Table 3 *(Continued)*

	LDL-cholesterol, mg dL^{-1}					HR per 1 SD	*P* for
	<80	80–99	100–119	120–139	140+	increment	interaction
Multivariable HR[a]	1.0	0.86 (0.52–1.43)	0.92 (0.56–1.50)	1.01 (0.61–1.68)	1.25 (0.76–2.07)	1.12 (0.97–1.29)	
HDL-cholesterol	No	22	59	81	62	96	320	
<54 mg dL^{-1}[c]	Multivariable HR[a]	1.0	1.51 (0.92–2.48)	1.60 (0.99–2.59)	1.36 (0.83–2.25)	1.99 (1.22–3.23)	1.20 (1.08–1.35)	0.73
Triglycerides	No	27	52	54	50	61	244	
<118 mg dL^{-1}[c]	Multivariable HR[a]	1.0	0.95 (0.59–1.52)	0.79 (0.49–1.27)	0.93 (0.57–1.51)	1.30 (0.80–2.10)	1.10 (0.95–1.27)	
Triglycerides	No	21	44	76	59	95	295	
≥118 mg dL^{-1}[c]	Multivariable HR[a]	1.0	1.34 (0.79–2.27)	1.73 (1.06–2.84)	1.38 (0.83–2.30)	1.85 (1.13–3.02)	1.21 (1.08–1.35)	0.61
Fasting (≥8 h	No	3	10	11	16	29	69	
after last meal)	Multivariable HR[a]	1.0	1.28 (0.35–4.76)	0.85 (0.23–3.12)	1.20 (0.34–4.25)	1.62 (0.47–5.61)	1.16 (0.91–1.50)	
Nonfasting (<8 h	No	45	86	119	93	127	470	
after last meal)	Multivariable HR[a]	1.0	1.18 (0.82–1.70)	1.32 (0.92–1.88)	1.18 (0.81–1.71)	1.64 (1.14–2.37)	1.19 (1.08–1.31)	0.94

[a]HR (95% CI) adjusted for gender, age and potential confounding factors. [b]Hypertensive was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 and/or as use of medication for hypertension. [c]Median value was used for cut-off point.

men. Our study showed a statistically significant age interaction (<50 years vs. ≥50 years) amongst women, whereas the number of cases was small (only five cases) amongst women aged <50 years. This result suggests an important role of menopause on the gender difference. Thirdly, men were more likely to have unhealthy lifestyles and unfavourable psychosocial factors compared with women and these risk factors may accelerate the effect of LDL-cholesterol on atherosclerosis development. In the present study, men were more likely to smoke and drink heavily compared with women.

It has remained a matter of debate in recent recommendations what range is optimal for LDL-cholesterol levels. A review article [26] declared that the optimal level of LDL-cholesterol is 50 to 70 mg dL^{-1}, because this range is observed amongst native hunter-gathers, healthy human neonates, free-living primates or wild mammals, all without atherosclerosis. Further, atherosclerosis progression and coronary heart disease events were minimized amongst participants in a cholesterol lowering trial to reduce the level to less than 70 mg dL^{-1}. However, NCEP-ATPIII [1, 2] recommended the clinical management and dietary therapy for low risk populations with ≥160 mg dL^{-1} of LDL-cholesterol and high risk populations with ≥100 mg dL^{-1} of LDL-cholesterol, because it was estimated that low cholesterol populations gain less absolute benefit from cholesterol lowering therapy than do high cholesterol populations. We identified an increased risk of mortality from coronary heart disease only in men with ≥140 mg dL^{-1} of LDL-cholesterol amongst this low cholesterol population. Our findings of men thus support the current suggestions by the NCEP-ATPIII that there may be an LDL-cholesterol threshold above 140 mg dL^{-1} for increased risk of coronary heart disease.

It is also a matter of debate why low LDL-cholesterol is associated with increased risk of all-cause mortality. A previous review showed the association between low total cholesterol levels and increased mortality from cancer and intraparenchymal haemorrhage [27]. Low LDL-cholesterol may be caused by cancer in most cases [27], but low LDL-cholesterol *per se* may increase the risk of intraparenchymal haemorrhage through the development of arteriolosclerosis [28].

A limitation of the current study is that we estimated LDL-cholesterol levels by using the Friedewald formula, which was formulated in fasting subjects without hypertriglyceridaemia [17]. However, there

Table 4 *Gender-specific multivariable hazard ratio (HR)[a] and 95% confidence interval (95% CI) of coronary heart disease according to lipid profiles*

	Lipid categories (Lower)				(Higher)	HR per 1 SD increment	*P* for interaction
LDL-cholesterol							
Range, mg dL^{-1}	<80	80–99	100–119	120–139	140+		
No for men	35	56	74	62	68	295	
Multivariable HR[a] for men	1.0	1.09 (0.71–1.68)	1.29 (0.85–1.95)	1.47 (0.95–2.26)	2.06 (1.34–3.17)	1.27 (1.13–1.43)	
No for women	13	40	56	47	88	244	
Multivariable HR[a] for women	1.0	1.29 (0.69–2.43)	1.10 (0.60–2.03)	0.83 (0.44–1.55)	1.16 (0.64–2.12)	1.06 (0.93–1.21)	0.06
Non-HDL-cholesterol							
Range, mg dL^{-1}	<110	110–129	130–149	150–169	170+		
No for men	48	57	56	52	82	295	
Multivariable HR[a] for men	1.0	1.17 (0.79–1.73)	1.10 (0.73–1.64)	1.42 (0.93–2.18)	2.15 (1.42–3.26)	1.28 (1.13–1.46)	
No for women	23	34	43	47	97	244	
Multivariable HR[a] for women	1.0	0.80 (0.47–1.37)	0.65 (0.39–1.09)	0.66 (0.39–1.11)	0.83 (0.50–1.37)	1.08 (0.94–1.25)	0.13
Total cholesterol							
Range, mg dL^{-1}	<160	160–179	180–199	200–219	220+		
No for men	50	57	56	53	79	295	
Multivariable HR[a] for men	1.0	1.02 (0.70–1.51)	0.90 (0.60–1.33)	1.18 (0.78–1.78)	1.89 (1.27–2.82)	1.26 (1.12–1.43)	
No for women	22	24	40	55	103	244	
Multivariable HR[a] for women	1.0	0.52 (0.29–0.93)	0.50 (0.29–0.85)	0.57 (0.34–0.95)	0.61 (0.37–1.00)	1.08 (0.94–1.25)	0.26

1SD of lipid profiles was 32.5 mg dL^{-1} (0.84 mmol L^{-1}) for LDL-cholesterol, 35.9 mg dL^{-1} (0.93 mmol L^{-1}) for non-HDL-cholesterol and 35.2 mg dL^{-1} (0.91 mmol L^{-1}) for total cholesterol. [a]HR (95% CI) adjusted for age and potential confounding factors.

was no change in the association between LDL-cholesterol and coronary heart disease after the exclusion of nonfasting subjects or persons with hypertriglyceridaemia at baseline, probably because the magnitude of subjects with hypertriglyceridaemia may be small in our cohort. Secondly, we used the mortality data based on death certificate diagnoses, not the incidence data. Thirdly, we did not measure menopausal status, which may have an important role in the mechanisms of gender difference. There was an age interaction (aged <50 years vs. aged ≥50 years) amongst women, suggesting that menopause may contribute to the gender difference. Finally, we did not measure psychosocial factors, which may contribute to gender-difference of association with risk of coronary heart disease [29–31]. The residual confounding and unmeasured effect modifier may affect the gender difference.

The strength of the present study is that we used lipid measurement values standardized in a single laboratory, which in turn was standardized by the CDC-NHLBI Lipid Standardized Program [15]. This justifies our assumption that misclassification bias due to errors in lipid measurement have been adequately reduced, and that the resultant accuracy lipid measurements are comparable with the results of previous well-standardized studies. The other strength is a statistical power sufficient to detect the association between LDL-cholesterol and mortality from coronary heart disease after the gender stratification. A previous Japanese study had too small number of cases to detect the association in women [22].

In conclusion, our large cohort study provides epidemiological evidence that, in a less obese population, higher concentrations of LDL-cholesterol are associated with increased risk of mortality from coronary heart disease for men, but not for women.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Long-term exposure to elevated blood pressure and mortality from cardiovascular disease in a Japanese population: the Ibaraki Prefectural Health Study

Hiroyuki Sasai[1,2,3], Toshimi Sairenchi[1,4], Fujiko Irie[5], Emiko Otaka[1], Hiroyasu Iso[6], Kiyoji Tanaka[2], Hitoshi Ota[1] and Takashi Muto[4]

High blood pressure (BP) has been well established as a leading risk factor for both cardiovascular disease and mortality in general. However, the effect of long-term exposure to elevated BP on mortality risks in Asian populations remains unclear. The purpose of this study was to investigate the effects of time-averaged BP levels over 5 years on subsequent cardiovascular disease mortalities in a Japanese population. A total of 46 484 adults (14 771 men and 31 713 women) aged 40–79 years, who had no history of stroke or heart disease and who underwent health checkups in Ibaraki prefecture, Japan, in 1993 and 1998 were followed up through 2005. Hazard ratios (HRs) for mortality were estimated using a Cox proportional hazard model. Multivariate HRs (95% confidence interval) associated with a 10 mm Hg increase in systolic BP were measured in 1993 and 1998, and their averages were 1.11 (1.05–1.16), 1.13 (1.07–1.18) and 1.17 (1.10–1.27), respectively. Multivariate HRs for a 10 mm Hg increase in time-averaged systolic BP were 1.12 (1.03–1.21) in men and 1.24 (1.13–1.35) in women. The subgroup analysis of antihypertensive use showed that multivariate HRs for time-averaged systolic BP were 1.20 (1.11–1.29) in sustained non-users and 1.17 (1.04–1.32) in sustained users. Similar results were also obtained for diastolic BP. In conclusion, long-term exposure to elevated BP substantially associates with excess risk for cardiovascular disease mortality among Japanese subjects, irrespective of antihypertensive medication use. Thus, appropriate management of BP is important in both users and non-users of antihypertensive medication.
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Keywords: antihypertensive medication use; cardiovascular disease; mortality; prospective cohort study; time-averaged blood pressure

INTRODUCTION

Elevated blood pressure (BP) is one of the major risk factors for mortality from cardiovascular disease (CVD) and all-cause comorbidity worldwide.[1–4] The excess risk for CVD and all-cause mortalities was substantially attributed to hypertension when compared with normal BP levels.[3] Therefore, management of hypertension is of utmost importance, not only in clinical practice but also in public health practice.

Atherosclerotic vascular disease evolves slowly and is undoubtedly related to the cumulative exposure of individuals to CVD risk factors over a lifetime.[5] High BP is a typical example of such a lifelong exposure. Consequently, previous investigations analyzing the relationship of BP to CVD mortality risk might be limited by a failure to effectively characterize or adequately quantify long-term vascular exposure. Some previous investigations have highlighted the importance of BP levels over time on incidence risk for CVD. The Framingham Heart Study[6] reported that recent antecedent BP (average of readings of all available examinations 1–10 years before baseline) is an important determinant of risk for future CVD events beyond current BP level. This effect was consistent in multiple subgroups, including men and women, older and younger age groups, as well as in lower and higher BP groups. The Physicians' Health Study,[7] a study of 11 150 men in the United States, aged 40–84 years, also demonstrated that 2-year diastolic BP change added information to current levels in relation to the risk of CVD. It remains uncertain, however, whether the results obtained in Western countries can be applied to Japanese populations because of the differences in intrinsic/extrinsic cultural and racial factors such as dietary habits by way of salt intake[8] and cardiovascular event rates[9,10] in Western countries and Japan. Therefore, it might be of interest to know whether long-term exposure to elevated BP (time-averaged BP within 5 years) in a population has a role in CVD risk prediction. Furthermore, to the

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best of our knowledge, few investigations exist with respect to the mortality risks associated with long-term exposure to BP in Asians.

Thus, the purpose of this study was to investigate the effects of long-term exposure to elevated BP on subsequent CVD and all-cause mortalities among the Japanese population. Furthermore, the present large prospective study tested whether the influences on mortality risks varied with antihypertensive medication use.

METHODS

Study design and population

The study population consisted of 97 078 adults (33 138 men and 63 940 women) aged 40–79 years and living in the Ibaraki prefecture of Japan, who availed themselves of annual community-based health checkups in 1993 (the Ibaraki Prefectural Health Study).[11,12] A total of 38 of the 85 municipalities in the prefecture were included in this study. The participation rate for health checkups was 36.4% in these areas and was similar to the rate for the Ibaraki prefecture overall in 1993 (35.8%). The study population accounted for 3% of the prefectural census population. Data were collected from anthropometry, BP measurements, blood samples, ECGs, interview questionnaires on smoking status, alcohol consumption, fasting status and medical history.

All participants attended a baseline visit in 1993, when BP and other health status data were collected. Participants with a history of heart disease, stroke, atrial fibrillation or with missing data were excluded from the study. The same examinations as at baseline were conducted among the 49 890 (55.2% of 90 361 participants who totally recruited after baseline examinations) adults who attended a second visit in 1998 (5 years later). At the second visit, participants with the health status mentioned above and/or with missing data were also excluded. The remaining 46 484 adults (14 771 men and 31 713 women) served as the basis for the analysis and their vital status was subsequently tracked until 2005 (7 years after the second visit). A detailed flow of the participants is presented in Figure 1. The study protocol was approved by the ethics committee of the Ibaraki prefectural office.

Assessments at baseline and at second visit

Systolic and diastolic BP levels were measured by trained observers using a standard mercury sphygmomanometer (cuff size 14×47 cm) on the right arm of seated participants who had rested for at least 5 min with their feet on the floor and arm supported at heart level. When systolic BP was greater than 150 mm Hg or diastolic BP was greater than 90 mm Hg, BP was measured again after several deep breaths, and the lower BP values, which were almost always observed after the second measurement, were used for analyses. Participants were considered hypertensive if they had systolic BP $\geqslant$ 140 mm Hg or diastolic BP $\geqslant$ 90 mm Hg according to the classification in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (the JNC 7 report).[13] Pulse pressure was computed as systolic BP minus diastolic BP. Time-averaged BP indices were also computed from the values in 1993 and 1998. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Blood samples were drawn from seated participants into two polyethylene terephthalate tubes: one tube with an accelerator and the other with sodium fluoride and ethylenediaminetetraacetic acid. Overnight fasting ($\geqslant$ 8 h) was not required. Serum triglyceride and serum total cholesterol levels were assayed on the basis of an enzyme method using an RX-30 device (Nihon Denshi, Tokyo, Japan) in 1993 and an H7350 device (Hitachi, Tokyo, Japan) in 1998. High-density lipoprotein cholesterol was measured by a phosphotungstic acid magnesium method using an MTP-32 device (Corona Electric, Ibaraki, Japan) in 1993 and with a direct measurement method using an H7350 device in 1998. The measurement of these lipids in the laboratory of the Ibaraki Health Service Association was standardized by the laboratory of the Osaka Medical Center for Health Science and Promotion under the laboratory network program of the US Centers for Disease Control and Prevention (Atlanta, Georgia).[14] Blood glucose levels were measured with a glucose oxidase electrode method using a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan) in 1993 and with a hexokinase/glucose-6-phosphate dehydrogenase method using an H7170 device (Hitachi, Tokyo, Japan) in 1998. Participants were considered diabetic if they had a blood glucose level $\geqslant$ 7.0 mmol l^{-1} during fasting or $\geqslant$ 11.1 mmol l^{-1} during non-fasting or if they reported being treated for diabetes mellitus. Atrial fibrillation was diagnosed on an ECG-8300 (in 1993) and an ECG-9332 (in 1998) cardiofax-V electrocardiogram (Nihon Kohden, Tokyo, Japan) by a trained physician.

An interview was conducted to ascertain antihypertensive and lipid medication uses, as well as treatment for diabetes mellitus, smoking status (never, past-smoker, smoked 1–19 cigarettes per day or $\geqslant$ 20 cigarettes per day), alcohol consumption (non-, sometimes, $<$ 60 g per day or $\geqslant$ 60 g per day), fasting status and any histories of heart disease or stroke.

Mortality surveillance

Mortality surveillances were conducted with systematic reviews of death certificates and resident registrations with the cooperation of public health centers and municipal government offices. The underlying causes of death were

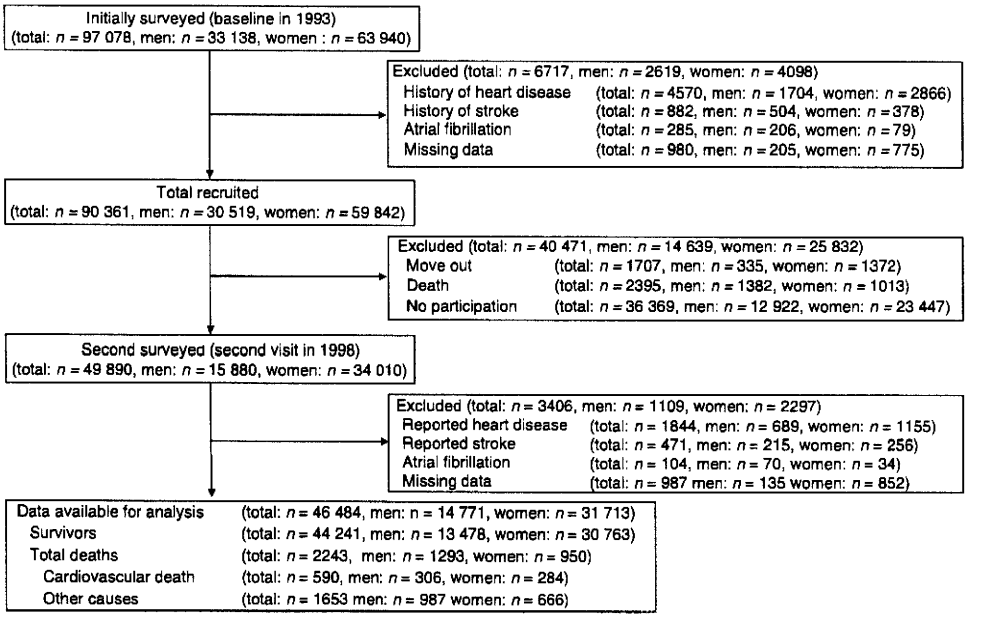

Figure 1 A detailed flow diagram of the study participants.

coded according to the International Classification of Diseases 10th revision (ICD-10). The follow-up surveillances after the second visit in 1998 were carried out until the end of 2005. There were 2243 participants who died during the follow-up phase. These individuals were censored at the date of death. The median follow-up duration for all participants was 7 years. Total CVD mortality was determined individually (codes I00-I99). The codes I00-99 indicate diseases of the circulatory system defined by ICD-10, including ischemic heart disease and cerebrovascular disease. The use of death certificate data was permitted by the Ministry of Health, Labour and Welfare of Japan.

Statistical analysis

To compare participants' physical characteristics at the second visit to the time-averaged BP categories according to the JNC 7 report, one-way analysis of variance was applied for continuous variables and a χ^2-test for categorical variables. Hazard ratios (HRs) (with the corresponding 95% confidence intervals (CI)) per 10 mm Hg increase of the time-averaged systolic BP and per 5 mm Hg increase of the time-averaged diastolic BP and pulse pressure for mortality from CVD and all causes were estimated using a Cox proportional hazards model. These values were chosen according to the previous study[15] and for ease of clinical interpretation. They did not mean a 10 or 5 mm Hg increase in BP indices from baseline to the second visit. HRs for BP indices at baseline and at the second visit were separately calculated and compared with the time-averaged models. The analysis was repeated with stratification for age (40–59 years, 60–79 years) in each gender. The analysis was also repeated with stratification for antihypertensive medication uses at baseline and at the second visit. All Cox models were adjusted for potential confounders (confer, footnotes of Tables 2, 3 and 4). A *P*-value less than 0.05 was regarded as statistically significant. The SAS statistical package version 9.1 (SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

During the 7-year follow-up after the second visit, there were 2243 deaths (1293 men and 950 women) from all causes, with 590 deaths (306 men and 284 women) from CVD. Gender- and age-specific numbers of all-cause deaths were 198 and 1095 among men aged 40–59 and 60–79 years, respectively. Similarly, there were 223 and 727 deaths for the same respective age groups in women. Gender- and age-specific numbers of CVD deaths were 36 and 270 among men aged 40–59 and 60–79 years, respectively. Similarly, there were 47 and 237 deaths for the same respective age groups in women.

Table 1 presents gender-stratified physical characteristics at the second visit based on time-averaged BP indices according to the classification of the JNC 7 report. All characteristics, except for total cholesterol in men, significantly differed across time-averaged BP categories.

Table 2 shows a comparison of BP indices at baseline, at second visit and their time-averaged values for mortality risks from CVD and all causes using all the study participants. Although systolic BP at baseline, at the second visit and their averages all exhibited significant

Table 1 Gender-stratified physical characteristics at the second visit in 1998 based on the time-averaged blood pressure categories according to the classification of the JNC 7 report

	Men (n=14 771)				*Women (n=31 713)*			
	Normal	*Pre-hypertension*	*Hypertension*	P	*Normal*	*Pre-hypertension*	*Hypertension*	P
Number of participants	2061	6660	6050		7173	14 513	10 027	
Age, year	59.8 (9.8)	63.7 (9.5)	66.7 (8.4)	<0.01	56.3 (8.6)	61.4 (9.0)	65.3 (8.5)	<0.01
Height, m	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	<0.01	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	<0.01
Weight, kg	58.8 (9.2)	60.3 (9.3)	60.8 (9.4)	<0.01	51.2 (7.2)	52.7 (7.9)	53.6 (8.4)	<0.01
Body mass index, $kg\,m^{-2}$	22.3 (2.9)	23.1 (2.9)	23.6 (3.0)	<0.01	22.3 (2.8)	23.4 (3.1)	24.2 (3.3)	<0.01
Systolic blood pressure, mm Hg	112.3 (8.9)	130.2 (9.5)	149.7 (13.2)	<0.01	111.4 (9.5)	130.7 (9.6)	149.8 (12.6)	<0.01
Diastolic blood pressure, mm Hg	69.1 (7.3)	77.0 (8.3)	84.9 (10.1)	<0.01	67.9 (7.3)	76.4 (8.0)	83.6 (9.9)	<0.01
Pulse pressure, mm Hg	43.2 (8.2)	53.1 (9.9)	64.8 (13.3)	<0.01	43.5 (8.0)	54.3 (9.8)	66.2 (12.9)	<0.01
Total cholesterol, $mmol\,l^{-1}$	5.0 (0.8)	5.0 (0.8)	5.0 (0.8)	0.26	5.4 (0.9)	5.5 (0.8)	5.6 (0.9)	<0.01
Triglyceride, $mmol\,l^{-1}$	1.4 (0.9)	1.6 (1.1)	1.7 (1.1)	<0.01	1.3 (0.7)	1.5 (0.8)	1.6 (0.9)	<0.01
HDL cholesterol, $mmol\,l^{-1}$	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	0.01	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	<0.01
Blood glucose, $mmol\,l^{-1}$	5.7 (1.7)	6.1 (1.9)	6.5 (2.2)	<0.01	5.4 (1.2)	5.7 (1.5)	6.1 (1.7)	<0.01
Antihypertensive medication use, %	2.1	14.4	41.1	<0.01	1.8	17.1	47.6	<0.01
Lipid medication use, %	2.0	2.7	4.5	<0.01	4.7	8.3	11.0	<0.01
Diabetes mellitus, %	2.7	3.8	4.8	<0.01	1.1	2.5	3.7	<0.01
Overnight fasting (≥8 h), %	45.3	35.6	32.5	<0.01	44.7	36.8	32.3	<0.01
Smoking status, %								
Never	23.8	23.3	22.9	<0.01	93.9	96.0	96.6	<0.01
Past	27.1	33.2	36.4		0.8	0.6	0.5	
Smoked 1–19 cigarettes per day	14.7	13.5	15.9		3.4	2.4	2.2	
Smoked ≥20 cigarettes per day	34.4	30.0	24.9		2.0	1.1	0.8	
Alcohol drinking, %								
Non	38.3	33.9	27.5	<0.01	82	85.7	88	<0.01
Sometimes	23.0	19.0	16.0		14.2	10.9	9.3	
<60 g per day	37.2	45.5	54.4		3.7	3.3	2.7	
≥60 g per day	1.5	1.7	2.1		0.1	0.0	0.0	

Abbreviation: HDL, high-density lipoprotein.
Means (s.d.) A one-way analysis of variance was applied for continuous variable and a chi-square test for categorical variables.

Table 2 Comparison of blood pressure indices at baseline, the second visit and their time-averaged value for mortality risks from cardiovascular disease and all causes among Japanese (n=46 484)

	Systolic blood pressure (HR per 10 mm Hg increase)	*Diastolic blood pressure (HR per 5 mm Hg increase)*	*Pulse pressure (HR per 5 mm Hg increase)*
Cardiovascular-disease mortality (person-years=329 263; number of deaths=590)			
Baseline in 1993	**1.11 (1.05, 1.16)**	**1.11 (1.06, 1.15)**	1.02 (0.99, 1.05)
Second visit in 1998	**1.13 (1.07, 1.18)**	**1.12 (1.07, 1.16)**	1.03 (1.00, 1.06)
Time-averaged value (1993 and 1998)	**1.17 (1.10, 1.24)**	**1.17 (1.11, 1.23)**	1.03 (1.00, 1.07)
All-cause mortality (person-years=329 263; number of deaths=2243)			
Baseline in 1993	**1.05 (1.03, 1.08)**	**1.04 (1.02, 1.06)**	1.02 (1.00, 1.04)
Second visit in 1998	1.03 (1.00, 1.06)	**1.03 (1.01, 1.06)**	1.00 (0.99, 1.02)
Time-averaged value (1993 and 1998)	**1.06 (1.03, 1.09)**	**1.05 (1.03, 1.08)**	1.02 (1.00, 1.04)

Systolic and diastolic blood pressure levels, and pulse pressure were entered in separate models. Hazard ratios (HRs) with 95% confidence intervals were adjusted for possible confounders measured at the second visit in 1998: gender, age, body mass index, total and high-density lipoprotein cholesterol, log-transformed triglycerides, blood glucose, treatment (yes or no) for hypertension and dyslipidemia, presence of diabetes (yes or no), smoking status (never, past-smoker, smoked 1–19 cigarettes per day or ⩾20 cigarettes per day), alcohol drinking (non-, sometimes, <60 g per day or ⩾60 g per day) and fasting status (<8 h or ⩾8 h). Bold values showed statistical significance (P<0.05).

relationships with CVD mortality, the time-averaged systolic BP had the greatest HRs compared with those at baseline and the second visit. Similar results were also obtained with diastolic BP. We observed relatively higher HRs in time-averaged systolic and diastolic BP levels for CVD mortality risks. However, this tendency seems to be much lower for all-cause mortality.

Table 3 presents gender- and age-stratified HRs for mortality from CVD and all causes according to the time-averaged BP indices. The HRs of time-averaged systolic and diastolic BP levels for CVD mortality were larger in men aged 40–59 years compared with men aged 60–79 years. In contrast, the HRs were similar among women aged 40–59 years and 60–79 years. We also detected that the effects of time-averaged BP indices on all-cause mortality were apparently lower than those from CVD. We were unable to observe a clear age-specific relationship between time-averaged BP indices and mortality from all causes.

Table 4 provided multivariate HRs for mortality from CVD according to the time-averaged BP indices stratified by antihypertensive medication use at baseline and the second visit. The positive associations between time-averaged systolic and diastolic BP levels and mortality from CVD were similarly observed in both sustained users and sustained non-users of antihypertensive medication.

DISCUSSION

This large cohort study demonstrated that each 10 mm Hg increase in time-averaged systolic BP and 5 mm Hg increase in time-averaged diastolic BP is associated with a 1.17-fold risk for CVD mortality. This suggests that long-term vascular exposure to elevated BP yields excess risks for CVD mortality. To the best of our knowledge, this is the first large prospective study to show the associations between long-term exposure to elevated BP and mortality from CVD among Asians. Furthermore, it appears that these effects remained unchanged according to the state of antihypertensive medication use.

The Framingham Heart Study[16] showed that each 1-SD increase in time-averaged systolic BP (available readings 1–10 years before baseline) exhibited significant associations with the risk of heart failure (HR (95% CI), 1.31 (1.1–11.15)) after adjusting for current BP. Vasan *et al.*[6] in the same cohort, revealed similar trends with respect to CVD events. Progression to hypertension from prehypertension or optimal BP categories was also reported to be associated with increased risk for cardiovascular outcomes by several previous studies.[17,18] For example, the Nurses' Health Study,[17] a study of 39 322 US female nurses, aged greater than 45 years, demonstrated that women who progressed to hypertension had a higher major CVD event risk than those who remained normotensive, according to the classification of the JNC 7 report. Similar results were also obtained in the Copenhagen MONICA cohort.[18] In addition, the Seven Countries Study (11.2% Japanese) and related cohorts have examined the impact of BP changes, not time-averaged BP, as an additional risk factor for CVD mortality.[15,19,20] Most findings suggest that a BP decrease is beneficial and an increase is harmful for both the incidence and mortality risks of CVD. For example, Menotti *et al.*[15] reported that a 10 mm Hg increase in systolic BP within a 10-year period corresponded to an increased risk for mortality from all causes (HR (95% CI), 1.11 (1.09–1.13)) and from CVD (HR (95% CI), 1.14 (1.10–1.17)) during the subsequent 25 years. These slight but significant relationships were consistent with the results of a clinical trial[21] using antihypertensive medication. Our results are also fully consistent with these previous studies. Although existing literature has been mainly based on the results of participants from European countries, our study showed for the first time that long-term exposure to elevated BP is associated with increased mortality risks from CVD.

There are several reasons why time-averaged BP may predict CVD mortality risk after controlling for potential confounders. First, time-averaged BP levels provide a somewhat more stable characterization of the true BP of an individual because it is less influenced by intraindividual physiological fluctuations and measurement error.[22] Second, time-averaged BP has been more clearly associated with the presence of cardiovascular target organ damage,[23] which serves as an intermediate for subsequent clinical CVD events.

In this study, we detected higher mortality risk for CVD in men aged 40–59 years than in men aged 60–79. However, this tendency was not observed in women. The reason for this association remains uncertain. We simply speculated that the weaker association between high BP and the risk of CVD deaths in older age groups might be partly due to elevated risk among older individuals with low BP from the effects of aging, such as increased fat mass and reduced physical activity.[24,25] However, the explanation is not specific for men or for women. Further research is needed to confirm these gender- and age-specific associations between long-term exposure to BP and CVD mortality in Asians.

The current study also revealed that extended elevated BP was a significant predictor for CVD deaths in individuals with sustained antihypertensive medication use (Table 4). The results highlighted the need for appropriate BP control in antihypertensive users by

Table 3 Gender- and age-stratified multivariate hazard ratios (HRs) for mortality from cardiovascular disease and all causes according to the time-averaged blood pressure indices

	Number of participants	*Person-years*	*Number of deaths*	*Systolic blood pressure (HR per 10 mm Hg increase)*	*Diastolic blood pressure (HR per 5 mm Hg increase)*	*Pulse pressure (HR per 5 mm Hg increase)*
Cardiovascular-disease mortality						
Men						
Subtotal	14771	103301	306	**1.12 (1.03, 1.21)**	**1.11 (1.03, 1.18)**	1.03 (0.98, 1.08)
Age 40–59 years	6368	45796	36	**1.65 (1.32, 2.06)**	**1.40 (1.17, 1.67)**	**1.25 (1.07, 1.45)**
Age 60–79 years	8403	57505	270	1.06 (0.97, 1.16)	1.07 (1.00, 1.16)	1.01 (0.95, 1.07)
Women						
Subtotal	31713	225962	284	**1.24 (1.13, 1.35)**	**1.24 (1.16, 1.33)**	1.04 (0.99, 1.10)
Age 40–59 years	18620	133666	47	**1.25 (1.01, 1.54)**	**1.23 (1.04, 1.47)**	1.07 (0.92, 1.25)
Age 60–79 years	13093	92296	237	**1.24 (1.13, 1.37)**	**1.26 (1.16, 1.36)**	1.04 (0.98, 1.10)
All-cause mortality						
Men						
Subtotal	14771	103301	1293	**1.05 (1.01, 1.09)**	1.03 (1.00, 1.07)	1.02 (1.00, 1.05)
Age 40–59 years	6368	45796	198	1.08 (0.97, 1.20)	1.04 (0.96, 1.14)	1.04 (0.97, 1.12)
Age 60–79 years	8403	57505	1095	**1.05 (1.00, 1.10)**	1.03 (0.99, 1.07)	1.02 (0.99, 1.05)
Women						
Subtotal	31713	225962	950	**1.07 (1.02, 1.13)**	**1.08 (1.04, 1.12)**	1.01 (0.98, 1.04)
Age 40–59 years	18620	133666	223	1.01 (0.91, 1.12)	1.04 (0.96, 1.13)	0.98 (0.91, 1.05)
Age 60–79 years	13093	92296	727	**1.09 (1.04, 1.16)**	**1.10 (1.05, 1.15)**	1.01 (0.98, 1.05)

Systolic and diastolic blood pressure levels, and pulse pressure were entered in separate models. HRs (95% confidence intervals) were adjusted for possible confounders measured at the second visit in 1998: age, body mass index, total and high-density lipoprotein cholesterol, log-transformed triglycerides, blood glucose, treatment (yes or no) for hypertension and dyslipidemia, presence of diabetes (yes or no), smoking status (never, past-smoker, smoked 1–19 cigarettes per day or ⩾20 cigarettes per day), alcohol drinking (non-, sometimes, <60 g per day or ⩾60 g per day) and fasting status (<8 h or ⩾8 h). Age was adjusted within age-stratified group owing to relatively large age range. Bold values showed statistical significance ($P<0.05$).

Table 4 Multivariate hazard ratios (HRs) for mortality from cardiovascular disease (CVD) according to the time-averaged (1993 and 1998) blood pressure indices, stratified by antihypertensive medication uses at baseline and the second visit

	Antihypertensive medication use (baseline/second visit)			
	No/No	*No/Yes*	*Yes/No*	*Yes/Yes*
Number of participants	34923	3924	689	6948
Number of deaths from CVD	340	68	18	164
Systolic blood pressure				
Means (s.d.), mm Hg	128.9 (14.5)	143.4 (12.5)	140.9 (13.5)	145.0 (12.5)
HRs per 10 mm Hg increase	**1.20**	1.08	0.95	**1.17**
95% confidence intervals	**1.11, 1.29**	0.89, 1.31	0.66, 1.36	**1.04, 1.32**
Diastolic blood pressure				
Means (s.d.), mm Hg	76.4 (8.5)	82.7 (8.5)	82.0 (8.8)	82.6 (8.6)
HRs per 5 mm Hg increase	**1.17**	**1.18**	1.03	**1.19**
95% confidence intervals	**1.09, 1.25**	**1.01, 1.37**	0.77, 1.38	**1.08, 1.31**
Pulse pressure				
Means (s.d.), mm Hg	52.5 (10.4)	60.6 (10.9)	58.9 (11.0)	62.4 (11.2)
HRs per 5 mm Hg increase	**1.07**	0.96	0.94	1.01
95% confidence intervals	**1.01, 1.12**	0.86, 1.08	0.75, 1.18	0.95, 1.09

Systolic and diastolic blood pressure levels, and pulse pressure were entered in separate models. HRs (95% confidence intervals) were adjusted for possible confounders measured at the second visit in 1998: age, body mass index, total and high-density lipoprotein cholesterol, log-transformed triglycerides, blood glucose, treatment for dyslipidemia (yes or no), presence of diabetes (yes or no), smoking status (never, past-smoker, smoked 1–19 cigarettes per day or ⩾20 cigarettes per day), alcohol drinking (non-, sometimes. <60 g per day or ⩾60 g per day), fasting status (<8 h or ⩾8 h). Bold values showed statistical significance ($P<0.05$).

therapeutic approaches, including dose management of drugs and lifestyle modification. In addition, we observed that elevated BP for a long period of time was significantly associated with increased risk of CVD deaths, even in sustained non-users of antihypertensive medication. This also demonstrated the clinical significance of controlling BP among drug-free individuals.

High BP is one of the leading risk factors for CVD mortality. Its contribution to general mortality is also significant.[3] In this study, however, the results did not show a strong relationship between time-averaged BP and all-cause mortality. This appears inconsistent with a previous study investigating BP and mortality risks.[20] This is likely because the proportion of CVD to all-cause mortality is much

smaller in Japan (approximately 30% in both genders) than in the United States[26] (approximately 50% in both genders).

The strength of this study is that we used a cohort that was large enough to conduct subgroup analyses. In addition, all blood samples were measured by the same laboratory, which is acknowledged by a known quality control program, as opposed to previous studies in which blood analysis was carried out in many different laboratories.[1]

Our study, however, had several limitations. First, the study samples were participants in annual health checkups for community residents that had a response rate of approximately 36%. Potential selection bias may be significant partly because of low participation rates (standardized mortality ratios=0.51 (95% CI: 0.49–0.54)). In addition, only 55.2% (49 890/90 361 persons) of those who received baseline measurements attended the second examination in 1998. However, the baselines BP were significant but differed slightly (systolic BP: 132.0 *vs.* 134.5 mm Hg, diastolic BP: 78.4 *vs.* 79.3 mm Hg) between those participants who had and those who had not attended health checkups in 1998. Although there were 1707 people who moved out (0.38% per year) from baseline to the second visit, the influence of migration on our results might be small because of the relatively low migration rate of this cohort. Second, the medical care status after incidence of CVD might be a confounding factor because incidence data were not available. We used death certificates, but did not validate the causes of death. The accuracy of our diagnoses of ischemic heart disease or heart disease as the cause of death is, therefore, uncertain. However, previous studies have shown that death certificate diagnosis with regard to stroke subtypes was valid owing to the high prevalence of computerized tomography scan or MRI used in hospitals in Japan.[27] Third, the regulating factor for BP levels was unclear during the 5-year follow-up period. For participants without antihypertensive medication, other factors such as physical activity[28] and dietary intake and composition[8] (sodium, magnesium, calcium or potassium) may have an influential role in their BP regulation over 5 years. For participants with antihypertensive medication, no information on changes in the intensity of antihypertensive treatment was available. This might be a possible confounder. However, this effect might be considerably small, as the same result was obtained in drug-free participants, as shown in Table 4.

In conclusion, long-term exposure to elevated BP (for example, high time-averaged BP indices) raised CVD mortality among Asians. This effect is not altered by the use of antihypertensive medication. Thus, BP maintenance is a crucial intervention for Japanese citizens in general, irrespective of antihypertensive medication use.

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V. 資　料

研究成果等普及啓発事業　研究成果発表会（一般向け）

「（市民公開講座）自分でできる生活習慣病の予防」

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研究協力者　長澤 晋哉　滋賀医科大学生活習慣病予防センター　特任助教

当厚生労働研究の６年間の成果を、一般市民向けに普及啓発することを目的に以下の組織と計画を構成し実施した。発表テーマは、「自分でできる生活習慣病の予防」として、高血圧、糖尿病、高コレステロール血症、慢性腎臓病、喫煙の計５項目について講演した。当日は、予想を上回る212人の市民が集まり、その多くは一般参加者であった。

高血圧については、大久保孝義（滋賀医科大学社会医学講座公衆衛生学部門准教授）が、「血圧が語るリスクサイン」と題して、家庭血圧の重要性や様々な血圧値の意義や測定値の見方などについて発表した。糖尿病については、斎藤重幸（札幌医科大学内科学第二講座講師）が、「地域の疫学研究からみた糖尿病と循環器疾患の予防：もし、糖尿病といわれたら」と題して、近年の糖尿病の疫学、予防法、および治療法について心構えも含め発表した。高コレステロール血症については、岡村智教（慶應義塾大学医学部衛生学公衆衛生学教授）が、「コレステロールと病気のふしぎ」と題して、動脈硬化を予防する有効な手段としてのコレステロール低下療法の重要性、さらに血清コレステロール値が低い場合における原因の考察の重要性について発表した。慢性腎臓病については、清原裕（九州大学大学院医学研究院環境医学分野教授）が、「今注目されている慢性腎臓病とは？」と題して、慢性腎臓病の重要性とその予防について、久山町研究成果などをもとに発表した。喫煙については、村上義孝（滋賀医科大学社会医学講座医療統計学部門准教授）が、「たばこは本当にからだに悪いの？」と題して、喫煙の健康に対する悪影響とわが国の喫煙率減少に必要な要点について発表した。

参加者の反応は非常に良く、講演後の質問も多かった。具体的には、変動した血圧値の評価方法、手首で測定する血圧計の信頼性、目標とすべきHDLコレステロール値、喫煙率減少への取り組み方法についてなどの質問であり、活発な議論を通し、市民との対話が実現できた。アンケートの結果では、参加者の９割以上が今回の発表会に満足し、今後もこのような機会があれば参加したい、との回答であった。

さらに本発表会では、一般市民の他、市町村の保健課、福祉課、医療関係者なども参加し、既に実施されている特定健診・特定保健指導において、有効な情報提供ができたと考えられた。

A. 主催

滋賀医科大学生活習慣病予防センター

B. 共催

財団法人循環器病振興財団

C. 後援

滋賀県、滋賀県医師会

D. 開催日時

平成23年2月19日（土）　14時00分～16時30分

E. 開催場所

ピアザ淡海（滋賀県大津市）

F. 発表テーマ

（市民公開講座）自分でできる生活習慣病の予防

G. プログラム

座長　：上島弘嗣　（滋賀医科大学生活習慣病予防センター）

三浦克之　（滋賀医科大学社会医学講座公衆衛生学部門）

午後

2：00～2：05・・・開会の挨拶

2：05～2：25・・・血圧が語るリスクサイン

大久保孝義（滋賀医科大学社会医学講座公衆衛生学部門）

2：25～2：45・・・地域の疫学研究からみた糖尿病と循環器疾患の予防

斎藤重幸（札幌医科大学内科学第二講座）

2：45～3：05・・・コレステロールと病気のふしぎ

岡村智教（慶應義塾大学医学部衛生学公衆衛生学）

～休憩～

3：15～3：35・・・今注目されている慢性腎臓病とは？

清原裕（九州大学大学院医学系研究院環境医学）

3：35～3：55・・・たばこは本当にからだに悪いの？

村上義孝（滋賀医科大学社会医学講座医療統計学部門）

3：55～4：25・・・総合討論と質疑応答

4：25～4：30・・・閉会の挨拶

市民公開講座 アンケート結果

参加者数 212 人

アンケート提出者数 174 人

1. 今回の市民公開講座を何で知りましたか。(%)

テレビ	0.0
新聞	5.2
広報	15.5
大学 HP	6.9
ちらし	47.1
紹介	12.6
その他	12.6
無回答	0.0

2. 今回の市民公開講座はいかがでしたか。(%)

大変良	53.4
良	37.9
普通	2.3
不良	0.0
無回答	6.3

3. 発表内容はいかがでしたか。(%)

分かり易い	84.5
普通	10.9
分かりにくい	0.0
無回答	4.6

4. 発表者1人あたりの発表時間はいかがでしたか。(%)

長い	3.4
適当	72.4
短い	16.7
無回答	7.5

5. またこのような市民公開講座に出席したいと思いますか。(%)

是非出席	53.4
都合次第	43.1
興味なし	0.0
無回答	3.4

6.　あなたの性別、年齢をお聞かせください。(%)

男性	35.6
女性	62.6
無回答	1.7
20 歳以下	0.6
21～30 歳	6.3
31～40 歳	8.6
41～50 歳	9.2
51～60 歳	11.5
61～70 歳	33.3
71～80 歳	27.0
81 歳以上	3.4
無回答	0.0

7.　あなたのお住まいはどちらですか？(%)

大津市	57.5
草津市	14.4
その他	27.6
無回答	0.6

8.　あなたの職業等をお聞かせください。(%)

会社員	8.6
公務員	8.6
教職員	3.4
医療関係者	7.5
学生	3.4
主婦	33.3
無職	13.2
その他	19.0
無回答	2.9


市民公開講座
自分でできる
生活習慣病の予防
ピアザ淡海
ピアザホール
当日、ご自由にお越しください
入場料無料
プログラム ～Program～
血圧が語るリスクサイン
大久保 孝義
地域の疫学研究からみた糖尿病と腎臓疾患の予防
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多注目されている慢性腎臓病とは？
清原 裕
たばこは本当にからだに悪いの？
村上 義孝
ピアザ淡海
滋賀医科大学生活習慣病予防センター

ポスター・チラシ


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市民公開講座
自分でできる
生活習慣病の予防
2階 ピアザホール
大津市保育協議会
2月第3土曜日研修会
3階 大会議室
PIAZZA
OMI


厚生労働科学研究　研究成果等普及啓発事業　市民公開講座
自分でできる生活習慣病の予防
主催：滋賀医科大学生活習慣病予防センター

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平成22年度厚生労働科学研究費補助金
循環器疾患・糖尿病等生活習慣病対策総合研究事業

「大規模コホート共同研究による
生活習慣病発症予防データベース構築と
その高度利用に関する研究」

平成22年度　総括・分担研究報告書

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