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ORIGINAL ARTICLE

Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women

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Blood pressure (BP) categories defined by systolic BP (SBP) and diastolic BP (DBP) are commonly used. However, the BP category-specific risk of cardiovascular disease (CVD) has not been thoroughly investigated in different age groups. The aim of this study was to assess long-term CVD risk and its impact according to BP categories and age group. Pooling individual data from 10 cohorts, we studied 67 309 Japanese individuals (40–89 years old) who were free of CVD at baseline: we categorized them as belonging to three age groups: 'middle-aged' (40–64 years), 'elderly' (65–74 years) and 'very elderly' (75–89 years). BP was classified according to the 2009 Japanese Society of Hypertension Guidelines. Cox models were used to estimate adjusted hazard ratios for CVD deaths. We observed 1944 CVD deaths over a mean follow-up of 10.2 years. In all age groups, the overall relationship between BP category and CVD risk was positive, with a greater strength observed for younger age groups. We observed a trend of increased risk from SBP/DBP $\geqslant$ 130/85 mm Hg in the very elderly, and a significant increase from SBP/DBP $\geqslant$ 120/80 mm Hg in the other age groups. The population attributable fractions (PAFs) of CVD death in reference to the SBP/DBP $<$ 120/80 mm Hg category ranged from 23.4% in the very elderly to 60.3% in the middle-aged. We found an overall graded increase in CVD risk with higher BP category in the very elderly. The PAFs suggest that keeping BP levels low is an important strategy for primary CVD prevention, even in an elderly population.
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INTRODUCTION

Epidemiological studies have shown that the effect of both systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the risk of cardiovascular disease (CVD) is continuous and consistent.[1,2] Because both SBP and DBP are independent predictors of CVD risk,[3–7] most guidelines for adult blood pressure (BP) management have proposed similar BP categorization systems with regard to the following: (1) BP categories are defined by taking both SBP and DBP into account, and (2) the most favorable BP category is SBP $<$ 120 mm Hg and DBP $<$ 80 mm Hg, irrespective of age.[8–11]

Although such BP categorization is widely used, there is only limited evidence assessing long-term CVD risk according to BP category, particularly for elderly populations. Given the worldwide trend of aging,[12] assessing the long-term risk of elevated BP and its impact on the aged population is increasingly important from both clinical and public health standpoints. The Framingham Heart Study (FHS) reported graded increases in major CVD risk across higher BP categories among 1932 participants aged $\geqslant$80 years.[13] However, the follow-up period was relatively short (mean, 2.7 years).[13] Therefore, long-term CVD risk was not fully assessed in that study. Other Western studies seeking to assess the BP category-specific risk of CVD events were based on subjects aged $\leqslant$75 years.[5,14–16] Epidemiological studies on long-term CVD risk among an elderly population have also been limited,[17,18] and hence needed,[19] in Asia.

The objectives of this study were (1) to estimate long-term CVD mortality risk according to BP categories defined by both SBP and DBP, (2) to examine whether the relationship between BP categories and CVD risk differs according to age group and (3) to compare the impact of increased BP on long-term CVD risk for different age groups by estimating population attributable fractions (PAFs). We focused particularly on an elderly population.

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METHODS

Design

This study is part of a pooling project in which individual participants' data from 13 observational cohorts across Japan were combined. The project was designed to examine the relationship between disease mortality and various exposure factors, including laboratory and lifestyle/behavioral factors. The project is called Evidence for Cardiovascular Prevention from Observational Cohorts in Japan. The inclusion criteria for the cohorts were as follows: collection of health examination measures, follow-up of almost 10 years and more than 1000 participants. Both nationwide and regional cohort studies were included. Other details are reported elsewhere.[20]

Study population

In all, 10 of 13 cohorts provided data on cause of death ($n=90\,528$). Of those, we used the following exclusion criteria for the present study: age <40 years or >89 years at baseline ($n=10\,528$); history of CVD at baseline ($n=5031$); missing values for SBP, DBP or both ($n=147$); and missing adjusting covariates ($n=7513$). Thus, 67 309 individuals from 10 cohort studies were pooled (Tanno-Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, the Radiation Effects Research Foundation cohort, Hsayama, JACC study, NIPPON DATA80 and NIPPON DATA90; see Supplementary Table S1 for the demographics of each cohort).

Death ascertainment

In accordance with the Family Registration Law in Japan, all death certificates are forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residence. Registration of death is required by law and believed to be complete. The underlying cause of death is coded according to the International Classification of Disease (ICD) for National Vital Statistics, based on the criteria proposed by the World Health Organization.[21]

Cause of death was sought in great detail using the available sources in each cohort study. In most studies, death certificates were reviewed and/or National Vital Statistics were used after obtaining permission. Other sources used in some studies included autopsy, medical records, health examination and questionnaires. The cause of death was coded based on either ICD-9 or ICD-10. The classification codes used in the study were as follows: death from CVD (390–459 by ICD-9; I00–I99 by ICD-10), total stroke (410–414 or 430–438; I20–I25 or I60–I69), ischemic stroke (433 or 434 or 437.8; I63 or I69.3), intracerebral hemorrhage (431–432; I61 or I69.1), coronary heart disease (410–414; I20–I25) and heart failure (428; I50).

BP measurement

Detailed information on the BP measurement method for each cohort is provided in Supplementary Table S2. BP measurements were obtained using a mercury sphygmomanometer when each participant was in a seated position in all but two cohort studies. In one cohort (Ohasama), an automated device was used.[22] In the other study (JACC), the BP values were based on self-recorded values after BP had been measured at a health check-up.[23] In most cohorts, BP was measured once with a participant in a seated position after rest.

BP categories

Participants were categorized according to the modified classification of the 2009 Japanese Society of Hypertension Guidelines (JSH2009).[10] The cutoff values for the BP classification were the same as those in the 2007 Guidelines from the European Society of Hypertension and the European Society of Cardiology (ESH-ESC 2007).[8] Optimal BP was defined as SBP <120 mm Hg and DBP <80 mm Hg; the corresponding SBP and DBP values were 120–129 and 80–84 mm Hg for normal/non-optimal BP, 130–139 or 85–89 mm Hg (whichever was greater) for high-normal BP, 140–159 or 90–99 mm Hg for grade I hypertension, 160–179 or 100–109 mm Hg for grade II hypertension, and $\geqslant 180$ or $\geqslant 110$ mm Hg for grade III hypertension, respectively.

Statistical analysis

We estimated multivariable adjusted hazard ratios (HRs) of death from total CVD and its subtypes for each BP category by Cox proportional hazard models, in reference to the optimal BP category. We constructed two models to adjust for potential confounders. First, we adjusted for age (years), sex and cohort (model 1). Second, we further adjusted for serum total cholesterol ($\mathrm{mmol\,l^{-1}}$), body mass index ($\mathrm{kg\,m^{-2}}$), smoking status (current, past, never)[24] and alcohol intake (current, past, never) (model 2).

To examine whether the relationship between BP category and risk of CVD death differed according to age, we divided participants into three groups based on their age at baseline: 'middle-aged' represented those 40–64 years old, 'elderly' represented those 65–74 years old and 'very elderly' represented those 75–89 years old. The HR and the corresponding PAF for CVD deaths were estimated for each BP category in each age group. To assess heterogeneity, we assumed a monotonic association between CVD risk and BP category and created pertinent variables. In assessing heterogeneity among cohorts, we created a Forest plot.

PAF was calculated as $\mathrm{pd}\times(\mathrm{RR}-1)/\mathrm{RR}$, where pd represents the proportion of exposed deaths in a specific BP category and RR is the corresponding multivariable-adjusted HR in reference to the optimal BP category.[25] Additionally, we calculated gender-specific mortality risks and PAFs for CVD, total stroke, ischemic stroke, intracerebral hemorrhage, coronary heart disease and heart failure according to the BP category. In testing statistical evidence of interaction between sex and BP category on the effect of CVD risk, we first visually confirmed the overall positive relationship between BP category and CVD risk in both sexes. Then, we created an ordinal variable for BP category and its interaction term with sex, and inserted them in the models.

We performed the following sensitivity analyses: (1) excluding those who died from any cause within the first 3 years as an attempt to eliminate potential reverse causality from low BP;[26,27] (2) restricting the subjects to non-users of antihypertensive medication at baseline; and (3) adding diabetes mellitus (DM) status (yes or no) to the models for those participants for whom diabetes-defining variables were available ($n=36\,393$). We defined DM as either a fasting glucose level of $\geqslant 126\,\mathrm{mg\,dl^{-1}}$ ($7.0\,\mathrm{mmol\,l^{-1}}$), a casual glucose level of $\geqslant 200\,\mathrm{mg\,dl^{-1}}$ ($11.1\,\mathrm{mmol\,l^{-1}}$), a Hb A1c level of $\geqslant 6.5\%$, a history of DM, or taking medication for DM.

All statistical analyses were performed using SAS version 9.13 (SAS Institute, Cary, NC, USA). All of the P values for statistical tests were two-tailed, and $P<0.05$ were regarded as statistically significant. The study protocol was approved by the internal review board at each study center.

RESULTS

The participants' characteristics at baseline according to BP category are shown in Table 1. The proportion of the participants ($n=67\,309$) in each BP category was 21.9 (optimal BP), 20.2 (normal/non-optimal BP), 21.3 (high-normal BP), 24.9 (grade I hypertension), 9.0 (Grade II hypertension) and 2.7% (grade III hypertension) at baseline. Compared with participants in higher BP categories, those in the optimal BP category tended to be younger and to have a lower body mass index and lower total cholesterol level at baseline. The number of participants categorized as middle-aged, elderly and very elderly was 49 935 (74.2%), 13 707 (20.4%) and 3667 (5.4%), respectively.

During a mean follow-up of 10.2 years, we observed 1944 CVD deaths: 917 from total stroke, 479 from ischemic stroke, 220 from intracerebral hemorrhage, 388 from coronary heart disease and 343 from heart failure in all age groups combined. In the Cox regression models, CVD risk increased almost continuously as the BP category advanced. In disease-specific analyses, the risk of total stroke and coronary heart disease increased similarly as the BP category advanced (see Supplementary Table S3). The PAF estimates indicated that the elimination of normal/non-optimal BP to grade III hypertension could have prevented almost half of the CVD deaths. The results were similar for both sexes, with no statistical evidence of interaction

Table 1 Baseline characteristics of participants according to blood pressure category

	Blood pressure category[a]						
Variable	*Optimal (N = 14764)*	*Normal/non-optimal (N = 13607)*	*High-normal (N = 14325)*	*Grade I hypertension (N = 16729)*	*Grade II hypertension (N = 6079)*	*Grade III hypertension (N = 1805)*	*Total (N = 67309)*
Women, %	66.1	60.0	56.8	55.4	53.6	51.2	58.7
Age, mean (s.d.), years	53.7 (9.7)	55.5 (10.0)	58.0 (10.0)	59.9 (10.0)	61.5 (10.0)	62.1 (10.4)	57.4 (10.3)
Body mass index, mean (s.d.), $kg\,m^{-2}$	22.2 (2.8)	23.0 (2.9)	23.3 (3.0)	23.7 (3.2)	24.0 (3.4)	24.1 (3.6)	23.2 (3.1)
Total cholesterol, mean (s.d.), $mmol\,l^{-1}$[b]	5.05 (0.91)	5.11 (0.93)	5.21 (0.94)	5.23 (0.97)	5.24 (0.99)	5.27 (1.05)	5.16 (0.95)
Smoking							
Never, %	69.5	66.2	64.4	63.1	61.1	58.0	65.1
Past, %	6.7	9.0	10.5	11.6	12.4	12.9	9.9
Current, %	23.8	24.8	25.2	25.3	26.5	29.1	25.1
Drinking							
Never, %	61.5	57.7	55.6	54.8	53.7	51.5	56.8
Past, %	2.7	2.5	2.8	2.8	3.0	3.2	2.8
Current, %	35.8	39.8	41.6	42.4	43.3	45.3	40.4

[a]Blood pressure categories were defined as follows; 'Optimal' as systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mm Hg for 'Normal/non-optimal,' 130–139 or 85–89 mm Hg (whichever was greater) for 'high-normal,' 140–159 or 90–99 mm Hg for 'grade I hypertension,' 160–179 or 100–109 mm Hg for 'grade II hypertension' and $\geqslant 180$ or $\geqslant 110$ mm Hg for 'grade III hypertension, respectively.'
[b]The conversion factor for total cholesterol level from $mmol\,l^{-1}$ to $mg\,dl^{-1}$ is 38.67.

(*P* for interaction by sex 0.95) (see Supplementary Table S4 and Supplementary Table S5 for sex-specific results).

The crude death rates, adjusted HRs and PAFs according to BP category for each age group are shown in Table 2. The overall relationship between BP category and CVD risk was positive and graded for all age groups, with a greater strength of association observed in the younger group (*P* value for heterogeneity <0.001). For both the middle-aged and elderly groups, compared with individuals in the optimal BP category, the CVD risk increased significantly for those in the normal/non-optimal BP category and continued to increase overall for those in higher BP categories. For the very elderly group, in contrast, both optimal and normal/non-optimal BP categories appeared to have the lowest CVD risk. The PAFs for CVD death in reference to the optimal BP category tended to be greater for younger groups, accounting for 60, 49 and 23% of all CVD deaths in the middle-aged, elderly and very elderly groups, respectively. There is no statistical evidence that these trends differ according to sex in any of the age groups (*P* values for interaction by sex were 0.23, 0.11 and 0.50 for the middle-aged, elderly and very elderly, respectively). (For sex-specific results by age group, see Supplementary Table S6 and Supplementary Table S7).

The Forest plot by cohort indicated an apparently stronger effect of BP in the YKK workers cohort than in other cohorts (Supplementary Figure S1). However, the confidence interval was wide, and the direction of association was the same as for the other cohorts. Furthermore, exclusion of this cohort did not change the results substantially (data not shown). In the Forest plot, we did not observe a clear difference among methods of BP measurement.

In the first sensitivity analysis, which excluded deaths within the first 3 years, the observed association between the BP category and CVD death became stronger for the very elderly group than it was in the main analysis, such that the CVD risk significantly increased for participants in the high-normal BP category and higher categories (Table 3). The results for other age groups were similar to those in the main analysis. In the second sensitivity analysis, which was restricted to non-users of antihypertensive medication at baseline (29 097 participants, 823 CVD deaths), we observed similar results to the main analysis for all age groups (see Supplementary Table S8). In the third sensitivity analysis, which included DM status in the model, the relationship between BP category and CVD risk was attenuated in both the elderly and very elderly groups, whereas the relationship was slightly strengthened in the middle-aged group (see Supplementary Table S9).

DISCUSSION

This pooled analysis of 10 well-qualified, prospective cohort studies in Japan enabled us to investigate the detailed relationship between BP categories and long-term CVD mortality risk over a broad age range. We found an overall positive relationship for all of the age groups that were studied. In the middle-aged and elderly groups, the risk was lowest for those in the optimal BP category. Importantly, even in the very elderly, the risk appeared to increase from the high-normal BP category to higher BP categories in a graded fashion. The relationship became stronger in this age group when the first 3 years of deaths were excluded. Another important finding of our study is that the impact of elevated BP, as measured by PAF, remained substantial in older groups, suggesting that maintaining optimal BP could have eliminated as many as one-quarter of CVD deaths in the very elderly group and half of those in the elderly group.

In many guidelines, BP categorization involves both SBP and DBP, and the same cutoff values are used irrespective of age.[8–11] However, only a few studies have examined BP category-specific CVD risk in an elderly population. To our knowledge, this is the first observational study that has demonstrated a long-term CVD risk and its impact according to BP category in a group of very elderly (aged $\geqslant 75$ years) Asian men and women. From North America/European regions, the FHS showed that major CVD risk increased in a graded fashion with advancing BP category among those aged $\geqslant 80$ years.[13] Most other studies from these regions have examined populations aged $\leqslant 75$ years.[5,14–16] The FHS observed 336 CVD events among 1932 elderly

Table 2 Cardiovascular death according to blood pressure categories by age group

	Optimal	*Normal/non-optimal*	*High-normal*	*Grade I hypertension*	*Grade II hypertension*	*Grade III hypertension*	*Total*
Very elderly (75–89 years)							
Number at risk	350	483	726	1251	616	241	3667
Person-years	2627	3786	5563	9655	4855	1810	28296
CVD deaths	38	45	105	206	137	60	591
Crude rate[a]	14.46	11.89	18.88	21.34	28.22	33.15	20.89
HR (95% CI)[b]	1	0.83 (0.54–1.28)	1.27 (0.87–1.84)	1.38 (0.97–1.97)	1.46 (1.01–2.12)	1.73 (1.14–2.64)	
PAF (%)[c]	—	−1.6	3.7	9.7	7.3	4.3	23.4
Elderly (65–74 years)							
Number at risk	1880	2227	3105	4290	1735	470	13707
Person-years	16086	19202	26249	38491	15973	4391	120392
CVD deaths	45	96	104	267	146	66	724
Crude rate[a]	2.80	5.00	3.96	6.94	9.14	15.03	6.01
HR (95% CI)[b]	1	1.76 (1.23–2.51)	1.40 (0.99–1.99)	2.20 (1.59–3.03)	2.64 (1.87–3.73)	3.96 (2.67–5.85)	
PAF (%)[c]	—	5.7	4.1	20.1	12.5	6.8	49.3
Middle-aged (40–64 years)							
Number at risk	12534	10897	10494	11188	3728	1094	49935
Person-years	132300	117254	109424	122301	40846	12756	534880
CVD deaths	51	87	102	194	124	71	629
Crude rate[a]	0.39	0.74	0.93	1.59	3.04	5.57	1.18
HR (95% CI)[b]	1	1.77 (1.25–2.51)	1.94 (1.38–2.73)	2.99 (2.17–4.11)	5.23 (3.71–7.35)	8.50 (5.81–12.43)	
PAF (%)[c]	—	6.0	7.9	20.5	15.9	10.0	60.3

Abbreviations: 95% CI, 95% confidence intervals; CVD, cardiovascular disease; HR, hazard ratio; PAF, population attributable fraction.
[a]Crude rate was expressed as per 1000 person-year.
[b]Hazard ratio was adjusted for age, sex, cohort, body mass index ($kg\,m^{-2}$), total cholesterol ($mmol\,l^{-1}$), smoking, and drinking (model 2).
[c]PAF estimate was based on the hazard ratio obtained by model 2.

Table 3 Risk of cardiovascular death in the subgroup with those died in the first 3 years excluded

	Optimal	*Normal/non-optimal*	*High-normal*	*Grade I hypertension*	*Grade II hypertension*	*Grade III hypertension*	*Total*
Very elderly (75–89 years)							
No. at risk	296	429	648	1087	518	190	3168
Person-years	2518	3655	5372	9298	4620	1712	27175
CVD deaths	20	34	81	150	94	40	419
Crude rate[a]	7.94	9.3	15.08	16.13	20.35	23.37	15.42
HR[b]	1	1.17 (0.67–2.04)	1.87 (1.14–3.05)	1.91 (1.19–3.07)	1.83 (1.12–3.01)	2.14 (1.23–3.72)	—
Elderly (65–74 years)							
No. at risk	1829	2141	2980	4136	1655	437	13178
Person-years	15970	18998	25923	38126	15789	4315	119120
CVD deaths	39	78	77	223	117	51	585
Crude rate[a]	2.44	4.11	2.97	5.85	7.41	11.82	4.91
HR[b]	1	1.62 (1.10–2.38)	1.19 (0.81–1.76)	2.01 (1.42–2.85)	2.26 (1.55–3.29)	3.28 (2.13–5.04)	—
Middle-aged (40–64 years)							
No. at risk	12440	10811	10400	11057	3657	1066	49431
Person-years	132096	117053	109187	121997	40667	12700	533700
CVD deaths	40	69	87	155	102	60	513
Crude rate[a]	0.3	0.59	0.8	1.27	2.51	4.72	0.96
HR[b]	1	1.75 (1.19–2.60)	2.08 (1.43–3.05)	2.91 (2.03–4.16)	5.21 (3.55–7.64)	8.39 (5.50–12.8)	—

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.
[a]Crude rate was expressed as per 1000 person-year.
[b]Hazard ratio (95% confidence interval) adjusted for age (years), sex, cohort, body mass index ($kg\,m^{-2}$), total cholesterol ($mmol\,l^{-1}$), smoking (current, never, past) and drinking (current, never, past).

over a mean of 2.7 years.[13] Compared with the FHS, we observed more than five times as many CVD events among twice as many elderly participants over a mean of 10.2 years. Furthermore, we used six BP categories compared with the four used in the FHS (based on a modified version of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines).[9] Our categorization allows us to show finer BP category-specific CVD risks, such as those for normal/non-optimal BP or high-normal BP categories. Nevertheless, our results were broadly consistent with those in the FHS. There are at least two large-scale meta-analyses with pooled data from individual participants that have studied the association between BP and CVD risk: the Prospective Studies Collaboration (PSC)[2] and the Asia Pacific Cohort Studies Collaboration (APCSC).[28] Although our results

are consistent with the results of these studies, our study differs significantly from both of these studies with respect to BP measurements. The PSC and the APCSC used either continuous DBP or SBP alone, whereas we used BP categories that accounted for both SBP and DBP. Several studies from Japan have reported both BP category-specific risk and/or PAF for CVD events.[29–33] Because of the small sample sizes, however, none of these studies sought detailed estimates for the very elderly population (aged $\geqslant$75 years), unlike the present study. A recent, large, prospective study from China showed both BP category-specific risk and PAF for CVD events.[18] However, this study provided only limited information with regard to BP category-specific risk and impact on the very elderly population because the authors grouped those aged $\geqslant$65 years together and used fewer BP categories (a modified JNC7 categorization similar to the FHS) than did our study.

When excluding the first 3 years of death in the very elderly, we observed a stronger overall relationship between BP category and CVD risk, with a significant increase in risk observed for the high-normal BP category and higher categories. This observation may suggest the presence of reverse causality, in which a poor health condition could have caused a lower BP.[34,35] Exclusion of the first few years of deaths from the analysis was proposed as one way to address reverse causality, particularly when analyzing an elderly population.[26,27,35] Therefore, the lack of difference in CVD risk between the two lowest BP categories in the very elderly group may be attributable to reverse causality. Another possible explanation is that there is an attenuated strength of association between BP and CVD risk in this age group compared with younger age groups.[3,28]

We observed a significant difference in the strength of the association between BP and CVD risk (that is, a difference in the relative risk of CVD) according to age group. Such heterogeneity by age in the effect of BP on CVD risk has been observed consistently in many large observational studies.[18,28,32,36] However, a recent meta-analysis of clinical trials by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) concluded that there was no evidence of statistical heterogeneity in the effect of BP-lowering therapy on CVD risk between younger and older subjects.[37] We speculate that this discrepancy could be due to differences between observational studies and clinical trials and/or due to a lack of statistical power in the BPLTTC study, as the authors of the study have noted.[37]

Regarding sex-specific differences, we observed that the absolute risk of CVD was generally higher in men than in women in all age groups, whereas the relative risk of CVD according to BP category (expressed as the HR) was similar between men and women (Supplementary Table S4–S7). These findings were consistent with those of previous large observational studies.[18,38]

The PAF estimates calculated in our study imply that, in a Japanese population, BP has a greater impact on CVD risk than does smoking[24,39,40] or elevated cholesterol.[41] Combined with the observed lower CVD risks associated with the lower BP categories, the results endorse maintaining a low BP throughout one's life as an important strategy for CVD prevention, both at an individual level and at the population level. It should be emphasized, however, that our results do not necessarily endorse pharmaceutical treatment for hypertension because the study was an observational study among a general population, and not an interventional study on a group of patients. In fact, recent studies indicate that the use of antihypertensive medication is unlikely to lower the risk of CVD to the same level as the risk for those who remain in low BP categories without such treatment.[42] Furthermore, evidence on pharmaceutical treatment for hypertension in the very elderly is still limited, as stated in the recent consensus document by the American College of Cardiology Foundation and the American Heart Association.[43]

Several limitations need to be considered when interpreting our results. First, we did not take into account the use or non-use of antihypertensive medication in the main analyses because of a substantial amount of missing information. However, the sensitivity analysis that was restricted to non-users of such medication at baseline showed similar results to the main analyses for all three age groups. Thus, it is unlikely that this limitation would materially change our inferences. Second, the study was based on a BP measurement on a single occasion, and it did not account for regression dilution bias.[2] Therefore, the results of the study are likely to underestimate the true association. Third, our estimates in the main analyses were not adjusted for DM. However, we found qualitatively similar results in the sensitivity analysis that adjusted for DM. Therefore, the influence of this limitation on our conclusion would likely be small. One strength of the study is that we pooled data from cohorts with a prospective design with a long follow-up period (over 10 years). Another strength is that the results are likely to be generalizable to a wide age range of adult men and women given that our samples were obtained from across the nation.

In summary, we observed a graded positive trend in CVD mortality risk starting from the high-normal BP category (SBP/DBP > 130/85 mm Hg) continuing up to the higher BP categories among the very elderly group and a significant increase in risk starting from the normal/non-optimal BP category (SBP/DBP > 120/80 mm Hg) up to the higher categories among the middle-aged and elderly groups. The strength of association between the BP category and CVD risk was attenuated but remained positive and graded in the very elderly. PAFs revealed that keeping BP levels low could prevent one-quarter of CVD deaths in the very elderly and one-half of those in the elderly. These findings suggest that maintaining low BP is an important strategy for primary CVD prevention in an elderly population, even among those aged 75–89 years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)

APPENDIX

The EPOCH-JAPAN Research Group

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); Executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura, Yoshitaka Murakami (Shiga University of Medical Science), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Akira Okayama (Japan Anti-Tuberculosis Association), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Aichi Medical University), Ichiro Tsuji (Tohoku University Graduate School of Medicine) and Michiko Yamada (Radiation Effects Research Foundation).