Original Article

Age-Specific Relationship between Blood Pressure and the Risk of Total and Cardiovascular Mortality in Japanese Men and Women

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To examine the impact of age on the relationship between blood pressure (BP) levels and each of cardiovascular disease mortality and all-cause mortality, a total of 30,226 men and 58,798 women aged 40–79 years who had no history of stroke or heart disease underwent health checkups in Ibaraki-ken, Japan, in 1993 and were followed through 2002. Risk ratios for mortality by BP category based on the 1999 WHO-ISH guidelines were calculated by age subgroups (40–59 years, 60–79 years) using a Cox proportional hazards model. Compared with optimal BP levels, the multivariate risk ratios of cardiovascular mortality for stage 2 or 3 hypertension were 5.99 (95% confidence interval: 2.13–16.8) in middle-aged men and 4.09 (1.70–9.85) in middle-aged women. These excess cardiovascular mortality risks were larger in the 40–59 years age group than in the 60–79 years age group for both genders (*p* for interaction = 0.01 for both). In men, the population attributable risk percents of cardiovascular mortality were 60% for younger men and 28% for older men, while for women they were 15% for younger women and 7% for older women. Weaker but significant excess risks of total mortality were observed for stage 2 or 3 hypertension in men of both age groups and in the older age group for women. The impact of BP on the risk of cardiovascular mortality was larger among middle-aged persons than among the elderly in both men and women. Our findings indicate the importance of BP control to prevent cardiovascular disease among middle-aged individuals. (*Hypertens Res* 2005; 28: 901–909)

***Key Words*: blood pressure, cardiovascular disease, aging, follow-up study**

Introduction

Elevated blood pressure is a common and powerful predisposing factor for stroke, coronary disease, cardiac failure and peripheral artery disease (*1*). In Japan, hypertension is a major public health problem, and in 2002, 31% of deaths were attributable to cardiovascular disease (*2*).

The 1999 World Health Organization–International Society (WHO-ISH) of Hypertension Guidelines for the Management of Hypertension (*3*) has been adopted in Japanese clinical practice. The relationship of systolic blood pressure (SBP) to all-cause mortality and mortality or incidence of cardiovascular disease among Caucasians has been reported to be age-dependent (*4–6*). A recent meta-analysis in which 8% of the subjects were Japanese has shown an age-dependent

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Table 1. Gender- and Age-Specific Baseline Characteristics According to Endpoint Categories among 30,226 Men and 58,798 Women, Ibaraki-Ken, Japan, 1993

Gender, age group, and variables	Survived*	Cardiovascular death	Non-cardiovascular death
Men			
Age 40–59 years			
No. of subjects	11,814	83	339
Systolic blood pressure (mmHg)**	131.1±16.4	143.8±17.7†	134.3±17.4†
Diastolic blood pressure (mmHg)**	81.0±11.2	86.2±±10.9†	82.2±10.4
Pulse pressure (mmHg)**	50.1±11.4	57.6±12.5†	52.1±11.8†
Hypertension medication (%)	8.8	25.3†	12.1†
Current smoker (%)	54.8	73.5†	63.1†
Current drinker (%)	56.6	67.5†	57.9
Total cholesterol (mg/dl)**	197.1±34.7	194.0±34.1	186.7±37.1†
High-density lipoprotein cholesterol (mg/dl)**	51.8±14.4	56.1±18.8†	52.4±15.8
Body mass index (kg/m^2)**	23.9±2.9	23.7±3.7	23.7±3.2
Diabetes mellitus (%)	6.2	8.4	12.4†
Atrial fibrillation (%)	0.2	3.6†	0.3
Proteinuria (%)	2.3	3.6	4.1†
Age 60–79 years			
No. of subjects	15,073	778	2,139
Systolic blood pressure (mmHg)**	139.4±17.1	144.2±18.1†	140.8±17.7†
Diastolic blood pressure (mmHg)**	80.9±10.3	82.2±10.5†	80.4±10.6†
Pulse pressure (mmHg)**	58.5±13.4	62.0±14.8†	60.5±14.0†
Hypertension medication (%)	25.8	37.4†	29.6†
Current smoker (%)	47.4	52.8†	55.9†
Current drinker (%)	49.4	44.1†	48.7
Total cholesterol (mg/dl)**	191.5±32.5	187.5±34.7†	184.0±33.2†
High-density lipoprotein cholesterol (mg/dl)**	52.9±14.8	52.5±15.8	53.1±16.1
Body mass index (kg/m^2)**	23.0±2.9	22.5±3.2†	22.3±3.1†
Diabetes mellitus (%)	7.8	11.4†	10.7†
Atrial fibrillation (%)	0.8	3.0†	1.2
Proteinuria (%)	3.3	7.3†	6.1†

relationship between SBP and cardiovascular mortality throughout the whole Asia-Pacific region (*7*). However, this age-dependency has not been studied in a cohort of exclusively Japanese men and women. The study of the age-specific relationship of blood pressure to cardiovascular disease in the Japanese population is important for public health in Japan, since it has been reported that the relationship of elevated blood pressure to cardiovascular disease in the Japanese population is different from that in Caucasians (*8*). Thus, we examined the gender- and age-specific relationships between blood pressure levels and risk of cardiovascular mortality and total mortality in a large Japanese cohort study.

Methods

Study Population

A total of 38 of 85 communities in Ibaraki-ken, Japan were adopted for use in this study (*9*). The rate of participation in health checkups was 36.4% for residents in the study area, which was similar to the rate of 35.8% for residents of Ibaraki-ken in 1993. In the present study, we enrolled 97,153 Japanese subjects (33,162 men and 63,991 women) aged 40–79 years who underwent the health checkups conducted by the Ibaraki Health Service Association in Ibaraki-ken in 1993. The standard mortality ratio (SMR) of all-cause mortality among the study participants was 95% (95% confidence interval [CI]: 86–103) for men and 100% (95% CI: 89–110) for women compared with the total Japanese population in 2000 (*2*). Data were collected from anthropometry measurements, blood pressure measurements, blood samples, urine dipsticks test, sulfosalicylic acid test, electrocardiogram, and interview questionnaires on smoking habit, daily alcohol intake, and a medical history of heart disease and stroke.

At baseline, we excluded 852 men and 2,146 women with incomplete data, and 2 men and 4 women who moved out of their community before their health checkups. We also excluded 2,082 men and 3,043 women with a history of heart

Table 1. (Continued)

Gender, age group, and variables	Survived*	Cardiovascular death	Non-cardiovascular death
Women			
Age 40–59 years			
No. of subjects	30,810	70	335
Systolic blood pressure (mmHg)**	126.5±17.0	138.6±19.3†	128.2±16.2
Diastolic blood pressure (mmHg)**	76.8±10.8	83.3±12.6†	77.6±10.0
Pulse pressure (mmHg)**	49.7±11.4	55.3±12.9†	50.6±11.7
Hypertension medication (%)	9.3	27.1†	11.9
Current smoker (%)	6.0	12.9†	6.3
Current drinker (%)	4.2	2.8	2.7
Total cholesterol (mg/dl)**	203.3±34.9	211.1±42.2	203.1±36.0
High-density lipoprotein cholesterol (mg/dl)**	58.2±14.0	54.4±16.5	56.9±14.7
Body mass index (kg/m^2)**	23.4±3.1	24.6±4.2†	23.8±3.4
Diabetes mellitus (%)	2.6	11.4†	5.4†
Atrial fibrillation (%)	0.0	0.0†	0.0
Proteinuria (%)	1.4	7.1†	2.1
Age 60–79 years			
No. of subjects	25,484	680	1,419
Systolic blood pressure (mmHg)**	137.6±17.0	142.9±18.2†	139.4±17.2†
Diastolic blood pressure (mmHg)**	78.9±10.1	80.2±11.4†	78.4±10.6
Pulse pressure (mmHg)**	58.7±13.3	62.7±14.2†	60.9±13.9†
Hypertension medication (%)	29.9	44.9†	36.8†
Current smoker (%)	3.3	7.6†	5.5†
Current drinker (%)	2.7	0.0	0.0
Total cholesterol (mg/dl)**	213.3±33.6	208.7±35.7†	207.6±36.9†
High-density lipoprotein cholesterol (mg/dl)**	55.3±13.7	55.2±13.8	55.3±14.4
Body mass index (kg/m^2)**	23.8±3.3	23.4±3.8†	23.4±3.6†
Diabetes mellitus (%)	5.2	12.2†	7.4†
Atrial fibrillation (%)	0.2	2.2†	0.4
Proteinuria (%)	2.0	7.6†	4.7†

*Including moving out cases. **Showing mean±SD. †$p<0.05$ *vs*. survived subjects.

disease or stroke. Therefore, a total of 30,226 men and 58,798 women were followed until the end of 2002. A total of 144 deaths (62 men and 82 women) of unknown causes were included in the analysis of all-cause mortality, and treated as censored cases for the analysis of cause-specific mortality. Persons who moved out of their community during the follow-up periods were censored at the date of their transference. The number of subjects moving out of communities during the follow-up was 555 (1.8%) in men and 2,109 (3.6%) in women. The mean follow-up period was 8.7 years in men and 8.9 years in women.

The protocol of this cohort study was approved by the Ibaraki Epidemiology Study Union Ethic Review Committee. The use of death certificate data was permitted by the Ministry of Health, Labour and Welfare of Japan.

Baseline Examinations

Baseline blood pressures were measured on the right arm of seated participants by trained observers using standard mercury sphygmomanometers. When the SBP was greater than 150 mmHg or the diastolic blood pressure (DBP) was greater than 90 mmHg, the blood pressure was measured again after several deep breaths, and the lower blood pressure values, which were almost always observed after the second measurement, were used. Pulse pressure was calculated as the SBP (mmHg) minus the DBP (mmHg). Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided by the square of the height (m). An interview was conducted to ascertain treatment of hypertension, treatment of diabetes, alcohol intake (never, sometimes, <66 g/day, or ≥66 g/day), smoking status (never smoked, former smoker, or current smoker) and, for current smokers, the number of cigarettes smoked per day.

At baseline, non-fasting 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.

Plasma glucose levels were measured using a glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan). Subjects were considered diabetic if they had a plasma glucose level ≥126 mg/dl during fasting or ≥200 mg/dl during non-fasting, or if they were being treated for diabetes mellitus. Serum total cholesterol and serum triglyceride levels were measured with an enzyme method using an RX-30 device (Nihon Denshi, Tokyo, Japan). High density lipoprotein cholesterol was measured with a phosphotungstic acid magnesium method using an MTP-32 device (Corona Electric, Hitachinaka, Japan). 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, USA) (*10*). Proteinuria was tested using dipsticks (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan). Samples trace positive for proteinuria were reexamined using the sulfosalicylic acid test, and were divided into four groups (–, 1+, 2+, 3+). Samples yielding results of “1+” or higher were defined as positive. Electrocardiograms were taken using an ECG-9332 device (Nihon Kohden, Tokyo, Japan) and analyzed by doctors.

Endpoint Determination

Mortality surveillance was done by reviewing certificates of residence provided by local government officials. The data from residence certificates and the data from health checkups were merged at a data management center of the local government, and were provided to the investigators. These data included the date of death, but the names and addresses of subjects were excluded. Mortality data were sent to the Ministry of Health, Labor and Welfare, and the underlying cause of death was coded as per the National Vital Statistics requirements based on the “International Statistical Classification of Diseases,” 9th revision (ICD-9) in 1993–1994 and the 10th revision (ICD-10) in 1995–2002. Record matching between the certificates of residence and death certificates was conducted based on residential area, gender, date of birth, and death date (*9*). All cardiovascular deaths were identified as code 390–459 in the ICD-9 and as code I00–I99 in the ICD-10. Registration of death is required by the Family Registration Law in Japan and is believed to be accurate throughout Japan. Therefore, all deaths that occurred in the cohort were documented by death certificates, except for subjects who died after they moved away from their original community, in which case the subject was treated as censored.

Statistical Analysis

Participants were classified into the following four categories with regard to their blood pressures according to the WHO-ISH guidelines (*3*): optimal (SBP <120 mmHg and DBP <80 mmHg), normal (120 mmHg ≤ SBP <130 mmHg and 80 mmHg ≤ DBP <85 mmHg), high normal (130 mmHg ≤ SBP <140 mmHg and 85 mmHg ≤ DBP <90 mmHg), stage 1 (140 mmHg ≤ SBP <160 mmHg and 90 mmHg ≤ DBP <100 mmHg), and stage 2 or stage 3 (SBP ≥160 mmHg or DBP ≥100 mmHg). Risk ratios for cardiovascular disease mortality and all-cause mortality according to blood pressure classification were calculated with reference to optimal blood pressure using the Cox proportional hazards regression model. Multivariate risk ratios with a 1 SD increment of SBP, DBP, and pulse pressure were also calculated.

Covariates included age (years), antihypertensive medication use (yes or no), serum total cholesterol level (mg/dl), serum high-density lipoprotein cholesterol level (mg/dl), body mass index (kg/m^2), diabetes mellitus (yes or no), alcohol intake (never, sometimes, <66 g/day, and ≥66 g/day), and smoking status (never smoked, former smoker, current smoker <20 cigarettes/day, and current smoker ≥20 cigarettes/day).

The analysis was repeated with stratification for each age subgroup (40–59 years, 60–79 years), and the significance of the interaction with the age subgroup was tested in multivariate models using the interaction terms of the age subgroup with the blood pressure classification (optimal, normal, high normal, stage 1, and stage 2 or 3). The significance of the interaction with age (years) was also tested using the interaction terms of age with SBP, DBP, and pulse pressure.

Furthermore, gender- and age-specific population attributable risks (PAR) of blood pressure were calculated as follows (*11*):

$$\mathrm{PAR} = 1 - \frac{1}{\Sigma(p \times \mathrm{RR})},$$

where p is the proportion of the population that is exposed, and RR is the relative risk of the population that is exposed. All statistical analyses were conducted using SAS, version 8.02 (SAS Institute, Inc., Cary, USA).

Results

The baseline characteristics of the study subjects are shown in Table 1. The mean values of SBP, DBP, and pulse pressure were higher in subjects who died from cardiovascular disease than in the surviving subjects in both gender and age subgroups. These differences were larger among subjects aged 40–59 years than in those aged 60–79 years in both genders.

During the follow-up through 2002, there were 3,339 total deaths that included 861 cardiovascular deaths among the 30,226 men (263,442 person-years), and 2,504 total deaths that included 750 cardiovascular deaths among the 58,798 women (521,575 person-years). The gender- and age-specific numbers of deaths from cerebrovascular disease were 31 among men aged 40–59 years, 376 among men aged 60–79 years, and 38 and 351 for these age groups in women, respectively. The respective numbers of deaths from ischemic heart disease were 34 and 219 in men, and 17 and 174 in women.

Table 2. Gender- and Age-Specific Multivariate Adjusted Risk Ratios of Mortality from Cardiovascular Disease and All-Causes According to Blood Pressure Stage among 30,226 Men and 58,798 Women, Ibaraki-Ken, Japan, 1993–2002

Gender, age group, and blood pressure classification	No. of person-years	Cardiovascular mortality				All-cause mortality			
		No. of death	Multivariate-adjusted risk ratio*	95% confidence interval	*p* for interaction	No. of death	Multivariate-adjusted risk ratio*	95% confidence interval	*p* for interaction
Men									
Age 40–59 years									
Optimal	19,437	5	1.00			56	1.00		
Normal	23,995	9	1.48	0.50–4.44		69	0.98	0.69–1.39	
High normal	23,532	19	2.89	1.07–7.86		101	1.32	0.95–1.84	
Stage 1	32,563	30	3.06	1.15–8.16		133	1.14	0.82–1.58	
Stage 2 or Stage 3	10,490	20	5.99	2.13–16.8		63	1.62	1.10–2.38	
Age 60–79 years					0.011				0.046
Optimal	13,279	43	1.00			214	1.00		
Normal	21,116	84	1.25	0.87–1.81		375	1.14	0.96–1.35	
High normal	31,639	127	1.20	0.84–1.70		515	1.01	0.86–1.19	
Stage 1	64,789	338	1.47	1.06–2.03		1,282	1.20	1.03–1.39	
Stage 2 or Stage 3	22,602	186	2.24	1.59–3.15		531	1.37	1.16–1.62	
Women									
Age 40–59 years									
Optimal	80,934	10	1.00			88	1.00		
Normal	64,393	8	0.86	0.34–2.20		98	1.27	0.95–1.70	
High normal	56,768	11	1.19	0.50–2.84		84	1.14	0.84–1.55	
Stage 1	60,590	26	2.02	0.93–4.38		100	1.10	0.81–1.50	
Stage 2 or Stage 3	15,363	15	4.09	1.70–9.85		35	1.46	0.96–2.22	
Age 60–79 years					0.010				0.895
Optimal	25,608	49	1.00			177	1.00		
Normal	37,445	72	0.91	0.63–1.31		276	1.01	0.83–1.22	
High normal	54,257	137	1.14	0.82–1.59		429	1.04	0.88–1.25	
Stage 1	97,958	292	1.21	0.89–1.65		893	1.12	0.95–1.32	
Stage 2 or Stage 3	28,259	130	1.61	1.15–2.26		324	1.28	1.06–1.55	

*Adjusted for age, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, diabetes mellitus (yes or no), body mass index, atrial fibrillation (yes or no), proteinuria (positive or negative), alcohol intake (never, sometimes, $<$66 g/day, and $\geq$66 g/day), and smoking status (never smoker, ex-smoker, current $<$20 cigarettes/day, current $\geq$20 cigarettes/day).

The gender- and age-specific proportions of deaths from cerebrovascular disease and ischemic heart disease among all cardiovascular deaths were approximately 80% in both gender and age subgroups.

Table 2 shows age- and gender-specific multivariate risk ratios of mortality from cardiovascular disease and all-cause mortality according to the blood pressure classification. The mortality rate of stage 2 or 3 hypertension was 7 to 8 times higher than the optimal blood pressure in subjects aged 40–59 years, while that in subjects aged 60–79 years was 2 to 3 times higher. The multivariate risk ratios of cardiovascular mortality among subjects with stage 2 or stage 3 hypertension as compared with optimal blood pressure were greater among subjects aged 40–59 years than among subjects aged 60–79 in both genders, and the interaction between the two age groups was significant ($p=0.01$ in both genders). A similar but weaker interaction between the age and the blood pressure category for total mortality was observed in men ($p=0.046$), but not in women ($p=0.895$). The results were essentially the same when persons on antihypertensive medication ($n=17{,}458$) were excluded (not shown in the table).

Gender- and age-specific multivariate risk ratios of cardiovascular disease mortality and all-cause mortality by a 1 SD increment of SBP (SD=17.3 mmHg for men and 17.1 mmHg for women), DBP (10.7 mmHg for men and 10.5 mmHg for women), and pulse pressure (13.4 mmHg for men 13.2 mmHg and for women) are shown in Table 3.

The multivariate risk ratios of cardiovascular mortality by a

Table 3. Gender- and Age-Specific Multivariate Adjusted Risk Ratios of Mortality from Cardiovascular Disease and All-Causes According to Systolic Blood Pressure Level, Diastolic Blood Pressure Level, and Pulse Pressure Level among 30,226 Men and 58,798 Women, Ibaraki-Ken, Japan, 1993–2002

Gender, systolic blood pressure*, pulse pressure, and age*	No. of person-years	Cardiovascular mortality				All-cause mortality			
		No. of death	Multivariate-adjusted risk ratio**	95% confidence interval	*p* for interaction	No. of death	Multivariate-adjusted risk ratio**	95% confidence interval	*p* for interaction
Men									
Systolic blood pressure									
Age 40–59 years	110,017	83	1.79	1.45–2.20	0.002	422	1.20	1.09–1.34	0.030
Age 60–79 years	153,425	778	1.23	1.14–1.32		2,917	1.09	1.05–1.13	
Diastolic blood pressure									
Age 40–59 years	110,017	83	1.44	1.16–1.77	0.045	422	1.14	1.03–1.26	0.050
Age 60–79 years	153,425	778	1.22	1.13–1.31		2,917	1.07	1.03–1.12	
Pulse pressure									
Age 40–59 years	110,017	83	1.65	1.32–2.06	0.010	422	1.15	1.03–1.28	0.158
Age 60–79 years	153,425	778	1.11	1.04–1.19		2,917	1.06	1.02–1.10	
Women									
Systolic blood pressure									
Age 40–59 years	278,048	70	1.47	1.16–1.86	<0.001	405	1.06	0.96–1.18	0.091
Age 60–79 years	243,527	680	1.19	1.10–1.28		2,099	1.08	1.04–1.13	
Diastolic blood pressure									
Age 40–59 years	278,048	70	1.44	1.15–1.82	<0.001	405	1.07	0.97–1.18	0.063
Age 60–79 years	243,527	680	1.19	1.11–1.28		2,099	1.06	1.02–1.11	
Pulse pressure									
Age 40–59 years	278,048	70	1.28	0.99–1.66	0.010	405	1.03	0.92–1.16	0.244
Age 60–79 years	243,527	680	1.07	1.00–1.15		2,099	1.05	1.01–1.09	

*Systolic blood pressure, diastolic blood pressure and pulse pressure were entered in separate models. **Risk ratio was associated with a 1 SD increase in blood pressure and was adjusted for age, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, diabetes mellitus (yes or no), body mass index, atrial fibrillation (yes or no), proteinuria (positive or negative), alcohol intake (never, sometimes, <66 g/day, and ≥66 g/day), and smoking status (never smoker, ex-smoker, current <20 cigarettes/day, current ≥20 cigarettes/day).

1 SD increment of SBP, DBP, and pulse pressure were greater among subjects aged 40–59 years than among subjects aged 60–79 years with significant interaction ($p=0.002$ in men and <0.001 in women for SBP, 0.045 and <0.001 for DBP, respectively, and 0.010 in both genders for pulse pressure). A similar but weaker interaction between age and the SBP for total mortality was observed in men but not in women ($p=0.030$ in men and 0.091 in women).

The gender- and age-specific population attributable risk percent of non-optimal blood pressure for cardiovascular mortality was larger in subjects aged 40–59 years than in subjects aged 60–79 years for both men and women (Table 4). However, such a trend was not observed for total mortality in either gender.

Discussion

This large prospective study showed the age-dependent relationship of blood pressure and pulse pressure levels with mortality from cardiovascular disease among Japanese men and women. The impact of SBP, DBP, and pulse pressure on cardiovascular disease was approximately two times larger among middle-aged subjects than among elderly subjects for both men and women. Furthermore, the burden on the whole population of non-optimal blood pressure for cardiovascular disease was also two times greater among middle-aged subjects than among elderly subjects of both genders. These results did not change when persons on antihypertensive medication were excluded. To our knowledge, this is the first large prospective study to show age-dependence in the relationship of blood pressure and pulse pressure to cardiovascular disease among Japanese men and women.

The First National Health and Nutrition Examination Survey (*12*) (NHANES I) showed that the impact of blood pressure levels—as classified by the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treat-

Table 4. Gender- and Age-Specific Population Attributable Risk Percent of Mortality from Cardiovascular Disease and All-Causes According to Blood Pressure Stage among 30,226 Men and 58,798 Women, Ibaraki-Ken, Japan, 1993–2002

Gender, age group, and blood pressure stage	Percentage of subjects	Cardiovascular mortality		All-cause mortality	
		Multivariate-adjusted risk ratio* and 95% confidence interval	Population attributable risk (%)	Multivariate-adjusted risk ratio* and 95% confidence interval	Population attributable risk (%)
Men					
Age 40–59 years					
Optimal	17.7	1.00		1.00	
Normal	21.7	N.S.		N.S.	
High normal	21.4	2.89 (1.07–7.86)		N.S.	
Stage 1	29.6	3.06 (1.15–8.16)	60	N.S.	
Stage 2 or Stage 3	9.6	5.99 (2.13–16.84)		1.62 (1.10–2.38)	6
Age 60–79 years					
Optimal	8.6	1.00		1.00	
Normal	13.7	N.S.		N.S.	
High normal	20.4	N.S.		N.S.	
Stage 1	42.4	1.47 (1.06–2.03)	28	1.20 (1.03–1.39)	12
Stage 2 or Stage 3	15.0	2.24 (1.59–3.15)		1.37 (1.16–1.62)	
Women					
Age 40–59 years					
Optimal	29.3	1.00		1.00	
Normal	23.2	N.S.		N.S.	
High normal	20.4	N.S.		N.S.	—
Stage 1	21.6	N.S.		N.S.	
Stage 2 or Stage 3	5.5	4.09 (1.70–9.85)	15	N.S.	
Age 60–79 years					
Optimal	10.5	1.00		1.00	
Normal	15.3	N.S.		N.S.	
High normal	22.3	N.S.		N.S.	
Stage 1	40.2	N.S.		N.S.	
Stage 2 or Stage 3	11.7	1.61 (1.15–2.26)	7	1.28 (1.06–1.55)	3

N.S.: not significant. *Adjusted for age, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, diabetes mellitus (yes or no), body mass index, atrial fibrillation (yes or no), proteinuria (positive or negative), alcohol intake (never, sometimes, <66 g/day, and ≥66 g/day), and smoking status (never smoked, ex-smoker, current <20 cigarettes/day, current ≥20 cigarettes/day).

ment of High Blood Pressure (JNC VI)—on cardiovascular mortality was greater in subjects aged 25–45 years than in those aged 46–77 years (both groups were of mixed gender). The results of our study are consistent with NHANES I.

Two large meta-analyses of cohort studies (*6*, *7*) have shown that the impact of baseline SBP on the risk of stroke and ischemic heart disease was greater in younger than in older subjects. One of the meta-analyses, the Prospective Studies Collaboration (*6*), reported that the effect of a 20 mmHg reduction of the baseline SBP or a 10 mmHg reduction of the baseline DBP on stroke, ischemic heart disease, and other vascular mortality was approximately two-fold greater in the 40–49 years age group than in the 80–89 years age group for both men and women. The Asia Pacific Cohort Studies Collaboration (*7*) also showed that the effect of a 10 mmHg reduction of the baseline SBP on stroke and ischemic heart disease was approximately two-fold greater in the 50–59 years age group than in the 70–89 years age group.

The weakening of the association between blood pressure levels and risk of cardiovascular disease in the older age groups may have been partly due to the elevated risk among normotensive individuals through the effects of aging; the mortality rates from cardiovascular disease were 13–15 times larger among older persons of optimal blood pressure than middle-aged persons of optimal blood pressure (Table 2).

In the present study, the age-dependency of the relationship of blood pressure levels with all-cause mortality was generally weak compared with the data from the United States (*4*). This is likely because the proportion of cardiovascular mortality to all-cause mortality is much smaller in Japan (approximately 30% in both genders) than in the United States (approximately 50% in both genders) (*2*).

Pulse pressure, which is used as an index of arterial stiffness (*13*), has been recognized as a cardiovascular risk factor (*14*, *15*). To our knowledge, the present study is the first to show a significant interaction among age, pulse pressure, and cardiovascular mortality. The NHANES I (*12*) showed that the risk of cardiovascular mortality for pulse pressure was larger in subjects 25–45 years of age than in those 46–77 years of age, although the *p* value for the interaction with age was not reported. That relative risk ratio per 10 mmHg of pulse pressure was 1.24 in younger subjects and 1.12 in older subjects. The Chicago Heart Association Detection Project in Industry Study (*16*) also showed that the relative risk of cardiovascular mortality with a higher pulse pressure was larger in middle-aged women than in elderly women, although in men the relative risk was similar in each age subgroup. The relative risk ratio per 1 SD of pulse pressure (13.7 mmHg in subjects 40–59 years of age and 16.2 mmHg in subjects 60–74 years of age) was 1.18 in subjects 40–59 years of age and 1.13 in subjects 60–74 years of age in women. In men, the relative risk ratio per 1 SD (12.4 mmHg, 13.3 mmHg and 15.4 mmHg, respectively) was 1.17 in subjects aged 18–39 years, 1.14 in subjects aged 40–59 years, and 1.16 in subjects aged 60–74 years. The *p* value for the interaction with age was not reported.

One strength of the present study was that we employed a large cohort for which gender and age stratification analysis was possible (*12*, *16*). In addition, all blood samples were measured by the same device, reagents, and quality control program, as opposed to previous studies in which blood analysis was done in many different laboratories (*6*).

Our study had several limitations. First, the subjects of this study were participants in a health checkup for community residents that had a response rate of approximately 40%. However, the potential selection bias may be small since the rate of all-cause mortality did not differ between the study subjects and the total Japanese population. Second, because the incidence data were not available, we used death certificates and did not validate the causes of death. The accuracy of our diagnosis of ischemic heart disease or heart disease as the cause of death was therefore uncertain. However, previous studies have shown that death certificate diagnosis with regard to stroke subtypes is valid due to the high prevalence of CT scan or MRI use in hospitals in Japan (*17*, *18*).

In conclusion, the impact of the blood pressure level on the risk of cardiovascular disease was larger among the middle-aged than among the elderly in Japan. Our findings underscore the importance of blood pressure control to prevent cardiovascular disease among middle-aged individuals.

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