TABLE 1. Age and sex-adjusted mean values or prevalence of risk factors according to blood pressure categories at baseline

Variable	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Age (years)	55.1±0.4	56.4±0.5	58.8±0.5	61.8±0.5	66.2±0.6	<0.001
Men (%)	32.4	42.9	45.4	47.8	44.0	<0.001
Systolic blood pressure (mmHg)	110.8±0.3	123.5±0.3	133.8±0.4	145.9±0.3	170.3±0.4	<0.001
Diastolic blood pressure (mmHg)	66.7±0.3	73.7±0.3	78.6±0.4	84.2±0.3	91.9±0.4	<0.001
Antihypertensive medication (%)	3.1	7.5	13.2	23.4	32.6	<0.001
Body mass index (kg/m^2)	21.4±0.1	22.6±0.1	23.4±0.1	23.6±0.1	23.9±0.2	<0.001
Total cholesterol (mmol/l)	5.24±0.04	5.31±0.05	5.49±0.05	5.38±0.04	5.34±0.06	0.02
HDL cholesterol (mmol/l)	1.33±0.01	1.29±0.01	1.30±0.01	1.28±0.01	1.28±0.02	0.009
Diabetes (%)	5.1	12.6	14.7	15.1	19.5	<0.001
Chronic kidney disease (%)	7.0	12.1	11.7	16.2	23.5	<0.001
Electrocardiogram abnormalities (%)	10.6	12.8	15.5	18.6	29.3	<0.001
Current drinking (%)	20.9	30.4	30.4	34.5	39.5	<0.001
Current smoking (%)	29.7	24.4	25.2	21.6	22.7	0.004
Regular exercise (%)	9.2	12.0	9.2	9.7	10.7	0.78

BP, blood pressure; HT, hypertension; HDL, high-density lipoprotein. All values are given as means±SE or as percentages. Neither age nor sex was adjusted for covariates.

lower range of prehypertension (hazard ratio 1.58, 95% CI 1.11–2.26). When lower and higher ranges of prehypertension were combined, multivariate-adjusted hazard ratio of total prehypertension (120–139/80–89 mmHg) for the development of CVD was 1.64 (95% CI 1.18–2.26). Similar findings were obtained after excluding those taking antihypertensive agents at baseline from the study participants (Table 4).

As shown in Table 3, the PAFs of prehypertension, stage 1 hypertension, and stage 2 hypertension for development of CVD were 13.2, 13.6, and 16.5%, respectively. Approximately one-third of excess cardiovascular events attributable to elevated BP occurred among participants with prehypertension. PAFs for stroke incidence (16.1, 17.8, and 17.8 for prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively) were larger than those for coronary heart disease (5.8, 8.0, and 12.6%).

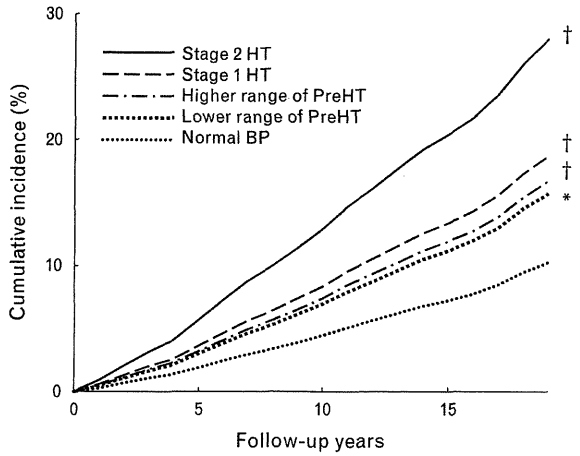


FIGURE 1 Age and sex-adjusted cumulative incidence of cardiovascular disease according to blood pressure categories. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. *$P<0.05$, †$P<0.01$ vs. normal BP.

Figure 2 shows the association of BP categories with the risk of CVD between two groups defined by the number of other cardiovascular risk factors (diabetes, hypercholesterolaemia, smoking, and chronic kidney disease). The multivariate-adjusted hazard ratio of CVD continuously increased with BP levels both among participants with 0–1 risk factor and those with 2–4 risk factors. However, stronger associations of prehypertension and hypertension with CVD were observed for participants with 2–4 risk factors compared to those with 0–1 risk factor ($P=0.04$ for heterogeneity).

DISCUSSION

In a long-term prospective study of a general Japanese population, we demonstrated that higher BP levels were associated with increased risks of CVD, and significantly higher incidence of CVD was observed from the lower range of prehypertension compared to normal BP. This association remained unchanged even after adjustment for other cardiovascular risk factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, ECG abnormalities, chronic kidney disease, smoking, drinking, and regular exercise. Because the prevalence rate of prehypertension was high, about one-third of the burden of CVD attributable to elevated BP was likely to occur from prehypertension. Furthermore, the effects of BP on the risks of CVD were stronger among 'high-risk' participants with multiple cardiovascular risk factors than among participants with 0–1 risk factor.

A number of large-scale cohort studies have demonstrated that prehypertension, particularly higher-range prehypertension, was associated with increased risks of CVD and death [4,20,21]. However, these studies were mainly conducted in Western populations, and it has been unclear to what extent these findings apply to Japanese populations. The Ohsaki study did not show significant effects of prehypertension on cardiovascular or total deaths in a general Japanese population [7]. The Evidence for

TABLE 2. Age and sex-adjusted incidence of cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n = 657$)	Lower range ($n = 545$)	Higher range ($n = 447$)	Stage 1 HT ($n = 626$)	Stage 2 HT ($n = 359$)	*P* for trend
Cardiovascular disease						
Total: no. of events/person-years	53/11148	76/8954	77/7142	127/9075	116/4440	
Age and sex-adjusted incidence	7.5	12.6*	12.1†	13.7‡	24.6‡	<0.001
Male: no. of events/person-years	24/3385	37/3747	47/3074	65/4108	56/1867	
Age-adjusted incidence	9.5	15.8	16.7†	17.8‡	32.6‡	<0.001
Female: no. of events/person-years	29/7763	39/5207	30/4068	62/4968	60/2573	
Age-adjusted incidence	6.1	10.4*	8.5	10.9†	19.5‡	<0.001
Stroke						
No. of events/person-years	31/11238	50/9048	53/7262	92/9183	79/4535	
Age and sex-adjusted incidence	4.1	8.2*	8.5†	9.9‡	16.8‡	<0.001
Ischaemic stroke						
No. of events/person-years	25/11238	36/9048	39/7262	66/9183	47/4535	
Age and sex-adjusted incidence	3.4	6.3	6.5*	6.9†	9.4†	<0.001
Haemorrhagic stroke						
No. of events/person-years	6/11238	14/9048	14/7262	26/9183	32/4535	
Age and sex-adjusted incidence	0.7	1.8*	2.0*	2.9†	7.4‡	<0.001
Coronary heart disease						
No. of events/person-years	26/11267	32/9225	29/7381	52/9596	48/4754	
Age and sex-adjusted incidence	3.7	5.1	4.0	5.2	8.7†	0.002

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension. Incidence, per 1000 person-years.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$ vs. normal BP.

Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) has reported a significant increase in all-cause mortality associated with prehypertension only among participants aged 50–69 [22]. The Jichi Medical School Cohort Study has shown a clear association between the higher range of prehypertension and incident CVD, but not for lower range of prehypertension [23]. In contrast, the Japan Atherosclerosis Longitudinal Study (JALS) and the

TABLE 3. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n = 657$)	Lower range ($n = 545$)	Higher range ($n = 447$)	Stage 1 HT ($n = 626$)	Stage 2 HT ($n = 359$)	*P* for trend
Cardiovascular disease						
Age and sex-adjusted HR	1.00	1.58 (1.11–2.25)	1.69 (1.19–2.40)	1.92 (1.39–2.65)	3.04 (2.17–4.25)	<0.001
Multivariate-adjusted HR	1.00	1.58 (1.11–2.26)	1.70 (1.18–2.44)	1.93 (1.37–2.72)	2.78 (1.93–4.01)	<0.001
PAF (%)		6.2 (1.3–10.9)	7.0 (2.1–11.7)	13.6 (6.9–19.8)	16.5 (11.0–21.7)	
Stroke						
Age and sex-adjusted HR	1.00	1.80 (1.15–2.81)	2.05 (1.31–3.19)	2.44 (1.62–3.69)	3.54 (2.31–5.44)	<0.001
Multivariate-adjusted HR	1.00	1.79 (1.14–2.82)	2.05 (1.30–3.24)	2.44 (1.59–3.75)	3.21 (2.03–5.08)	<0.001
PAF (%)		7.2 (1.5–12.6)	8.9 (3.2–14.3)	17.8 (10.0–24.9)	17.8 (11.3–23.9)	
Ischaemic stroke						
Age and sex-adjusted HR	1.00	1.57 (0.94–2.61)	1.76 (1.06–2.92)	1.99 (1.25–3.17)	2.27 (1.37–3.75)	<0.001
Multivariate-adjusted HR	1.00	1.48 (0.88–2.49)	1.63 (0.97–2.73)	1.80 (1.10–2.94)	1.77 (1.02–3.05)	0.03
PAF (%)		5.5 (−1.9 to 12.3)	7.0 (−0.6 to 14.1)	13.8 (2.8–23.5)	9.6 (0.7–17.7)	
Haemorrhagic stroke						
Age and sex-adjusted HR	1.00	2.74 (1.05–7.15)	3.18 (1.22–8.31)	4.38 (1.79–10.74)	10.06 (4.13–24.53)	<0.001
Multivariate-adjusted HR	1.00	2.96 (1.13–7.74)	3.76 (1.42–9.98)	5.26 (2.10–13.18)	11.97 (4.73–30.32)	<0.001
PAF (%)		10.1 (0.8–18.4)	11.2 (2.4–19.1)	22.9 (11.3–32.9)	31.9 (20.6–41.6)	
Coronary heart disease						
Age and sex-adjusted HR	1.00	1.27 (0.76–2.14)	1.17 (0.69–1.99)	1.42 (0.88–2.29)	2.28 (1.40–3.72)	0.002
Multivariate-adjusted HR	1.00	1.23 (0.72–2.10)	1.11 (0.64–1.94)	1.35 (0.81–2.25)	1.97 (1.14–3.41)	0.02
PAF (%)		3.2 (−6.5 to 8.9)	1.6 (−8.8 to 7.5)	7.2 (−5.3 to 18.1)	12.6 (2.8–21.5)	

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses were adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

TABLE 4. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories in participants without antihypertensive medication, 1988–2007

	Blood pressure category					
		Prehypertension				
Endpoint	Normal BP (n = 642)	Lower range (n = 510)	Higher range (n = 388)	Stage 1 HT (n = 474)	Stage 2 HT (n = 227)	P for trend
Cardiovascular disease						
No. of events	47	67	64	92	70	
Age and sex-adjusted HR	1.00	1.67 (1.15–2.42)	1.83 (1.26–2.67)	2.03 (1.42–2.89)	3.41 (2.33–4.98)	<0.001
Multivariate-adjusted HR	1.00	1.72 (1.17–2.51)	1.85 (1.25–2.74)	2.06 (1.42–3.01)	3.31 (2.19–4.99)	<0.001
PAF (%)		8.2 (2.3–13.8)	8.7 (3.0–14.0)	13.9 (6.9–20.4)	14.4 (9.2–19.3)	
Stroke						
No. of events	29	44	42	65	50	
Age and sex-adjusted HR	1.00	1.78 (1.16–2.85)	1.99 (1.24–3.20)	2.38 (1.53–3.71)	4.02 (2.51–6.43)	<0.001
Multivariate-adjusted HR	1.00	1.81 (1.13–2.91)	2.00 (1.22–3.25)	2.41 (1.52–3.83)	3.82 (2.31–6.32)	<0.001
PAF (%)		8.6 (1.5–15.1)	9.1 (2.4–15.3)	16.5 (8.1–24.2)	16.0 (9.7–22.0)	
Ischaemic stroke						
No. of events	23	31	32	47	25	
Age and sex-adjusted HR	1.00	1.56 (0.91–2.68)	1.83 (1.07–3.14)	2.01 (1.21–3.34)	2.23 (1.25–4.00)	0.003
Multivariate-adjusted HR	1.00	1.54 (0.89–2.65)	1.69 (0.97–2.95)	1.84 (1.07–3.14)	1.84 (0.98–3.45)	0.04
PAF (%)		6.8 (−2.3 to 15.1)	8.3 (−0.8 to 16.5)	13.5 (1.8–23.9)	7.2 (−0.5 to 14.4)	
Haemorrhagic stroke						
No. of events	6	13	10	18	25	
Age and sex-adjusted HR	1.00	2.63 (1.00–6.94)	2.51 (0.91–6.93)	3.75 (1.48–9.55)	12.37 (4.99–30.66)	<0.001
Multivariate-adjusted HR	1.00	2.83 (1.07–7.51)	3.00 (1.07–8.45)	4.60 (1.76–11.99)	15.28 (5.88–39.74)	<0.001
PAF (%)		11.7 (0.3–21.8)	9.3 (−0.4 to 17.9)	19.6 (7.1–30.3)	32.4 (19.9–43.1)	
Coronary heart disease						
No. of events	22	27	27	37	25	
Age and sex-adjusted HR	1.00	1.34 (0.76–2.35)	1.51 (0.86–2.65)	1.55 (0.91–2.63)	2.34 (1.31–4.20)	0.008
Multivariate-adjusted HR	1.00	1.38 (0.77–2.46)	1.46 (0.80–2.65)	1.47 (0.83–2.62)	2.25 (1.19–4.28)	0.03
PAF (%)		5.3 (−4.8 to 14.5)	6.1 (−4.0 to 15.3)	8.6 (−4.4 to 20.0)	10.1 (1.7–17.7)	

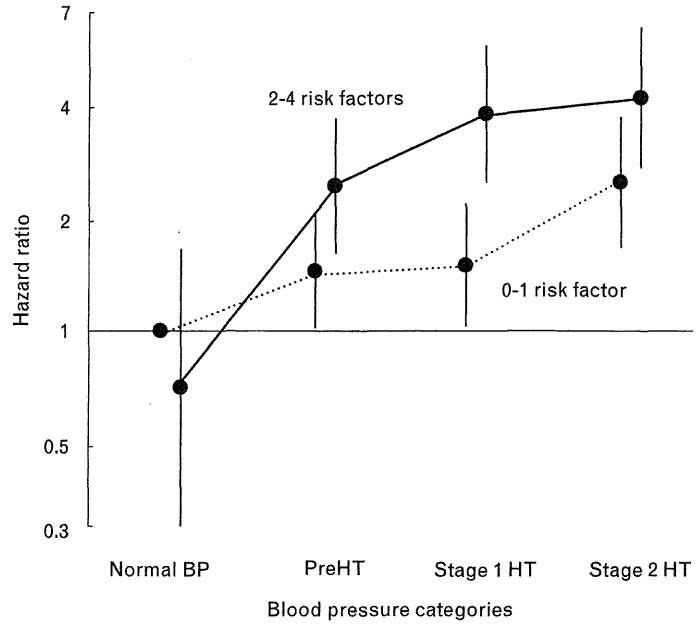
Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses are adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

Japan Public Health Center-based Prospective (JPHC) Study have demonstrated clear associations between BP and stroke incidence, with significant increase from the lower range of prehypertension [6,24]. The Suita Study has also reported that both higher and lower ranges of prehypertension were associated with increased risks of stroke and total CVD among Japanese men [25]. The present analysis from the Hisayama Study confirmed the hypothesis generated from previous cohort studies that prehypertension is not innocent even in the lower range of 120–129/80–84 mmHg, and that this level of BP definitely promotes systemic arteriosclerosis, resulting in incident stroke, coronary heart disease, and other manifestations of cardiovascular events. These findings could also be supported by our previous findings that prehypertension increased the risk of renal arteriosclerosis and arteriolar hyalinosis in an autopsy series of Hisayama residents [26].

In the present study, the highest risks of CVD were observed among patients with stage 1 and 2 hypertension. The third highest risk was among patients with higher range of prehypertension, and the fourth highest among those with lower range of prehypertension. These findings are directly in line with the results of large-scale cohort studies [6,24,25]. They confirm that the risks of CVD is slightly higher among patients with higher range of prehypertension than among those with lower range of prehypertension and support the European and Japanese guidelines for management of hypertension [27,28] which distinguish these two groups as high-normal and normal BP.

In the present analysis, the prevalence of prehypertension was as high as 38% of the total population. As a result, the PAF of prehypertension for development of CVD was similar to those of stage 1 and 2 hypertension. This finding is compatible with the results of several other cohort studies [6,25]. These results suggest that approximately one-third of the burden of excess CVD attributable to elevated BP levels comes from prehypertension. Therefore, in order to reduce the enormous burden of CVD, a high-risk strategy to treat patients with hypertension should be complemented with population strategies to lower BP levels which include lifestyle modifications such as weight loss in the overweight, physical activity, moderation of alcohol intake, a diet with increased fresh fruit and vegetables and reduced saturated fat content, reduction of dietary sodium intake, and increased dietary potassium intake [1,27,28].

Another important finding from the present analysis of the Hisayama Study is that the effects of prehypertension on the risks of CVD were larger among 'high-risk' participants with multiple cardiovascular risk factors than among 'lower-risk' participants with only a few risk factors. Furthermore, the risk of CVD among these 'high-risk' participants with prehypertension was equivalent to that among participants with stage 2 hypertension who have only a few risk factors. Therefore, a pharmaceutical



N of events/person-years				
0-1 risk factor	47/9785	107/13 142	81/7315	66/3122
2-4 risk factors	6/1363	46/2954	46/1760	50/1300

FIGURE 2 Multivariate-adjusted hazard ratios for cardiovascular disease according to blood pressure categories and the number of risk factors. Risk factors included diabetes, hypercholesterolaemia, smoking, and chronic kidney disease. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. Hazard ratios were adjusted for age, sex, body mass index, high-density lipoprotein cholesterol, electrocardiogram abnormalities, drinking, and regular exercise. $P=0.04$ for heterogeneity in the effects of blood pressure categories between participants groups defined by the number of risk factors.

treatment to lower BP may be necessary for participants with prehypertension who are at high risk of CVD as well as for hypertensive patients. In fact, several randomized controlled trials of BP-lowering have demonstrated that patients with high cardiovascular risk benefit from BP-lowering treatment regardless of whether they were hypertensive or not [29–32]. These findings support the concept of treating patients with high cardiovascular risk who have BP levels of prehypertension, which is recommended by current national and international guidelines [27,28].

The strengths of our study include its longitudinal population-based study design, no true loss to follow-up for a long period, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD subtypes. In contrast, the present study was limited by the fact that BP was only measured at baseline and that BP during the follow-up period was not considered for the analysis. However, this limitation is not likely to invalidate the findings observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of the true relationship. The participants of the present analysis were leaner compared to more westernized populations that exist today. Further studies are required to determine whether the findings obtained from the present study are applicable to more westernized populations.

In conclusion the present study confirmed the strong and continuous associations between BP levels and the incidence of CVD in a general Japanese population. The lowest incidence of CVD was observed among individuals with normal BP, and even a slight increase in BP (e.g. lower range of prehypertension) was associated with significantly higher risks of CVD. Approximately one-third of excess CVD events attributable to elevated BP were likely to occur among individuals without hypertension. These results support the current guidelines for management of hypertension which recommend lifestyle modification with/without BP-lowering agents for moderate to high-risk patients with prehypertension as well as hypertensive patients [1,27,28].

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Conflicts of interest

There are no conflicts of interest.

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