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Blood pressure and the risk of stroke, cardiovascular disease and all-cause mortality among Japanese: The JPHC Study

Running head: Blood Pressure and cardiovascular disease

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ABSTRACT

Background- Little is known about the influence of blood pressure (BP) on cardiovascular disease (CVD) outcomes among Asian populations.

Methods- We examined population attributable fractions (PAF) and hazard ratios associated with BP in relation to stroke and coronary heart disease (CHD) incident and mortality within a cohort of 33,372 Japanese men and women aged 40-69 years, free of prior diagnosis of cancer and CVD. The BP was classified based on modified criteria of the 2003 European Society of Hypertension-European Society of Cardiology guidelines. A total of 943 stroke events, 182 CHD events, 262 stroke deaths, and 120 CHD deaths occurred between the baseline questionnaire (1990-1994) and the end of follow-up in December 31, 2003.

Results- BP levels were linearly associated with incidence and mortality of CVD in men and women. According to the PAF estimation, the elimination of normal to severe hypertension would prevent 64% of stroke incidence in men and 50% in women; 67% of stroke mortality in men and 29% in women; and 38% of total CVD mortality in men and 36% in women. The PAF estimate for total stroke incidence was the highest for mild hypertension, and the smaller for moderate to severe hypertension in both sexes.

Conclusions- Compared to contributions of normal BP, high normal BP, and mild hypertension to the occurrence of stroke events were greater than those made by moderate and severe hypertension, highlighting the importance of primary prevention and of treatment for low to moderate degrees of hypertension.

Key words: cardiovascular disease, hypertension, follow-up studies

INTRODUCTION

Cardiovascular disease (CVD) remains a major public health burden in Japan (28% of deaths),[1] although mortality from stroke and coronary heart disease (CHD) has declined since the 1960s.[2] This decline may be attributable to the steady decline in the prevalence of hypertension, which in turn is probably due to nationwide hypertension control and lifestyle changes (e.g. lowering sodium intake) in Japan.[1] Hypertension is an established major risk factor for onset of CVD and as well as a prognostic factor [3-7] and it can readily be detected.[8] In fact, a recent study has suggested that primary prevention of hypertension could reduce CVD deaths four times more than could secondary prevention.[9]

Identifying the population attributable fraction (PAF) associated with hypertension can offer significant insights into primary and secondary prevention of CVD. However, although there have been many reports on the PAF for CVD associated with hypertension from Western countries [7, 10, 11], there have been far fewer from Asian countries. [12] Because prevalence of risk factors varies for different populations, a highly potent factor in one country could be less important in another where it is less common. Previous epidemiological studies have confirmed that hypertension is associated with higher relative risks for stroke and heart failure than for CHD.[9, 13] In Japan, where stroke is more common than CHD, elevated blood pressure (BP) may have a greater impact on CVD morbidity and mortality than other risk factors (i.e. hyperlipidemia and cigarette smoking). Yet, few studies have examined the PAFs associated with BP categories used in clinical practice on CVD and all-cause mortality [12]and CVD incidence. We therefore investigated the estimated PAFs and hazard ratios (HR) associated with BP levels on stroke and CHD incidence and mortality from CVD occurrence and mortality in a large-scale Japanese cohort study.

MATERIALS AND METHODS

Study Cohort

The first cohort of the Japan Public Health Center-based Prospective Study (JPHC Study) was initiated in 1990 (Cohort-I) the second in 1993 (Cohort-II) in 11 public health center areas throughout the country.[14] Two public health center areas (Tokyo and Osaka) were excluded from the present study because CVD incidence data were not available. The study population of the present study was defined as all residents (n =116,896) aged 40-59 years for Cohort-I and 40-69 years for Cohort-II at baseline. Of these residents, 220 were excluded because of non-Japanese nationality (n=51), late reports of emigration occurring before the start of the follow-up period (n=166), and incorrect birth date (n=3). As a result, 116,676 residents remained eligible for the study. We informed the detail of the study to all study subjects. The protocol of the study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. A baseline self-administered questionnaire on various lifestyles was given to the residents in 1990, 1993 and 1994, and the 95,374 who responded were included in the study cohort. The overall response rate was 82%.

Baseline Questionnaire Survey and Health Examination

The questionnaire covered personal and family medical history, psychosocial factors such as perceived stress, household structure, as well as occupation, behavioral patterns and lifestyle factors such as smoking and alcohol habits, dietary habits, and physical activity.

Data for both systolic and diastolic BP were available for 34,654 men and women who participated health examinations conducted by municipal governments during the same year as the baseline survey. Arterial BP was measured with a standard mercury sphygmomanometer applied to the right arm of the seated participant after a 5-min rest. We used the modified classification of BP from the 2003 European Society of

Hypertension-European Society of Cardiology guidelines.[15] Regardless of antihypertensive medication use, optimal BP was defined as systolic pressure <120 mmHg and diastolic pressure <80 mmHg; the corresponding values for normal BP were 120-129 mmHg or 80-84 mmHg, for high normal BP 130-139 mmHg or 85-89 mmHg, for mild hypertension 140-159 mmHg or 90-99 mmHg, for moderate hypertension 160-179 mmHg or 100-109 mmHg, and for severe hypertension ≥180 mmHg or ≥110 mmHg.

We excluded 1,282 participants from the analysis due to previous history of myocardial infarction (MI), angina pectoris, stroke, or cancer at study baseline. Eventually, altogether 11,684 men and 21,688 women were entered in the analysis.

Confirmation of CHD and Stroke Incidence

A total of 64 hospitals were registered in the sampling area of the study cohort. All were major hospitals capable of treating patients with acute CHD and stroke. Physicians blinded to the patents' lifestyle data reviewed the medical records at each hospital. Acute CHD and stroke events were included in the study if they occurred after the date of return of the baseline questionnaire and before January 1, 2004.

The details of the surveillance for CHD were described previously.[16] Briefly, MI was confirmed in the medical records according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project,[17] which requires evidence from ECGs, cardiac enzymes, and/or autopsy. When such a workup was not performed but typical chest pain (20 min or longer) was reported, a probable diagnosis of MI was made. In the absence of such a diagnosis, deaths that occurred within 1 hour from onset of symptoms were regarded as sudden cardiac deaths.

Stroke was confirmed according to the criteria of the National Survey of Stroke,[18] which requires the presence of focal neurological deficits of sudden or rapid onset lasting at

least 24 hours or until death. Strokes were further classified as subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH), or ischemic stroke (thrombotic or embolic). All registered hospitals were equipped with computer tomographic scanning and/or magnetic resonance scanning equipment. A definite diagnosis was established on the basis of examination of CT or MRI images and/or autopsy.

Confirmation of CHD and Stroke Mortality

All death certificates are submitted to the Ministry of Health, Labor, and Welfare and coded for the National Vital Statistics. Registration of death is required by the Family Registration Law and is believed to be complete in Japan. The underlying causes of deaths were defined according to the International Classification of Diseases, 10th Revision (ICD-10) as follows: deaths from stroke (I60-I69), CHD (I20-I25), CVD (I01-I99), and cancer (C00-C97). Other causes (non-CVD and non-cancer) and all causes were also included in the analyses as well as CHD and stroke deaths if they occurred after the date of return of the baseline questionnaire and before January 1, 2004.

During the follow-up period, 2,254 of the study subjects died, 1,370 moved out of the study areas, and 79 were lost to follow-up.

Statistical analysis

Person-years for the follow-up period were counted from the date of the return of the baseline survey until one of the endpoints described hereafter. For the analysis of CHD or stroke incidence, person-years were censored at the date of disease diagnosis, the date of emigration from the study area, the date of death, or the end of the study period (December 31, 2003), whichever came first. For the analysis of deaths, person-years were censored at the date of emigration from the study area, the date of death, or the end of the study period, whichever

came first. For persons who were lost to follow-up, the last confirmed date of their presence in the study area was used as the censoring date.

Analysis of covariance and chi-square tests were used to compare sex-specific age-adjusted mean values and percentages for CVD risk factors. For this study, outcomes were defined as newly occurring CHD and stroke incidence or deaths during the study period. HRs and their 95% confidence intervals (95% CI) were calculated after adjustment for age and other potential risk factors by means of Cox proportional hazards models. The risk factors included age (years), public health center areas, smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, <150g/wk, 150-299g/wk, 300-449g/wk, or ≥450g/wk), body mass index (BMI, kg/m^2 in quintiles), antihypertensive medication use (yes or no), history of diabetes (yes or no), and serum total cholesterol levels (<4.14, 4.14-4.64, 4.65-5.16, 5.17-5.68, 5.69-6.20 and ≥6.21 mmol/L). We also calculated PAF to examine the contribution of the BP and its components to the risk of CVD, using multivariable HRs of statistical significance and the proportion of cases in each BP category.[19] PAF was estimated as pd × (HR−1)/HR, where pd is the proportion of cases falling into the category and the HR is the HR for the category relative to optimal BP.

We tested the assumption of proportional hazards by using both the time-dependent covariate method and the linear correlation test and found no violation of proportionality. The SAS statistical package Version 9.1 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

During the 393,493 person-years of follow-up (median follow-up period=11.0 years) among the 33,372 subjects, a total of 182 cases of incident CHD and 912 incident strokes were included in the analyses for the incidence. For the analyses of mortality, 120 CHD deaths, 209 stroke deaths, 97 CHD deaths, 456 CVD deaths, 850 cancer deaths, 485 deaths from other causes, and 1,791 all-cause deaths were included during the 405,326 person-years of the follow-up period (median follow-up period=11.0 years) among 33,372 subjects.

BP levels in relation to CVD risk factors were examined separately for men and women (Table 1). Subjects were categorized into six levels of BP: optimal (23%), normal (22%), high normal (21%), mild (25%), moderate (7%), or severe hypertension (2%). Both men and women with optimal BP were younger than other subjects, more likely to be current smokers, and to have lower BMI, lower serum total cholesterol levels, lower antihypertensive medication use, lower history of diabetes and lower ethanol intake.

The HRs and PAF for stroke, stroke subtypes (IPH, SAH, ischemic stroke), and CHD are presented in Table 2. For men, there were linear associations between BP levels and the incidence of total stroke, IPH and ischemic stroke and CHD. Similar linear relationships were observed for total stroke, IPH and ischemic stroke, and all endpoints in women except CHD incidence. There was no significant linear association between BP and risk of SAH in either men or women. Figure 1 also showed PAF, which represented the proportion of new stroke events in the entire cohort that would be prevented if normal to severe hypertension were eliminated. The elimination of normal to severe hypertension would prevent 64% of new stroke events in men: 6.1% from normal BP, 12.2% from high normal BP, 29.0% from mild hypertension, 11.5% from moderate hypertension, and 5.2% from severe hypertension, and 50% in women: 6.6%, 11.8%, 16.6%, 9.9% and 4.9%, respectively. The PAF estimate for total stroke incidence was the highest for mild hypertension, and was equal to or greater than

that for moderate to severe hypertension in both men and women. Further, the PAF estimate was similar for high normal and moderate hypertension in both sexes.

Table 3 shows the HRs and PAF estimates of mortality from stroke, CHD, cancer, CVD, other causes and all causes by BP category. We found linear relationships between BP levels and mortality from stroke and total CVD in both men and women and from all causes in men. Moderate and severe hypertension was significantly associated with increased risk of mortality from CHD and other causes in men, and severe hypertension with mortality from other causes in women. There was no significant association between BP and cancer mortality in either sex. According to the PAF estimation, the elimination of normal to severe hypertension would prevent 67% of stroke mortality in men and 29% in women, and 38% of total CVD mortality in men and 36% in women. The PAF estimate for total CVD mortality was the highest for mild hypertension, and was equal to or greater than that for moderate to severe hypertension.

For analysis of the PAF estimates of incidence and mortality from total CVD, further stratification by age group (40-64 and 65-69 years) was examined (data not shown). The PAF estimate for total CVD incidence was the highest for mild hypertension in both younger and older subjects. The PAF estimate for total CVD mortality was the highest for mild hypertension in younger subjects, even though no excess PAF estimate was found in older subjects.

We also examined whether the PAF estimates for any of the outcomes for non-antihypertensive medication users were different from the estimates for total subjects. There were no differences between the PAF estimates for untreated subjects and total subjects (data not shown). For instance, normal, high normal, mild, moderate and severe categories accounted for 36% overall of total CVD mortality. The PAF estimate for total CVD mortality was the highest for mild hypertension (15%), and slightly larger than that for moderate to

severe hypertension (13%).

DISCUSSION

In this large prospective analysis of a Japanese population, we found, after adjustment for cardiovascular risk factors, a linear relationship between BP and risks of stroke, IPH, ischemic stroke in both men and women and CHD in only men. Similarly, statistically significant linear relationships were detected between BP and risk of mortality from stroke, CVD and all causes for both men and women. The overall PAF of total stroke incidence from normal to severe hypertension (compared to optimal BP) was 64% in men and 50% in women. The overall PAF of CVD incidence and mortality from mild hypertension was equal to or greater than that from moderate to severe hypertension.

Hypertension has been shown to produce a strong predisposition to all of the major atherosclerotic CVD events.[7, 13] Further, clinical trials have documented striking reductions in stroke incidence as a result of antihypertensive medication therapy.[20, 21] Other preventive strategies such as antiplatelet therapy, lipid lowering, and smoking cessation have not been shown to reduce the risk of stroke to the same degree.[22-25] In addition, the potential benefits of hypertension control for reducing CVD may be greater than those of any other prevention strategies. For instance, the PAF of stroke incidence from smoking was 17% in men and 5% in women [26] and that of CHD incidence from smoking was 46% in men and 9% in women,[27] whereas the PAF of stroke incidence from elevated BP was 64% in men and 50% in women and that of CHD incidence from elevated blood pressure was 41% in men and 33% in women in the present study.

Antihypertensive medication treatment is usually initiated for patients with moderate and severe hypertension. However, it should be realized that, whereas HRs of stroke and CHD are greater for moderate and severe hypertension, mild hypertension includes the vast majority of hypertensive individuals. In fact, the PAF estimates for stroke and CHD are higher for mild hypertension because it is so common. A prevention of events in the

population is suboptimal if mild hypertension is inadequately controlled. A previous study reported that the elimination of normal (systolic pressure 120-129 mmHg and diastolic pressure 80-84 mmHg) and high normal BP (systolic pressure 130-139 mmHg or diastolic pressure 85-89 mmHg) would prevent 14% and 16% respectively of either incident ischemic stroke or CHD.[11] Our data similarly showed that the PAF estimates for the normal and high normal BP groups for incidence stroke or CHD to be 6% and 11%, respectively.

There are several limitations to our study. First, the proportion of subjects with data for both systolic and diastolic BP at baseline was only 30%, although the study subjects were selected from the general population. A previous report documented that non-participants had an unhealthier lifestyle than respondents, and were less likely to have undergone BP measurement in the health examination.[28] Thus, the prevalence of hypertension could be underestimated, but as a previous report suggested,[29] it is still uncertain whether HRs of CVD associated with hypertension was overestimated, underestimated or not. An exact effect of potential selection bias on PAFs is uncertain, but it is unlikely to change an overall picture of the findings. Second, since the study was not designed to analyze the effect of transitions, we were not able to assess changes in BP as a predictor of CVD outcomes. The strength of the relationship between BP and CVD outcomes may thus have been underestimated. Third, although the present study is a large-scale nationwide representative sample of the general population, we excluded subjects from Tokyo and Osaka (first and second largest cities in Japan) due to incomplete event registration. Thus, it is uncertain whether our results are generalizable to metropolitan areas of Japan. Fourth, it was possible that we have had missed some of end points in the present study. Within the sampling areas of the JPHC study, a total of 78 hospitals formed the register of events. All were major hospitals with the capability of treating patients with acute CHD, stroke or cancer events. In the JPHC study, 97% of registered strokes and 92% of registered MIs were treated at these 78 hospitals and a few

missing reports from hospitals or cases treated at outside of registered hospitals.[30] Furthermore, the JPHC Study involved local public health centers to systematically obtain hospital records and death certificates, which may have enhanced the accuracy of the JPHC stroke and MI registry. Finally, the numbers of events in some subsets such as women with CHD and men with SAH were small although the overall population was large. For that reason, conclusions related to these endpoints may have been limited.

The strengths of our study are its prospective design and large sample size, yielding robust statistical power for detecting the effects of BP stratified by gender.

To summarize, we found that BP was linearly associated with incidence and mortality from CVD. The overall effect of the normal, high normal, and mild hypertension categories for occurrence of stroke events was greater than that of the moderate and severe hypertension categories for both men and women. Our findings highlight the importance of control of low-to-moderate degrees of hypertension for primary prevention.

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Competing Interests:

None declared.

REFERENCES

1. Statistics and Information Department, Minister's Secretariat Ministry of Health, Labour and Welfare Japan: Statistical Abstracts on Health and Welfare in Japan 2003. Tokyo, Health and Welfare Statistics Association, 2004, pp 218-223.
2. Iso H, Shimamoto T, Kitamura A, Iida M, Komachi Y. Trends of cardiovascular risk factors for primordial prevension. Prev Med 1999; 29: S102-S105.
3. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, Kojima S. Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation. 1989; 79: 503-515.
4. MacMahon S, Peto R, Cutler J, Colliins R, Sorlie P, NeatonJ, Abbott R, Godwin J, Dyer A, Stmler J. Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-774.
5. Stamler J, Stamler R, Neaton D. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. Arch Intern Med. 1993; 153; 598-615.
6. Whelton PK. Epidemiology of hypertension. Lancet 1994; 344: 101-106.
7. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 1996; 275: 1571-1576.
8. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull 1994; 50: 272-298.
9. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ 2005; 331: 614.
10. Wilhelmsen L. Cardiovascular monitoring of a city over 30years. Eur Heart J 1997; 18: 1220-1230.

11. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. Am J Med 2006; 119: 133-141.
12. Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, Saito Y, Ota H, Nose T. Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. Hypertens Res 2005; 28: 901-909.
13. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903–1913.
14. Tsugane S, Sobue T. Baseline survey of JPHC study-design and participation rate. Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001; 11 (suppl): S24-S29.
15. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011-1053.
16. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; for the JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese, The Japan Public Health Center-Based (JPHC) study cohort I. Circulation 2006; 113:195-202.
17. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. for WHO MONICA Project. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates and case fatality in 38 populations from 21 countries in 4 continents. Circulation 1994; 90:583-612.

18. Walker AE, Robins M, Weinfeld FD. The national Survey of Stroke: clinical findings. Stroke. 1981; 119: 837-839.
19. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998; 88: 15-19.
20. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; 265: 3255–3264.
21. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757–764.
22. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81–106.
23. Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. Arch Intern Med 2003; 163: 669–676.
24. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. JAMA 1993; 269: 232–236.
25. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. JAMA 2002; 288: 1388–1395.
26. Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S; Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Group. Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. Stroke 2004; 35: 1248-1253.

27. Baba S, Iso H, Mannami T, Sasaki S, Okada K, Konishi M; Shoichiro Tsugane; JPHC Study Group. Cigarette smoking and risk of coronary heart disease incidence among middle-aged Japanese men and women: the JPHC Study Cohort I. Eur J Cardiovasc Prev Rehabil 2006; 13: 207-213.
28. Iwasaki M, Otani T, Yamamoto S, Inoue M, Hanaoka T, Sobue T, Tsugane S; JPHC Study Group. Background characteristics of basic health examination participants: the JPHC Study Baseline Survey. J Epidemiol 2003; 13: 216-225.
29. Iwasaki M, Yamamoto S, Otani T, Inoue M, Hanaoka T, Sobue T, Tsugane S; Japan Public Health Center-based Prospective Study Group. Generalizability of relative risk estimates from a well-defined population to a general population. Eur J Epidemiol. 2006; 21:253-262.
30. Yamagishi K, Ikeda A, Iso H, Inoue M, and Tsugane S. Self-reported stroke and myocardial infarction had adequate sensitivity in a population-based prospective study (JPHC Study). J Clin Epidemiol 2008 (in press).

APPENDIX

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Table1. Distributions of baseline characteristics according to blood pressure classification in a cohort of 33,372 men and women.

	Blood pressure classification						
	Optimal	Normal	High normal	Mild	Moderate	Severe	P-value
Men							
No. at risk	2,058	2,456	2,483	3,371	1,028	288	
Age, year	51.9	53.1	54.6	56.0	56.5	56.3	<0.001
Current smoker, %	52.1	45.9	44.6	43.2	40.3	44.5	<0.001
Ethanol intake, g/week	188.6	218.3	238.1	284.3	319.9	341.5	<0.001
Mean body mass index, kg/m2	22.3	23.3	23.6	24.2	24.5	24.8	<0.001
Antihypertensive medication use, %	3.3	6.0	11.1	21.3	33.1	38.4	<0.001
History of diabetes, %	5.1	5.2	7.1	7.2	6.4	5.3	0.007
Serum total cholesterol levels, mmol/l	4.8	5.0	5.0	5.1	5.1	5.2	<0.001
Women							
No. at risk	5,536	4,867	4,441	5,124	1,390	330	
Age, year	50.9	52.9	54.5	56.5	57.5	58.0	<0.001
Current smoker, %	4.5	2.9	3.1	2.8	2.8	4.6	<0.001
Ethanol intake, g/week	7.8	11.4	9.0	11.3	12.9	9.6	0.04
Mean body mass index, kg/m2	22.7	23.5	24.1	24.6	25.1	25.5	<0.001
Antihypertensive medication use, %	4.4	7.7	14.8	26.6	40.2	48.1	<0.001
History of diabetes, %	2.0	2.2	3.2	3.3	3.7	3.9	<0.001
Serum total cholesterol levels, mmol/l	5.2	5.3	5.4	5.4	5.4	5.5	<0.001

Optimal blood pressure was defined as systolic pressure <120 mmHg and diastolic pressure <80 mmHg; the corresponding values for normal blood pressure were 120-129 mmHg or 80-84 mmHg, for high normal blood pressure 130-139 mmHg or 85-89 mmHg, for mild hypertension 140-159 mmHg or 90-99 mmHg, for moderate hypertension 160-179 mmHg or 100-109 mmHg, and for severe hypertension ≥180 mmHg or ≥110 mmHg.

Table2. Age- and sex-adjusted and multivariable hazard ratios and 95% confidence intervals for incidence of stroke, stroke subtypes, and coronary heart disease according to blood pressure classification.

	Blood pressure classification						
	Optimal	Normal	High normal	Mild	Moderate	Severe	P for trend
Men							
Person-years	24,823	29,222	28,908	38,404	11,522	3,060	
Stroke, n	27	62	94	189	71	29	
Age-adjusted HR (95%CI)	1	1.83(1.17-2.88)	2.58(1.68-3.97)	3.68(2.46-5.53)	4.52(2.89-7.05)	7.05(4.17-11.94)	<0.001
Multivariable HR (95%CI)	1	1.87(1.19-2.94)	2.60(1.68-4.01)	3.63(2.39-5.51)	4.27(2.69-6.78)	6.72(3.90-11.59)	<0.001
PAF, %		6.1	12.2	29.0	11.5	5.2	
Intraparenchymal hemorrhage, n	7	12	30	58	24	10	
Age-adjusted HR (95%CI)	1	1.41(0.56-3.59)	3.44(1.51-7.85)	4.86(2.21-10.70)	6.64(2.85-15.47)	10.53(3.99-27.78)	<0.001
Multivariable HR (95%CI)	1	1.36(0.53-3.45)	3.43(1.49-7.88)	4.89(2.19-10.95)	6.49(2.71-15.53)	10.25(3.77-27.88)	<0.001
PAF, %		-	15.1	32.7	14.4	6.4	
Subarachnoid hemorrhage, n	3	6	10	10	6	1	
Age-adjusted HR (95%CI)	1	1.71(0.43-6.86)	2.92(0.80-10.65)	2.22(0.60-8.13)	4.46(1.10-18.05)	2.81(0.29-27.24)	0.05
Multivariable HR (95%CI)	1	-	-	-	-	-	-
PAF, %		-	-	-	-	-	
Ischemic stroke, n	17	44	54	121	41	18	
Age-adjusted HR (95%CI)	1	2.01(1.15-3.52)	2.22(1.29-3.84)	3.46(2.08-5.77)	3.81(2.16-6.73)	6.42(3.30-12.48)	<0.001
Multivariable HR (95%CI)	1	2.11(1.20-3.70)	2.21(1.27-3.84)	3.27(1.93-5.53)	3.38(1.88-6.10)	5.76(2.89-11.48)	<0.001
PAF, %		7.8	10.0	28.5	9.8	5.0	
Coronary heart disease, n	11	18	20	45	20	9	
Age-adjusted HR (95%CI)	1	1.33(0.63-2.82)	1.41(0.68-2.96)	2.29(1.18-4.45)	3.32(1.58-6.98)	5.68(2.34-13.78)	<0.001
Multivariable HR (95%CI)	1	1.35(0.64-2.88)	1.32(0.62-2.80)	1.98(0.99-3.98)	2.69(1.23-5.89)	3.74(1.47-9.53)	<0.001

(Cont. table2)

PAF, %		-	-	-	10.2	5.4	
Women							
Person-years	66,873	58,455	52,992	59,724	15,832	3,678	
Stroke, n	43	73	100	136	62	26	
Age-adjusted HR (95%CI)	1	1.74(1.19-2.53)	2.41(1.68-3.45)	2.63(1.86-3.73)	4.34(2.92-6.45)	7.65(4.67-12.53)	<0.001
Multivariable HR (95%CI)	1	1.67(1.14-2.43)	2.08(1.44-3.00)	2.17(1.51-3.11)	3.35(2.21-5.07)	5.60(3.34-9.39)	<0.001
PAF, %		6.6	11.8	16.6	9.9	4.9	
Intraparenchymal hemorrhage, n	10	18	28	36	17	11	
Age-adjusted HR (95%CI)	1	1.88(0.87-4.09)	3.01(1.46-6.23)	3.19(1.56-6.49)	5.50(2.48-12.16)	15.04(6.29-36.0)	<0.001
Multivariable HR (95%CI)	1	1.81(0.83-3.95)	2.70(1.29-5.65)	2.69(1.29-5.62)	4.19(1.83-9.61)	10.3(4.07-25.9)	<0.001
PAF, %		-	14.7	18.8	10.8	8.3	
Subarachnoid hemorrhage, n	17	19	22	30	11	3	
Age-adjusted HR (95%CI)	1	1.22(0.64-2.36)	1.51(0.80-2.86)	1.76(0.96-3.25)	2.40(1.10-5.21)	2.80(0.81-9.67)	0.01
Multivariable HR (95%CI)	1	1.32(0.68-2.57)	1.53(0.79-2.94)	1.77(0.93-3.39)	2.35(1.03-5.34)	2.91(0.81-10.53)	0.02
PAF, %		-	-	-	-	-	
Ischemic stroke, n	16	36	50	70	34	12	
Age-adjusted HR (95%CI)	1	2.19(1.22-3.96)	2.99(1.70-5.26)	3.23(1.86-5.59)	5.60(3.06-10.22)	8.14(3.82-17.36)	<0.001
Multivariable HR (95%CI)	1	1.98(1.10-3.59)	2.37(1.33-4.21)	2.36(1.34-4.17)	3.86(2.06-7.22)	5.22(2.37-11.47)	<0.001
PAF, %		8.2	13.3	18.5	11.6	4.4	
Coronary heart disease, n	6	4	15	22	10	2	
Age-adjusted HR (95%CI)	1	0.64(0.18-2.27)	2.33(0.90-6.04)	2.57(1.03-6.44)	4.14(1.48-11.58)	3.37(0.67-16.94)	<0.001
Multivariable HR (95%CI)	1	-	-	-	-	-	-
PAF, %		-	-	-	-	-	

Variables for multivariable adjustment were age, body mass index, smoking status, ethanol intake, antihypertensive medication use, history of diabetes, serum total cholesterol levels, and public health center areas. *Multivariable hazard ratios were not presented due to small the number of cases. HR indicates hazard ratios; CI, confidence intervals.

Table3. Age- and sex-adjusted and multivariable hazard ratios and 95% confidence intervals for mortality of stroke, coronary heart disease, total cardiovascular disease, cancer, other causes and all causes according to blood pressure classification.

	Blood pressure classification						
	Optimal	Normal	High normal	Mild	Moderate	Severe	P for trend
Men							
Person-years	25,526	30,018	29,967	39,843	12,008	3,273	
Stroke, n	6	15	19	42	19	7	
Age-adjusted HR (95%CI)	1	1.95(0.76-5.04)	2.22(0.89-5.58)	3.42(1.45-8.07)	5.00(1.99-12.58)	6.83(2.29-20.41)	<0.001
Multivariable HR (95%CI)	1	2.15(0.83-5.56)	2.47(0.97-6.26)	3.83(1.58-9.27)	5.45(2.09-14.17)	7.36(2.36-22.98)	<0.001
PAF, %		-	-	28.7	14.4	5.6	
Coronary heart disease, n	6	11	8	19	10	5	
Age-adjusted HR (95%CI)	1	1.44(0.53-3.90)	0.94(0.33-2.73)	1.57(0.62-3.95)	2.68(0.97-7.42)	4.96(1.50-16.34)	0.01
Multivariable HR (95%CI)	1	1.45(0.53-3.96)	0.85(0.29-2.51)	1.47(0.56-3.90)	2.18(0.74-6.43)	3.41(0.95-12.19)	0.06
PAF, %		-	-	-	-	-	
Total cardiovascular disease, n	24	34	43	86	46	20	
Age-adjusted HR (95%CI)	1	1.11(0.66-1.87)	1.26(0.76-2.08)	1.76(1.12-2.78)	3.06(1.86-5.02)	4.93(2.72-8.95)	<0.001
Multivariable HR (95%CI)	1	1.17(0.69-1.98)	1.30(0.78-2.17)	1.74(1.08-2.81)	2.78(1.64-4.71)	4.27(2.27-8.03)	<0.001
PAF, %		-	-	14.4	11.6	6.1	
Cancer, n	60	93	111	153	55	15	
Age-adjusted HR (95%CI)	1	1.19(0.86-1.65)	1.25(0.91-1.71)	1.18(0.87-1.59)	1.37(0.95-1.98)	1.38(0.78-2.43)	0.15
Multivariable HR (95%CI)	1	1.26(0.91-1.75)	1.33(0.97-1.84)	1.23(0.90-1.68)	1.46(1.00-2.15)	1.48(0.83-2.65)	0.12

(Cont. table3)

PAF, %		-	-	-	3.6	-	
Other cause mortality, n	41	58	60	97	36	15	
Age-adjusted HR (95%CI)	1	1.10(0.74-1.64)	1.01(0.68-1.51)	1.13(0.78-1.64)	1.36(0.87-2.14)	2.10(1.16-3.79)	0.05
Multivariable HR (95%CI)	1	1.19(0.80-1.79)	1.11(0.74-1.67)	1.34(0.91-1.97)	1.72(1.07-2.75)	2.47(1.33-4.58)	0.004
PAF, %		-	-	-	4.9	2.9	
All cause mortality, n	125	185	214	336	137	50	
Age-adjusted HR (95%CI)	1	1.15(0.91-1.44)	1.18(0.94-1.47)	1.27(1.04-1.57)	1.68(1.32-2.15)	2.27(1.63-3.15)	<0.001
Multivariable HR (95%CI)	1	1.22(0.97-1.54)	1.25(1.00-1.57)	1.36(1.10-1.69)	1.81(1.40-2.33)	2.36(1.67-3.32)	<0.001
PAF, %		-	4.1	8.5	5.8	2.7	
Women							
Person-years	68,741	60,023	54,461	61,264	16,363	3,839	
Stroke, n	14	17	17	32	16	5	
Age-adjusted HR (95%CI)	1	1.18(0.58-2.41)	1.16(0.57-2.37)	1.69(0.89-3.21)	2.99(1.44-6.22)	3.80(1.35-10.68)	<0.001
Multivariable HR (95%CI)	1	1.25(0.61-2.57)	1.08(0.52-2.24)	1.54(0.78-3.03)	2.52(1.15-5.51)	2.80(0.94-8.30)	0.01
PAF, %		-	-	-	9.6	-	
Coronary heart disease, n	3	4	10	14	6	1	
Age-adjusted HR (95%CI)	1	1.22(0.27-5.46)	2.89(0.79-10.55)	2.92(0.83-10.32)	4.34(1.07-17.64)	2.82(0.29-27.53)	0.02
Multivariable HR (95%CI)	1	-	-	-	-	-	-
PAF, %		-	-	-	-	-	
Total cardiovascular disease, n	24	29	42	67	33	8	
Age-adjusted HR (95%CI)	1	1.15(0.67-1.97)	1.60(0.97-2.66)	1.93(1.20-3.10)	3.33(1.95-5.68)	3.22(1.44-7.23)	<0.001
Multivariable HR (95%CI)	1	1.17(0.68-2.02)	1.48(0.88-2.48)	1.74(1.06-2.86)	2.77(1.57-4.88)	2.39(1.03-5.53)	<0.001
PAF, %		-	-	14.1	10.4	2.3	

(Cont. table3)

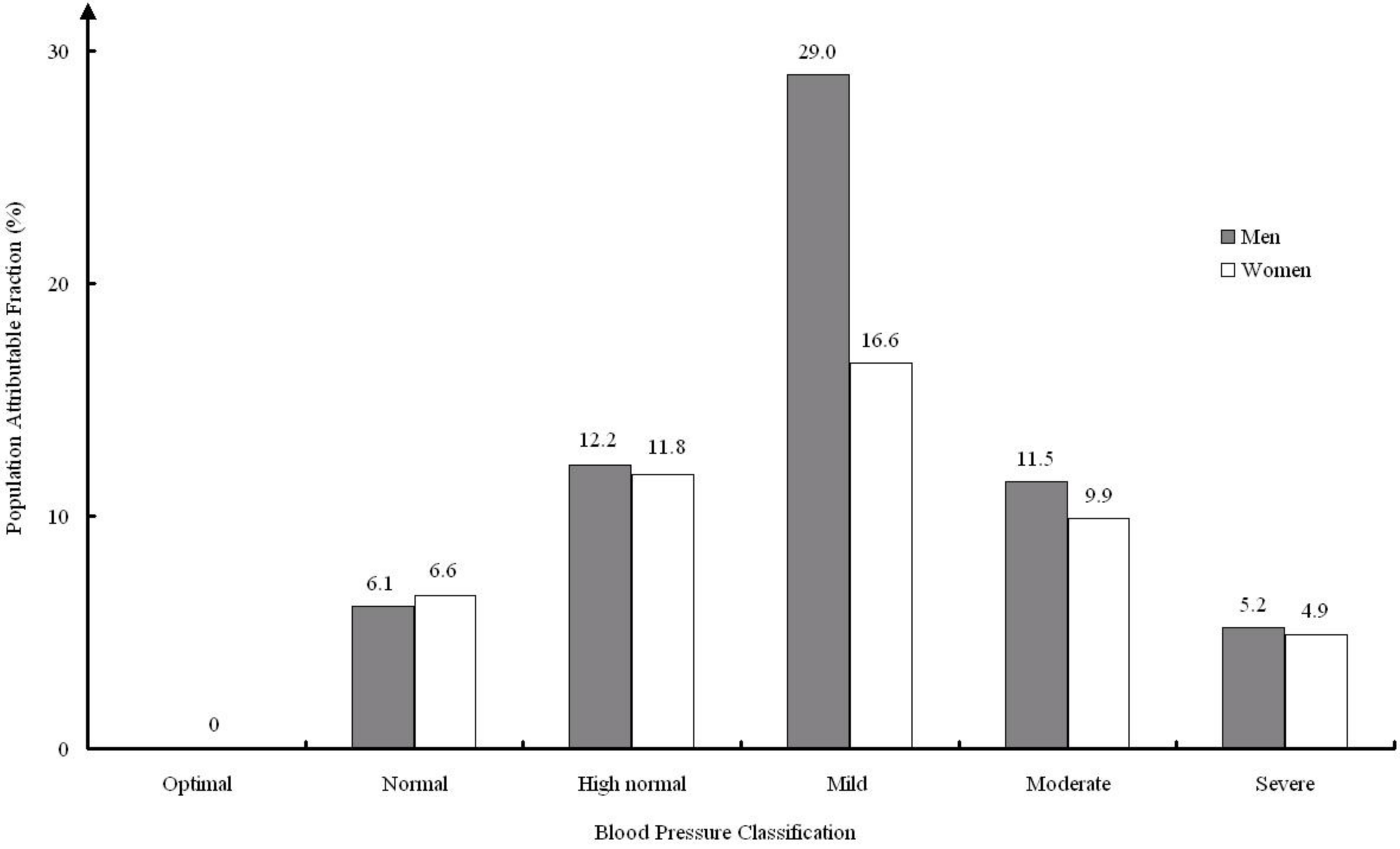
Cancer, n	80	72	76	104	24	7	
Age-adjusted HR (95%CI)	1	0.89(0.65-1.22)	0.93(0.67-1.27)	0.99(0.73-1.33)	0.81(0.51-1.28)	0.96(0.44-2.09)	0.77
Multivariable HR (95%CI)	1	0.85(0.62-1.18)	0.86(0.62-1.19)	0.91(0.66-1.25)	0.74(0.46-1.19)	0.84(0.38-1.87)	0.40
PAF, %		-	-	-	-	-	
Other cause mortality, n	36	35	30	53	18	6	
Age-adjusted HR (95%CI)	1	0.95(0.59-1.51)	0.79(0.49-1.29)	1.08(0.70-1.67)	1.30(0.73-2.31)	1.75(0.73-4.19)	0.22
Multivariable HR (95%CI)	1	1.04(0.65-1.66)	0.88(0.53-1.44)	1.28(0.81-2.01)	1.55(0.85-2.83)	2.14(0.87-5.28)	0.07
PAF, %		-	-	-	-	-	
All cause mortality, n	140	136	148	224	75	21	
Age-adjusted HR (95%CI)	1	0.95(0.75-1.20)	1.01(0.80-1.27)	1.18(0.95-1.46)	1.39(1.05-1.85)	1.58(0.99-2.50)	0.002
Multivariable HR (95%CI)	1	0.95(0.75-1.21)	0.97(0.77-1.24)	1.14(0.91-1.43)	1.31(0.97-1.76)	1.42(0.88-2.28)	0.02
PAF, %		-	-	-	-	-	

Variables for multivariable adjustment were age, body mass index, smoking status, ethanol intake, antihypertensive medication use, history of diabetes, serum total cholesterol levels, and public health center areas. *Multivariable hazard ratios were not presented due to small the number of cases. HR indicates hazard ratios; CI, confidence intervals.

Figure legend:

Figure 1.

Sex-specific population attributable fraction (%) for total stroke incidence by blood pressure category.


30
20
10
0
Population Attributable Fraction (%)
Men
Women
0
6.1
6.6
12.2
11.8
29.0
16.6
11.5
9.9
5.2
4.9
Optimal
Normal
High normal
Mild
Moderate
Severe
Blood Pressure Classification