Low Systolic Blood Pressure and Vascular Mortality Among More Than 1 Million Korean Adults

Sang-Wook Yi, MD, PhD; Yejin Mok, PhD; Heechoul Ohrr, MD, PhD; Jee-Jeon Yi, PhD; Young Duk Yun, MD; Jihwan Park, BA; Sun Ha Jee, PhD

Background—The association between low systolic blood pressure (SBP) and vascular disease is unclear, especially in nonclinical populations.

Methods and Results—We studied 1 235 246 individuals who participated in routine medical examinations between 1992 and 1995. The hazard ratios (HRs) were adjusted for potential confounders. During 22.7 million person-years of follow-up, 34 816 individuals died of atherosclerotic vascular diseases. An increase in SBP was directly related to an increase in vascular mortality at SBP above ≈100 mmHg. The group with the lowest SBP (<90 mm Hg) had a higher HR for mortality from atherosclerotic vascular disease (HR, 1.53; 95% confidence interval, 1.15–2.03) in comparison with those with an SBP of 90 to 99 mm Hg. The HR associated with the lowest SBP was 2.54 (95% confidence interval, 1.51–4.29) for ischemic heart disease and 1.21 (95% confidence interval, 0.79–1.85) for stroke. Regarding stroke subtype, mortality from hemorrhagic stroke (HR per 10 mm Hg increase, 0.53; 95% confidence interval, 0.29–0.96), rather than mortality from ischemic stroke (HR per 10 mm Hg increase, 1.00; 95% confidence interval, 0.51–1.97), was inversely associated with SBP when SBP fell to <100 mm Hg. Even when excluding the first 5 years of follow-up, the HRs associated with the lowest SBP did not decrease. The inverse association between SBP and vascular mortality in the range <100 mm Hg tended to be apparent in people aged 60 to 95 years in comparison with individuals aged 30 to 59 years.

Conclusions—J-curve associations exist between SBP and vascular mortality, which reach a nadir at ≈100 mm Hg. SBP of <90 mm Hg may portend death from vascular disease, particularly from ischemic heart disease. **(*Circulation*. 2016;133:2381-2390. DOI: 10.1161/CIRCULATIONAHA.115.020752.)**

Key Words: blood pressure ■ cohort studies ■ hypotension ■ mortality ■ vascular diseases

Blood pressure (BP) has been reported to be directly related to mortality from vascular disease down to at least 115/75 mm Hg with no clear threshold level.[1] Evidence from previous research suggests that low BP is a predictor of mortality in various clinical settings, and J- or U-curve associations between BP and vascular mortality have been reported among the elderly and those with vascular or other diseases.[2–9] Low BP, even a single incidence of isolated hypotensive BP in certain situations, can predict mortality,[10] but despite the evidence, physicians often ignore low BP.[10,11] There is no doubt, however, that a J-curve association between BP and mortality exists, even in the general population with no known comorbid diseases, because adequate perfusion to vital organs is difficult to sustain below a certain BP. In nonclinical populations, a few studies have found that low BP was associated with a higher mortality from vascular disease.[12–14] However, it is unclear whether and in what range of BP a J-curve occurs. We conducted a large prospective cohort study with >1 million participants to demonstrate whether a J-curve association exists between systolic BP (SBP) and mortality from vascular disease in a nonclinical population. We focused on SBP, because SBP has been shown to be a better predictor of mortality from vascular disease than diastolic BP (DBP) or pulse pressure in prospective studies among the general population.[1,15,16]

Clinical Perspective on p 2390

Methods

Study Participants

The Korean Cancer Prevention Study comprises 1 329 525 individuals (482 618 women) aged 30 to 95 years who underwent at least 1 routine medical examination by the Korean Medical Insurance Corporation

Received July 15, 2015; accepted April 19, 2016.

From Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Gangneung, Gangwon-do, Republic of Korea (S.-W.Y,); Institute for Clinical and Translational Research, Catholic Kwandong University, Gangneung, Gangwon-do, Republic of Korea (S.-W.Y,); Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea (Y.M., S.H.J.); Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea (Y.M., S.H.J.); Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea (H.O.); Institute for Occupational and Environmental Health, Catholic Kwandong University, Republic of Korea (J.-J.Y.); National Health Insurance Service, Wonju, Republic of Korea (Y.D.Y.); and Department of Applied Statistics, Graduate School, Yonsei University, Seoul, Republic of Korea (J.P.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.020752/-/DC1.

Correspondence to Sun Ha Jee, PhD, Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, Republic of Korea. E-mail jsunha@yuhs.ac

(a former branch of the National Health Insurance Service) between 1992 and 1995.[17–19] For participants who underwent ≥2 examinations, data from the first examination were used. Approximately 96% of South Koreans are covered by the National Health Insurance Service, through which all Korean citizens are eligible to participate in regular health examinations. Six hundred ninety-six individuals who died during the year of enrollment were dropped from the sample. Other participants that were excluded consisted of 43 411 individuals whose records were missing information on body mass index (BMI), alcohol intake, blood pressure, fasting blood glucose levels, or total cholesterol levels; 49 483 persons who self-reported having cancer, liver disease, cardiovascular diseases (hypertension, heart disease, or stroke), or a respiratory disease at or before the baseline survey; and 689 persons with an extremely low BMI (<15.0 kg/m^2) or an extremely short stature (≤1.3 m). Thus, 1 235 246 individuals (445 239 women) were finally included in the study. The institutional review boards of Yonsei University and the Johns Hopkins University Bloomberg School of Public Health approved the study.

Data Collection

All participants underwent medical examinations at local hospitals. A standard mercury sphygmomanometer was used to measure BP in a seated position, and the SBP and DBP were measured as the first and fifth Korotkoff sounds, respectively. Total cholesterol and glucose levels were assayed from a fasting serum specimen, and each participating hospital in the examination had external quality control procedures that were supervised by the Korean Association of Laboratory Quality Control. The status of cigarette smoking (never, former, current), alcohol intake (grams of ethanol per day), and current participation in physical exercise (yes or no) were also collected by using self-reported questionnaires. Height and weight were measured while the participants wore light clothing without shoes, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Follow-Up and Outcomes

Mortality of participants from 1993 through December 31, 2012 was confirmed with death records from the National Statistical Office of Korea.[20] The follow-up was performed through record linkage at the national level and was complete. The main outcomes for this study were death from atherosclerotic vascular diseases (I10–I15 [hypertensive diseases], I20–I25, I44–I52, I60–I69, I70–I74 [diseases of arteries], R96 [other sudden death with cause unknown]), ischemic heart diseases (I20–I25), total stroke (I60–I69), hemorrhagic stroke (I60–I62), and ischemic stroke (I63), as defined by the *International Classification of Diseases, Tenth Revision*. More details of the diseases for each *International Classification of Diseases, Tenth Revision* code are presented in Table I in the online-only Data Supplement.

Statistical Analysis

SBP was classified into 8 groups (mm Hg <90 [range, 60–89], 90–99 [reference group], 100–109, 110–119, 120–139, 140–159, 160–179, and ≥180 [range, 180–290]). The SBP category with the lowest vascular risk was used as the referent group. χ^2 tests and 1-way analysis of variance were performed to compare the differences between SBP groups.

Cox proportional hazards models were used to evaluate the association between SBP at baseline and mortality, and the analyses were adjusted for the following covariates: age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/d; 0, 1–20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous). The HRs of restricted cubic spline transformation of continuous confounders with 3 knots (5th, 50th, and 95th percentiles) with death from atherosclerotic vascular disease were plotted (Figure I in the online-only Data Supplement). DBP was adjusted for as a continuous variable by using restricted cubic splines with 5 knots (50, 60, 70, 80, and 90 mm Hg) to examine whether the effects of SBP are independent of those of DBP. HRs of restricted cubic spline transformation of SBP with 5 knots (80, 90, 100, 110, and 120 mm Hg) and 90 mm Hg as a reference were also plotted. The nonlinear associations of SBP with vascular mortality were assessed with a likelihood ratio test, in which we compared the model with only the linear term with the model with both the linear and the cubic spline terms.

A stratified analysis was performed according to age at entry (≥60 or <60 years) to examine whether association varied according to age group.[1,13,21] Sex-stratified analysis was also done. In additional analyses, we excluded all deaths (n=23 372) that had occurred in the first 5 years of follow-up.[12] These analyses ensured sensitivity in our results. The interaction of age or sex with SBP on mortality was assessed by including an interaction term (age × SBP or sex × SBP) in the analysis stratified by SBP (<100 or ≥100 mm Hg), assuming a linear inverse association at <100 mm Hg and a linear positive association at ≥100 mm Hg. Proportional assumption was tested by using Schoenfeld residuals. The survival curve according to SBP was plotted using the life-table method (Figure II in the online-only Data Supplement).

Two-sided *P* values were calculated, and the statistical significance level was set at 0.05. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

A total of 154 882 deaths (crude death rate, 683 deaths per 100 000 person-years) occurred during 22 674 299 person-years (mean, 18.4 person-years) of follow-up, and of these, 34 816 died of atherosclerotic vascular diseases (154 deaths per 100 000 person-years). At enrollment, the mean (standard deviation) age was 46.6 (11.6) years, and the mean SBP was 123.4 (17.2) mm Hg (Table 1). Participants with SBP <90 mm Hg tended to be women and had the lowest levels of DBP, total cholesterol, fasting glucose, and BMI of all SBP groups. They were also older than those with SBPs of 90 to 139 mm Hg (Table II in the online-only Data Supplement). The proportion of current smokers and current drinkers was highest in individuals with SBPs of 120 to 139 mm Hg.

Both low and high SBPs were associated with higher atherosclerotic vascular mortality (Figures 1 and 2), and the lowest atherosclerotic vascular mortality was associated with an SBP of 90 to 109 mm Hg, which rose thereafter as the SBP increased; the mortality was also higher in those with an SBP <90 mm Hg (hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.15–2.03; Table 2). The HR associated with an SBP below 90 mm Hg, in comparison with 90 to 99 mm Hg, was 2.54 (95% CI, 1.51–4.29) for ischemic heart disease, and 1.21 (95% CI, 0.79–1.86) for stroke. Among stroke subtypes, the HR associated with an SBP <90 mm Hg was 1.64 for hemorrhagic stroke mortality and 0.76 for ischemic stroke mortality.

After exclusion of the first 5 years of follow-up, the association between the lowest SBP group and vascular mortality did not weaken (Figure III in the online-only Data Supplement). When DBP (restricted cubic splines with 5 knots at 50, 60, 70, 80, and 90 mm Hg), and restricted cubic splines of continuous confounders (age, total cholesterol, BMI, and fasting glucose) with 3 knots at the 5th, 50th, and 95th percentile of each variable were added, the observed associations with low SBP were generally unchanged (Figure IV in the online-only Data Supplement).

When stratified by age group, higher HRs associated with the lowest SBP for atherosclerotic vascular mortality and ischemic heart disease in comparison with the reference

Table 1. Baseline Characteristics of Participants

Variables	n (%)
Person-years, person-year (%)	22 674 299 (100.0)
Age, mean (SD), y	46.6 (11.6)
SBP, mean (SD), mm Hg	123.4 (17.2)
DBP, mean (SD), mm Hg	80.0 (11.7)
BMI, mean (SD), kg/m^2	23.2 (2.8)
Total cholesterol,* mean (SD), mg/dL	192.4 (38.4)
Fasting glucose,† mean (SD), mg/dL	92.0 (24.7)
Sex	
Women	445 239 (36.0)
Men	790 007 (64.0)
Exercise	
No	934 474 (75.7)
Yes	300 772 (24.5)
Smoking	
Current smoker	483 708 (39.2)
Never smoker	581 615 (47.1)
Past smoker	169 923 (13.8)
Drinking, g ethanol/d	
0	565 743 (45.8)
1–19	440 644 (35.7)
≥20	228 859 (18.5)
SBP, mm Hg‡	
<90	1862 (0.2)
90–99	21 414 (1.7)
100–109	107 283 (8.7)
110–119	283 313 (22.9)
120–139	573 091 (46.4)
140–159	186 067 (15.1)
160–179	47 204 (3.8)
≥180	15 012 (1.2)

BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SD, standard deviation.

*To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

†To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259.

‡The range of the lowest and highest SBP groups was 60–89 mm Hg and 180–290 mm Hg, respectively.

were statistically significant in older participants aged 60 to 95 years, but not in younger participants aged 30 to 59 years (Figure 3, Figures V and VI in the online-only Data Supplement, Table III in the online-only Data Supplement). In addition, in stratified analyses by SBP assuming linear associations (Tables IV through VI in the online-only Data Supplement), in the range <100 mm Hg, HR of atherosclerotic vascular mortality for each 10 mm Hg increase in SBP was 0.65 (95% CI, 0.50–0.84) and 0.89 (95% CI, 0.53–1.49), respectively, in participants aged 60 to 95 years versus those aged 30 to 59 years (Figure 4, Table V in the online-only Data Supplement). However, when interactions between age and SBP were evaluated by using interaction terms of age and SBP, the *P* value was >0.05 for each type of vascular mortality given an SBP <100 mm Hg. In individuals aged 60 to 95 years, and in those aged 30 to 59 years, as well, vascular mortality increased as SBP increased to >90 to 99 mm Hg, and the association between high SBP and vascular mortality was greater among individuals <60 years than it was among those aged 60 to 95 years. The *P* values for the linear interaction between age and SBP were <0.001 for vascular mortality given an SBP of 100 to 290 mm Hg.

In analyses stratified by sex, the HRs associated with the lowest SBP for atherosclerotic vascular diseases were 1.63 (95% CI, 1.13–2.34) in women and 1.37 (95% CI, 0.87–2.14) in men (Figures VII through IX in the online-only Data Supplement, Table VII in the online-only Data Supplement). However, *P* values of linear interaction between men and women in the range <100 mm Hg were generally >0.05 (Table VI in the online-only Data Supplement).

We tested the proportional assumption and found no evidence of a violation of the proportional assumption for the dummy variable of SBP <90 mm Hg for any cause of vascular mortality. However, evidence indicated that several variables including several dummy SBP variables may have nonproportional HRs over the follow-up time period. For such variables, analysis was done by stratifying according to the variables (not dummy SBP variables such as alcohol consumption and exercise). In addition, time-dependent covariables for dummy SBP variables (which were generated using the Model Statement of the PROC PHREG procedure) were included to address nonproportionality.[22] In addition, we analyzed individuals who survived as of January 1, 2003 to examine whether the association of SBP in 2003 to 2012 was different from that during the entire follow-up period (1993–2012). The associations with low SBP were unchanged (Figure X in the online-only Data Supplement).

Discussion

Investigation of a healthy Korean population without known preexisting illnesses exhibited J-curve associations between SBP and death from atherosclerotic vascular diseases, with a nadir at 90 to 109 mm Hg for vascular mortality. An SBP <90 mm Hg was associated with ≈50% higher mortality from atherosclerotic vascular disease, especially ischemic heart disease (≈150% higher mortality), in comparison with an SBP of 90 to 99 mm Hg.

Association Between Low SBP and Vascular Mortality

This study revealed that SBPs <90 mm Hg are related to an increased risk of vascular mortality. The majority of previous reports on the J-curve association between BP and vascular mortality studied clinical patients with vascular disease,[2–6,9,23] and, although similar findings have been reported in Korean nonclinical populations, those results are limited by a small number of deaths in the lowest SBP categories and the self-reported nature of BP measurements.[13,14] The current study clearly showed that J-curve associations exist between SBP and vascular mortality, especially mortality from ischemic heart disease, in Korean adults.

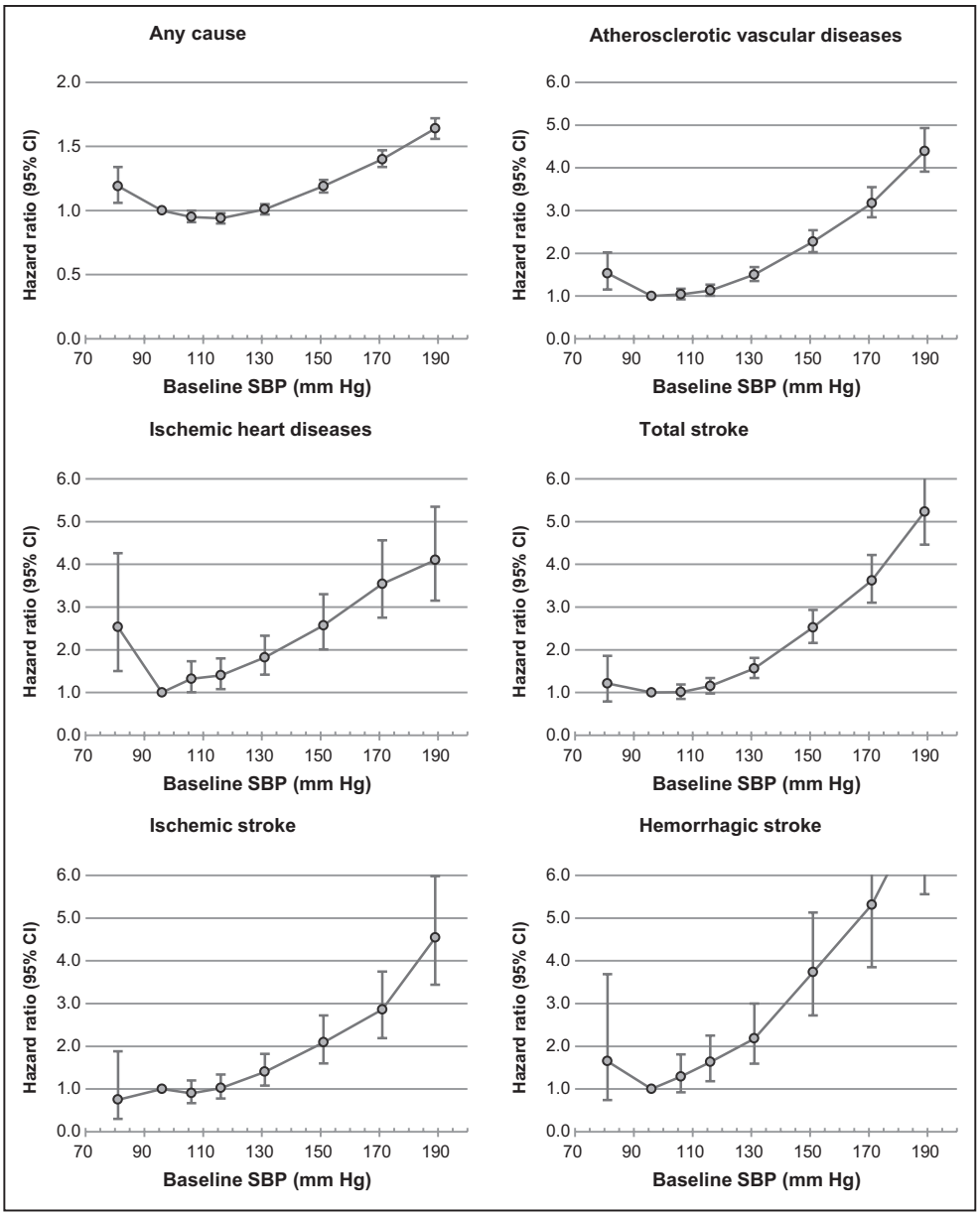


Figure 1. Sex- and age-adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group. Eight categories of SBP (reference, 90–99 mm Hg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. A different *y*-axis scale was used for all-cause mortality and vascular mortality. CI indicates confidence interval.

However, these associations do not guarantee a causal relationship. It is possible that a low SBP could be a consequence of concurrent frailty or chronic disease, even though the participants in our study constituted a nonclinical population with no known preexisting diseases, such as cancer, heart disease, or stroke. Furthermore, the population of the current study was generally healthier than the average Korean population.[17] Because individuals with underlying conditions who have a low SBP, even if undiagnosed at the time of study entry, may die prematurely, we additionally excluded patients who died during the first 5 years of follow-up. After such exclusion, the relative risk of mortality associated with low SBP increased, albeit modestly, relative to those of the main analysis. Therefore, reverse causality may not be solely responsible for the association between low SBP and death from vascular disease. However, because a comprehensive cardiovascular evaluation was not conducted for each participant, the possibility of some of the participants with the lowest SBP having undiagnosed cardiovascular disease and taking BP-lowering medications cannot be completely ruled out.

Second, in recent studies involving individuals with various diseases, index event bias (or collider-stratification bias) has been suggested as an explanation for the seemingly paradoxical associations.[4,24–26] This study included healthy individuals without evident cardiovascular diseases[24–26] and adjusted for most major risk factors for vascular disease[4]; thus, the observed associations are unlikely to be the result of this type of selection bias. When further analysis that included

Table 2. Multivariable Adjusted* HRs for All-Cause and Cardiovascular Mortality by SBP Group

Causes of Death (ICD-10)	SBP Groups, mm Hg	No. of Deaths	Death Rate†	*P* Value	HR	(95% CI)
Any cause	<90	302	931	0.007	1.18	(1.05–1.33)
	90–99	2253	580		1.00	(Reference)
	100–109	8963	449	0.122	0.96	(0.92–1.01)
	110–119	22 693	426	0.075	0.96	(0.92–1.00)
	120–139	63 011	592	0.023	1.05	(1.01–1.10)
	140–159	37 636	1148	<0.001	1.25	(1.19–1.30)
	160–179	14 368	1852	<0.001	1.48	(1.42–1.55)
	≥180	5656	2422	<0.001	1.73	(1.65–1.82)
Atherosclerotic vascular diseases (I10–I15, I20–I25, I44–I52, I60–I69, I70–I74, R96)	<90	57	176	0.003	1.53	(1.15–2.03)
	90–99	326	84		1.00	(Reference)
	100–109	1355	68	0.525	1.04	(0.92–1.17)
	110–119	3631	68	0.035	1.13	(1.01–1.27)
	120–139	12 474	117	<0.001	1.50	(1.34–1.67)
	140–159	10 012	305	<0.001	2.25	(2.01–2.51)
	160–179	4706	606	<0.001	3.13	(2.8–3.5)
	≥180	2255	966	<0.001	4.30	(3.83–4.84)
Ischemic heart diseases (I20–I25)	<90	18	55	<0.001	2.54	(1.51–4.29)
	90–99	64	16		1.00	(Reference)
	100–109	357	18	0.052	1.30	(1–1.7)
	110–119	975	18	0.020	1.35	(1.05–1.74)
	120–139	3254	31	<0.001	1.71	(1.34–2.2)
	140–159	2306	70	<0.001	2.35	(1.83–3.02)
	160–179	1009	130	<0.001	3.19	(2.47–4.11)
	≥180	391	167	<0.001	3.63	(2.78–4.74)
Total stroke (I60–I69)	<90	24	74	0.384	1.21	(0.79–1.85)
	90–99	172	44		1.00	(Reference)
	100–109	683	34	0.908	1.01	(0.85–1.19)
	110–119	1897	36	0.068	1.16	(0.99–1.35)
	120–139	6668	63	<0.001	1.58	(1.36–1.84)
	140–159	5807	177	<0.001	2.55	(2.19–2.97)
	160–179	2848	367	<0.001	3.66	(3.14–4.27)
	≥180	1439	616	<0.001	5.28	(4.5–6.19)
Ischemic stroke (I63)	<90	5	15	0.557	0.76	(0.31–1.9)
	90–99	57	15		1.00	(Reference)
	100–109	197	10	0.427	0.89	(0.66–1.19)
	110–119	535	10	0.984	1.00	(0.76–1.32)
	120–139	1949	18	0.022	1.36	(1.05–1.77)
	140–159	1650	50	<0.001	1.99	(1.53–2.6)
	160–179	788	102	<0.001	2.70	(2.06–3.54)
	≥180	442	189	<0.001	4.23	(3.2–5.58)
Hemorrhagic stroke (I60–I62)	<90	7	22	0.230	1.64	(0.73–3.66)
	90–99	39	10		1.00	(Reference)
	100–109	212	11	0.128	1.30	(0.93–1.84)

(*Continued*)

Table 2. Continued

Causes of Death (ICD-10)	SBP Groups, mm Hg	No. of Deaths	Death Rate†	*P* Value	HR	(95% CI)
	110–119	678	13	0.002	1.66	(1.2–2.3)
	120–139	2207	21	<0.001	2.26	(1.64–3.1)
	140–159	1778	54	<0.001	3.90	(2.84–5.36)
	160–179	799	103	<0.001	5.57	(4.03–7.7)
	≥180	392	168	<0.001	8.14	(5.85–11.33)

CI indicates confidence interval; HR, hazard ratio; ICD-10, *International Classification of Diseases, 10th Revision*; and SBP, systolic blood pressure.

*Adjustment for age at entry (continuous), sex, smoking status (never, former, current smoker), alcohol intake (g/d; 0, 1–20, >20), physical activity (yes, no), total cholesterol (mg/dL; continuous), fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

†Crude death rate per 100 000 person-years

participants with preexisting diseases, with no conditioning on the manifest cardiovascular disease status (namely, no adjustment for disease status), was done to minimize collider-stratification bias and increase generalizability,[24,26] the association between vascular mortality and low SBP did not weaken (Figure XI in the online-only Data Supplement). Meanwhile, in additional analysis among people with known preexisting cardiovascular diseases (n=15 277), the inverse association in the low-SBP range was stronger than that in the healthy population (Figure XII in the online-only Data Supplement).

Third, a wide pulse pressure, rather than a low DBP, has been suggested as 1 possible explanation for the J-curve associations.[27] Because our study analyzed the SBP, where the wide pulse pressure hypothesis is irrelevant, and the associations with low SBP were maintained after additional adjustment for pulse pressure in the current study, and in previous research, as well,[2,5] a wide pulse pressure cannot explain the J-curve associations between SBP and vascular mortality.

The findings of a strong association of low SBP with death from ischemic heart disease and a weak association with death from stroke are consistent with the results of previous research conducted on individuals with vascular disease,[2,4–6] and on the nonclinical populations, as well.[13,14] However, the association observed between low SBP and stroke mortality, for example, the inverse association of SBP <100 mm Hg in people aged 60 to 95 years, may conflict with the results of previous research.[2,4,6] This inconsistency may be mainly attributable to the differences in the subtype of stroke common to Korean populations versus European populations. According to Korean national mortality statistics, hemorrhagic stroke was a leading subtype of stroke mortality up until 2001. In younger populations (eg, those <70 years), the same is true in the present day. Of our participants, more individuals died of hemorrhagic stroke (n=6112) than of ischemic stroke (n=5623). In contrast, ischemic stroke accounts for the majority of strokes in populations of European origin.[28,29] In the current study, the HR associated with an SBP <90 mm Hg was 1.65 (95% CI, 0.74–3.69) for mortality from hemorrhagic stroke, but was 0.75 (95% CI, 0.30–1.88) for ischemic stroke mortality in all participants. In the range <100 mm Hg, each 10 mm Hg increase in SBP was inversely associated with mortality from hemorrhagic stroke (HR, 0.53; 95% CI, 0.29–0.96), but not from ischemic stroke (HR, 1.00; 95% CI, 0.51–1.97).

In addition, the positive association of SBP <90 mm Hg with vascular mortality in comparison with the reference group, and the inverse associations of SBP with vascular mortality in the range <100 mm Hg, were statistically significant in participants aged 60 to 95 years, but not in their younger counterparts, in accordance with previous results.[4,13,14] However, it cannot be stated conclusively that the association in the range <100 mm Hg in people aged 30 to 59 years was different from that in people aged 60 to 95 years, especially for ischemic heart disease mortality, because the *P* values for the interaction between age and SBP were >0.05.

Association of Low DBP and Low Pulse Pressure With Vascular Mortality

In the general population, the associations of DBP and pulse pressure with vascular mortality have been shown to be weaker than the associations of SBP with vascular mortality.[1,15,16] In an additional analysis of our data, there was some evidence to suggest J-curve associations between DBP and atherosclerotic vascular mortality. However, the J-curve associations of DBP per se were weaker than those of SBP, in contrast to several studies on patients with manifest cardiovascular diseases,[2,4] and the associations disappeared or were substantially weakened after adjustment for SBP (Figures XIII through XV in the online-only Data Supplement). Pulse pressure seemed to have no apparent J-curve association with atherosclerotic vascular mortality (Figures XVI and XVII in the online-only Data Supplement).

Potential Mechanisms

An SBP <90 mm Hg may lead to hypoperfusion of the coronary arteries and thus cause cardiac events that then result in death from ischemic heart disease. In cases of ischemic stroke, although a low SBP (<90 mm Hg) may cause a reduction in cognitive performance,[30] it may not be sufficiently low to cause ischemic brain injury because a mean atrial pressure >45 to 50 mm Hg may be sufficient for brain survival.[31] For a hemorrhagic stroke, resulting from the mass effect from hematoma expansion and perihemorrhagic edema, an elevated intracranial pressure can increase the intracranial venous pressure.[32,33] A low SBP that cannot compensate for the increase in venous pressure may result in insufficient perfusion of the brain tissue and subsequent death.[32] Furthermore, systolic hypotension <90 mm Hg is well known to be a poor prognostic factor in patients with traumatic brain injury, which can also cause intracranial hemorrhage.[34] Meanwhile, the mechanisms through which low SBP may cause hemorrhagic stroke are currently unclear.

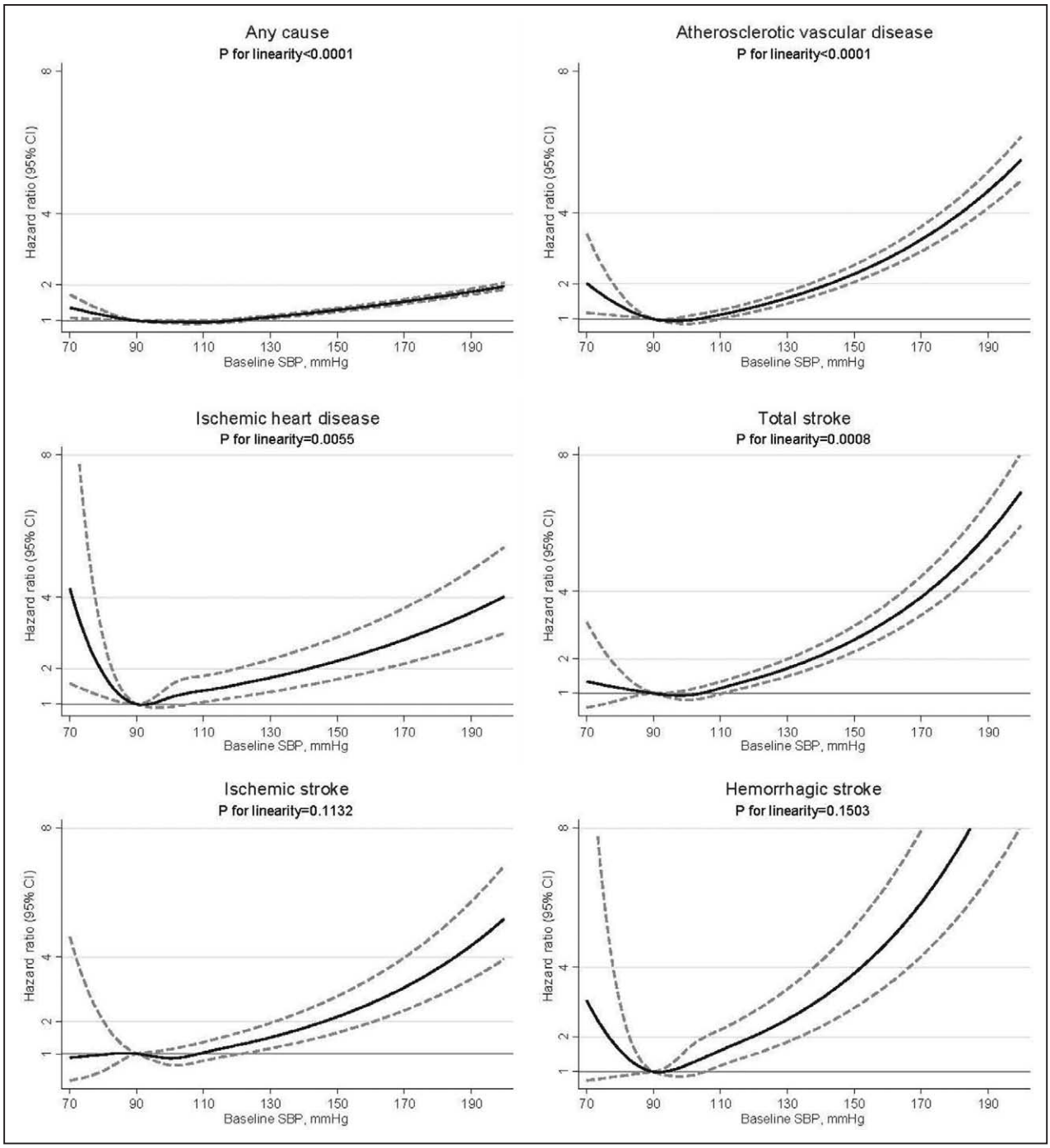


Figure 2. Multivariable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of systolic blood pressure (SBP) with 5 knots (80, 90, 100, 110, and 120 mm Hg) and 90 mm Hg as a reference. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. CI indicates confidence interval.

Strengths and Limitations of This Study

The strengths of this study include its prospective design, a large number of participants, long-term duration, complete follow-up, and a homogeneous ethnic group. It also has several limitations. First, the procedure with which BP measurements were taken for the current study may not be ideal; there are higher published standards for BP research.[35] However, because the potential errors in the BP measurements are mostly likely to be random according to vascular mortality,[36,37] overestimation of the relative risk associated with a low SBP is unlikely to be a major concern. Second, BP was measured only once. Thus, the relative risks associated with SBP may be underestimated in the current study because of a regression dilution bias.[38] Third, the causes of death were not verified independent from national death records. However, in Korea, cause of death on the death certificate was reported to be reasonably valid in comparison with medical records.[20] In addition, because potential misclassification tends not to depend on SBP, this issue is unlikely to cause an overestimation of the risk associated with low SBP.[39] Fourth, despite the large

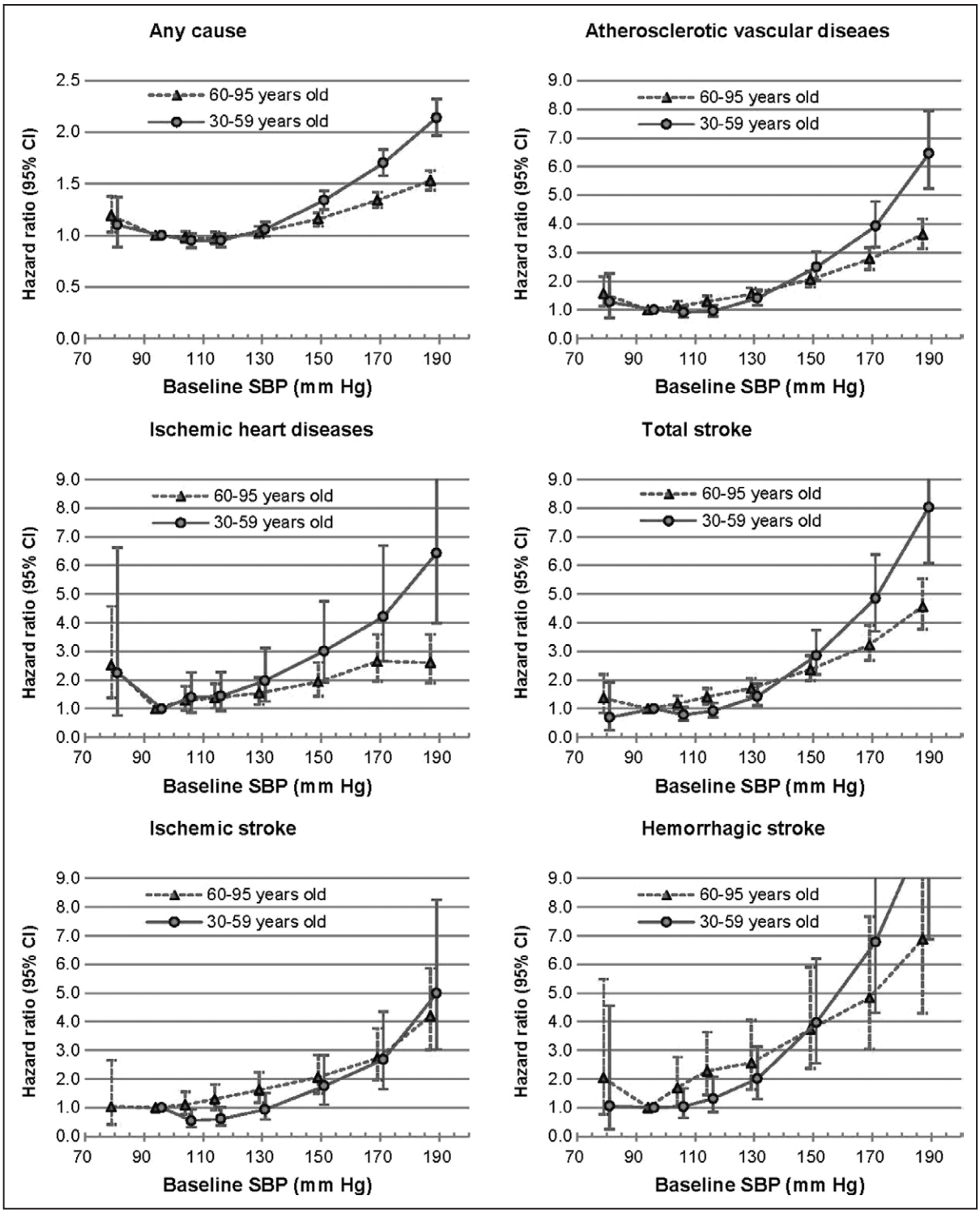


Figure 3. Multivariable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group according to age. Eight categories of SBP (reference, 90–99 mm Hg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. No death was observed from ischemic stroke in persons aged 30 to 59 years with SBP 60 to 89 mm Hg. A different *y*-axis scale was used for all-cause mortality and vascular mortality. The numeric version of this figure is available in Table III in the online-only Data Supplement. CI indicates confidence interval.

number of participants, the number of cause-specific vascular deaths in those with the lowest SBP was small, which may result in a decreased statistical power in some of the analyses. Fifth, given the observational nature of the study, definite causal inference is limited. In addition, although persons with self-reported hypertension, heart disease, stroke, cancer, liver disease, or respiratory disease were excluded from the study, lack of information on several potential confounders such as

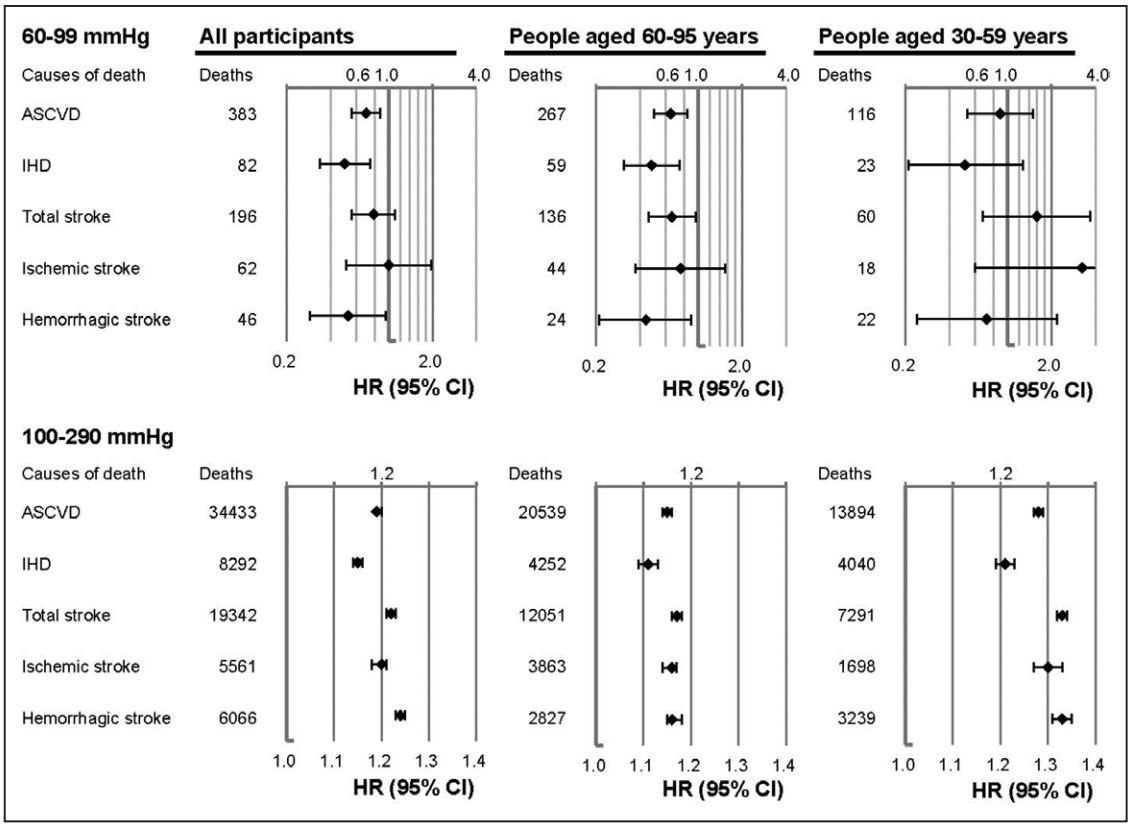


Figure 4. Multivariable adjusted hazard ratios for all-cause and vascular mortality per 10 mm Hg increase in SBP across SBP groups (60–99 and 100–290 mm Hg), stratified by age at entry (60–95 and 30–59 years). Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. The numeric version of this figure is available in Tables IV and V in the online-only Data Supplement. ASCVD indicates atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; and IHD, ischemic heart disease.

BP medication use, and detailed cardiovascular and other disease status, is another limitation. Finally, the generalizability of the findings to the global population may be limited because all participants were Korean. Further research is thus needed to confirm whether this J-curve association exists among other ethnic groups. It is also worth mentioning that our study population is healthier and has a higher socioeconomic status (employees of the government or schools, or their dependents) than the general population in Korea.[17] We do not, however, think that the expected low death rate of a healthier population substantially impacts the association between SBP and vascular mortality.

Conclusion

In healthy Korean adults, a J-curve association exists between SBP and all-cause and vascular mortality. In persons with SBP >100 mm Hg, increases in SBP increase vascular mortality, whereas in persons with SBP <90 mm Hg, decreases in SBP are associated with higher vascular mortality, especially mortality from ischemic heart disease. Death from hemorrhagic stroke may also be associated with low SBP. Therefore, individuals with low SBPs should be clinically followed. Further research is required to confirm this association in other ethnic/regional populations.

Acknowledgments

We thank the staff at the National Health Insurance Service of Korea.

Sources of Funding

This study was funded with a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C2686). The funder had no role in the study design and data collection, in analyzing and interpreting data, or in the decision to submit this work for publication.

Disclosures

None.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
2. Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, LaRosa JC; Treating to New Targets Steering Committee and Investigators. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J*. 2010;31:2897–2908. doi: 10.1093/eurheartj/ehq328.
3. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP; INDANA Project Steering Committee. INdividual Data ANalysis of Antihypertensive intervention. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med*. 2002;136:438–448.
4. Dorresteijn JA, van der Graaf Y, Spiering W, Grobbee DE, Bots ML, Visseren FL; Secondary Manifestations of Arterial Disease Study Group. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. *Hypertension*. 2012;59:14–21. doi: 10.1161/HYPERTENSIONAHA.111.179143.
5. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively

lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006;144:884–893.
6. Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, Schumacher H, Weber M, Böhm M, Williams B, Pogue J, Koon T, Yusuf S; ONTARGET investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens*. 2009;27:1360–1369. doi: 10.1097/HJH.0b013e32832d7370.
7. Rönnback M, Isomaa B, Fagerudd J, Forsblom C, Groop PH, Tuomi T, Groop L; Botnia Study Group. Complex relationship between blood pressure and mortality in type 2 diabetic patients: a follow-up of the Botnia Study. *Hypertension*. 2006;47:168–173. doi: 10.1161/01.HYP.0000199667.30253.b7.
8. Mancia G, Grassi G, Zanchetti A. Antihypertensive treatment and blood pressure in diabetic and nondiabetic patients: the lower, the better? *Diabetes Care*. 2011;34 Suppl 2:S304–S307. doi: 10.2337/dc11-s244.
9. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Systolic blood pressure and mortality after stroke: too low, no go? *Stroke*. 2015;46:1307–1313. doi: 10.1161/STROKEAHA.115.008821.
10. Seamon MJ, Feather C, Smith BP, Kulp H, Gaughan JP, Goldberg AJ. Just one drop: the significance of a single hypotensive blood pressure reading during trauma resuscitations. *J Trauma*. 2010;68:1289–1294; discussion 1294–1295.
11. Arbous MS, Grobbee DE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, Werner FM, Meursing AE. Mortality associated with anaesthesia: a qualitative analysis to identify risk factors. *Anaesthesia*. 2001;56:1141–1153.
12. Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. *Hypertension*. 2005;45:240–245. doi: 10.1161/01.HYP.0000152079.04553.2c.
13. Yi SW, Hong S, Ohrr H. Low systolic blood pressure and mortality from all-cause and vascular diseases among the rural elderly in Korea; Kangwha cohort study. *Medicine (Baltimore)*. 2015;94:e245. doi: 10.1097/MD.0000000000000245.
14. Yi SW, Ohrr H. Low systolic blood pressure and mortality from all causes and vascular diseases among older middle-aged men: Korean Veterans Health Study. *J Prev Med Public Health*. 2015;48:105–110. doi: 10.3961/jpmph.15.003.
15. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:243–250. doi: 10.1161/CIRCULATIONAHA.108.797936.
16. Sull JW, Yi SW, Nam CM, Choi K, Ohrr H. Binge drinking and hypertension on cardiovascular disease mortality in Korean men and women: a Kangwha cohort study. *Stroke*. 2010;41:2157–2162. doi: 10.1161/STROKEAHA.110.586347.
17. Jee SH, Kivimaki M, Kang HC, Park IS, Samet JM, Batty GD. Cardiovascular disease risk factors in relation to suicide mortality in Asia: prospective cohort study of over one million Korean men and women. *Eur Heart J*. 2011;32:2773–2780. doi: 10.1093/eurheartj/ehr229.
18. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst*. 2004;96:1851–1856. doi: 10.1093/jnci/djh334.
19. Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS. Smoking and cancer risk in Korean men and women. *Cancer Causes Control*. 2004;15:341–348. doi: 10.1023/B:CACO.0000027481.48153.97.
20. Won TY, Kang BS, Im TH, Choi HJ. The study of accuracy of death statistics. *J Korean Soc Emerg Med*. 2007;18:256–262.
21. Hakala SM, Tilvis RS, Strandberg TE. Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. *Eur Heart J*. 1997;18:1019–1023.
22. Allison PD. Survival Analysis Using SAS: A Practical Guide, 2nd ed. Cary, NC: SAS Institute; 2010.
23. D'Agostino RB, Belanger AJ, Kannel WB, Cruickshank JM. Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *BMJ*. 1991;303:385–389.
24. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, Poole C. Illustrating bias due to conditioning on a collider. *Int J Epidemiol*. 2010;39:417–420. doi: 10.1093/ije/dyp334.
25. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA*. 2011;305:822–823. doi: 10.1001/jama.2011.163.
26. Lajous M, Bijon A, Fagherazzi G, Boutron-Ruault MC, Balkau B, Clavel-Chapelon F, Hernán MA. Body mass index, diabetes, and mortality in French women: explaining away a "paradox". *Epidemiology*. 2014;25:10–14. doi: 10.1097/EDE.0000000000000031.
27. Kannel WB, Wilson PW, Nam BH, D'Agostino RB, Li J. A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol*. 2004;94:380–384. doi: 10.1016/j.amjcard.2004.04.043.
28. Ayala C, Croft JB, Greenlund KJ, Keenan NL, Donehoo RS, Malarcher AM, Mensah GA. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995-1998. *Stroke*. 2002;33:1197–1201.
29. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol*. 2003;2:43–53.
30. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol*. 2012;2012:367516.
31. McDonald JL. Systolic and mean arterial pressures during manual and mechanical CPR in humans. *Ann Emerg Med*. 1982;11:292–295.
32. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265.
33. Staykov D, Wagner I, Volbers B, Hauer EM, Doerfler A, Schwab S, Bardutzky J. Natural course of perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2011;42:2625–2629. doi: 10.1161/STROKEAHA.111.618611.
34. Fuller G, Hasler RM, Mealing N, Lawrence T, Woodford M, Juni P, Lecky F. The association between admission systolic blood pressure and mortality in significant traumatic brain injury: a multi-centre cohort study. *Injury*. 2014;45:612–617. doi: 10.1016/j.injury.2013.09.008.
35. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111:697–716. doi: 10.1161/01.CIR.0000154900.76284.F6.
36. Hessel PA. Terminal digit preference in blood pressure measurements: effects on epidemiological associations. *Int J Epidemiol*. 1986;15:122–125.
37. Wen SW, Kramer MS, Hoey J, Hanley JA, Usher RH. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *J Clin Epidemiol*. 1993;46:1187–1193.
38. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150:341–353.
39. Yi SW, Odongua N, Nam CM, Sull JW, Ohrr H. Body mass index and stroke mortality by smoking and age at menopause among Korean postmenopausal women. *Stroke*. 2009;40:3428–3435. doi: 10.1161/STROKEAHA.109.555144.

CLINICAL PERSPECTIVE

Physicians often ignore low blood pressure. Previous research suggests that low blood pressure is a predictor of mortality in the elderly and in individuals with vascular or other diseases. However, it is unclear whether and in what range low blood pressure increases the risk of death from any cause and from vascular diseases, especially in healthy general populations. The current prospective cohort study that includes 1 235 246 healthy Korean adults aged 30 to 95 years with 20 years of follow-up demonstrated that low systolic blood pressure (SBP) increases overall and vascular mortality. The association between low SBP (>90 mm Hg) and vascular mortality was prominent for ischemic heart disease, whereas it was weak for total stroke. Death from hemorrhagic stroke may also be related to low SBP. Our study establishes low SBP as a risk factor for death from vascular diseases or any cause in a general population. Therefore, individuals with low SBPs should not be ignored, but should be clinically followed to ensure better health and to minimize death from vascular diseases and other causes.

Low Systolic Blood Pressure and Vascular Mortality Among More Than 1 Million Korean Adults

Sang-Wook Yi, Yejin Mok, Heechoul Ohrr, Jee-Jeon Yi, Young Duk Yun, Jihwan Park and Sun Ha Jee

Circulation. 2016;133:2381-2390; originally published online April 27, 2016;
doi: 10.1161/CIRCULATIONAHA.115.020752
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Low Systolic Blood Pressure and Vascular Mortality among Over One Million Korean adults

Sang-Wook Yi, MD, PhD, Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Republic of Korea; **Yejin Mok**, PhD, Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Republic of Korea; **Heechoul Ohrr**, MD, PhD, Department of Preventive Medicine, Graduate School of Public Health, Yonsei University, Republic of Korea; **Jee-Jeon Yi**, PhD, Institute for Occupational and Environmental Health, Catholic Kwandong University, Republic of Korea; **Young Duk Yun**, MD, National Health Insurance Service, Seoul, Republic of Korea; **Jihwan Park,** BA, Department of Applied Statistics, Graduate School, Yonsei University, Seoul, Republic of Korea; **Sun ha Jee**, PhD, Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Republic of Korea

Supplemental Table 1. ICD-10 code and related diseases analyzed in the study.

ICD-10 code	Diseases
I10-I15	Hypertensive diseases
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension
I20-I25	Ischemic heart diseases
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischemic heart diseases
I25	Chronic ischemic heart disease
I44-I52	other forms of heart disease likely related to atherosclerosis
I44	Atrioventricular and left bundle-branch block
I45	Other conduction disorders
I46	Cardiac arrest
I47	Paroxysmal tachycardia
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I51	Complications and ill-defined descriptions of heart disease
I52	Other heart disorders in diseases classified elsewhere
I60-I69	Total stroke
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequele of cerebrovascular disease
I70-I74	Diseases of arteries
I70	Atherosclerosis

I71	Aortic aneurysm and dissection
I72	Other aneurysm and dissection
I73	Other peripheral vascular diseases
I74	Arterial embolism and thrombosis
R96	Other sudden death, cause unknown

ICD-10, International classification of diseases and related health problems, 10th revision.

Supplemental Table 2. Baseline characteristics and follow-up years by category of systolic blood pressure

	(SBP; mm Hg)	< 90	90-99	100-109	110-119	120-139	140-159	160-179	≥180	
Variables	**Classification**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p-value**
Participants	Number (%)[a]	1,862 (0.2)	21,414 (1.7)	107,283 (8.7)	283,313 (22.9)	573,091 (46.4)	186,067 (15.1)	47,204 (3.8)	15,012 (1.2)	
Person-years	Person-year (%)[a]	32,450 (0.1)	388,778 (1.7)	1,997,605 (8.8)	5,327,718 (23.5)	10,640,094 (46.9)	3,278,231 (14.5)	775,934 (3.4)	233,489 (1.0)	<0.001
Age	Mean (SD), years old	51.2 (11.5)	46.9 (11.8)	44.2 (11.2)	43.5 (10.6)	45.8 (11.1)	51.8 (11.4)	56.7 (10.7)	58.8 (10.3)	<0.001
SBP	Mean (SD), mm Hg	80.3 (3.3)	90.4 (1.5)	100.2 (1.2)	110.1 (0.8)	124.2 (5.0)	143.1 (4.7)	163.4 (4.8)	187.9 (11.8)	<0.001
DBP	Mean (SD), mm Hg	53.8 (7.0)	60.2 (5.2)	65.6 (6.3)	72.0 (5.6)	81.4 (6.9)	90.9 (8.0)	100.8 (10.5)	110.4 (14.1)	<0.001
BMI (kg/m^2)	Mean (SD)	21.7 (2.8)	21.9 (2.7)	22.1 (2.6)	22.6 (2.6)	23.4 (2.7)	24.1 (2.9)	24.4 (3.1)	24.6 (3.2)	<0.001
Total cholesterol[b]	Mean (SD), mg/dL	184.4 (36.1)	184.5 (36.8)	185.1 (36.4)	187.5 (36.7)	192.8 (38.0)	199.8 (40.1)	203.9 (41.7)	206.1 (42.7)	<0.001
Fasting glucose[c]	Mean (SD), mg/dL	88.3 (22.1)	87.9 (22.0)	88.2 (21.4)	89.0 (21.0)	91.9 (23.9)	96.7 (29.2)	99.6 (32.4)	101.3 (34.4)	<0.001
Sex	Women	1,393 (74.8)	15,124 (70.6)	60,609 (56.5)	111,796 (39.5)	169,852 (29.6)	59,503 (32.0)	19,835 (42.0)	7,127 (47.5)	<0.001
	Men	469 (25.2)	6,290 (29.4)	46,674 (43.5)	171,517 (60.5)	403,239 (70.4)	126,564 (68.0)	27,369 (58.0)	7,885 (52.5)	
Exercise	No	1,529 (82.1)	17,467 (81.6)	86,204 (80.4)	221,345 (78.1)	430,424 (75.1)	133,125 (71.5)	33,638 (71.3)	10,742 (71.6)	<0.001
	Yes	333 (17.9)	3,947 (18.4)	21,079 (19.6)	61,968 (21.9)	142,667 (24.9)	54,942 (29.5)	13,566 (28.7)	4,270 (28.4)	
Smoking	Current smoker	430 (23.1)	4,832 (22.6)	31,440 (29.3)	109,058 (38.5)	245,139 (42.8)	73,223 (39.4)	15,276 (32.4)	4,310 (28.7)	<0.001
	Never smoker	1,310 (70.4)	15,140 (70.7)	66,410 (61.9)	140,317 (49.5)	243,541 (42.5)	82,317 (44.2)	24,223 (51.3)	8,357 (55.7)	
	Past smoker	122 (6.6)	1,442 (6.7)	9,433 (8.8)	33,938 (12.0)	84,411 (14.7)	30,527 (16.4)	7,705 (16.3)	2,345 (15.6)	
Drinking,	0	1,414 (75.9)	15,196 (71.0)	65,567 (61.1)	139,046 (49.1)	234,924 (41.0)	78,252 (42.1)	23,283 (49.3)	8,061 (53.7)	<0.001
g ethanol/day	1-19	416 (22.3)	5,295 (24.7)	31,578 (29.4)	98,740 (34.9)	214,901 (37.5)	68,413 (36.8)	16,330 (34.6)	4,971 (33.1)	
	≥ 20	32 (1.7)	923 (4.3)	10,138 (9.4)	45,527 (16.1)	123,266 (21.5)	39,402 (21.2)	7,591 (16.1)	1,980 (13.2)	

Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

[*] The percent value is calculated using the number in each SBP category compared to that in all participants.

[†] To convert glucose from mg/dL to mmol/L, multiply by 0.0555

[‡] To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259

P-values were calculated by chi-squared tests and one-way analysis of variance between eight SBP groups

Supplemental Table 3. HRs[*] for all-cause and vascular mortality by SBP group according to age (Numerical version of Figure 3).

		60-95 years (n=177,790)				30-59 years (n=1,057,456)			
Causes of death (ICD-10)	SBP groups, mmHg	No. of death	Death rate[†]	p-value	HR (95% CI)	No. of death	Death rate[†]	p-value	HR (95% CI)
Any cause	<90	211	3,260	0.017	1.19 (1.03-1.38)	91	350	0.386	1.10 (0.89-1.37)
	90-99	1,402	2,730		1.00 (Reference)	851	252		1.00 (Reference)
	100-109	4,666	2,627	0.540	0.98 (0.93-1.04)	4,297	236	0.129	0.95 (0.88-1.02)
	110-119	9,758	2,565	0.364	0.97 (0.92-1.03)	12,935	261	0.148	0.95 (0.89-1.02)
	120-139	28,208	2,739	0.288	1.03 (0.98-1.09)	34,803	362	0.108	1.06 (0.99-1.13)
	140-159	20,829	3,152	<0.001	1.16 (1.09-1.22)	16,807	642	<0.001	1.34 (1.25-1.43)
	160-179	9,275	3,704	<0.001	1.34 (1.27-1.42)	5,093	969	<0.001	1.70 (1.58-1.83)
	≥180	3,830	4,338	<0.001	1.53 (1.44-1.63)	1,826	1258	<0.001	2.14 (1.97-2.32)
Atherosclerotic	<90	44	680	0.006	1.57 (1.14-2.17)	13	50	0.400	1.28 (0.72-2.28)
vascular diseases	90-99	223	434		1.00 (Reference)	103	31		1.00 (Reference)
(I10-I15, I20-I25,	100-109	863	486	0.096	1.13 (0.98-1.31)	492	27	0.394	0.91 (0.74-1.13)
I44-I52, I60-I69,	110-119	2,075	545	<0.001	1.29 (1.12-1.48)	1,556	31	0.714	0.96 (0.79-1.18)
I70-I74, R96)	120-139	6,824	663	<0.001	1.55 (1.35-1.77)	5,650	59	0.001	1.41 (1.16-1.72)
	140-159	6,064	918	<0.001	2.06 (1.8-2.35)	3,948	151	<0.001	2.49 (2.04-3.03)
	160-179	3,185	1,272	<0.001	2.77 (2.42-3.17)	1,521	289	<0.001	3.92 (3.2-4.79)
	≥180	1,528	1,731	<0.001	3.63 (3.15-4.18)	727	501	<0.001	6.45 (5.24-7.94)
Ischemic heart	<90	14	216	0.003	2.51 (1.38-4.57)	4	15	0.140	2.25 (0.77-6.62)
diseases	90-99	45	88		1.00 (Reference)	19	6		1.00 (Reference)
(I20-I25)	100-109	202	114	0.125	1.29 (0.93-1.78)	155	9	0.165	1.40 (0.87-2.26)
	110-119	463	122	0.044	1.37 (1.01-1.86)	512	10	0.118	1.44 (0.91-2.28)
	120-139	1,468	143	0.004	1.55 (1.15-2.09)	1,786	19	0.003	1.98 (1.26-3.11)
	140-159	1,234	187	<0.001	1.94 (1.44-2.62)	1,072	41	<0.001	3.01 (1.91-4.75)
	160-179	651	260	<0.001	2.65 (1.95-3.59)	358	68	<0.001	4.21 (2.65-6.69)
	≥180	234	265	<0.001	2.61 (1.89-3.59)	157	108	<0.001	6.43 (3.99-10.38)
Total Stroke	<90	20	309	0.195	1.37 (0.85-2.2)	4	15	0.493	0.70 (0.25-1.93)
(I60-I69)	90-99	116	226		1.00 (Reference)	56	17		1.00 (Reference)
	100-109	466	262	0.113	1.18 (0.96-1.45)	217	12	0.110	0.79 (0.59-1.06)
	110-119	1,176	309	<0.001	1.41 (1.16-1.71)	721	15	0.525	0.92 (0.7-1.2)
	120-139	3,917	380	<0.001	1.71 (1.42-2.06)	2,751	29	0.008	1.43 (1.1-1.87)
	140-159	3,593	544	<0.001	2.37 (1.97-2.85)	2,214	85	<0.001	2.86 (2.19-3.74)
	160-179	1,913	764	<0.001	3.23 (2.68-3.9)	935	178	<0.001	4.85 (3.7-6.37)
	≥180	986	1,117	<0.001	4.57 (3.77-5.54)	453	312	<0.001	8.03 (6.07-10.62)
Ischemic Stroke	<90	5	77	0.929	1.04 (0.41-2.65)	0	0		0.00
(I63)	90-99	39	76		1.00 (Reference)	18	5		1.00 (Reference)
	100-109	148	83	0.615	1.10 (0.77-1.56)	49	3	0.028	0.55 (0.32-0.94)
	110-119	376	99	0.121	1.30 (0.93-1.81)	159	3	0.051	0.61 (0.38-1)
	120-139	1,310	127	0.003	1.62 (1.18-2.23)	639	7	0.809	0.94 (0.59-1.51)
	140-159	1,123	170	<0.001	2.06 (1.49-2.84)	527	20	0.020	1.76 (1.1-2.83)
	160-179	579	231	<0.001	2.72 (1.96-3.77)	209	40	<0.001	2.68 (1.65-4.35)
	≥180	327	370	<0.001	4.20 (3.01-5.86)	115	79	<0.001	4.99 (3.03-8.25)

Hemorrhagic	<90	5	77	0.155	2.04 (0.76-5.48)	2	8	0.934	1.06 (0.25-4.55)
Stroke	90-99	19	37		1.00 (Reference)	20	6		1.00 (Reference)
(I60-I62)	100-109	108	61	0.034	1.70 (1.04-2.76)	104	6	0.887	1.04 (0.64-1.67)
	110-119	303	80	0.001	2.28 (1.44-3.63)	375	8	0.223	1.32 (0.84-2.08)
	120-139	913	89	<0.001	2.57 (1.63-4.05)	1,294	13	0.002	2.01 (1.29-3.13)
	140-159	858	130	<0.001	3.74 (2.37-5.9)	920	35	<0.001	3.97 (2.54-6.19)
	160-179	427	171	<0.001	4.83 (3.05-7.66)	372	71	<0.001	6.78 (4.31-10.67)
	≥180	218	247	<0.001	6.88 (4.3-11.01)	174	120	<0.001	10.97 (6.88-17.47)

Abbreviation: CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th revision; SBP, systolic blood pressure

* Adjustment for age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/day; 0, 1-20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

† Crude death rate per 100,000 person-years.

Supplemental Table 4. HRs* per 10 mmHg increase in SBP for vascular mortality given SBP range.

Causes of death	No. of death	p-value	HR for each 10 mmHg increase in SBP (95% CI)
In the range SBP < 100 mmHg			
Any cause	2,555	0.014	0.88 (0.80-0.97)
Atherosclerotic vascular diseases	383	0.002	0.70 (0.56-0.88)
Ischemic heart diseases	82	0.001	0.50 (0.34-0.75)
Total Stroke	196	0.172	0.79 (0.56-1.11)
Ischemic Stroke	62	0.994	1.00 (0.51-1.97)
Hemorrhagic stroke	46	0.038	0.53 (0.29-0.96)
In the range SBP ≥ 100 mmHg			
Any cause	152,327	<0.001	1.08 (1.08-1.08)
Atherosclerotic vascular diseases	34,433	<0.001	1.19 (1.19-1.20)
Ischemic heart diseases	8,292	<0.001	1.15 (1.14-1.16)
Total Stroke	19,342	<0.001	1.22 (1.21-1.23)
Ischemic Stroke	5,561	<0.001	1.20 (1.18-1.21)
Hemorrhagic stroke	6,066	<0.001	1.24 (1.23-1.25)

Abbreviation: CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure

* Adjustment for age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/day; 0, 1-20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

Supplemental Table 5. HRs* per 10 mmHg increase in SBP for vascular mortality across SBP ranges stratified by age group.

Causes of death (ICD-10)	60-95 years			30-59 years			
	No. of death	p-value	HR for each 10 mmHg increase in SBP (95% CI)	No. of death	p-value	HR for each 10 mmHg increase in SBP (95% CI)	p for interaction†
In the range SBP < 100 mmHg							
Any cause	1,613	0.019	0.87 (0.77-0.98)	942	0.427	0.93 (0.77-1.12)	0.502
Atherosclerotic vascular diseases	267	0.001	0.65 (0.50-0.84)	116	0.664	0.89 (0.53-1.49)	0.939
Ischemic heart diseases	59	0.001	0.48 (0.31-0.75)	23	0.147	0.51 (0.21-1.27)	0.792
Total Stroke	136	0.030	0.66 (0.46-0.96)	60	0.284	1.59 (0.68-3.69)	0.310
Ischemic Stroke	44	0.443	0.76 (0.37-1.54)	18	0.174	3.24 (0.6-17.64)	0.482
Hemorrhagic stroke	24	0.026	0.44 (0.21-0.90)	22	0.555	0.72 (0.24-2.18)	0.992
In the range SBP ≥ 100 mmHg							
Any cause	76,566	<0.001	1.06 (1.05-1.06)	75,761	<0.001	1.11 (1.11-1.12)	<0.001
Atherosclerotic vascular diseases	20,539	<0.001	1.15 (1.14-1.16)	13,894	<0.001	1.28 (1.27-1.29)	<0.001
Ischemic heart diseases	4,252	<0.001	1.11 (1.09-1.13)	4,040	<0.001	1.21 (1.19-1.23)	<0.001
Total Stroke	12,051	<0.001	1.17 (1.16-1.18)	7,291	<0.001	1.33 (1.32-1.34)	<0.001
Ischemic Stroke	3,863	<0.001	1.16 (1.14-1.17)	1,698	<0.001	1.30 (1.27-1.33)	<0.001
Hemorrhagic stroke	2,827	<0.001	1.16 (1.15-1.18)	3,239	<0.001	1.33 (1.31-1.35)	<0.001

Abbreviation: CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure

* Adjustment for age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/day; 0, 1-20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

† p values for interaction between SBP and age were calculated by introducing a linear interaction term (the product of age and SBP).

Supplemental Table 6. HRs* per 10 mmHg increase in SBP for vascular mortality across SBP ranges stratified by sex.

Causes of death (ICD-10)	Men			Women			
	No. of death	p-value	HR for each 10 mmHg increase in SBP (95% CI)	No. of death	p-value	HR for each 10 mmHg increase in SBP (95% CI)	p for interaction†
In the range SBP < 100 mmHg							
Any cause	1,362	0.034	0.86 (0.75-0.99)	1,193	0.247	0.92 (0.79-1.06)	0.696
Atherosclerotic vascular diseases	167	0.073	0.72 (0.50-1.03)	216	0.016	0.69 (0.51-0.93)	0.891
Ischemic heart diseases	39	0.011	0.46 (0.25-0.84)	43	0.037	0.56 (0.32-0.96)	0.661
Total Stroke	87	0.884	1.04 (0.59-1.86)	109	0.042	0.64 (0.42-0.98)	0.220
Ischemic Stroke	30	0.395	1.64 (0.53-5.12)	32	0.419	0.71 (0.31-1.63)	0.247
Hemorrhagic stroke	17	0.144	0.47 (0.17-1.29)	29	0.111	0.53 (0.24-1.16)	0.825
In the range SBP ≥ 100 mmHg							
Any cause	104,560	<0.001	1.09 (1.08-1.09)	47,767	<0.001	1.07 (1.06-1.07)	<0.001
Atherosclerotic vascular diseases	21,270	<0.001	1.22 (1.21-1.23)	13,163	<0.001	1.16 (1.15-1.17)	<0.001
Ischemic heart diseases	5,709	<0.001	1.17 (1.15-1.18)	2,583	<0.001	1.13 (1.11-1.15)	0.611
Total Stroke	11,549	<0.001	1.26 (1.25-1.27)	7,793	<0.001	1.18 (1.17-1.19)	<0.001
Ischemic Stroke	3,335	<0.001	1.23 (1.21-1.25)	2,226	<0.001	1.16 (1.14-1.18)	<0.001
Hemorrhagic stroke	3,671	<0.001	1.28 (1.26-1.30)	2,395	<0.001	1.20 (1.18-1.22)	0.005

Abbreviation: CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure

* Adjustment for age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/day; 0, 1-20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

† p values for interaction between SBP and sex were calculated by introducing a linear interaction term (the product of sex and SBP).

Supplemental Table 7. HRs* for all-cause and vascular mortality by SBP group according to sex

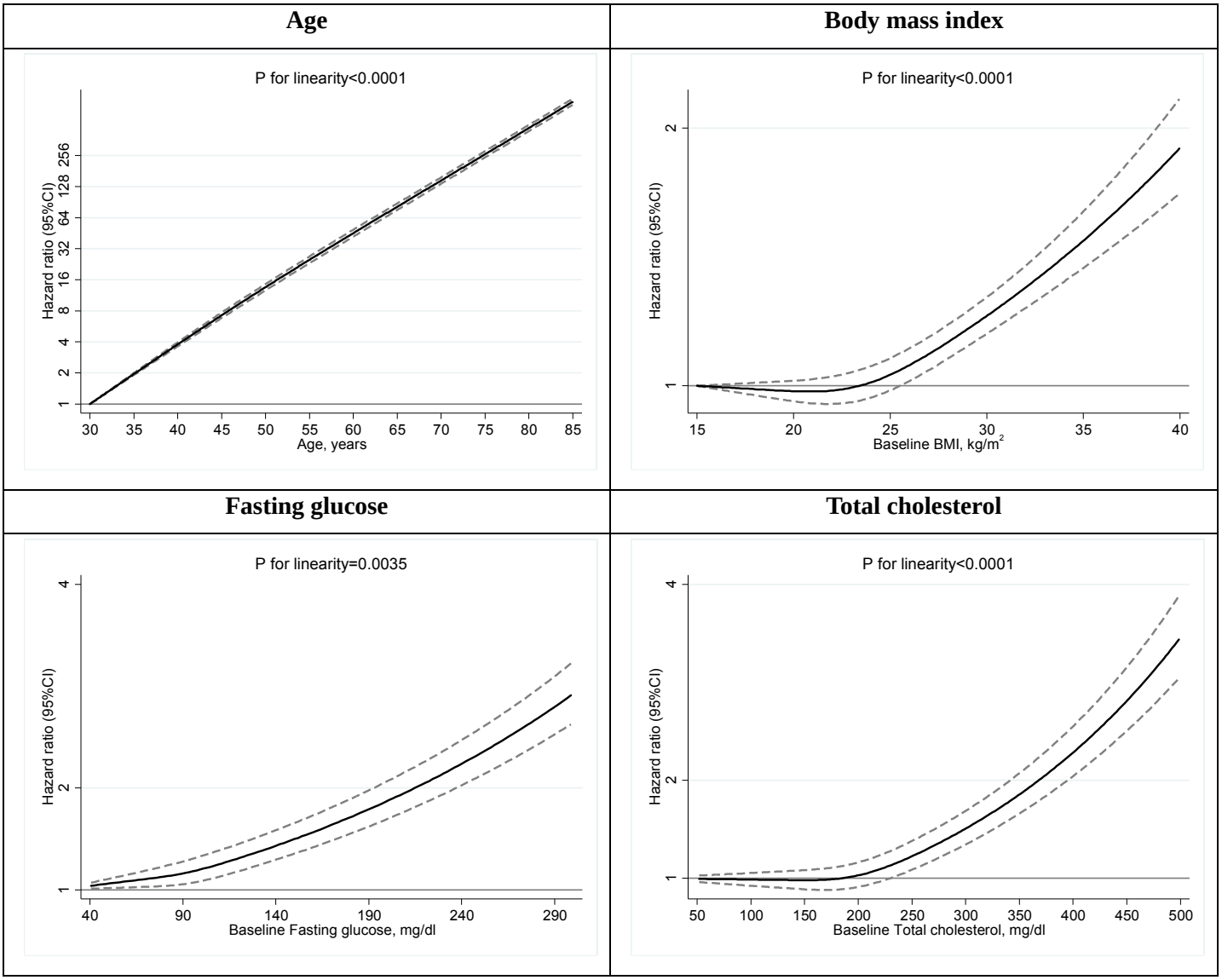
		Men (n=790,007)				Women (n=445,239)			
Causes of death (ICD-10)	SBP groups, mmHg	No. of death	Death rate†	p-value	HR (95% CI)	No. of death	Death rate†	p-value	HR (95% CI)
Any cause	<90	165	2,222	0.009	1.24 (1.06-1.46)	137	547	0.290	1.10 (0.92-1.32)
	90-99	1,197	1,083		1.00 (Reference)	1,056	379		1.00 (Reference)
	100-109	5,356	617	0.003	0.91 (0.86-0.97)	3,609	319	0.904	1.00 (0.93-1.07)
	110-119	15,461	476	<0.000	0.87 (0.82-0.93)	7,232	348	0.515	1.02 (0.96-1.09)
	120-139	45,459	601	0.183	0.96 (0.91-1.02)	17,554	570	0.002	1.10 (1.04-1.17)
	140-159	26,148	1,158	<0.001	1.17 (1.11-1.24)	11,488	1,125	<0.001	1.26 (1.18-1.34)
	160-179	8,850	1,956	<0.001	1.38 (1.3-1.47)	5,518	1,706	<0.001	1.53 (1.43-1.64)
	≥180	3,286	2,694	<0.001	1.66 (1.55-1.77)	2,370	2,125	<0.001	1.69 (1.57-1.82)
Atherosclerotic	<90	22	296	0.174	1.37 (0.87-2.14)	35	140	0.008	1.63 (1.13-2.34)
vascular diseases	90-99	145	131		1.00 (Reference)	181	65		1.00 (Reference)
(I10-I15, I20-I25,	100-109	706	81	0.935	1.01 (0.84-1.2)	649	57	0.590	1.05 (0.89-1.23)
I44-I52, I60-I69,	110-119	2,194	68	0.563	1.05 (0.89-1.24)	1,437	69	0.044	1.17 (1-1.37)
I70-I74, R96)	120-139	8,036	106	<0.001	1.40 (1.19-1.65)	4,439	144	<0.001	1.56 (1.34-1.81)
	140-159	6,438	285	<0.001	2.26 (1.92-2.67)	3,574	350	<0.001	2.09 (1.8-2.43)
	160-179	2,645	585	<0.001	3.13 (2.65-3.7)	2,061	637	<0.001	3.00 (2.57-3.5)
	≥180	1,251	1,026	<0.001	4.72 (3.97-5.6)	1,004	900	<0.001	3.69 (3.15-4.33)
Ischemic heart	<90	8	108	0.023	2.46 (1.13-5.35)	10	40	0.009	2.57 (1.27-5.22)
diseases	90-99	31	28		1.00 (Reference)	33	12		1.00 (Reference)
(I20-I25)	100-109	207	24	0.215	1.27 (0.87-1.85)	150	13	0.1614	1.31 (0.9-1.91)
	110-119	683	21	0.121	1.33 (0.93-1.91)	292	14	0.195	1.27 (0.89-1.82)
	120-139	2,348	31	0.005	1.66 (1.17-2.37)	906	29	0.004	1.67 (1.18-2.37)
	140-159	1,648	73	<0.001	2.46 (1.73-3.52)	658	64	<0.001	1.99 (1.4-2.83)
	160-179	590	130	<0.001	3.10 (2.16-4.46)	419	130	<0.001	3.15 (2.21-4.5)
	≥180	233	191	<0.001	3.96 (2.72-5.77)	158	142	<0.001	2.98 (2.04-4.36)
Total Stroke	<90	7	94	0.510	0.77 (0.36-1.67)	17	68	0.091	1.56 (0.93-2.62)
(I60-I69)	90-99	80	72		1.00 (Reference)	92	33		1.00 (Reference)
	100-109	324	37	0.262	0.87 (0.68-1.11)	359	32	0.260	1.14 (0.91-1.43)
	110-119	1,061	33	0.851	0.98 (0.78-1.23)	836	40	0.006	1.35 (1.09-1.68)
	120-139	4,063	54	0.007	1.36 (1.09-1.69)	2,605	85	<0.001	1.84 (1.49-2.26)
	140-159	3,680	163	<0.001	2.42 (1.94-3.02)	2,127	208	<0.001	2.55 (2.06-3.14)
	160-179	1,628	360	<0.001	3.54 (2.82-4.43)	1,220	377	<0.001	3.65 (2.95-4.52)
	≥180	793	650	<0.001	5.45 (4.32-6.86)	646	579	<0.001	4.93 (3.96-6.15)
Ischemic Stroke	<90	1	13	0.245	0.31 (0.04-2.25)	4	16	0.741	1.19 (0.42-3.4)
(I63)	90-99	29	26		1.00 (Reference)	28	10		1.00 (Reference)
	100-109	87	10	0.068	0.68 (0.44-1.03)	110	10	0.556	1.13 (0.75-1.72)
	110-119	304	9	0.377	0.84 (0.58-1.23)	231	11	0.382	1.19 (0.81-1.76)
	120-139	1,193	16	0.450	1.15 (0.8-1.67)	756	25	0.012	1.62 (1.11-2.36)
	140-159	1,054	47	0.001	1.86 (1.28-2.69)	596	58	<0.001	2.05 (1.4-2.99)
	160-179	446	99	<0.001	2.48 (1.7-3.62)	342	106	<0.001	2.88 (1.96-4.25)
	≥180	251	206	<0.001	4.34 (2.95-6.38)	191	171	<0.001	3.98 (2.67-5.94)

Hemorrhagic	<90	2	27	0.758	1.26	(0.29-5.51)	5	20	0.215	1.84 (0.7-4.82)
Stroke	90-99	15	14		1.00	(Reference)	24	9		1.00 (Reference)
(I60-I62)	100-109	100	12	0.481	1.22	(0.71-2.09)	112	10	0.184	1.35 (0.87-2.1)
	110-119	376	12	0.182	1.42	(0.85-2.39)	302	15	0.003	1.89 (1.24-2.86)
	120-139	1,395	18	0.007	2.03	(1.22-3.37)	812	26	<0.001	2.42 (1.61-3.64)
	140-159	1,144	51	<0.001	3.85	(2.31-6.41)	634	62	<0.001	3.60 (2.39-5.43)
	160-179	447	99	<0.001	5.56	(3.32-9.31)	352	109	<0.001	5.23 (3.45-7.92)
	≥180	209	171	<0.001	8.57	(5.07-14.49)	183	164	<0.001	7.23 (4.71-11.11)

Abbreviation: CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th revision; SBP, systolic blood pressure

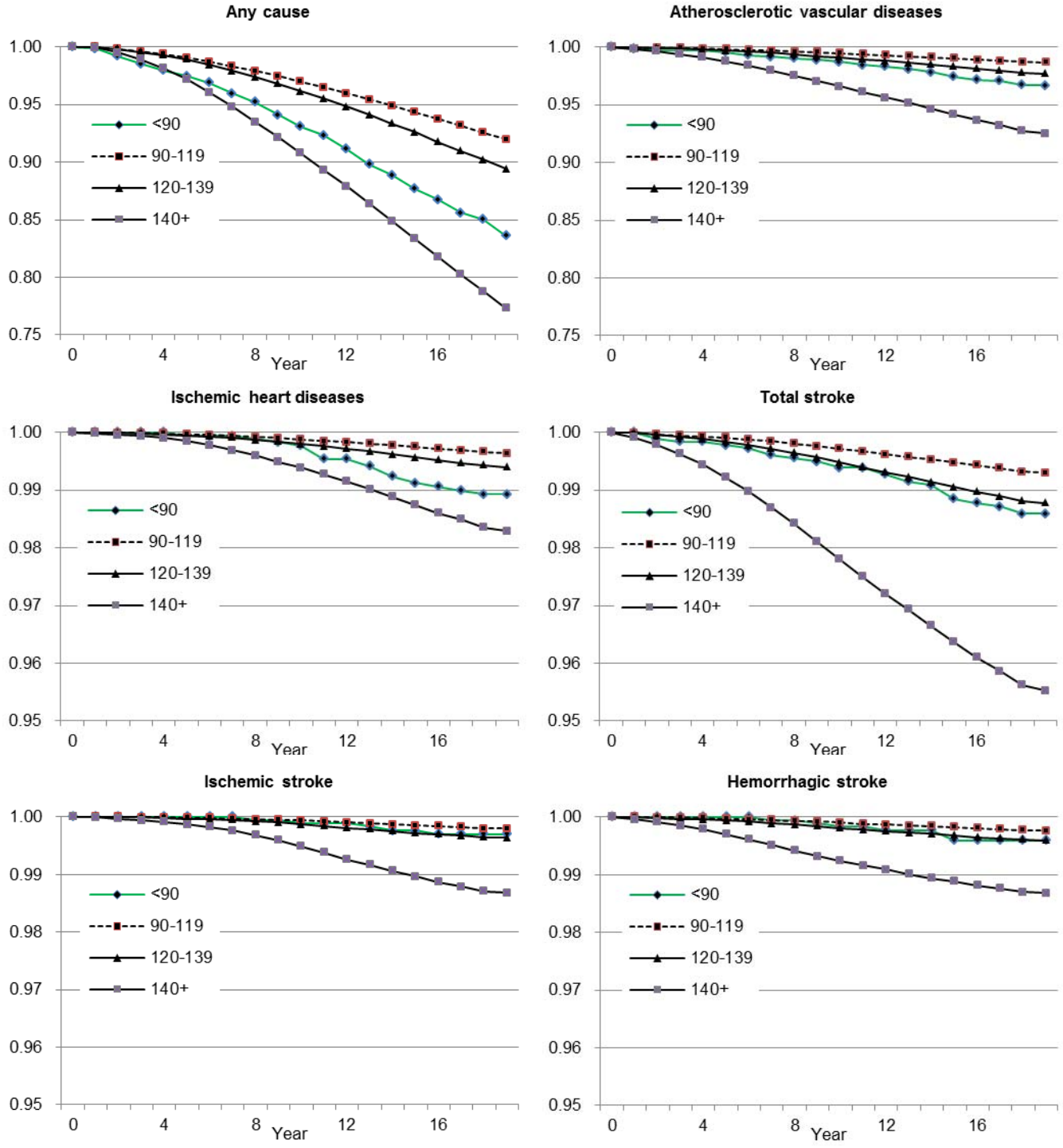
* Adjustment for age at entry (continuous); sex; smoking status (never, former, current smoker); alcohol intake (g/day; 0, 1-20, >20); physical activity (yes, no); total cholesterol (mg/dL; continuous); fasting serum glucose (mg/dL; continuous), and BMI (kg/m^2; continuous).

† Crude death rate per 100,000 person-years.



Supplemental Figure 1. Sex- and age- (when applicable) adjusted hazard ratios for mortality from atherosclerotic vascular diseases by restricted cubic splines of continuous confounding variables with three knots (5th, 50th, and 95th percentiles).

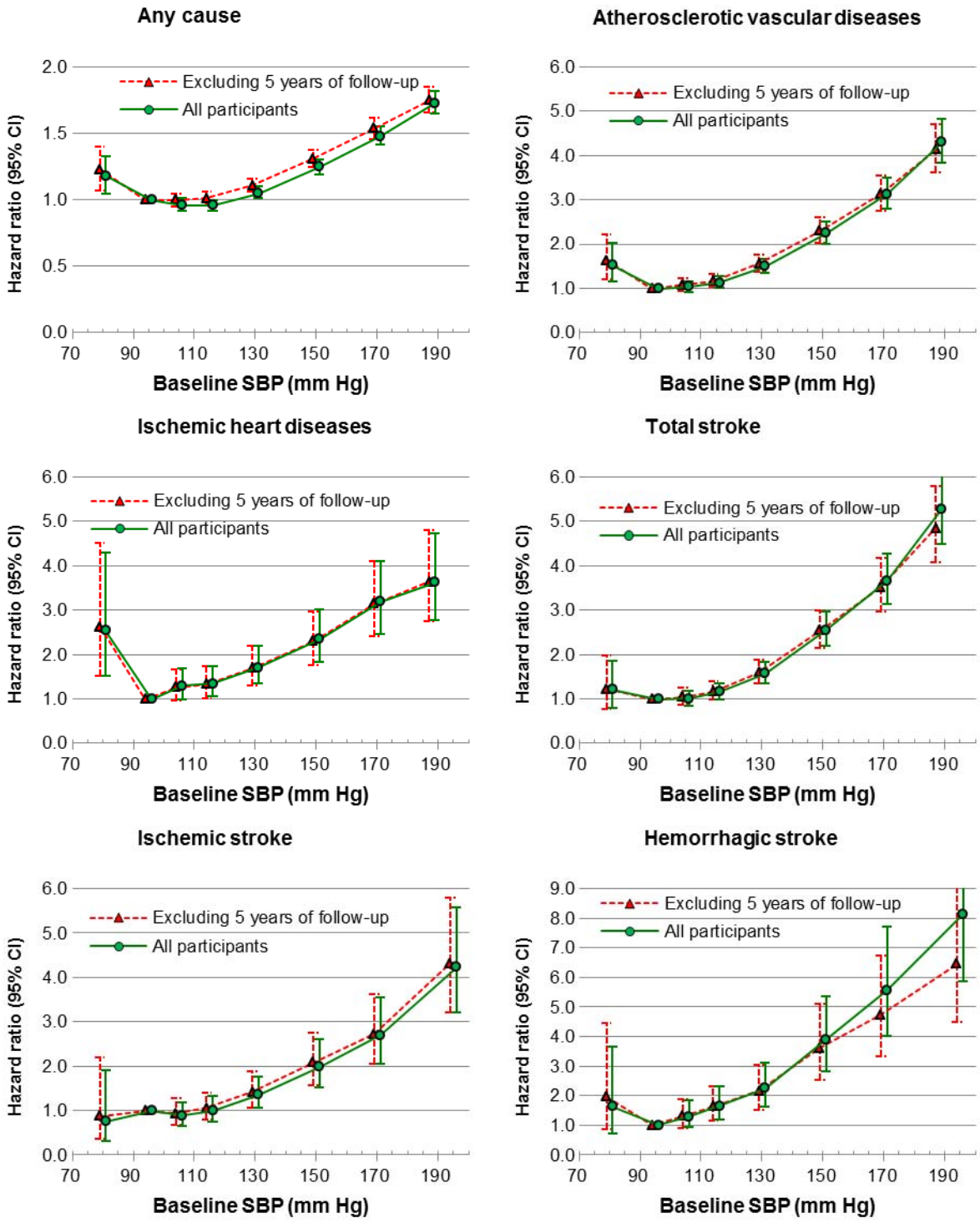
P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term with that with both the linear and the cubic spline terms



Years / SBP group	0	2	4	6	8	10	12	14	16	18
< 90 mmHg	1,862	1,836	1,818	1,788	1,754	1,721	1,673	1,636	1,596	1,332
90-119 mmHg	412,010	410,520	408,328	405,268	401,783	397,829	393,455	388,926	384,021	343,352
120-139 mmHg	573,091	570,817	567,302	561,526	555,061	547,655	539,669	530,997	521,704	469,910
≥140 mmHg	248,283	245,762	241,580	235,714	229,139	222,137	214,818	207,285	199,510	173,605

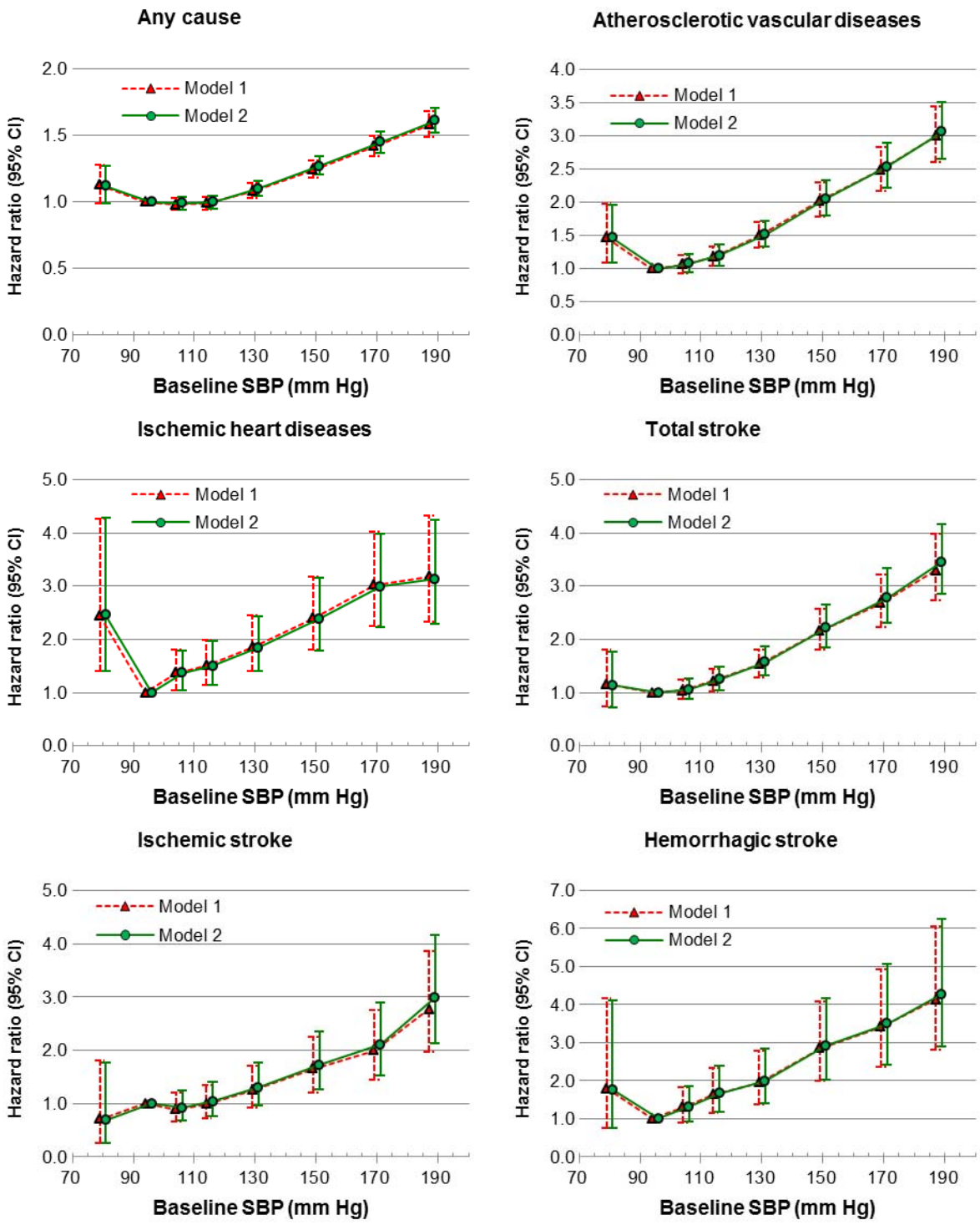
Supplemental Figure 2. Life-table survival curve for all-cause and vascular mortality by systolic blood pressure (SBP) group.

Four categories of SBP (mmHg, <90, 90-109, 110-119, and ≥120) were used. The survival rate was calculated using life-table method with a time interval of one year. A different Y-axis scale was used for subtypes of vascular mortality.



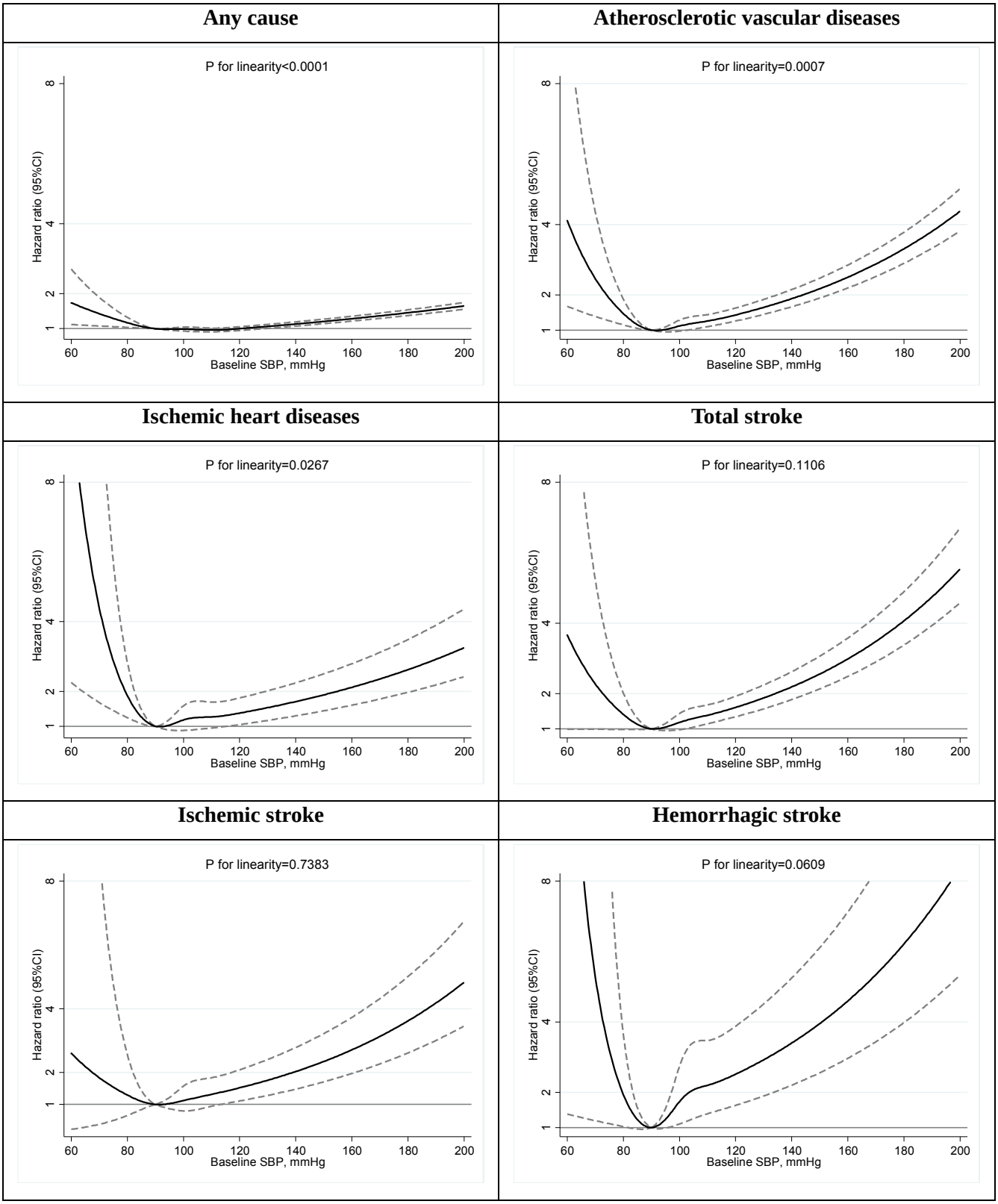
Supplemental Figure 3. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group in all participants (graphical version of Table 2) and survivors after 5 years of follow-up.

Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index.



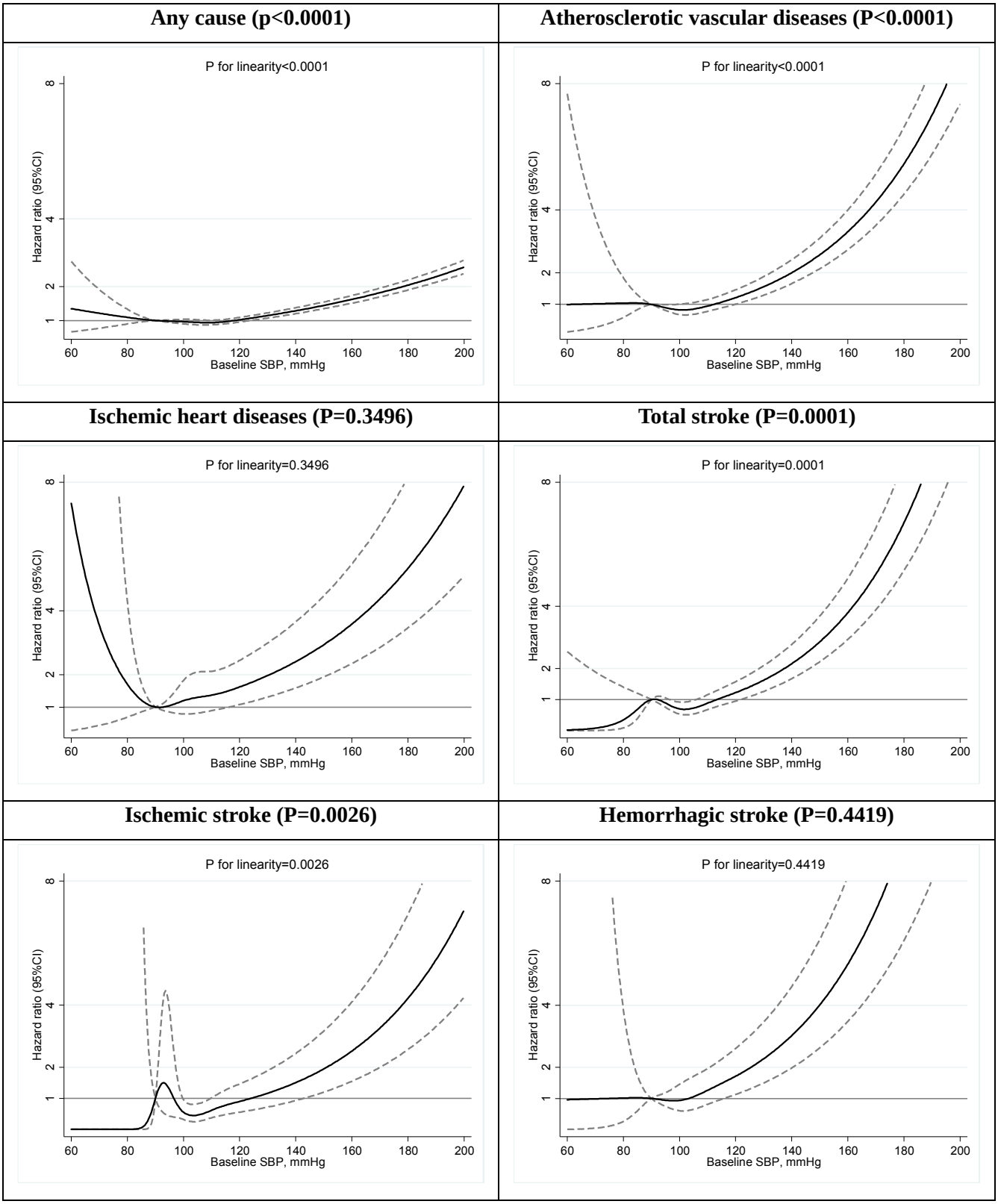
Supplemental Figure 4. Diastolic blood pressure (DBP) and multi-variable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group in all participants (to examine whether the associations were independent of DBP).

Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. In **Model 1**, adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, body mass index, and **restricted cubic splines of DBP with five knots (50, 60, 70, 80, 90 mmHg)**. In **Model 2**, all covariables used in Model 1 were included, while **continuous confounders (age, total cholesterol, fasting glucose, and body mass index) were included as cubic splines with three knots (5th, 50th, and 95th percentiles)**.



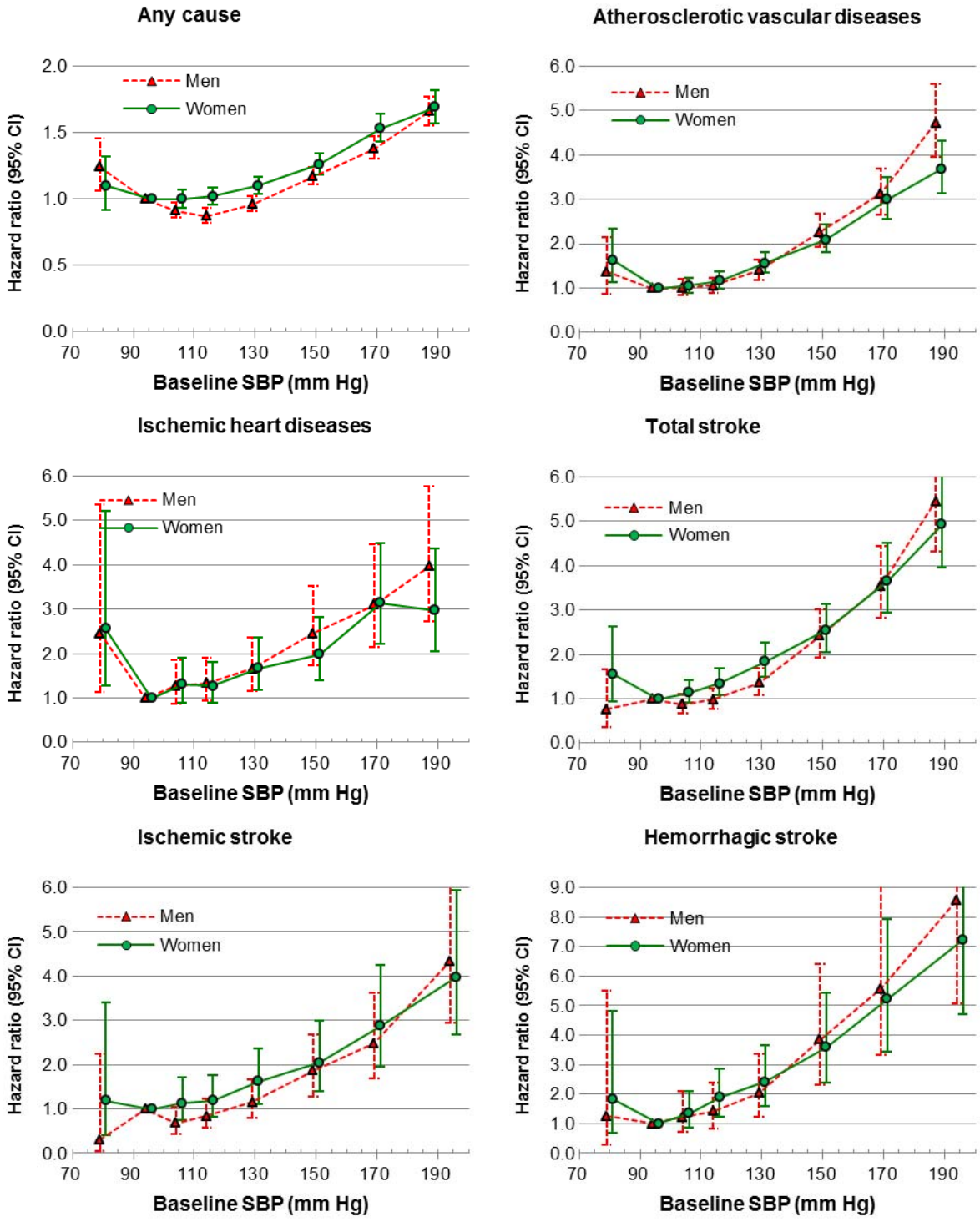
Supplemental Figure 5. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of systolic blood pressure (SBP) with five knots (80, 90, 100, 110, and 120 mmHg) and 90 mmHg as a reference in participants aged 60-95 years.

Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term with the model with both the linear and the cubic spline terms.



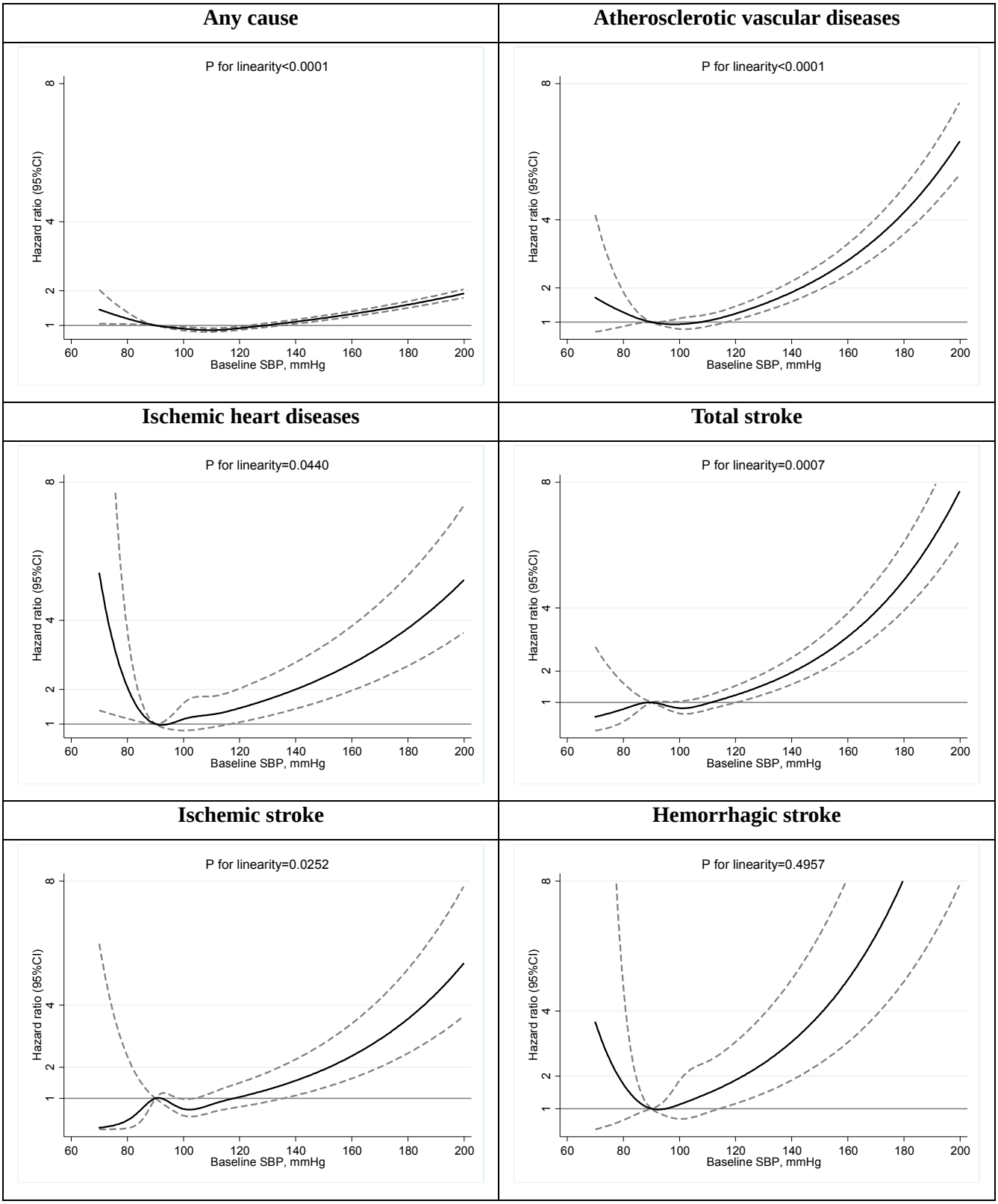
Supplemental Figure 6. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of systolic blood pressure (SBP) with five knots (80, 90, 100, 110, and 120 mmHg) and 90 mmHg as a reference in participants aged 30-59 years.

Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term to the model with both the linear and the cubic spline terms.



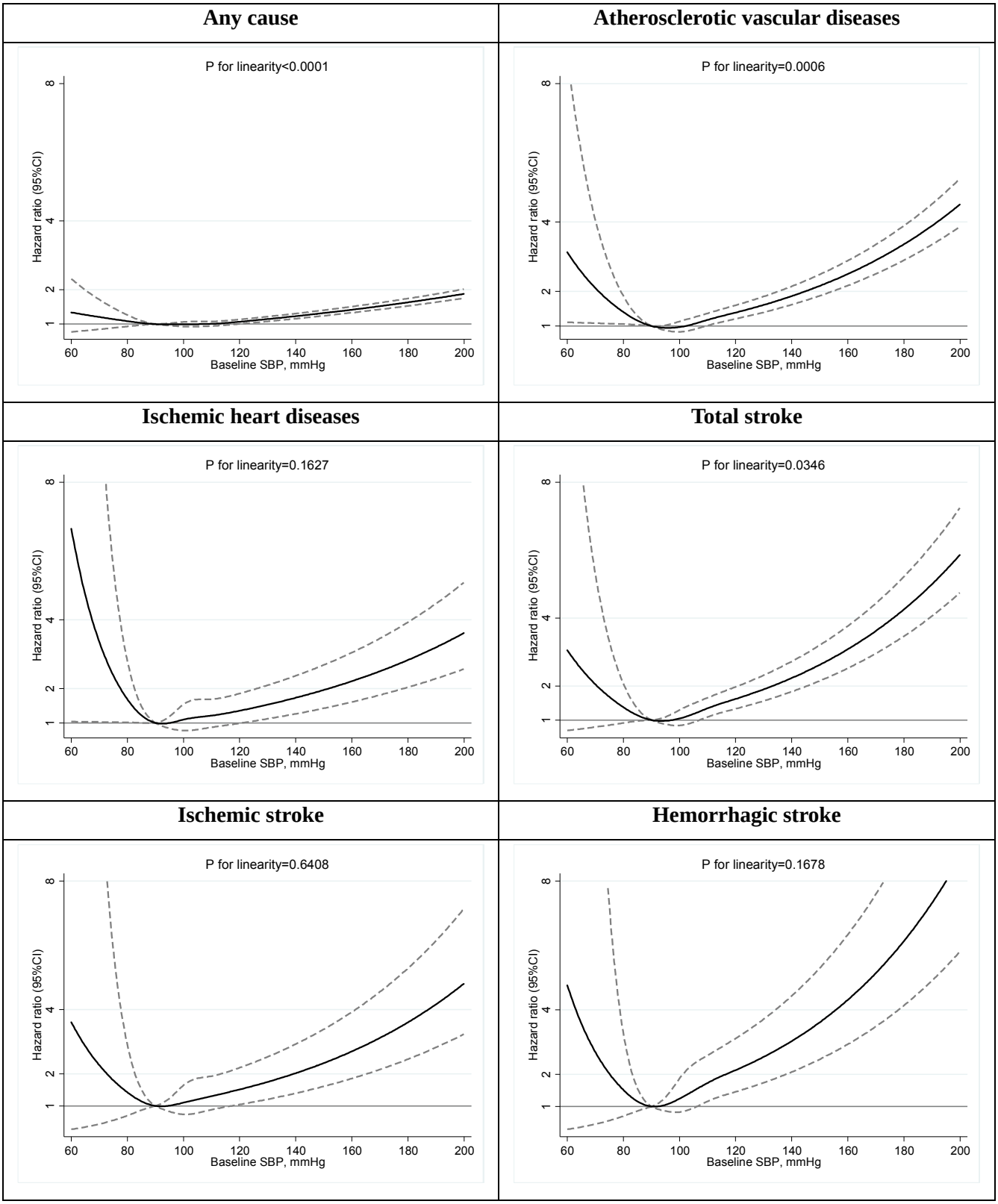
Supplemental Figure 7. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group according to sex.

Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index.



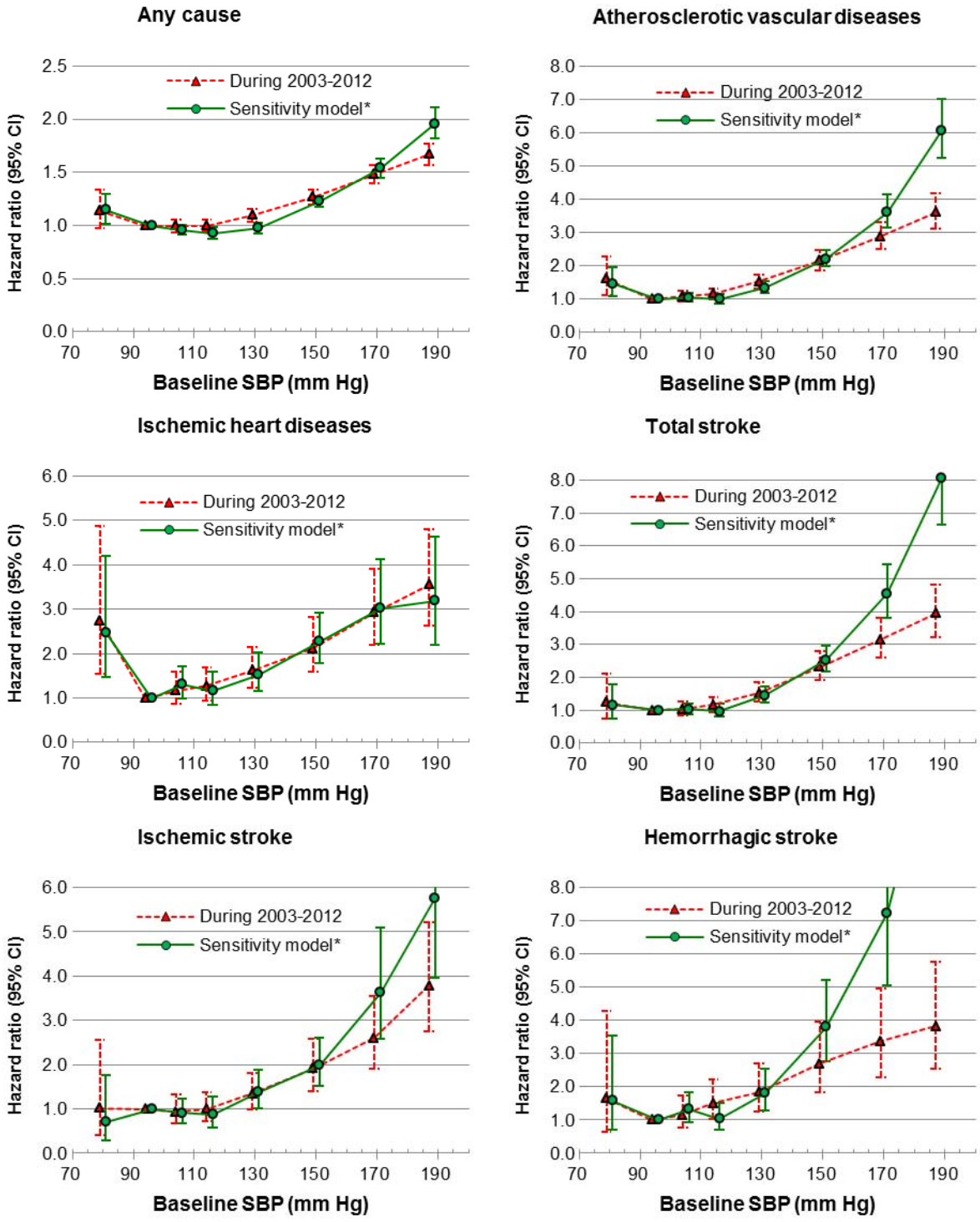
Supplemental Figure 8. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of systolic blood pressure (SBP) with five knots (80, 90, 100, 110, and 120 mmHg) and 90 mmHg as a reference in men.

Adjustment was made for age at entry, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term to the model with both the linear and the cubic spline terms.



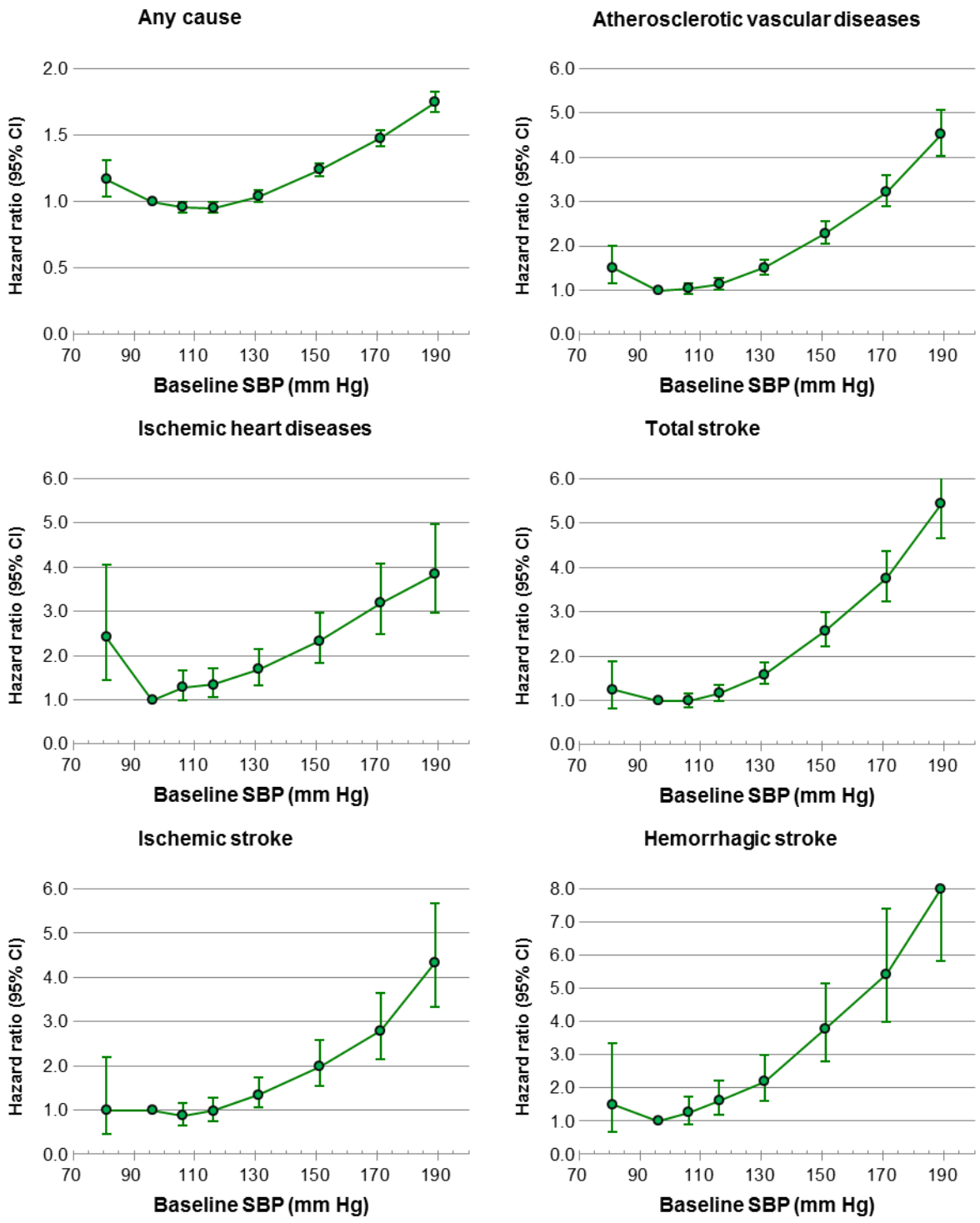
Supplemental Figure 9. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of systolic blood pressure (SBP) with five knots (80, 90, 100, 110, and 120 mmHg) and 90 mmHg as a reference in women.

Adjustment was made for age at entry, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term to the model with both the linear and the cubic spline terms.

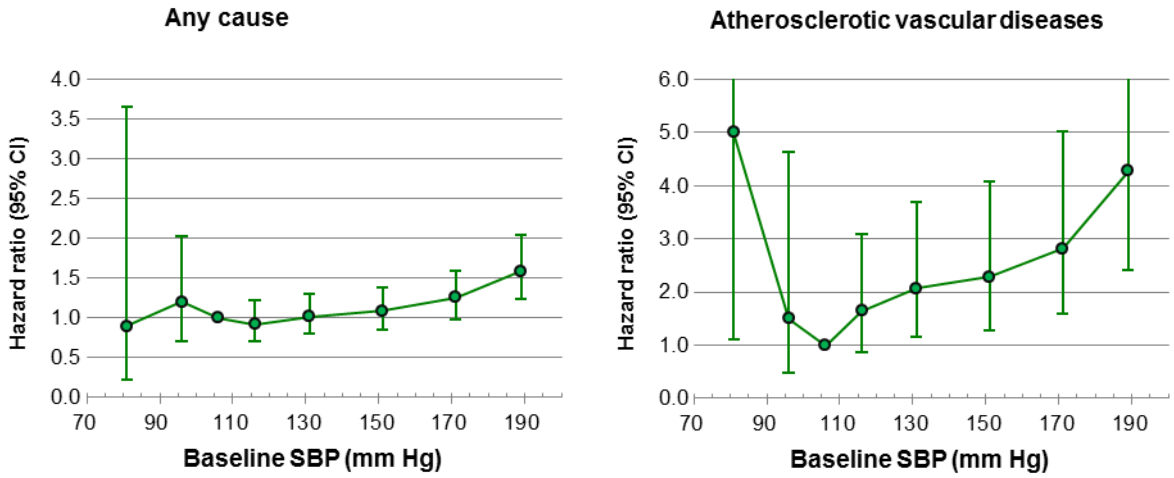


Supplemental Figure 10. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group in all participants and in survivors as of January 1, 2003 (follow-up during 2003-2012) (Sensitivity analysis, cox assumption).

Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. **In survivors as of January 1, 2003 (follow-up during 2003-2012)**, adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. **In the sensitivity model among all-participants**, co-variables that may cause non-proportional hazards over the follow-up time (violation of proportional hazard assumption) were stratified, while for several dummy variables of SBP with potential violations of assumption, time-dependent co-variables (which were generated using Model Statement of PROC PHREG procedure) were introduced in order to address non-proportionality. In the sensitivity model, analysis (PROC PHREG) stratified by age (years; <35, 35-44, 45-54, 55-64, 65-74, 75-84, ≥85), sex, exercise, alcohol intake (g/day; 0, 1-20, >20), total cholesterol (mg/dL; <200, 200-239, ≥240), and BMI (kg/m2; <18.5, 18.5-22.9, 23.0-24.9, ≥ 25.0), was done after adjustment for age, fasting glucose (mg/dL, continuous), smoking status, and several time-dependent dummy SBP co-variables (mmHg; 110-119, 120-139, 160-179, and ≥180).

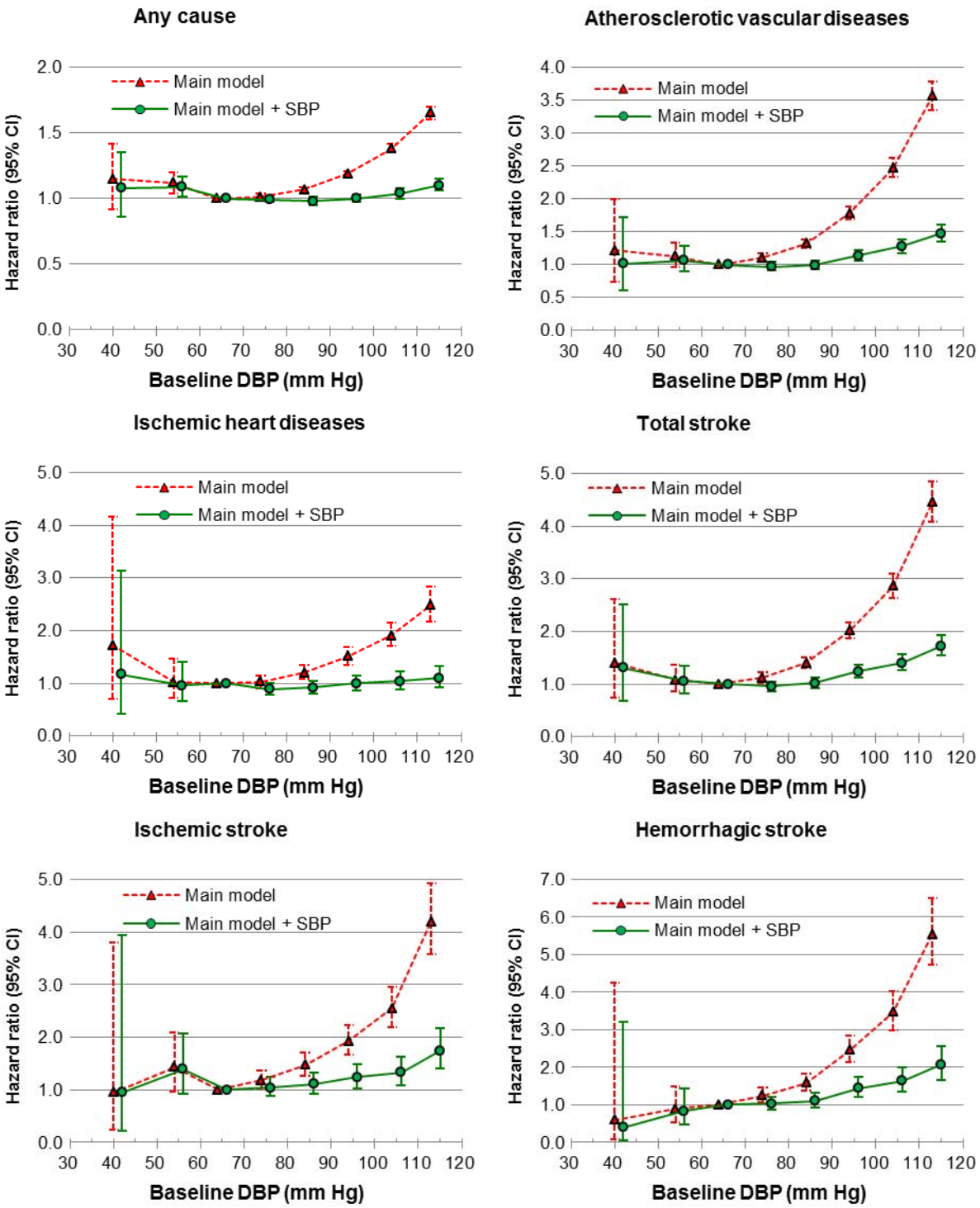


Supplemental Figure 11. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by systolic blood pressure (SBP) group in all study participants and in individuals with known diseases (excluded in the main analysis, n=49,483) combined (Sensitivity analysis, collider stratification bias).
Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index.



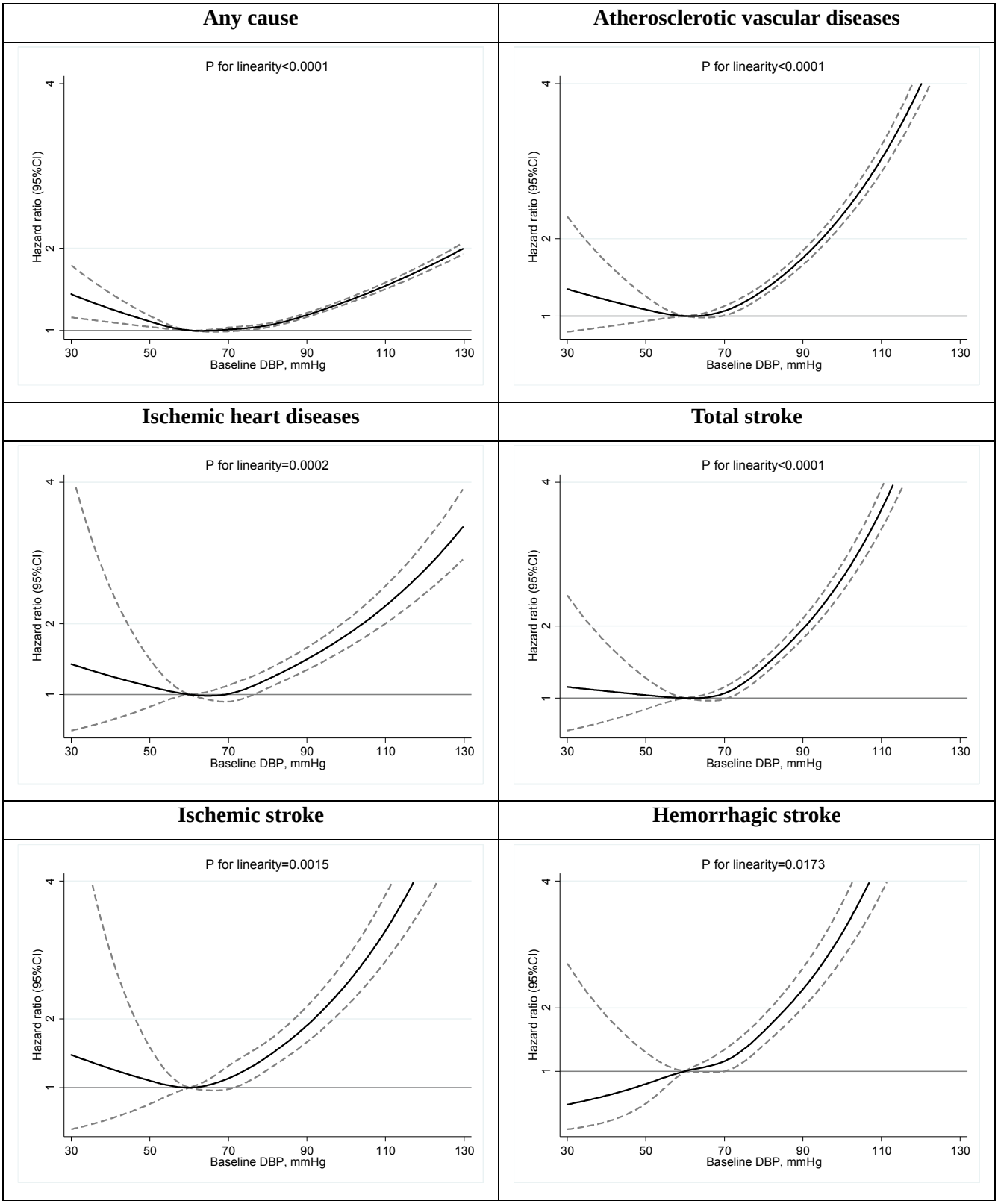
Supplemental Figure 12. Multi-variable adjusted hazard ratios for all-cause and atherosclerotic vascular mortality by systolic blood pressure (SBP) group in individuals with known cardiovascular diseases (hypertension, heart diseases, or stroke; excluded in the main analysis; n=15,277) (Sensitivity analysis).

Eight categories of SBP (reference: 90-99 mmHg) were used. The midpoint was used as a representative value for each SBP category, except for both ends (80 and 188), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index.



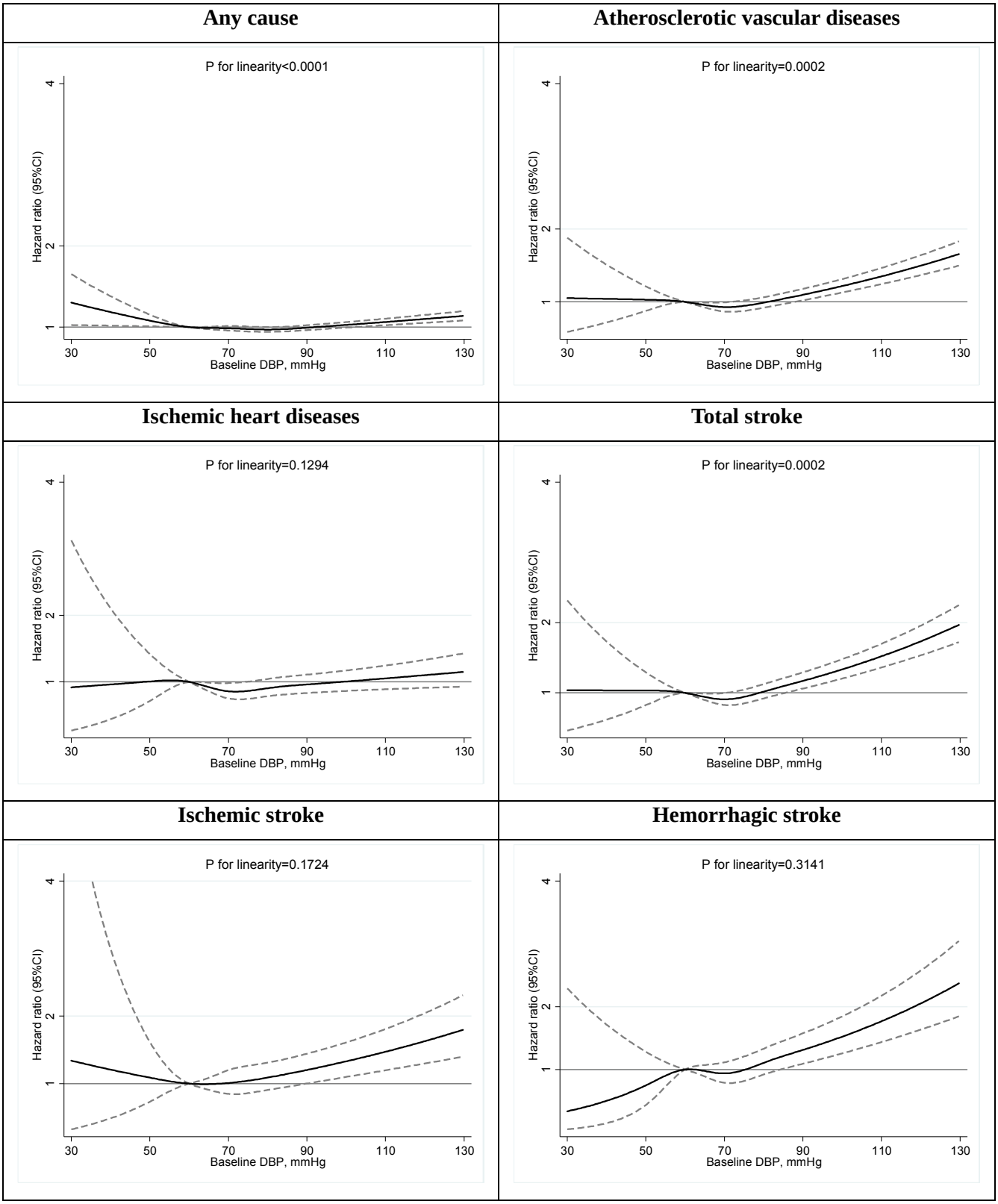
Supplemental Figure 13. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by diastolic blood pressure (DBP) group in all participants (to examine whether the associations were independent of SBP).

Eight categories of DBP (mmHg; <50, 50-59, 60-69 [reference], 70-79, 80-89, 90-99, 100-109, ≥110) were used. The midpoint was used as a representative value for each DBP category, except for both ends (41 and 114), for which the average of all participants was used. In the **Main model**, adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. In the **Main model +SBP,** additional adjustment was made for **restricted cubic splines of systolic blood pressure (SBP) with five knots (80, 90, 100, 110, and 120 mmHg)**.



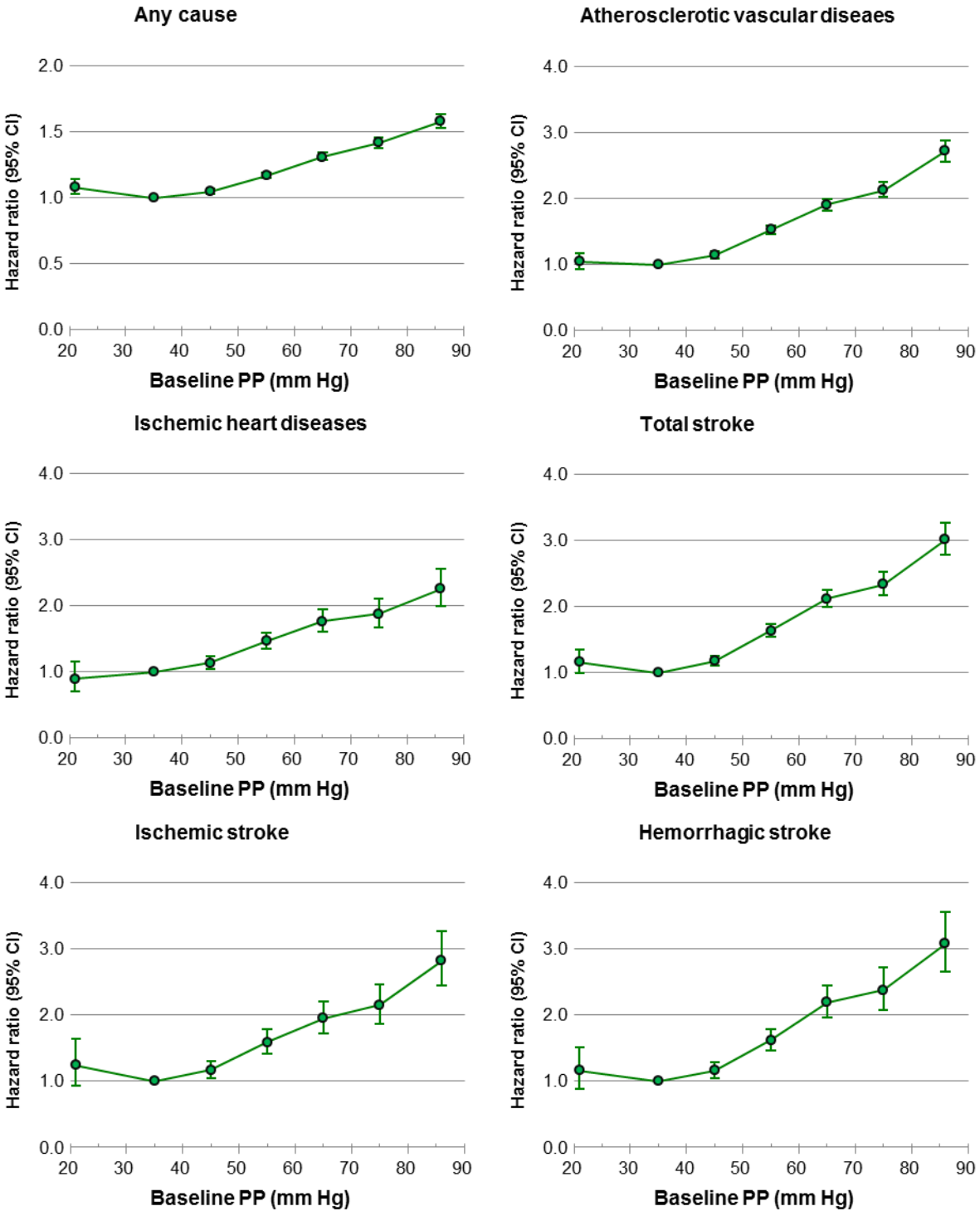
Supplemental Figure 14. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of diastolic blood pressure (DBP) with five knots (50, 60, 70, 80, and 90 mmHg) and 60 mmHg as a reference.

Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term with the model with both the linear and the cubic spline terms.



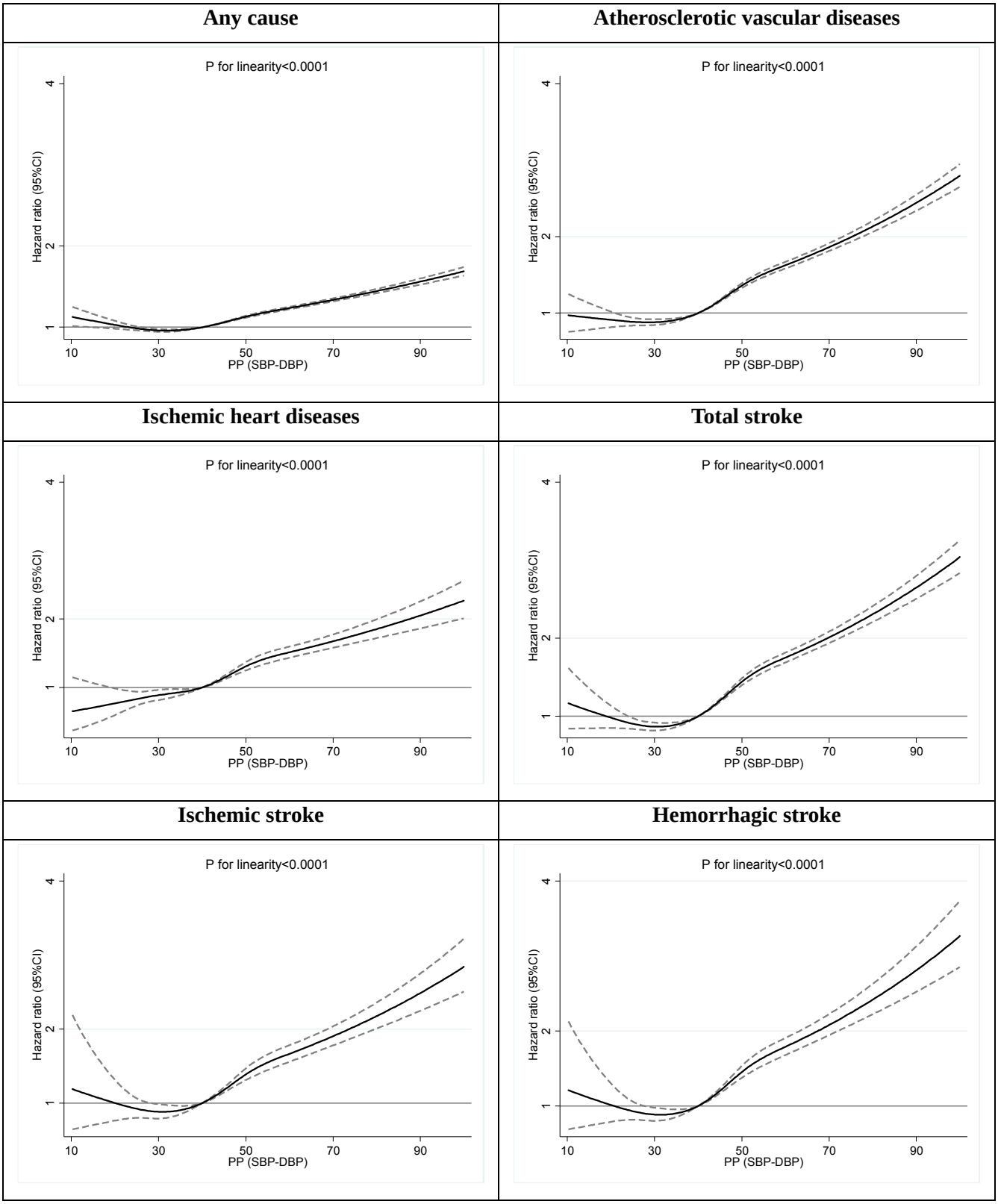
Supplemental Figure 15. Systolic blood pressure and multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of diastolic blood pressure (DBP) with five knots (50, 60, 70, 80, and 90 mmHg) and 60 mmHg as a reference.

Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, body mass index, and restricted cubic splines of systolic blood pressure with five knots (80, 90, 100, 110, and 120 mmHg). P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term to that with both the linear and the cubic spline terms.



Supplemental Figure 16. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by pulse pressure (PP) groups in all participants.

Seven categories of PP (mmHg; <30, 30-39 [reference], 40-49, 50-59, 60-69, 70-79, ≥80) were used. The midpoint was used as a representative value for each PP category, except for both ends (21 and 86), for which the average of all participants was used. Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index.



Supplemental Figure 17. Multi-variable adjusted hazard ratios for all-cause and vascular mortality by restricted cubic splines of pulse pressure (PP) with five knots (20, 30, 40, 50, and 60 mmHg) and 40 mmHg as a reference.

Adjustment was made for age at entry, sex, smoking status, alcohol intake, physical activity, total cholesterol, fasting serum glucose, and body mass index. P-values for linearity were calculated using the likelihood ratio test, comparing the model with only the linear term to the model with both the linear and the cubic spline terms.