Chronic Arsenic Exposure Increases Mortality from Ischemic Heart Disease and Stroke:

A Follow-up Study on 26,851 Residents in Taiwan

Chih-Hao Wang, M.D. Ph.D.,
Chi-Ling Chen, PhD.,
Lin-I Hsu, PhD.,
Hung-Yi Chiou, PhD,
Yu-Mei Hsueh, PhD
Shu-Yuan Chen, PhD.,
Meei-Maan Wu, PhD.,
Chuhsing Kate Hsiao, PhD.,
Chien-Jen Chen, ScD.

for the Blackfoot Disease Study Group

Author affiliation: Cardinal Tien Hospital, College of Medicine, Fu-Jen Catholic University (C.-H.W.); Graduate Institute of Epidemiology, National Taiwan University, Taipei (C.-L.C., L.-I.H., C.K.H., C.-J.C.); School of Public Health, Taipei Medical University, Taipei (H.-I.C., Y.-M.H.); Division of Biostatistics and Bioinformatics, National Health Research Institutes, Taipei (S.-Y.C.); and Institute of Biomedical Sciences, Academia Sinica (M.-M.W.).

Members of the Blackfoot Disease Study Group appear at the end of this article.

Corresponding Author: Chien-Jen Chen, ScD, College of Public Health, National Taiwan University, 1 Jen-Ai Rd, Section 1, Taipei 10018, Taiwan (cjchen @ha.mc.ntu.edu.tw).
ABSTRACT

Context  Chronic arsenic exposure has been found to increase the risk of atherosclerotic diseases. Previous studies were limited by ecological correlation, or cross-sectional studies and a small number of cases.

Objectives  To elucidate the dose-response relationship between ingested arsenic and cardiovascular mortality in a large-scale follow-up study.

Design, Setting, and Participants  This study enrolled 10,133 and 16,718 residents aged 40 and older from arsenic-exposed and unexposed areas respectively for an average follow up period of 12 years. Traditional risk factors and arsenic exposure via drinking water were evaluated through health examination and structured questionnaire interview.

Main Outcome Measure  Deaths from ischemic heart disease and stroke were ascertained up to December 31, 2004 through linkage with national death certification profiles. Cox's proportional hazards regression analyses were used to estimate multivariate-adjusted relative risks of mortality.

Results  There were 109,490 and 207,205 person-years observed for exposed and unexposed cohorts, respectively. There was a significant dose-response relationship between the mortality from ischemic artery disease and stroke and the arsenic level in drinking water (P<0.001 trend test). The relative risk was 1.80 (95% confidence interval, 1.36 – 2.38) for the highest arsenic level compared with the lowest.

Conclusions  There was a significant dose-response relationship between the cardiovascular mortality and the arsenic level in drinking water. Arsenic is a dominant risk factor for cardiovascular mortality.
Key words: arsenic, ischemic heart disease, stroke, risk factors
Arsenic is a ubiquitous metalloid in the crust of the earth, and human exposure to inorganic arsenic is mainly through ingestion of drinking water contaminated with naturally occurring arsenic. Chronic arsenic poisoning is becoming an emerging epidemic in Asia, and over 100 million people are exposed to underground water with high concentration of arsenic. The magnitude of this arsenic calamity has projected to be the largest in history of environmental disaster that will be more serious than those at Chernobyl, Ukraine in 1986 and Bhopal, India in 1984. In the United States, over 350,000 people are estimated to be exposed to water contaminated with arsenic greater than 50 μg/L and over 2.5 million to water with arsenic greater than 25 μg/L.

Long-term exposure to ingested arsenic has been documented to induce various cancers and cardiovascular diseases. The maximum contamination level for arsenic in drinking water has recently been lowered from 50 to 10 μg/L by the US Environmental Protection Agency. However, there remains argument on the scientific basis of this new regulatory standard and its adequacy for protection of public health.

Ingested inorganic arsenic has long been documented to cause blackfoot disease, a unique endemic peripheral vascular disease in southwestern Taiwan. Clinically, the disease begins with coldness and/or numbness of lower extremities, progresses over years to intermittent claudication, and ends with dry gangrene and spontaneous amputation of distal parts of affected extremities. Pathologically, the disease is compatible with thromboangiitis obliterans (30 percents) or arteriosclerosis obliterans (70 percents) with a fundamental change of an excessively severe systemic arteriosclerosis. The pleiotropism of arsenic-induced adverse health effects may be characterized by its associations with hypertension, diabetes mellitus, carotid atherosclerosis, ischemic heart disease, stroke and various cancers in a dose-response relationship.
However, the biological gradient between ingested arsenic and the mortality from ischemic heart disease and stroke has never been reported by a large-scale follow-up study.

This follow-up study aimed to elucidate the dose-response relationship between arsenic level in drinking water and mortality from ischemic heart disease and stroke among residents aged 40 and older in arsenic-exposed and unexposed areas. Risk factors were also examined.

METHODS

Exposed Cohorts Exposed-cohorts consisted of two study cohorts recruited from southwestern and northeastern Taiwan with an average follow up of 12 years to elucidate the dose-response relationship between ingested arsenic exposure and cardiovascular mortality.

Southwestern Cohort The recruitment of study subjects from two arsenic-exposed areas has been described in detail previously. In brief, a total of 2,051 residents aged 40 and older were recruited from four arsenic-exposed townships (Peimen, Hsuehchia, Putai and Ichu) in southwestern Taiwan, where residents started using high-arsenic well water in early 1910s. Residents living in the same village of these townships shared few wells of the village. A public water supply system using surface water was implemented in this area since early 1960s, but its coverage remained low until early 1970s. Artesian well water was not used for drinking and cooking after mid-1970s.

Northeastern cohort A total of 8,082 residents aged 40 and old were recruited from four arsenic-exposed townships (Chiaohsi, Chuangwei, Wuchieh and Tungshan) in northeastern Taiwan, where residents started using arsenic-contaminated well water in late 1940s. Residents in these townships had their own tube wells in their backyards. A public water supply system using surface water was implemented in this northeastern endemic area in early 1990s, and its coverage was as
high as 95% in 2000.

**Unexposed cohort** A total of 16,718 residents aged 40 or more years old were recruited from seven unexposed townships including Sanchi, Chutung, Putze and Kaoshu in Taiwan Island, as well as Paisha, Huhsi and Makung in Penghu archipelagos. The residents in these townships used tap water for cooking and drinking. The seven non-endemic townships were randomly selected and are compatible with the eight endemic townships in many aspects. Most residents in the endemic and non-endemic areas were engaged in farming, or fishery etc. The average socioeconomic status, living environments, life style, dietary pattern, and accessibility to health care facility are comparable in these three concurrent cohorts.

The mean (standard deviation) of age was 58.6 (10.7) and 52.6 (7.1) for the exposed and unexposed cohort, respectively. The corresponding proportion of men was 51 and 49% respectively.

**Enrollment of Study Subjects**

The enrollment of study subjects in exposed and unexposed cohorts has been depicted in details previously. All subjects participated voluntarily in the study with informed consent. Household-visits were conducted to interview subjects in the exposed cohort on the basis of structured questionnaire. A subcohort was invited to participate the health examinations. There were 1,132 subjects in southwestern and 1,132 in northeastern exposed cohorts participated the health examination. All study subjects in the unexposed cohort were personally interviewed and physically examined in local health stations.

**Arsenic Exposure and Traditional Risk Factors**
The well-trained public health nurses conducted the standardized interview of participants on the basis of person-to-person conversation. Information obtained from the interview including socioeconomic and demographic characteristics, alcohol intake, cigarette smoking, physical activities, dietary consumption, residential history, water consumption history, and personal and family history of hypertension, diabetes, cardiovascular diseases and cancers. Cigarette smoking was defined as a habit of smoking cigarettes daily for six or more months. Habitual alcohol drinking was defined as a habit of drinking alcoholic beverage more than three days a week for six or more months.

The estimation of ingested arsenic of study subjects in the exposed cohort has been described previously. The arsenic level in water of artesian wells of southwestern exposed area was obtained from previous studies conducted in early 1960s. As residents in this area shared few wells in the same village, the median arsenic level in water of shared wells was used as the exposure level of arsenic for villagers in this village. The average arsenic exposure level in drinking water of the study subject was derived by the formula \( \frac{\sum (C_i \times D_i)}{\sum D_i} \); where \( C_i \) was the median arsenic level in water of shared wells of a village in which the subject inhabited, and \( D_i \) was the duration of drinking artesian well water in the village during the period \( i \). The arsenic level in water of tube wells of northeastern arseniasis-endemic area was tested in early 1990s. The arsenic level in drinking water of study subjects in the northeastern exposed cohort was based on the arsenic level in water of their own tube wells in their backyards. Residents in unexposed areas used tap water for cooking and drinking, and the arsenic level in drinking water have been reported to be <10 \( \mu g/L \).

**Laboratory Examinations**

Fasting blood samples were collected from study subjects who participated the health
examination. The blood was used for testing of serum level of total cholesterol, and triglycerides by standardized auto-analyzers. Glucose tolerance test was also performed. Diabetes mellitus was defined as 1) a fasting serum glucose level ≥ 140 mg/dL, 2) a two-hour glucose level ≥ 200 mg/dL, or 3) a history of diabetes mellitus regularly treated with oral hypoglycemic agents or insulin. Anthropometric characteristics including height, weight, waist circumference, hip circumference, and systolic and diastolic blood pressures were measured according to a standard protocol. Blood pressure was measured three times with a mercury sphygmomanometer with subjects sitting. The average of three measurements was used to define the status of hypertension. Hypertension was defined as 1) an average systolic blood pressure ≥ 160 mmHg, 2) an average diastolic blood pressure ≥ 95 mmHg, or 3) a history of hypertension regularly treated with anti-hypertensive agents. Hyperlipidemia was defined as 1) a serum total cholesterol level ≥ 240 mg/dL, or 2) a serum triglycerides level ≥ 200 mg/dL. Overweight was defined as a body mass index ≥ 25 kg/m².

Ascertainment of Causes of Death

Causes of death of study subjects were ascertained through data linkage with national death certification profiles. It is mandatory to register any event of birth, education, marriage, employment, and death in Taiwan. The registration information of each household is double-checked annually by household registration officers. All death certificates are issued by clinical doctors in private practice or in hospitals. The death certification profiles in Taiwan have been considered complete, updated and precise. Causes of deaths were classified according to the codes of the International Classifications of Diseases, 9th Edition. The codes were 410-414 for ischemic heart disease and 430-438 for stroke.
Statistical Analysis

Mortality from ischemic heart disease and stroke were the hard end points. The prevalence of traditional risk factors for ischemic heart disease and stroke was compared between exposed and unexposed cohorts, using logistic regression analysis to test for the difference in the prevalence after adjustment for age and gender. Cox's proportional hazards regression analyses were performed to estimate the multivariate-adjusted relative risks with 95% confidence intervals for arsenic exposed and unexposed cohorts\textsuperscript{21}. Because ingested arsenic could induce hypertension, diabetes mellitus and hyperlipidemia, only age, gender and smoking were adjusted in the analyses to avoid over-adjustment\textsuperscript{10,11}. The dose-response relationship between the arsenic level in drinking water and mortality from ischemic heart disease and stroke was tested by a trend test.

RESULTS

Mortality from Ischemic Heart Disease and Stroke

A total of 109,490 and 207,205 person-years were observed for exposed and unexposed cohorts respectively during the mean follow up period of 12 years. The number of deaths from ischemic heart disease and stroke was 502 and 296, respectively. Figure 1 shows the age-specific mortality from ischemic heart disease and stroke for exposed and unexposed cohorts. The mortality was higher in exposed cohort than unexposed cohort for most age groups, showing an age-gender-adjusted relative risk of 1.5 (95 % CI of 1.2-1.7, $P<0.001$). Table 1 shows relative risk of mortality from ischemic heart disease and stroke by arsenic level in drinking water. There was a significant dose-response relationship between the arsenic level in drinking water and the mortality from ischemic heart disease and stroke ($p$ for trend $<0.001$). The age-gender-smoking-adjusted
relative risk (95% CI) was 1.80 (1.36-2.38), 1.34 (1.08-1.66) and 0.95 (0.74-1.21) for study subjects who drank water with an arsenic level of ≥ 500, 50-499 and 10-49 μg/L, respectively, compared with those with a level <10 μg/L.

**Traditional Risk Factors for Ischemic Heart Disease and Stroke**

Table 1 shows the prevalence of traditional risk factors for ischemic heart disease and stroke among health examinees in exposed and unexposed cohorts. The exposed cohort had a higher prevalence of hypertension, diabetes mellitus and hyperlipidemia than the unexposed cohort. The differences remained statistically significant after adjustment for age and gender (P<0.001).

As shown in table 3 traditional risk factors such as cigarette smoking, diabetes mellitus, hypertension, and hyperlipidemia were all significantly associated with an increased mortality from ischemic heart disease in the unexposed cohort. Table 4 showed the risk factors of cigarette smoking, diabetes mellitus, and hypertension were significantly associated with an increased mortality from stroke in the unexposed cohort.

**COMMENT**

Previous findings on the increased risk of atherosclerotic diseases such as peripheral vascular disease, ischemic heart disease and stroke were mostly reported by ecological correlation studies or cross-sectional surveys. They were limited by ecological fallacy, a small number of affected patients or difficulty in delineation of causal temporality. This study followed a large number of residents in arsenic-exposed and unexposed areas in Taiwan concurrently, and found a significant dose-response relationship between ingested arsenic and mortality from ischemic heart disease and stroke. This is the first large scale long-term follow-up study demonstrated a
biological gradient between ingested arsenic via drinking water and mortality from ischemic heart disease and stroke. Because ingested arsenic was known to induce various lethal cancers, accordingly cancer death was the competing cause of mortality. Thus, the cardiovascular mortality induced by ingested arsenic might be more than underestimated. In addition, residents in the exposed area had stopped consumption of high-arsenic artesian well water before their participation in this study. The increased cardiovascular mortality observed during this follow-up period suggests that arsenic may still exert persistent or irreversible adverse effects in arsenic-exposed subjects even after discontinuation of ingestion of arsenic-contaminated water.

Exposed cohort had a significantly higher prevalence of hypertension, diabetes mellitus and hyperlipidemia than unexposed cohort as reported previously. Previous studies had shown that hypertension, diabetes mellitus and hyperlipidemia can be induced by chronic ingestion of arsenic in a dose-responses manner.\textsuperscript{10,11,12} Therefore, the multivariate-adjusted relative risk of cardiovascular mortality did not include these three factors to avoid over-adjustment. Both hyperlipidemia and cigarette smoking seemed to play a less important role in the development of lethal ischemic heart disease and stroke in the exposed cohort. However, the difference in the sample size of exposed and unexposed cohorts may also restrict further interpretation.

Previously, the pathology of blackfoot disease has been extensively studied in 51 patients from southwestern exposed area.\textsuperscript{9} The universal finding is the systemic arteriosclerosis involving large, medium and small arteries. Severe atherosclerosis of ischemic and other medium-sized arteries, and repeated and extensive myocardial infarction were found. In an autopsy study at Antofagasta of Chile, infants or children free of traditional risk factors except chronically exposed to ingested arsenic were found to have systemic arterial intimal thickening in small and medium arteries involving the heart, gastrointestinal tract, liver, skin and pancreas.\textsuperscript{22} These findings suggest that
ingestion of arsenic via contaminated drinking water was capable of inducing severe systemic atherosclerosis in the absence of traditional risk factors.

Atherogenesis, thrombogenesis and arrhythmogenesis are the three major adverse cardiovascular effects induced by chronic arsenic poisoning and may contribute to the increased mortality from ischemic heart disease and stroke. Molecular and cellular mechanisms of arsenic-induced atherogeneis and thrombogeneis are associated with increased oxidative stress, inflammatory cytokines and process, coagulation activity of endothelium and impaired vascular nitric oxide homeostasis and enhanced aggregation activities of platelets. The genetically modified atherosclerosis-susceptible mouse models suggest that arsenic may accelerate atherosclerosis and amplify inflammatory cytokines. Mechanism of arsenic-induced arrhythmogenesis may involve QT prolongation, and torsades de pointes electrocardiographically, prolongation of action potential duration, and interference of potassium ionic channel.

In conclusion, we had demonstrated that a dose response relationship between ingested arsenic and mortality from ischemic heart disease and stroke in a larger scale long-term follow up study. Ingested arsenic is a dominant risk factor for cardiovascular mortality.

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Author Contributions:
Dr C.-J. Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: C.-H. Wang, H-I Chiou, Y-M Hsueh, C.-J. Chen.

Acquisition of data: C.-H. Wang, C-L Chen, L-I Hseu, H-I Chiou, Y-M Hsueh, C.-J. Chen.

Analysis and interpretation of data: C.-H. Wang, C-L Chen, C-K Hsiao, C.-J. Chen.

Drafting of the manuscript: C.-H. Wang.

Critical revision of the manuscript for important intellectual content: C.-H. Wang, C-L Chen, H-I Chiou, Y-M Hsueh, S.-Y. Chen, M-M Wu, C.-J. Chen.

Statistical analysis: C.-H. Wang, C-L Chen, C-K Hsiao

Obtained funding: C.-J. Chen.

Administrative, technical, or material support: H-I Chiou, Y-M Hsueh, C.-J. Chen.

Study supervision: C.-J. Chen.

The Blackfoot Disease Study Group: Department of Cardiology, Cardinal Tien Hospital, College of Medicine, Fu-Jen Catholic University, Taipei, Taiwan (Chih-Hao Wang, MD, PhD); Graduate Institute of Epidemiology, College of Public Health (Chien-Jen Chen, ScD, Chi-Ling Chen, PhD, Lin-I Hsu, PhD,) Wei-Liang Shih, MS, Yi-Hsiang Hsu, MS, Chia-Yen Chen, BS, Yu-Chin Cheng, BS, and Li-Hua Wang, BS) and Graduate Institute of Medical Technology, College of Medicine (Cheng-Yeh Lee, MS), National Taiwan University, Taipei; School of Public Health, Taipei Medical University, Taipei, Taiwan (Hung-Yi Chiou, PhD, Yu-Mei Hsueh, PhD, Meei-Maan Wu, PhD, Iuan-Horng Wang, MS, Yu-Chun Lin, MS); Division of Biostatistics and Bioinformatics, National Health Research Institute, Taipei, Taiwan (Shu-Yuan Chen, PhD); Division of Environmental Health and Occupational Medicine, National Health Research Institute, Kaohsiung, Taiwan (Wei-Lin Chou, MS); Department of Dermatology, National Taiwan University Hospital, Taipei (Mei-Ping Tseng, MS).
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The National Science Council and Department of Health, Executive Yuan, Taiwan, were not involved in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
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TABLE 1. AGE-GENDER-SMOKING-ADJUSTED RELATIVE RISKS OF MORTALITY FROM ISCHEMIC HEART DISEASE AND STROKE BY ARSENIC LEVEL IN DRINKING WATER

<table>
<thead>
<tr>
<th>Arsenic Level in Drinking Water (μg/L)</th>
<th>Number of Subjects+</th>
<th>Number of Deaths</th>
<th>Age-Gender-Adjusted Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>19360</td>
<td>428</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>10 – 49</td>
<td>2130</td>
<td>84</td>
<td>0.95 (0.74 – 1.21)</td>
</tr>
<tr>
<td>50 – 499</td>
<td>2317</td>
<td>116</td>
<td>1.34 (1.08 – 1.66)</td>
</tr>
<tr>
<td>≥500</td>
<td>1165</td>
<td>60</td>
<td>1.80 (1.36 – 2.38)</td>
</tr>
</tbody>
</table>

P for trend*                              P<0.001
FIGURE 1. Mortality from ischemic heart disease and stroke during follow-up in arsenic-exposed and unexposed cohorts by age.
### Table 2. Prevalence of Risk Factors in Arsenic-Exposed and Unexposed Cohorts

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Arsenic-Exposed Cohort (N=2,264)</th>
<th>Unexposed Cohort (N=16,676)</th>
<th>Age-Gender-Adjusted Odds Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>700</td>
<td>4959</td>
<td>1.16 (1.01 – 1.33)</td>
<td>0.037</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>380</td>
<td>574</td>
<td>4.70 (4.04 – 5.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>455</td>
<td>1354</td>
<td>2.40 (2.11 – 2.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>753</td>
<td>4131</td>
<td>1.71 (1.54 – 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overweight</td>
<td>731</td>
<td>6699</td>
<td>0.90 (0.81 – 1.00)</td>
<td>0.050</td>
</tr>
</tbody>
</table>
**Table 3. Multivariate-adjusted Relative Risks of Mortality from Ischemic Heart Disease in Arsenic-Exposed and Unexposed Cohorts**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Unexposed Cohort</th>
<th>Arsenic-Exposed Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk</td>
<td>Relative Risk</td>
</tr>
<tr>
<td></td>
<td>(95% Confidence Interval)</td>
<td>(95% Confidence Interval)</td>
</tr>
<tr>
<td>Age in one-year</td>
<td>1.13 (1.09 – 1.17) P&lt;0.001</td>
<td>1.02 (0.97 – 1.07) P=0.409</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>0.55 (0.33 – 0.94) P=0.027</td>
<td>0.52 (0.13 – 2.00) P=0.339</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.61 (1.01 – 2.56) P=0.046</td>
<td>0.90 (0.21 – 3.86) P=0.886</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>3.28 (1.92 – 2.61) P&lt;0.001</td>
<td>2.31 (0.77 – 6.93) P=0.135</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>2.22 (1.41 – 3.50) P=0.001</td>
<td>1.79 (0.59 – 5.37) P=0.302</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.82 (1.24 – 2.67) P=0.002</td>
<td>1.56 (0.54 – 4.50) P=0.411</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.28 (0.87 – 1.89) P=0.203</td>
<td>0.84 (0.28 – 2.50) P=0.750</td>
</tr>
</tbody>
</table>
**Table 4. Multivariate-Adjusted Relative Risks of Mortality from Stroke in Arsenic-Exposed and Unexposed Cohorts**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Unexposed Cohort</th>
<th>Arsenic-Exposed Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk</td>
<td>Relative Risk</td>
</tr>
<tr>
<td></td>
<td>(95% Confidence Interval)</td>
<td>(95% Confidence Interval)</td>
</tr>
<tr>
<td>Age in one-year increment</td>
<td>1.10 (1.07 – 1.12)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.11 (0.72 – 1.71)</td>
<td>P=0.642</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.40 (1.58 – 3.65)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.95 (1.86 – 4.68)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.07 (1.42 – 3.02)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.18 (0.86 – 1.62)</td>
<td>P=0.314</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.29 (0.96 – 1.75)</td>
<td>P=0.094</td>
</tr>
</tbody>
</table>