even after arsenic levels in the drinking water are reduced.

Key words: hypertension, arsenic, water consumption, environmental health, obesity, prevention, risk factors

Abbreviations:

As: Arsenic

As(III): arsenite

As(V): arsenate

BMI: body mass index

CV: coefficient of variation

DMA: dimethylarsinic acid

HDL: high density lipoprotein

HPLC: high-performance liquid chromatography

LDL: low density lipoprotein

MMA: monomethylarsonic acid

TRG: triglycerides

1. Introduction

Inorganic arsenic is ubiquitous and raises global health concerns because of the increasing dependence on groundwater for daily drinking (Smith et al., 2002). Arsenic contamination has been found in many countries in Southeast Asia, North America, South America, and Europe (Nordstrom, 2002). Arsenic in drinking water has been found to be associated with an increased prevalence of hypertension (Chen et al., 1995), cardiovascular disease (Tseng et al., 2003; Tseng, 2008), cerebrovascular disease risk (Wang et al., 2002), and other conditions, including renal disease and neurological dysfunction (Wang et al., 2003). We are particularly interested in evaluating the remaining risk for an increased incidence of hypertension following a substantial reduction in arsenic ingestion after introduction of treated tap water to arseniasis-endemic communities.

Hypertension is recognized as a major risk factor for a number of diseases (Kannel,

1996), including stroke (Hu et al., 2005), ischemic heart disease (Rodgers et al., 2000; Mehler et al., 2003), and end-stage renal failure (Iseki et al., 2000). Hypertension prevalence and incidence have both been shown to be increasing worldwide (Ueshima et al., 2000; Callow, 2005). Preventing hypertension would in turn prevent its associated vascular complications and related heath-care costs (Rodgers et al., 2000; Mehler et al., 2003). Arsenic in drinking water may soon join obesity, cigarette smoking, and salt intake as an important modifiable lifestyle factor that can be altered in an effort to prevent cardiovascular disease.

Before 1970, local residents of an arseniasis-endemic area in southwestern Taiwan drank artesian well water. This was preferable to the highly saline, shallow well water available between 1910 and 1970 (Lo et al., 1977). After 1970, the tap water supply system gradually began to cover these areas. The arsenic level at these sites has been routinely checked, and the exposure to the residents was substantially reduced to meet the regulatory concentration of 10 ppb. To evaluate changes in hypertension risk, we followed a geographically stable population with documented previous ingestion of arsenic from artesian well water (Chen et al., 1995). This 13-year (1990-2003) follow-up cohort provides a unique opportunity to assess hypertension occurrence two to three decades after high arsenic exposure, with conventional risk factors being considered.

2. Materials and Methods

2.1 Subjects

The Human Ethical Committee of the National Health Research Institutes in Taiwan approved the study protocol. Before participation, each subject provided informed consent after receiving a detailed explanation of the study and its potential consequences.

Subjects were from a community-based cohort established by Chen et al. (1995) in 1990 from three villages in the Budai Township in southwestern Taiwan's Chiayi County. This township had a high (9.6%–13.6%) prevalence of blackfoot disease (Wu et al., 1961) and a median arsenic concentration in its artesian well water ranging from 700 to 930 μg/L (Kuo, 1964; Chen et al., 1995), which is much higher than the current water standard of 10 μg/L in Taiwan and the United States. Local residents relied on artesian wells for daily drinking water into the 1960s because of the high salinity of shallow wells in this coastal region. A tap water supply system with a reduced arsenic concentration was implemented in the study area in the early 1960s; however, coverage remained low until the early 1970s.

Initially, 1571 subjects over the age of 30 were interviewed in 1988–89. Each subject was a registered resident at the local household-registration office and lived at least 5 days a week in the three study villages (Chen et al., 1995). A total of 898 residents participated in health examinations, including cardiovascular disease risk assessments (i.e. blood pressure, lipids, etc.) in 1989-90 (Figure 1). A cohort of 779 residents with blood pressure records and contact addresses both available in 1990 were studied. We excluded 289 subjects diagnosed

with hypertension and investigated the 490 non-hypertensive subjects. Subjects were invited for health checkups in 1993, 1996, and 2002/03. By 2002/03, 382 (78%) of these subjects were successfully followed and 138 had been lost to follow-up because they were untraceable (i.e. changes in their national-identification numbers) or had refused to be followed. If there were missing data on hypertension and related parameters for certain subjects in 1990, we utilized the data from 1993 and then from 1996. Similarly, if subjects had missing data in 2002/03, we used data from 1996 (and so forth) to obtain the longest follow-up duration for each individual. Thirty subjects died during the 1990–2002/03 follow-up periods. Only 2 (0.6%) of the 352 living subjects had moved away from this study township between 1990 and 2002/03.

The present report detailing the 110 new hypertensive subjects examined previous and current arsenic exposure as well as conventional risk factors. Among the 352 subjects studied, 195 provided morning urine samples in 2002/03 for standardized analyses of arsenic species, with 184 of them having sufficient urine volume for the 4-species measurements as well as creatinine (182 available).

2.2 Hypertension and related parameters

The World Health Organization standard protocol for measuring blood pressure (Rose et al., 1982) was used at baseline and follow-up. Systolic and diastolic blood pressures (BPs)

were measured three times using an arm mercury sphygmomanometer with a suitable cuff size after subjects had rested for 20 minutes or longer. The average of three measurements was used for data analysis. The criteria of the 7th Joint National Committee report (Chobanian et al., 2003) for hypertension (systolic BP >140 mmHg, diastolic BP >90, or on anti-hypertensive therapy) was used at both baseline and follow-up. A standardized questionnaire was used to acquire demographic factors, artesian well water usage, dietary habits, lifestyle, and personal and family history of hypertension and cardiovascular diseases at baseline (Chen et al., 1995). Education was utilized as an index of socioeconomic status and was based on duration of formal schooling: <1 year, 1–8 years, and ≥9 years. Body mass index and waist girth were used as an obesity index. Subjects were encouraged to provide early-morning urine samples to health examiners; if they did not, this was recorded. Venous blood was obtained after a 10-hour fast. Fasting serum was analyzed for glucose, triglycerides (TRG), and low- and high-density lipoproteins (LDL, HDL). There were missing data for some observations, ranging from 6 missing observations for glucose up to 27 for HDL, because of limited serum volume. Urinary creatinine (used to adjust for urinary arsenic) was analyzed in the central laboratory of the Kaohsiung Medical Center using a Beckman SYNCHRON LX20 (Beckman Coulter, Fullerton, CA). The coefficient of variation (CV) ranged between 0.4% and 3.4% with means of 2.8% and 2.2% for day-to-day and within run, respectively.

2.3 Inorganic arsenic ingestion levels

*2.3.1 Arsenic ingestion from artesian well water***.**

We utilized arsenic concentrations for the artesian well water as provided by the National Taiwan University group (Kuo, 1964). The water-contained arsenic recovery efficiencies were 95% or greater and were obtained using a PerkinElmer UV-VIS spectrophotometer incorporating a Klett-Summerson colorimeter. The data were validated and utilized for the evaluation of arsenic exposure in the community (Chen et al., 1995). For villages that used more than one artesian well as a source of potable water, median levels of water arsenic concentration across wells were used. The arsenic levels in artesian well water within the study area have been reported to be stable (Lo et al., 1977). During the 1950s–70s, most blocks had several artesian wells available within walking distance. Therefore, we utilized the median concentration for each subject who might walk around and use an available well. We recorded each subject's residential history to identify the arsenic median concentration for each period of time. We used the new concentration when residents moved from one village to another during the exposure period. We then adopted an index of cumulative arsenic exposure (micrograms per liter years) as defined by the sum of products derived by multiplying the arsenic concentration (in micrograms per liter) in well water by the duration of water consumption (in years) during consecutive periods of living in the three

studied villages. For 72 subjects, we set the cumulative arsenic as missing because they had changed houses within the township, thus making the concentration of well water unidentifiable.

2.3.2 Urinary arsenic species.

We collected morning urine samples in 2002/03, and from these we measured arsenic species using urinary creatinine adjustment to evaluate the arsenic methylation pattern in relation to the incidence of hypertension. Different levels or proportions of arsenic species were utilized as the metabolic status. Subjects were told not to eat seafood for three days before the test, to avoid an acute spike in organic arsenic.

Urinary samples were stored in a freezer at -20°C until analysis. We quantified four arsenic species in urine samples collected at follow-up—arsenite (AsIII), arsenate (AsV), monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA)—using high-performance liquid chromatography (HPLC) coupled with flow injection atomic absorption spectrometry (Lin et al., 1998). The HPLC system consisted of a solvent delivery pump (PU-1580; Jasco, Tokyo, Japan), a silica-based anion-exchange column (Nucleosil 10 SB, 250 mm×4.6 mm; Phenomenex, Torrance, CA), and a guard column packed with the same material. A flow injection analysis system (FIAS-400; PerkinElmer, Waltham, MA) was the on-line interface to the continuous hydride generation system (Analyst 100; PerkinElmer, Waltham, MA). Stock solutions (1000 mg/L) of As(III), As(V), MMA, and DMA were prepared in 0.2% v/v

sulfuric acid from sodium As(III) (Merck, Germany), disodium hydrogen As(V) (Merck, Germany), sodium dimethylarsenate trihydrate (Merck, Germany), and disodium methylarsenate (Chem Service, West Chester, PA), respectively, and stored at 4°C until use. The retention times for As(III), MMA, DMA, and As(V) were 2.9, 5.5, 9.2, and 13.2 min, respectively. Within-day and between-day precision (coefficient of variance, CV%) for As(III), As(V), MMA, and DMA ranged from 1.0% to 3.7%. Furthermore, by spiking the four arsenic species into urine samples, recoveries for As(III), As(V), MMA, and DMA were determined to be 99.0%, 98.9%, 99.0%, and 99.0% and 103.7%, 101.3%, 100.1%, and 102.0% for quality control recoveries, respectively; while detection limits (signal to noise ratio 3:1) were 0.75, 1.47, 1.19, and 0.76 μg/L, respectively.

2.4 Statistical Methods

Mortality statistics were obtained from the Department of Health, Taiwan. We utilized national-identification numbers for this data link to calculate cause-specific death rates. The standardized mortality ratio (SMR) was calculated using the number of observed deaths divided by the number of expected deaths. The expected numbers of deaths were calculated by mean mortality multiplied by the number of studied population by each age group at 5-year ranges from 30 to 84 during 1994–2003 (Department of Health, 1994-2003). For the age-adjusted incidence of hypertension, we used the baseline mid-year total population in

Taiwan in 1991 as the reference population for direct methods of standardization. We used the Student's t-test, or Mann Whitney test if the data did not follow a normal distribution, and Chi-square test to compare continuous and categorical variables, respectively, between those followed and those lost to follow-up. Logistic regression analyses were used to evaluate the relative risk for hypertension occurrence. Age was used as a continuous variable for the adjustment (i.e. relative risk). We carried out general linear regression and Cox's proportional hazard model when assessing the risk factors for increased blood pressure. All statistical analyses were performed using SPSS 11.0 (SPSS Inc., 2001).

3. Results

A total of 382 subjects (382/490=78%) were followed successfully during 1990–2002/03 (Figure 1). Mortality was as high as 11.3 per 1000 person years in this cohort, which was 1.23 times higher than the Taiwan mortality as demonstrated by the SMR (Table 1). Cancer was responsible for over half of the total deaths (17/30=57%), with an SMR of 1.76. Cardiovascular and type 2 diabetes causes were responsible for approximately one quarter of the total deaths (8/30=27%), with an SMR of 2.02. Table 2 describes the baseline characteristics of lost and followed subjects by gender. Distribution among hypertension-related factors was similar between the groups with the exception of cigarette smoking, with a lower rate observed in the followed men.

Table 3 illustrates the incidence of hypertension according to risk factors. The incidence of hypertension increased with age. Incidence increased 1.74 fold (p=0.027) for those with a BMI greater than or equal to 24 kg/m^2 with age adjustment. The incidence of hypertension also increased 1.75 fold for those with a waist girth ≥90 cm for men and ≥80 cm for women (p=0.037). Lipids were found not to be related to hypertension occurrence. A higher education level tended to be related to decreased risk for hypertension occurrence, but this effect diminished with age adjustment. The incidence of hypertension tended to increase with cumulative arsenic levels, but this became insignificant after adjusting for age. We found that the incidence of hypertension was positively associated with a higher concentration of As(V) (age adjusted relative risk [RR]=2.26 for upper tertile, *p*=0.051) and negatively associated with a high proportion of MMA (the RR=0.5 for upper tertile, *p*=0.077). A higher ratio of As(V) relative to the total of four arsenic species was related to the incidence of hypertension with a RR of around 2 and was borderline significant after adjusting for age. Table 4 showed that As(V) remained significantly associated with the incidence of hypertension (RR=2.39, *p*=0.041) when age and gender were considered. As(V) had a RR of 2.36 (p=0.05) when BMI was also adjusted for and a RR of 2.29 (p=0.06) when glucose was also adjusted for. Some may suspect an over adjustment while glucose was in the model; thus, we provided both data sets. There is a positive correlation between As(V) concentration and total urinary arsenic level, but this is not statistically significance (r=0.15, *p*=0.84 by

Spearman correlation) and might be a result of other sources of arsenic exposure (i.e. beverages, vegetables, etc.). We also examined the association between follow-up blood pressure levels and arsenic exposure. In general, the trend was clearer in lean subjects than in those with a BMI over 24 kg/m^2. Figure 2 is an example of diastolic blood pressures at follow-up by cumulative arsenic in subjects with a BMI <24 kg/m^2 (β=0.25, p=0.035 adjusted for age, sex, cigarette smoking, education, and serum glucose). A similar pattern was obtained when using blood pressure increases from baseline to follow-up according to arsenic exposure (data not shown). We found that a greater statistical power would be advantageous for these types of analyses.

In the final multivariate model (Table 5), As(V) concentration (p=0.047) was significantly associated with the incidence of hypertension after the multiple adjustment. Figure 3 demonstrates that subjects with As(V) ≥1.68 (μg/g creatinine) and BMI ≥26 kg/m^2 experienced around a 3-fold (7.23%/2.77%) increase in the incidence of hypertension compared to those with As(V) <1.68 and BMI <26, after age adjustment using 5-year age groups of the Taiwan data as a reference. Cox's proportional hazard model was also utilized in the regression analyses, and the conclusions are essentially the same.

4. Discussion

This is the first long-term follow-up study of residents with previous exposure to high arsenic levels mainly through drinking water to be conducted two to three decades after exposure. The incidence of hypertension might be underestimated in this study because of selection survival, since cardiovascular diseases were the most common causes of death among residents after those related to cancer. Nonetheless, we still found a higher incidence of hypertension in our cohort when compared to the general population in Taiwan (Yeh et al., 2001). The incidences in a community-based longitudinal study (also performed in rural areas) were 25.1, 46.1, and 57.2 per 1,000 person-years for men aged 35–49, 50–64, and 65–74 years, respectively. Our corresponding rates were 27.4, 65.6, and 69.1, respectively. In addition, the incidence of hypertension in our cohort reached 78.5 per 1,000 person-years for those more than 55 years of age, which is much higher than in the general population (>50 years: 46.1 per 1,000 person-years [/00], >65 years: 57.2/00, >75 years: 73.3/00 in men; 37.1, 79.3, and 50.2 for women, respectively) (Yeh et al., 2001). There might be migrants among these populations who tended to be younger, healthier, and less hypertensive. On the other hand, sick or older residents might have moved to the cities where their children work (allowing their children to take care of them), which is common in Taiwan. Thus, the relative risk tends to be overestimated in the previous case and underestimated in the latter. With the limited immigration effect and the consistent age-stratification and age-adjustment, the

present study is not likely to be biased by these factors.

The relationships of age and obesity to the occurrence of hypertension are consistent with previous studies (Gillum et al., 1998; Gus et al., 2001). Our results also indicated that subjects who excrete higher amounts of MMA tend to experience a lower risk of hypertension, but this lower risk is not significant after multiple adjustments. This is consistent with the results of previous studies for hypertension prevalence (Huang et al., 2007) and skin lesions (McCarty et al., 2007), and this might be a result (in part) of different study designs—perspective cohort vs. cross-sectional, respectively. Subjects with both above-median levels of As(V) and a BMI over 26 kg/m^2 experienced the highest age-adjusted incidence of around 7.2%. Arsenic methylation capacity is suggested to play a role in the development of hypertension, and there is recent evidence that the proportion of arsenic species is associated with genomic polymorphisms in the As(III) methyltransferase (AS3MT) gene in groups with both low (Lindberg et al., 2007) and high (Schläwicke Engström et al., 2007) exposure to arsenic. Urine storage, technical improvements in arsenic analysis, and exposure levels also need to be considered when comparing results between studies. Future studies addressing appropriate exposure makers at baseline and with sufficient follow-up for cardiovascular diseases may help verify our current findings. Genetic factors associated with inorganic arsenic metabolism also need to be examined, particularly for those subjects who are sensitive to hypertension occurrence.

Using the cumulative index for drinking of artesian well water, there is generally a positive association between the increased risk of hypertension and previous arsenic exposure, but it is without statistical significance after adjustments for all other risk factors. There is potential, however, for underestimating the relative risk from previous arsenic exposure, because of selective survival, missing data due to loss of contact with subjects, and reduced statistical power. In addition, median arsenic levels in artesian well water were used when a village had more than one well. Variability from the median within these villages might potentially lead to exposure misclassification in some subjects. We think this misclassification would not differ in high- and low-exposure groups; thus, the relative risk might also be underestimated because of it being diluted by subjects changing from high-to-low or low-to-high groups at the same time. In addition, residents within an endemic area might tend to have similar exposure histories and dietary habits. A suitable cohort (i.e. with socioeconomic status similar to that in the exposure area) from a control unexposed area would be advantageous for more accurately estimating relative risks.

An interventional study by Pi et al. showed that vascular dysfunction could be reversed by reducing arsenic exposure (Pi et al., 2005). This observation suggests the possibility that the cardiovascular effects of arsenic exposure may be similarly effected. Our findings indicated that a moderate increase in the incidence of hypertension might be partly relate to a delayed risk reduction associated with exposure reduction, similar to the cessation

lag that has been calculated for transitional cell carcinoma and arsenic (Chen and Gibb, 2003). Part of this increased risk may also result from community exposure to locally produced food and its higher background arsenic levels (Lin et al., 2001). Thus, hypertension and other cardiovascular effects still need to be monitored for decades after a population acquires treated tap water. Subjects without formal education, perhaps a marker of low socioeconomic status, appear to have a higher risk for hypertension; however, this risk factor was not significant after adjusting for other factors. Other socioeconomic factors such as job title, exercise habits, and dietary patterns were quite similar among these village residents. Residents also had similarly low BMI due to their strenuous jobs, such as those in the fishing industry. Heavy smokers might have expired as a result of smoking related deaths, including bladder cancer, lung cancer, or cardiovascular disease. Thus, we could not find independent and significant results for these factors.

The present relative risk for hypertension incidence as it relates to arsenic may be moderate compared to arsenic exposure related to cancers, such as that of the bladder (Biggs et al., 1998; Yuan et al., 2007). However, the risk to specific populations that is attributable to arsenic exposure may be considerable, as the prevalence of hypertension in Taiwan is high (Ueshima et al., 2000). For example, in 1995 Taiwan's age-standardized mortality rate was 7.0 per 100,000 persons for hypertension and 2.8 for bladder cancer (Department of Health, 1994-2003). Hypertension is also a major risk factor for cardiovascular diseases; thus, its

relation to a modifiable environmental factor is noteworthy (Bhatnagar, 2006).

5. Conclusions

This first cohort study addressing the incidence of hypertension as it relates to reduced arsenic ingestion suggests that a slightly increased risk of hypertension might result from a moderate increase in arsenic exposure above background. Furthermore, arsenic methylation patterns might play a role in the development of arsenic-related hypertension. Therefore, the monitoring of arsenic exposure and related cardiovascular diseases is necessary in arsenic exposure areas even after the arsenic levels in the drinking water are reduced.

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Table 1. Causes of Death among Subjects from a Southwestern Taiwan Arseniasis-Endemic Area in 2003

Cause of death	ICD code	Deaths	Mortality rate (per 1000 person*yrs)	95% CI	SMR	95% CI
CVD	250, 410-429, 430-438	8	3.0	1.3, 5.9	2.02	2.01, 2.04
Cardiovascular disease	410-429	5	1.9	0.6, 4.4	2.13	2.12, 2.15
Malignant neoplasms	140-149, 150-159,160-165, 170-175,179-189, 190-199	17	6.4	3.7, 10.2	1.76	1.74, 1.78
Other	i.e. pneumonia, liver cirrhosis	5	1.9	0.6, 4.4	1.53	1.52, 1.55
All causes	Total	30	11.3	7.6, 16.1	1.23	1.22, 1.25

CVD: cardiovascular diseases including cardio- and cerebral-vascular diseases and type 2 diabetes mellitus.

SMR: standardized mortality ratio using the national population as a reference with 5-year age groups, from 30 to 84, during 1994–2003.

Table 2. Characteristics at Baseline in 1990 for Those Followed in 2002/03 and Those Lost to Follow-up [a].

Characteristics	Women (n=288)				Men (n=202)			
	Lost (97)		Followed (191)		Lost (41)		Followed (161)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age (yr)	49.00	46.92, 51.07	48.01	46.60, 49.42	47.12	44.00, 50.24	48.17	46.67, 49.66
BMI (kg/m^2)	23.83	23.21, 24.45	23.95	23.42, 24.47	23.30	22.30, 24.29	23.61	23.15, 24.06
Waist girth (cm)	76.70	74.69, 78.70	77.56	76.35, 78.78	83.75	81.33, 86.17	82.68	81.41, 83.96
Systolic BP (mmHg)	115.5	113.5, 117.9	112.0	110.3, 113.7	115.6	111.9, 119.8	116.2	114.5, 117.9
Diastolic BP (mmHg)	72.94	71.40, 74.48	71.84	70.74, 72.94	75.63	73.10, 78.17	74.83	73.67, 75.99
Serum glucose (mmol/l)	5.93	5.42, 6.44	5.55	5.33, 5.78	6.31	5.26, 7.36	5.62	5.41, 5.82
Well As conc. (μg/l)	501.8	412.0, 591.6	511.3	454.2, 568.4	603.9	492.9, 714.9	571.3	516.0, 626.51
Yrs. of drinking well water	20.17	17.38, 22.95	18.71	16.87, 20.54	17.51	13.19, 21.83	17.89	15.67, 20.12
Cumulative As (mg/l * yrs)	11.80	9.18, 14.41	11.06	9.43, 12.69	14.03	10.32, 17.74	12.73	10.93, 14.53
Cigarette smoking [b]	0	0%	0	0%	27	65.9%	74	46.0%*

As: arsenic; BMI: body mass index; BP: blood pressure. * $p<0.05$: followed men have a lower cigarette-smoking rate ($p=0.023$). [a] Differences for all other characteristics are not significant between followed and lost groups, except for the cigarette-smoking rate in men.

[b] Subjects who used to smoke more than 3 days per week.

Table 3. Incidence of Hypertension (per 1000 person-years) by Related Factors in an Arseniasis-Endemic Area of Southwestern Taiwan.

Factor	Group	N	Person- yrs	Incidence	95% CI	Crude RR	Age-adj.[a]	95% CI	*p* [b]
Age (years)	<45	142	997	26.1	16.1, 36.1	1.00	-	-	-
	45-55	102	797	37.6	24.2, 51.1	1.86*	-	-	-
	>55	108	683	79.1	58.0, 100	4.86***	-	-	-
Gender	Male	161	1092	47.6	34.7, 60.6	1.00	1.00	-	-
	Female	191	1385	41.9	31.1, 52.7	0.91	0.85	0.53, 1.38	0.511
BMI (kg/m^2)	<24	176	1293	34.8	24.6, 45.0	1.00	1.00	-	-
	≥24	176	1184	54.9	41.6, 68.2	1.71	1.74	1.07, 2.84	0.027*
Waist girth (cm) [c]	Less	254	1844	36.3	27.6, 81.4	1.00	1.00	-	-
	Greater	98	633	67.9	47.6, 156	2.18	1.75	1.04, 2.96	0.037*
Systolic BP (mmHg)	(<130)	314	2274	40.5	32.2, 48.7	1.00	1.00	-	-
	(≥130)	38	203	88.7	47.7, 130	2.17	1.57	0.75, 3.31	0.235
S. glucose (mmol/l)	<6.11	310	2165	43.4	34.6, 52.2	1.00	1.00	-	-
	≥6.11	36	245	61.2	30.2, 92.2	1.64	1.18	0.55, 2.53	0.672
HDL (mmol/l)	≤0.905	14	92	54.3	6.7, 102	1.00	1.00	-	-
	>0.905	311	2078	45.2	36.1, 54.4	0.78	0.86	0.26, 2.81	0.798
LDL (mmol/l)	≤3.35	194	1365	44.0	32.8, 55.1	1.00	1.00	-	-
	>3.35	130	967	39.3	26.8, 51.8	0.92	0.80	0.49, 1.38	0.455
TRG (mmol/l)	<1.44	275	1967	40.7	31.8, 49.6	1.00	1.00	-	-
	≥1.44	72	455	63.7	40.5, 86.9	1.64	1.35	0.75, 2.43	0.312
Cigarette smoking [d]	No	278	1993	44.2	35.1, 53.2	1.00	1.00	-	-
	Yes	74	484	45.5	26.5, 64.4	0.91	1.11	0.61, 2.00	0.742
Education (years)	<1	97	676	60.7	42.1, 79.2	1.00	1.00	-	-
	1-8	168	1258	35.8	25.3, 46.2	0.50*	0.67	0.38, 1.20	0.180
	≥9	87	543	44.2	26.5, 61.9	0.52#	1.03	0.51, 2.09	0.939

As conc.: arsenic concentration; As(V): penta-valent arsenic; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MMA: monomethylarsonic acid; S. glucose: serum glucose; TRG: triglycerides.

# $p<0.1$, * $p<0.05$, *** $p<0.001$.

[a] Age as continuous variable being adjusted. [b] *p* value for the age-adjusted relative risk as compared to the reference group. [c] ≥90 cm for men and ≥80 for women. [d] Subjects who used to smoke more than 3 days per week.

Table 3. Hypertension Incidence (per 1000 person-years) by Related Factors in an Arseniasis-Endemic Area of Southwestern Taiwan (continued).

Factor	Group	N	Person-yrs	Incidence	95% CI	Crude RR	Age-adj.[a]	95% CI	*p*[b]
Cumulative arsenic level (mg/l*yr)	<5.6	91	583	34.3	19.3, 49.3	1.00	1.00	-	-
	5.6-15.6	94	703	39.8	25.1, 54.6	1.51	1.08	0.53, 2.19	0.832
	>15.6	95	689	56.6	38.8, 74.4	2.47	1.06	0.46, 2.43	0.890
Years of drinking well water	<20	173	1198	30.9	20.9, 71.7	1.00	1.00	-	-
	20-30	101	769	54.6	38.1, 126	2.62	148	0.79, 2.78	0.221
	>30	77	508	61.0	39.5, 144	2.48	1.06	0.49, 2.29	0.892
As conc. in well water (μg/l)	<538	93	618	38.8	23.3, 54.4	1.00	1.00	-	-
	538-700	103	721	54.1	37.1, 71.1	1.75	1.28	0.66, 2.48	0.464
	>700	83	634	36.3	21.5, 51.1	1.10	0.82	0.40, 1.68	0.595
iAs ratio	<0.10	65	589	39.0	23.1, 62.1	1.00	1.00		
	0.10-0.17	65	604	46.4	29.2, 75.5	1.38	1.23	0.58, 2.60	0.587
	>0.17	65	644	31.1	17.4, 8.5	0.81	0.84	0.39, 1.80	0.646
oAs ratio	<0.83	65	644	31.1	17.4, 48.5	1.00	1.00		
	0.83-0.90	65	604	46.4	29.2, 75.5	1.70	1.47	0.69, 3.14	0.317
	>0.90	65	589	39.0	3.1, 62.1	1.23	1.20	0.56, 2.57	0.646
As(V) (μg/g creatinine)	＜1.17	57	569	29.9	15.7, 44.1	1.00	1.00	-	-
	1.17-2.67	57	488	41.0	23.0, 58.9	1.27	1.50	0.65, 3.47	0.339
	＞2.67	57	555	46.8	28.8, 64.9	1.97	2.26	1.00, 5.11	0.051#
As(V) ratio	<0.03	57	562	30.2	15.9, 44.6	1.00	1.00	-	-
	0.03-0.08	57	504	47.6	28.6, 66.7	1.71	2.12	0.92, 4.89	0.078#
	>0.08	57	546	40.3	23.5, 57.1	1.48	1.82	0.80, 4.16	0.154
MMA ratio	<0.06	65	582	48.1	30.3, 78.4	1.00	1.00		
	0.06-0.12	65	601	41.6	25.3, 66.9	0.83	0.72	0.34, 1.52	0.389
	>0.12	65	654	27.5	14.8, 42.3	0.51	0.50	0.23, 1.08	0.077
DMA ratio	<0.71	65	629	31.8	17.9, 49.7	1.00	1.00		
	0.71-0.81	65	624	38.5	23.1, 61.5	1.32	1.15	0.53, 2.47	0.723
	>0.81	65	544	49.6	30.9, 80.5	1.60	1.52	0.71, 3.25	0.276

Table 4. Arsenic Ingestion and Incidence of Hypertension in an Arseniasis-Endemic Area of Southwestern Taiwan.

Arsenic	Group	N	RR [a]	95% CI	*p*	RR [b]	95% CI	*p*	RR [c]	95% CI	*p*
Cumulative	<5.6	91	1.00	-	-	1.00	-	-	1.00	-	-
arsenic level	5.6-15.6	94	1.08	0.53, 2.19	0.839	1.18	0.57, 2.44	0.659	1.15	0.55, 2.40	0.710
(mg/l*yr)	>15.6	95	1.02	0.44, 2.35	0.968	1.19	0.51, 2.80	0.689	1.18	0.50, 2.77	0.709
Years of	<20	173	1.00	-	-	1.00	-	-	1.00	-	-
drinking	20-30	101	1.53	0.81, 2.90	0.188	1.55	0.81, 2.98	0.188	1.50	0.78, 2.89	0.229
well water	>30	77	1.05	0.48, 2.29	0.898	1.14	0.51, 2.52	0.753	1.16	0.52, 2.58	0.717
As conc. in	<538	93	1.00	-	-	1.00	-	-	1.00	-	-
well water	538-700	103	1.21	0.62, 2.36	0.586	1.21	0.62, 2.40	0.579	1.18	0.60, 2.34	0.631
(μg/l)	>700	83	0.78	0.38, 1.61	0.499	0.80	0.39, 1.68	0.561	0.83	0.40, 1.74	0.618
iAs ratio	<0.10	65	1.00	-	-	1.00	-	-	1.00	-	-
	0.10-0.17	65	1.22	0.58, 2.58	0.605	1.22	0.56, 2.66	0.609	1.24	0.57, 2.71	0.591
	>0.17	65	0.84	0.39, 1.81	0.658	0.76	0.34, 1.66	0.485	0.72	0.32, 1.60	0.413
oAs ratio	<0.83	65	1.00	-	-	1.00	-	-	1.00	-	-
	0.83-0.90	65	1.45	0.68, 3.10	0.339	1.62	0.73, 3.59	0.234	1.73	0.77, 3.88	0.181
	>0.90	65	1.19	0.55, 2.56	0.658	1.32	0.60, 2.91	0.485	1.40	0.63, 3.12	0.413
As(V) (μg/g	＜1.17	57	1.00	-	-	1.00	-	-	1.00	-	-
creatinine)	1.17-2.67	57	1.54	0.67, 3.58	0.312	1.37	0.58, 3.25	0.478	1.45	0.60, 3.48	0.409
	＞2.67	57	2.39	1.04, 5.49	0.041*	2.36	1.00, 5.59	0.050#	2.29	0.96, 5.49	0.063#
As(V) ratio	<0.03	57	1.00	-	-	1.00	-	-	1.00	-	-
	0.03-0.08	57	2.11	0.91, 4.86	0.081#	2.07	0.88, 4.89	0.098#	2.32	0.95, 5.63	0.064#
	>0.08	57	1.85	0.81, 4.23	0.147	1.79	0.76, 4.20	0.183	1.75	0.73, 4.22	0.210
MMA ratio	<0.06	65	1.00	-	-	1.00	-	-	1.00	-	-
	0.06-0.12	65	0.73	0.35, 1.53	0.400	0.75	0.35, 1.60	0.452	0.78	0.36, 1.70	0.528
	>0.12	65	0.49	0.22, 1.06	0.068	0.53	0.24, 1.18	0.119	0.59	0.26, 1.33	0.204
DMA ratio	<0.71	65	1.00	-	-	1.00	-	-	1.00	-	-
	0.71-0.81	65	1.16	0.54, 2.49	0.711	1.22	0.55, 2.68	0.627	1.05	0.47, 2.35	0.898
	>0.81	65	1.56	0.73, 3.34	0.254	1.56	0.70, 3.45	0.273	1.43	0.64, 3.20	0.383

As conc.: arsenic concentration; As(V): penta-valent arsenic; MMA: monomethylarsonic acid.

[a] Age, as a continuous variable, and gender adjusted. [b] Age, gender, and BMI adjusted. [c] Age, gender, BMI, and glucose (≥6.11mmol/l) adjusted. # $p<0.1$, * $p<0.05$.

Table 5. Hypertension Incidence and Related Factors in an Arseniasis-Endemic Area of Southwestern Taiwan by Multivariate Analysis.

Factor	Group	RR	95% CI	*p*
Age (years)		1.08	1.03, 1.13	0.001**
Gender	Male	1.00		
	Female	0.84	0.34, 2.08	0.699
BMI		1.19	1.05, 1.34	0.005**
Education (years)	<1	1.00		
	1-8	0.96	0.40, 2.30	0.931
	≥9	1.12	0.32, 3.92	0.855
Cigarette smoking	No	1.00		
	Yes	1.30	0.44, 3.84	0.632
As(V) (μg/g creatinine)	＜1.20	1.00		
	1.20-2.67	1.38	0.57, 3.34	0.473
	＞2.67	2.43	1.01, 5.86	0.047*

As(V): penta-valent arsenic; BMI: body mass index.

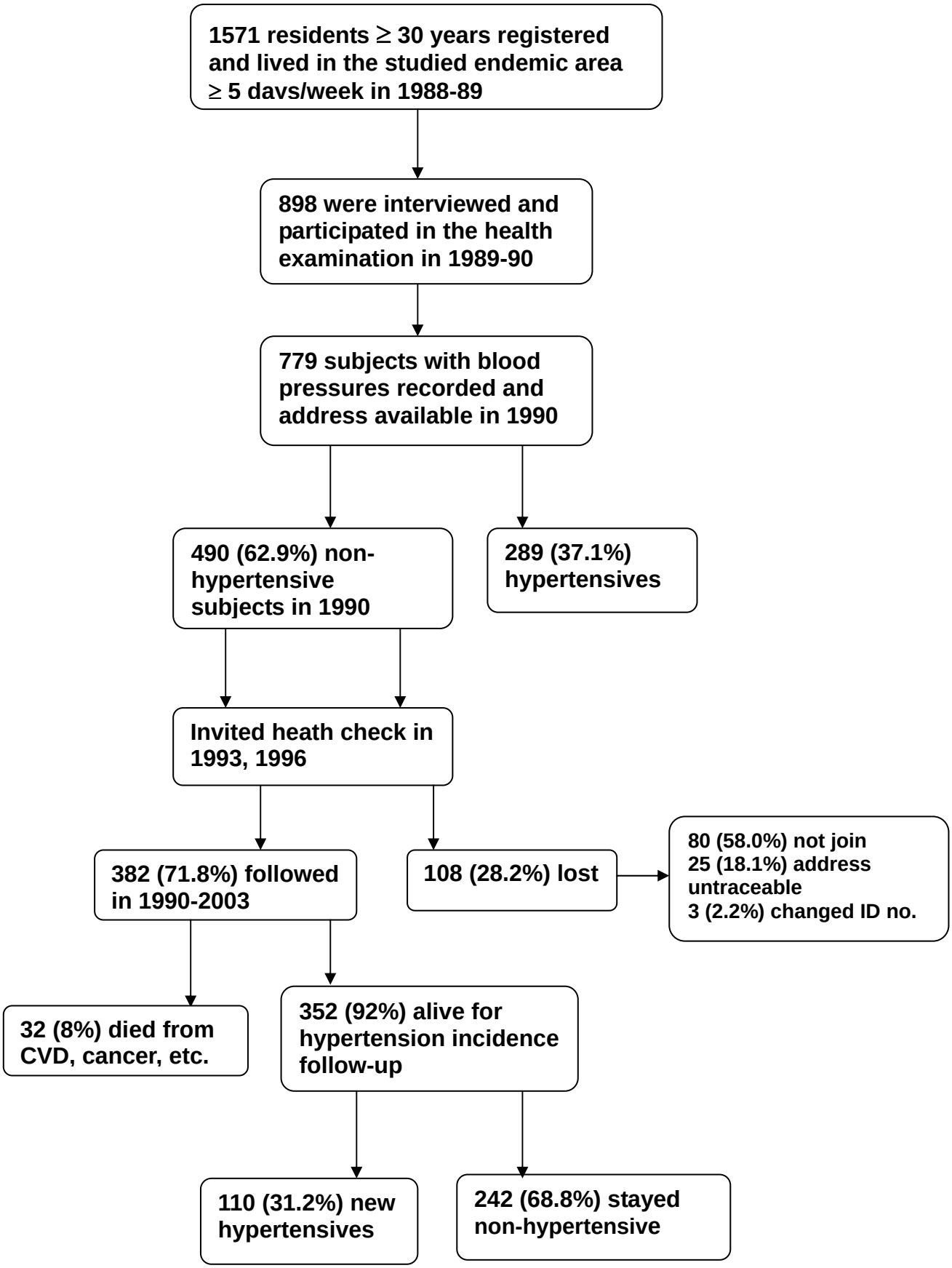
* $p<0.05$, ** $p<0.01$.

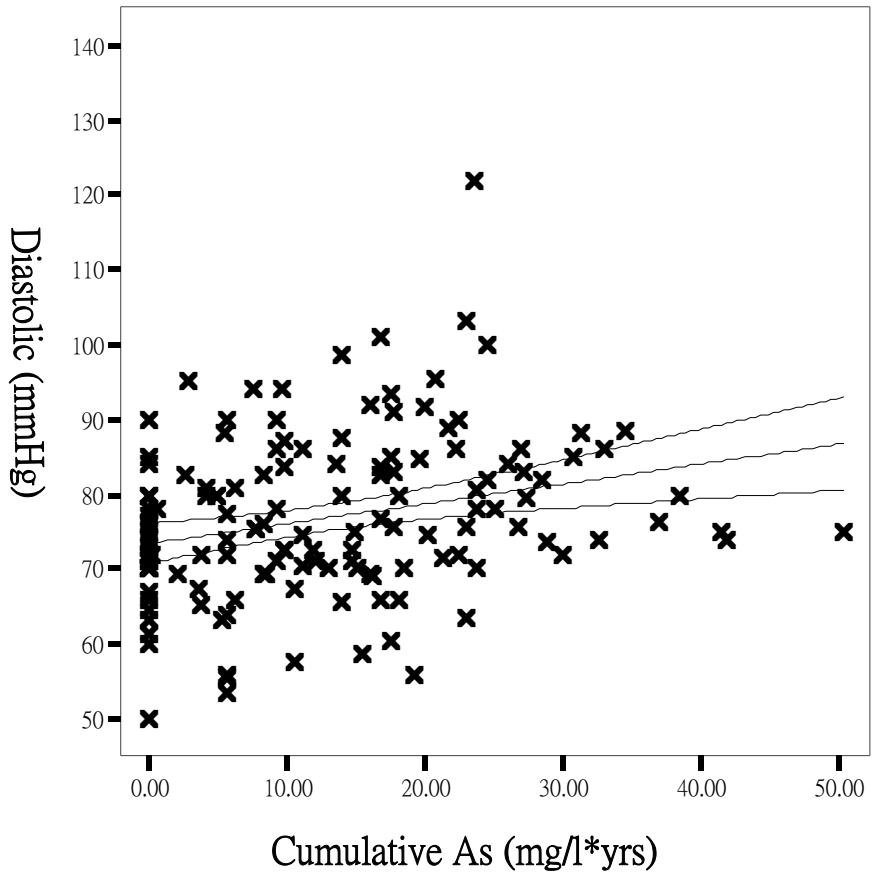
FIGURE LEGENDS

Figure 1. Follow-up flow chart for the incidence of hypertension in an arseniasis-endemic area of southwestern Taiwan, 1990–2002/03.

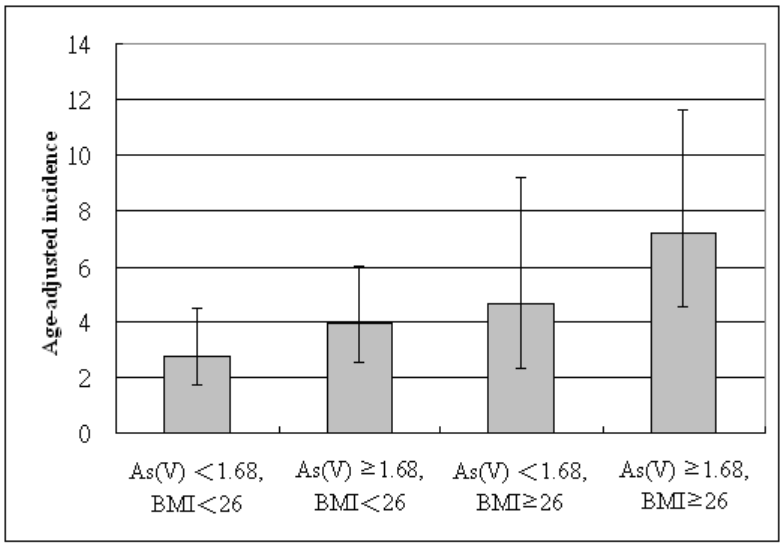
Figure 2. Diastolic blood pressures at follow-up by cumulative arsenic in subjects with a BMI <24 kg/m^2 (n=141; β=0.25 by age, sex, cigarette smoking, BMI, education, and plasma glucose; p=0.035 for the β, R=0.42, p<0.001 for R)

Figure 3. Age-adjusted hypertension incidence (%) by urinary As(V) concentration (μg/g creatinine) and BMI (kg/m^2) in an arseniasis-endemic area.


1571 residents ≥ 30 years registered and lived in the studied endemic area ≥ 5 davs/week in 1988-89
898 were interviewed and participated in the health examination in 1989-90
779 subjects with blood pressures recorded and address available in 1990
490 (62.9%) non-hypertensive subjects in 1990
289 (37.1%) hypertensives
Invited heath check in 1993, 1996
382 (71.8%) followed in 1990-2003
108 (28.2%) lost
80 (58.0%) not join
25 (18.1%) address untraceable
3 (2.2%) changed ID no.
32 (8%) died from CVD, cancer, etc.
352 (92%) alive for hypertension incidence follow-up
110 (31.2%) new hypertensives
242 (68.8%) stayed non-hypertensive



95% Confidence intervals for β estimates are indicated.



Median of As(V): 1.68 (ug/g creatinine).

Error bars represent 95% confidence intervals.