Relation of Blood Pressure and All-Cause Mortality in 180 000 Japanese Participants

Pooled Analysis of 13 Cohort Studies

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Abstract—Hypertension is a leading cause of death because of cardiovascular disease and predominantly affects total mortality. To reduce avoidable deaths from hypertension, we need to collect blood pressure data and assess their impact on total mortality. To examine this issue, a meta-analysis of 13 cohort studies was conducted in Japan. Poisson regression was used for estimating all-cause mortality rates and ratios. In the model, blood pressure data were treated as continuous (10-mm Hg increase) and categorical (every 10 mm Hg) according to recommendations of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension. Potential confounders included body mass index, smoking, drinking, and cohort. The impact of hypertension was measured by the population-attributable fraction. After excluding participants with cardiovascular disease history, 176 389 participants were examined in the analysis. Adjusted mortality rates became larger as the blood pressure increased, and these were more distinct in younger men and women. Hazard ratios also showed the same trends, and these trends were more apparent in younger men (hazard ratio [unit: 10-mm Hg increase] aged 40 to 49 years: systolic blood pressure 1.37 (range: 1.15 to 1.62); diastolic blood pressure 1.46 [range: 1.05 to 2.03]) than older ones (hazard ratio: aged 80 to 89 years: systolic blood pressure 1.09 [range: 1.05 to 1.13]and diastolic blood pressure 1.12 [range: 1.03 to 1.22]). Population-attributable fraction of hypertension was ≈20% when the normal category was used as a reference level and was 10% when we included the prehypertension group in the reference level. In conclusion, high blood pressure raised the risk of total mortality, and this trend was higher in the younger Japanese population. (***Hypertension*****. 2008;51:1483-1491.)**

Key Words: pooled analysis ■ total mortality ■ cohort study ■ blood pressure ■ population attributable fraction

High blood pressure is a well-established leading cause of cardiovascular disease mortality. The contribution of hypertension to total mortality is also large,[1] and the importance of management of hypertension is widely accepted not only in clinical practice but also in public health practice. Before measures for reducing hypertension are implemented, more information about the relationship between hypertension and total mortality is needed. For example, one study found that the hazard ratio of cardiovascular disease in those with high blood pressure was larger in younger than in older participants,[2] suggesting that the contribution of high blood pressure to mortality differed at different ages. The examination of this important issue requires a large number of participants, and a single cohort study estimating this contribution is limited by small sample size. The Joint National Committee of Hypertension 7 (JNC-7) also mentioned the importance of the risk of mortality and the contribution of prehypertension to total mortality.[3] The relation between blood pressure and total mortality is, therefore, of great interest. It is difficult to address this issue in a single cohort study, because few events can be observed in cohorts subgrouped, eg, by age or prehypertension status. A large-scale cohort study could answer these questions, but the huge amount of cost and effort involved represent serious obstacles. Meta-analysis using data on individual participants[4] is an efficient way to deal with this issue, and the approach has been used in studies of cardiovascular disease epidemiology.[2,5,6]

In Japan, meta-analysis of individual participants' data for cardiovascular disease was conducted in the Japanese population. The study, called Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN), included 13 cohort studies of existing Japanese cohorts. The total number of EPOCH-JAPAN participants was 188 321, with ≈10 years of follow-up. The purpose of this study was to examine sex- and age-specific hazard ratios and the effect of blood pressure on total mortality and to estimate the contribution of high blood pressure to all-cause death by

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Table 1. Baseline Characteristics of Study Participants in Each Cohort: EPOCH-JAPAN

Cohort Name	Geographic Location (Prefecture)	Source of Baseline Survey, Year, Reference(s)	Follow-Up Periods		No. of Participants	Age at Study Entry		Blood Pressure			
								Systolic		Diastolic	
			Average	SD		Average	SD	Average	SD	Average	SD
Men											
Tanno-Sobetsu	Hokkaido	1977[7,8]	18	5	840	51	7	132	20	82	10
Osaki	Miyagi	1994[9]	6	1	6918	63	10	133	17	80	11
Ohasama	Iwate	1987[10]	10	3	1122	61	11	135	17	76	11
Oyabe	Ishikawa	1988[11]	10	2	1509	61	10	131	20	79	11
YKK workers	Toyama	1990[12]	11	2	3177	51	6	121	15	74	12
SPMI cohort	Shiga	1989–1991[13]	9	3	1939	54	8	133	18	81	11
Suita	Osaka	1989[14,15]	6	2	2339	60	11	131	21	80	12
RERF cohort	Hiroshima	1986[16]	14	5	1506	60	13	135	22	85	12
Hisayama	Fukuoka	1988[17]	10	3	1113	58	12	135	20	81	11
JACC study	Nationwide‡	1988–1990[18]	9	2	11 041	58	10	135	19	81	11
NIPPON DATA80	Nationwide‡	1980[19]	16	5	3161	56	11	142	22	85	12
NIPPON DATA90	Nationwide‡	1990[20]	9	2	2759	57	11	140	20	85	12
Ibaraki	Ibaraki	1993[21,22]	10	2	33 134	61	10	137	17	81	11
Total			10	3	70 558	60	10	135	19	81	11
Women											
Tanno-Sobetsu	Hokkaido	1977[7,8]	18	4	971	51	7	134	20	82	10
Osaki	Miyagi	1994[9]	6	1	9312	62	9	130	18	78	11
Ohasama	Iwate	1987[10]	10	2	1678	60	10	130	17	73	11
Oyabe	Ishikawa	1988[11]	10	1	3208	58	10	126	20	75	11
YKK workers	Toyama	1990[12]	11	2	1724	50	6	115	15	70	11
SPMI cohort	Shiga	1989–1991[13]	9	3	2596	55	8	132	17	79	10
Suita	Osaka	1989[14,15]	6	2	2619	58	11	129	22	77	12
RERF cohort	Hiroshima	1986[16]	15	5	3121	63	12	135	23	81	12
Hisayama	Fukuoka	1988[17]	11	3	1518	59	12	133	22	76	11
JACC study	Nationwide‡	1988–1990[18]	10	2	19 210	57	9	132	19	78	11
NIPPON DATA80	Nationwide‡	1980[19]	17	4	4020	56	11	139	22	81	12
NIPPON DATA90	Nationwide‡	1990[20]	10	2	3697	58	12	138	20	81	12
Ibaraki	Ibaraki	1993[21,22]	10	2	63 909	59	10	132	18	78	11
Total			10	3	117 583	58	10	132	19	78	11

(*Continued*)

*In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-smokers were classified as never-smokers.
†In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-drinkers were classified as never-drinkers.
‡In this nationwide cohort study, study participants were from all areas of Japan.

performing a meta-analysis of the data from 13 population-based cohort studies conducted in Japan.

Study Participants and Methods

Study Cohorts

The EPOCH-JAPAN Study is the pooled analysis of 13 cohort studies examining the relation between health measures (laboratory measures and lifestyle and behavioral factors) and disease (mortality and incidence) in the Japanese population. The criteria for inclusion of meta-analysis were as follows: collection of health examination measures, follow-up of ≈10 years, and a number of participants >1000 persons. Both nationwide and single-site cohort studies were included. The name of each cohort study[7–22] is listed in Table 1. Inclusion criteria for participants were age at entry (40 to 90 years old) and availability of information about sex, age at entry, systolic blood pressure, and diastolic blood pressure. Since the end of follow-up varied between cohorts, we limited age ranges of follow-up from 40 to 90 years, and the end of the observation period was set at age 90 years.

Statistical Methods

Hazard ratios for total mortality were estimated in men and women separately. Participants were stratified into 10-year age groups from 40 to 80 years, and a statistical model was made to analyze the data of each age group separately. They were also divided on the basis of systolic blood pressure (SBP) into 10-mm Hg groups from <120 mm Hg to ≥160 mm Hg and on the basis of diastolic blood pressure (DBP) into 10-mm Hg groups from <70 mm Hg to ≥100 mm Hg. The lowest blood pressure group (<120 mm Hg for SBP and <70 mm Hg for DBP) served as the reference group.

A Poisson regression model was constructed for each sex and age group. When we analyzed the sex-combined results, we included sex in the model. In the model, we analyzed continuous and categorical

Table 1. Continued

Smoking Status*				Drinking Status†				Body Mass Index		No. of All-Cause Mortality
Never	Past	Current	Missing	Never	Past	Current	Missing	Average	SD	
228	0	522	90	214	0	533	93	23	3	130
1413	1996	3188	321	1048	556	5114	200	24	3	548
585	0	537	0	459	0	663	0	23	3	250
689	0	820	0	392	416	701	0	23	3	270
809	494	1874	0	562	38	2577	0	23	3	73
544	229	1164	2	398	0	1529	12	23	3	150
423	772	1105	39	504	99	1699	37	23	3	169
191	417	721	177	203	86	963	254	22	3	614
228	329	556	0	369	70	673	1	23	3	180
2392	2639	5590	420	2074	572	8069	326	23	3	1402
578	655	1922	6	657	219	2279	6	22	3	994
605	708	1446	0	962	206	1591	0	23	3	412
7376	9190	16 567	1	9629	2039	21 465	1	23	3	4688
16 061	17 429	36 012	1056	17 471	4301	47 856	930	23	3	9880
804	0	65	102	792	0	76	103	24	3	85
6706	120	355	2131	5617	225	1646	1824	24	3	302
1639	0	39	0	1584	0	94	0	24	3	194
3126	0	82	0	2770	399	39	0	23	3	255
1693	9	22	0	1320	7	397	0	22	3	18
2467	14	87	28	2049	0	520	27	23	3	65
2173	87	279	80	1727	39	783	70	23	3	85
2602	96	296	127	1605	47	951	518	23	4	889
1382	31	105	0	1366	17	133	2	23	3	123
16 989	208	656	1357	14 559	223	3535	893	23	3	997
3573	91	352	4	3236	59	717	8	23	3	790
3284	87	326	0	3443	35	219	0	23	3	312
60 357	462	3088	2	57 783	125	5999	2	24	3	3762
106 795	1205	5752	3831	97 851	1176	15 109	3447	24	3	7877

blood pressure data to estimate the hazard ratio. Body mass index, smoking status (smokers, ex-smokers, or never-smokers), drinking status (drinkers, ex-drinkers or never-drinkers), and cohort were included in the model as confounders. Person-years of observation was separated into 5 categories (1 for every 10 years from age 40 to age 80 years) and used as an offset variable in Poisson regression. Multivariate adjusted mortality rates were estimated from the Poisson regression. Mortality rates among groups were calculated after adjusting for the population-averaged effects of confounders (eg, smoking, drinking, and mean body mass index).

The MacMahon and Peto method was used to correct for regression dilution bias of blood pressure.[4,23] The dilution factors of blood pressure were derived from longitudinal blood pressure measurements made by the Ohasama Study that followed 1900 participants from 1999 to 2002. From the data, the calculated regression dilution ratio was 0.59 for SBP and 0.48 for DBP. Hazard ratio for total mortality according to the JNC-7 definition was also estimated in the analysis. The prehypertension ($120 \leq SBP < 140$ mm Hg or $80 \leq DBP < 90$ mm Hg), hypertension stage 1 ($140 \leq SBP < 160$ mm Hg or $90 \leq DBP < 100$ mm Hg), and hypertension stage 2 (160 mm Hg$\leq$SBP or 100 mm Hg$\leq$DBP) groups were compared with the normal reference groups (<120 mm Hg for SBP and <80 mm Hg for DBP).

The population-attributable fraction of high blood pressure according to the JNC 7 classification was calculated from the hazard ratio. Two reference levels (the normal and below prehypertension [normal plus prehypertension]) and the excess hazard ratio were used to calculate the population-attributable fraction. The prevalence of hypertension was set as the total number of participants in this study.[24] All of the statistical analysis was performed using SAS release 9.13 (SAS Institute Inc).

Results

Table 1 shows baseline characteristics of participants in each cohort. There were 188 141 participants (men: 70 558; women: 117 583). Average age at study entry was 59.6 years in men and 58.4 years in women, and the average follow-up

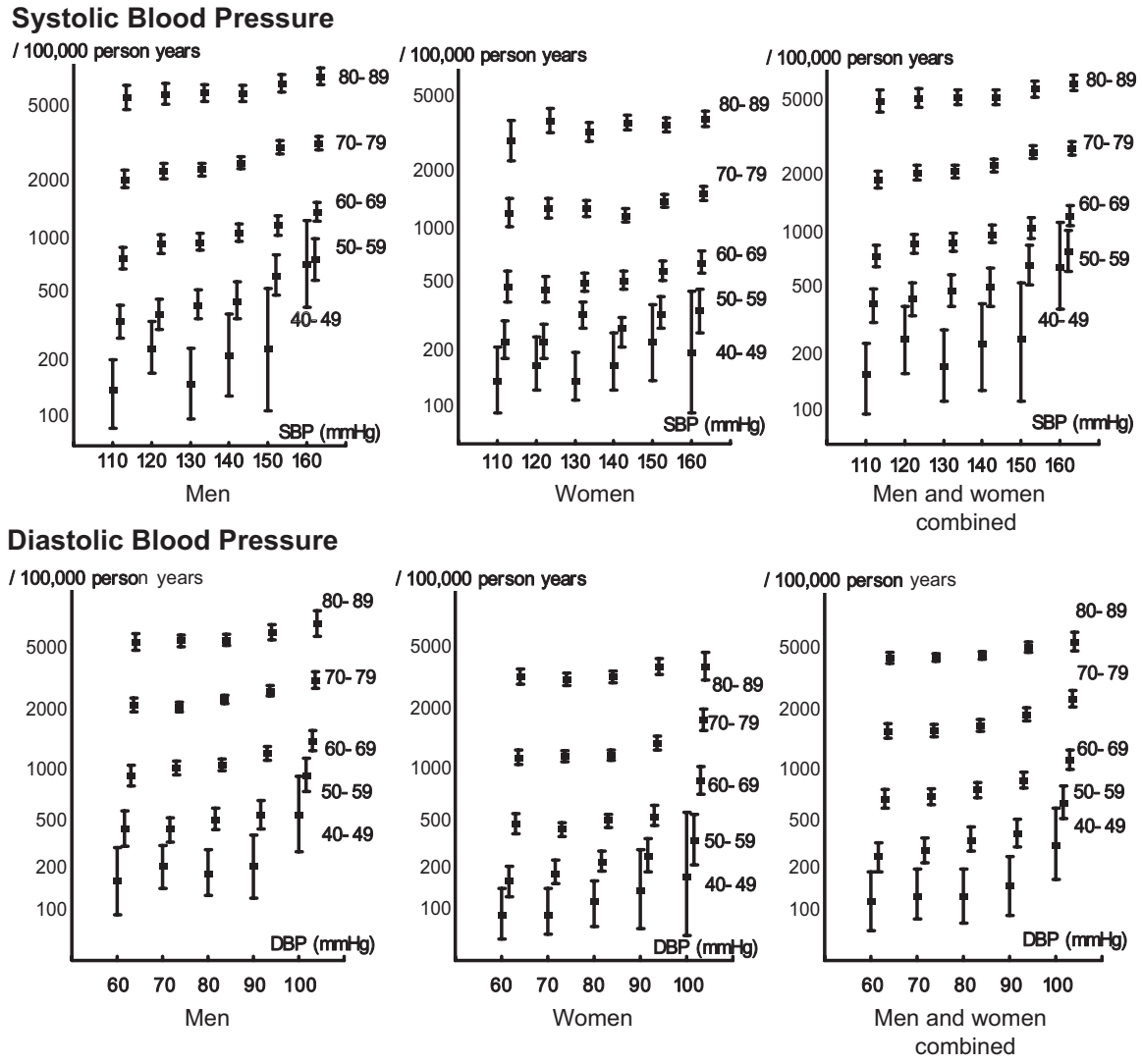

Figure. Relation between blood pressure and multivariate-adjusted mortality rate by age range. Each dot represents a multivariate estimate of mortality rate after adjusting for smoking, drinking, and body mass index, and each line shows the 95% CI. The number of events in each age category are as follows: men aged 40 to 49 years: 137; age 50 to 59 years: 566; age 60 to 69 years: 1900; age 70 to 79 years: 3782; age 80 to 89 years: 2183; women aged 40 to 49 years: 128; age 50 to 59 years: 518; age 60 to 69 years: 1392; age 70 to 79 years: 2708; age 80 to 89 years: 2258.

period was 9.6 years in men and 9.9 years in women. The total number of deaths (all-cause) was 17 757 (men: 9880; women: 7877). The characteristics of the cohorts were similar, and no apparent differences in hazard ratio were found at each blood pressure level. In our study, we analyzed participants without cardiovascular disease history. Because there was no information of cardiovascular disease history in the Tanno-Sobetsu cohort, we excluded these participants, and, therefore, 176 389 (male: 65 463; female: 110 926) participants were investigated in our study.

The Figure shows the relation between blood pressure and multivariate-adjusted hazard rate for total mortality. In almost every age group, mortality rate was higher at a higher SBP level and higher DBP levels. The difference in absolute mortality rate between the highest and lowest blood pressure groups was larger in older than in younger participants. The results did not change even when we excluded the participants who did not take antihypertensive medication.

Table 2 shows the multivariate-adjusted mortality ratio for all-cause mortality for each 10-mm Hg blood pressure increase. In all of the age groups and categories, the hazard ratios were statistically significant. The hazard ratio was larger in the younger group than in the older group. The effect of modifying age was apparent when we included the interaction terms of age and blood pressure into the model (men: $P<0.01$ in both SBP and DBP; women: $P=0.02$ in SBP and $P=0.05$ in DBP). Although we excluded body mass index or alcohol drinking from confounding factors, our result did not changed largely.

Table 3 shows the multivariate-adjusted hazard ratio for all-cause mortality according to JNC-7 criteria. Although they fluctuated in some categories to some extent, hazard ratio gradually increased in all of the sex and age categories. With some exceptions, the hazard ratio in groups with hypertension was consistently higher for almost every age range in both men and women.

Table 2. Multivariate-Adjusted Hazard Ratio of All-Cause Mortality According to Age and 10-mm Hg Blood Pressure Increase During an Average 9.8 Years of Follow-Up

Sex	Age Category, y	No. of Deaths	SBP Hazard Ratio (95% CI)	DBP Hazard Ratio (95% CI)
Men	40 to 49	137	1.37 (1.15 to 1.62)	1.46 (1.05 to 2.03)
	50 to 59	566	1.23 (1.14 to 1.33)	1.42 (1.21 to 1.65)
	60 to 69	1900	1.16 (1.11 to 1.21)	1.28 (1.17 to 1.40)
	70 to 79	3782	1.14 (1.11 to 1.17)	1.21 (1.13 to 1.29)
	80 to 89	2183	1.09 (1.05 to 1.13)	1.12 (1.03 to 1.22)
Women	40 to 49	128	1.19 (1.00 to 1.41)	1.40 (1.00 to 1.95)
	50 to 59	518	1.16 (1.07 to 1.26)	1.38 (1.17 to 1.64)
	60 to 69	1392	1.21 (1.15 to 1.27)	1.29 (1.16 to 1.44)
	70 to 79	2708	1.12 (1.08 to 1.16)	1.25 (1.15 to 1.35)
	80 to 89	2258	1.07 (1.03 to 1.11)	1.12 (1.03 to 1.22)
Men and women combined	40 to 49	265	1.27 (1.13 to 1.44)	1.42 (1.12 to 1.80)
	50 to 59	1084	1.20 (1.14 to 1.27)	1.40 (1.25 to 1.58)
	60 to 69	3292	1.18 (1.15 to 1.22)	1.29 (1.20 to 1.38)
	70 to 79	6490	1.13 (1.11 to 1.16)	1.22 (1.16 to 1.29)
	80 to 89	4441	1.08 (1.05 to 1.11)	1.12 (1.05 to 1.19)

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking and body mass index. To correct regression dilution bias, parameter estimates were multiplied by regression dilution factors (SBP: 0.59; DBP: 0.48). Unadjusted hazard ratios of SBP were as follows: men aged 40 to 49: 1.21 (1.09 to 1.34), 50 to 59: 1.14 (1.08 to 1.19), 60 to 69: 1.09 (1.07 to 1.12), 70 to 79: 1.08 (1.06 to 1.10), 80 to 89: 1.05 (1.03 to 1.08); women aged 40 to 49: 1.11 (1.00 to 1.23), 50 to 59: 1.10 (1.04 to 1.15), 60 to 69: 1.12 (1.09 to 1.15), 70 to 79: 1.07 (1.05 to 1.09), 80 to 89: 1.04 (1.02 to 1.07); men and women combined aged 40 to 49: 1.16 (1.08 to 1.25), 50 to 59: 1.12 (1.08 to 1.16), 60 to 69: 1.11 (1.09 to 1.13), 70 to 79: 1.08 (1.06 to 1.09), 80 to 89: 1.05 (1.03 to 1.06). Unadjusted hazard ratios of DBP were as follows: men aged 40 to 49: 1.20 (1.02 to 1.40), 50 to 59: 1.18 (1.10 to 1.27), 60 to 69: 1.13 (1.08 to 1.18), 70 to 79: 1.09 (1.06 to 1.13), 80 to 89: 1.06 (1.01 to 1.10); women aged 40 to 49: 1.17 (1.00 to 1.38), 50 to 59: 1.17 (1.08 to 1.27), 60 to 69: 1.13 (1.07 to 1.19), 70 to 79: 1.11 (1.07 to 1.15), 80 to 89: 1.06 (1.01 to 1.10); men and women combined aged 40 to 49: 1.18 (1.06 to 1.33), 50 to 59: 1.18 (1.11 to 1.24), 60 to 69: 1.13 (1.09 to 1.17), 70 to 79: 1.10 (1.08 to 1.13), 80 to 89: 1.06 (1.03 to 1.09).

The population-attributable fraction for each age range was similar in men and women. In men, except for age 80 to 89 years, 10.5%, the population-attributable fraction was ≈20% to 30%. Except for the lowest population-attributable fraction in women aged 40 to 49 and aged 80 to 89 years, the population-attributable fraction was ≈10% to 20%. For the overall population, the population-attributable fraction of nonnormal blood pressure was 22.7% in men and 17.9% in women. The population-attributable fraction became smaller when the reference was the combination of normal and prehypertension groups as compared with the normal group alone.

Discussion

On the basis of a meta-analysis of individual data from 176 389 Japanese participants, we confirmed that high blood pressure affects total mortality in all age categories. We found that there was an apparent effect modification by age and blood pressure and that hazard ratio was higher in younger than in older groups. We also examined the impact of primary prevention of high blood pressure on total mortality by calculating the population-attributable fraction and found that it was considerable in both men and women.

Blood pressure values are known to be relatively higher in Japan than other developed countries. This situation still exists although values have dropped dramatically.[25] One third of Japanese men and women died from cardiovascular diseases,[26] and Japan has one of the highest stroke mortalities among developed countries.[27] Thus, the contribution of high blood pressure to all-cause mortality should be higher in Japan than other countries. Thus, it should be important to know how many all-cause deaths are attributable to high blood pressure in different age groups. Our huge data set from 180 000 participants can be used to show the health consequence of high blood pressure in Japan. Each of our cohort studies was well administered and provided reliable data sets. The cohort studies were conducted all over Japan, confirming that our results are applicable to the general population in Japan.

Prospective studies collaboration showed that the relation of blood pressure to cardiovascular disease mortality was stronger in younger than in older subjects.[2] Recent studies in Japan showed that risk (all causes and cardiovascular disease) of high blood pressure in the Japanese population has increased.[21,28,29] The increasing trends in age-specific[28] and age-adjusted[29] hazard ratios were observed in nationwide cohort studies, and sex- and age- (aged 40 to 59 years and aged 60 to 79 years) specific hazard ratios showed increasing trends in the large-scale cohort study of the Ibaraki prefecture.[21] These studies raised the possibility that the association of blood pressure with all-cause mortality was stronger in the younger than in the older Japanese population. A data set from a huge population after fine age stratification could be used to prove findings that were never shown in Asian (Japanese) populations. We found significant interaction between age and blood pressure for all-cause mortality. This

Table 3. Multivariate Adjusted Hazard Ratio of All-Cause Mortality According to JNC-7 Classification, During Average 9.8 Years of Follow-Up

Sex	Age Category	Variable	Classification of Blood Pressure				PAF (%) (Reference: Normal)	PAF (%) (Reference: Normal+ Prehypertension
			Normal	Prehypertention	Hypertension (Stage 1)	Hypertension (Stage 2)		
Men	40 to 49	Total deaths	23	67	26	21	30.2	8.8
		Person-years	18 883	36 082	15 004	4899		
		Hazard ratio	1	1.45	1.28	3.38		
		95% CI		(0.89 to 2.38)	(0.70 to 2.34)	(1.76 to 6.50)		
	50 to 59	Total deaths	101	222	144	99	18.9	13.1
		Person-years	32 508	66 316	38 648	15 206		
		Hazard ratio	1	1.11	1.27	2.24		
		95% CI		(0.87 to 1.41)	(0.97 to 1.67)	(1.67 to 3.02)		
	60 to 69	Total deaths	198	691	644	367	25.7	11.3
		Person-years	28 313	79 508	69 671	30 000		
		Hazard ratio	1	1.26	1.39	1.82		
		95% CI		(1.07 to 1.48)	(1.18 to 1.64)	(1.52 to 2.18)		
	70 to 79	Total deaths	341	1194	1485	762	21.3	13.9
		Person-years	16 141	55 249	60 031	25 027		
		Hazard ratio	1	1.12	1.36	1.60		
		95% CI		(0.99 to 1.27)	(1.20 to 1.53)	(1.40 to 1.83)		
	80 to 89	Total deaths	182	660	844	497	10.5	7.0
		Person-years	2812	10 787	13 091	6082		
		Hazard ratio	1	1.05	1.11	1.31		
		95% CI		(0.88 to 1.25)	(0.93 to 1.31)	(1.09 to 1.57)		
Women	40 to 49	Total deaths	48	53	21	6	9.6	5.6
		Person-years	56 053	59 660	17 701	4817		
		Hazard ratio	1	1.09	1.42	1.44		
		95% CI		(0.73 to 1.62)	(0.83 to 2.45)	(0.60 to 3.45)		
	50 to 59	Total deaths	119	227	122	50	23.8	8.6
		Person-years	86 823	126 087	59 029	18 531		
		Hazard ratio	1	1.33	1.56	1.85		
		95% CI		(1.06 to 1.68)	(1.19 to 2.04)	(1.30 to 2.64)		
	60 to 69	Total deaths	204	513	435	240	22.3	13.8
		Person-years	66 277	146 391	108 093	36 453		
		Hazard ratio	1	1.16	1.35	2.13		
		95% CI		(0.98 to 1.37)	(1.14 to 1.62)	(1.74 to 2.60)		
	70 to 79	Total deaths	289	876	1037	506	11.8	13.3
		Person-years	28 708	91 539	91 441	33 945		
		Hazard ratio	1	0.98	1.20	1.48		
		95% CI		(0.85 to 1.12)	(1.05 to 1.38)	(1.27 to 1.72)		
	80 to 89	Total deaths	195	689	841	533	5.7	6.2
		Person-years	4702	17 815	21 342	10 758		
		Hazard ratio	1	0.99	1.07	1.17		
		95% CI		(0.84 to 1.18)	(0.90 to 1.27)	(0.98 to 1.40)		
Men and women combined	40 to 49	Total deaths	71	120	47	27	18.1	7.6
		Person-years	74 936	95 742	32 705	9716		
		Hazard ratio	1	1.22	1.28	2.48		
		95% CI		(0.90 to 1.65)	(0.86 to 1.91)	(1.53 to 4.04)		

(*Continued*)

Table 3. Continued

Sex	Age Category	Variable	Classification of Blood Pressure: Normal	Prehypertention	Hypertension (Stage 1)	Hypertension (Stage 2)	PAF (%) (Reference: Normal)	PAF (%) (Reference: Normal+Prehypertension
	50 to 59	Total deaths	220	449	266	149	22.1	11.3
		Person-years	119 331	192 403	97 677	33 737		
		Hazard ratio	1	1.22	1.42	2.15		
		95% CI		(1.03 to 1.45)	(1.17 to 1.72)	(1.72 to 2.69)		
	60 to 69	Total deaths	402	1204	1079	607	24.8	13.2
		Person-years	94 590	225 899	177 764	66 453		
		Hazard ratio	1	1.22	1.39	1.95		
		95% CI		(1.09 to 1.37)	(1.23 to 1.57)	(1.70 to 2.23)		
	70 to 79	Total deaths	630	2070	2522	1268	17.4	14.0
		Person-years	44 849	146 788	151 472	58 972		
		Hazard ratio	1	1.06	1.29	1.54		
		95% CI		(0.96 to 1.16)	(1.18 to 1.41)	(1.40 to 1.17)		
	80 to 89	Total deaths	377	1349	1685	1030	7.3	6.6
		Person-years	7513	28 602	34 433	16 840		
		Hazard ratio	1	1.01	1.08	1.22		
		95% CI		(0.90 to 1.15)	(0.96 to 1.22)	(1.08 to 1.39)		

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking, and body mass index. Classification of blood pressure status is according to JNC 7 guidelines (unit: mm Hg). Normal: SBP$<$120 and DBP$<$80; prehypertension: 120$\leq$SBP$<$140 and 80$\leq$DBP$<$90; hypertension (stage 1): 140$\leq$SBP$<$160 and 90$\leq$DBP$<$100; hypertension (stage 2): 160$\leq$SBP and 100$\leq$DBP, participants with hypertensive medication. Normal blood pressure level was set as the reference level. Population attributable fraction (PAF) was calculated in 2 ways. The reference level was set at (1) the normal blood pressure level and (2) below prehypertension (normal and prehypertension) level. Weighted averages of age-specific PAF, of which weights were person-years in each age category, were calculated as common PAFs. Common PAF was 22.7% in men, 17.9% in women, and 20.6 % in men and women combined (reference: normal) and 11.9% in men, 10.9% in women, and 11.9 % in men and women combined (reference: normal+prehypertension).

suggests that aggressive primary prevention of high blood pressure by all-cause mortality reduction benefits younger more than older people, although the absolute level of all-cause mortality was lower in younger than in older participants. As a consequence, absolute risk reduction should be lower in younger than in older people. Conversely, although the hazard ratio of high blood pressure was relatively lower in the elderly, absolute risk reduction should be higher in older than in younger people. Thus, the risk of hypertension should be age dependent. Because risk reduction is smaller in younger people, the high-risk approach might not be cost-effective. Therefore, the population approach is more suitable in younger than in older individuals. Conversely, for older individuals, the high-risk approach might be more beneficial.

The impact of lower blood pressure on the total mortality was determined by the population-attributable fraction. The study by Sairenchi et al[21] showed that the population-attributable fraction is ≈10% in men and 3% in women. In our study, the EPOCH-JAPAN estimated an age-specific population-attributable fraction for the contribution of blood pressure. In younger age ranges, a large number of deaths can be avoided by lowering blood pressure. This impact of blood pressure decreased with increasing age. When the prehypertension group was used for reference, the population-attributable fraction was ≈10% in each group. This proportion showed that lowering blood pressure is still effective even when all of the participants have prehypertension, which is a level of blood pressure that is achievable in practice.

We confirmed that all-cause mortality is consistently higher in individuals with prehypertension than in individuals with normal blood pressure. Thus, recommending lifestyle modification for them might reduce their all-cause mortality. However, because the absolute risk difference between normal blood pressure and prehypertension was not large, and population-attributable fraction was small, antihypertensive medication for them might not be recommended. Thus, we considered that the JNC-7 recommendation to modify lifestyle is the appropriate measure for prehypertension participants.

Hypertension is a leading cause of cardiovascular disease mortality and, thus, is a main contributor to total mortality. One of the advantages of selecting total mortality as an end point is that there is no misclassification issue in all-cause deaths compared with disease-specific ones. Although the interpretation of hypertension effect on total mortality was not intuitive, our examination of total mortality provided substantial information for public health purposes.

There were limitations in this study. First, the pooled data of most of the cohort studies were from baseline surveys performed during community health examinations. Participants in the cohort study volunteered to receive their health examinations, and for that reason their characteristics might be somewhat different from those of nonparticipants. This would influence the absolute measure of effect (mortality rate) and might underestimate the risk. However, these differences have little effect on relative measures of effect (such as hazard ratio). Thus, we considered that comparing

hazard ratios between age groups or population-attributable fractions might be largely unaffected. Second, we did not adjust for diabetes in this study. Because diabetes is an obesity-related risk factor for hypertension, we might have overestimated the risk posed by hypertension, per se. However, because prevalence of diabetes was very low during the baseline period in Japan, we believe that not adjusting for diabetes should have no substantial effect on our result.

In conclusion, high blood pressure raised the risk of total mortality, and this increase was higher relatively, but not absolutely, in younger than in older individuals. A relatively large amount of the population-attributable fraction was observed in the younger age group. Blood pressure management is an important preventive measure for the Japanese population regardless of age.

Perspectives

The present study showed the relation between blood pressure and total mortality in the Japanese population in detail. The results showed that apparent relation between blood pressure and total mortality was present not only in the elderly but also in a younger age group for both men and women. The result encourages us that blood pressure management was an important preventive measure for Japanese participants regardless of age. Furthermore, the people with prehypertension showed high hazard ratios in most age groups. This detailed information would provide effective public health policy and clinical practice not only in the Japanese but also in the Asian population.

Appendix

Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group is composed of the following individuals: chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); writing committee: Yoshitaka Murakami, Atsushi Hozawa, Tomonori Okamura, and Hirotsugu Ueshima; statistical analysis: Yoshitaka Murakami; secretariat: Yoshitaka Murakami; and the executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Medicine), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Kazunori Kodama (Radiation Effects Research Foundation), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (National Cardiovascular Center), Akira Okayama (Japan Anti-Tuberculosis Association), Shigeyuki Saitoh (Sapporo Medical University), Akiko Tamakoshi (National Center for Geriatrics and Gerontology), Ichiro Tsuji (Tohoku University Graduate School of Medicine), and Yoko Izumi (Ibaraki Prefecture).

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Disclosures

None.

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