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ORIGINAL RESEARCH

Age-Specific Associations Between Systolic Blood Pressure and Cardiovascular Disease: A 10-Year Diabetes Mellitus Cohort Study

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BACKGROUND: The relationship between systolic blood pressure (SBP) and cardiovascular disease (CVD) among patients with diabetes mellitus remains unclear. The study aimed to explore age-specific associations between SBP and CVD.

METHODS AND RESULTS: A population-based retrospective cohort study was conducted on 180 492 Chinese adults with type 2 diabetes mellitus in 2008–2010, with follow-up to 2017. Age-specific associations (<50, 50–59, 60–69, and 70–79 years) between the average SBP in the previous 2 years and CVD risk were assessed by adjusted Cox proportional hazards regression with age-specific regression dilution ratios and patient characteristics stratified by subgroups. During a median follow-up of 9.3 years (1.5 million person-years), 32 545 patients developed a CVD, with an incidence rate of 23.4 per 1000 person-years. A positive and log-linear association between SBP and CVD risk was observed among the 4 age groups without evidence of a threshold down to 120 mm Hg, but the magnitude of SBP effect on CVD attenuated with increased age. The CVD risk in the age group <50 years was ≈22% higher than the age group 70 to 79 years (hazard ratio [HR], 1.33 [95% CI, 1.26–1.41] versus HR, 1.09 [95% CI, 1.07–1.11]). Each 10-mm Hg higher SBP was associated with 12% (HR, 1.12 [95% CI, 1.10–1.13]), 11% (HR, 1.11 [95% CI, 1.10–1.13]), and 20% (HR, 1.20 [95% CI, 1.17–1.22]) higher risk of all composite CVD events, individual CVD, and CVD mortality, respectively.

CONCLUSIONS: There is a significant log-linear relationship between baseline SBP and the risk of CVD among patients with diabetes mellitus in China. The risk increases from an SBP of 120 mm Hg onward. Age influences this relationship significantly, with younger patients (<50 years) having a greater risk of CVD for a similar rise in SBP as compared with those who are older. These findings suggest that differential target blood pressures stratified by age maybe useful.

Key Words: blood pressure ■ cardiovascular disease ■ diabetes mellitus ■ hypertension ■ mortality

Diabetes mellitus (DM) is a lifelong disease with a global prevalence of 8.8% (425 million) in 2017 and is estimated to increase to 9.9% (629 million) by 2045.[1] An estimated 1.6 million annual deaths were caused directly by DM, and it is well recognized that patients with DM have a greater risk of cardiovascular disease (CVD).[2] While the incidence of CVD in older adults has decreased over the past decades, the steady or even increasing trend was observed in younger adults.[3] One key risk factor in the relationship between DM and CVD has been attributed to inadequate blood pressure (BP) control.[4] A targeted standard for the optimal BP range has been widely debated but remains controversial.

BP management to lower and achieve a targeted systolic BP (SBP) has been a major focus in most

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CLINICAL PERSPECTIVE

What Is New?

- This study in patients with diabetes mellitus in China suggests that the age of the patient significantly influences the strength of association between systolic blood pressure and risk of cardiovascular disease.
- For all age groups, the risk increases with the increase in systolic blood pressure from 120 mm Hg onward.
- This excess risk is significantly greater among younger patients as compared with older patients.

What Are the Clinical Implications?

- Our study suggests that age has a greater influence on the strength of the relationship between systolic blood pressure and the risk of cardiovascular disease. This may suggest that stratified blood pressure targets as per age of the patient may be beneficial.

Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
BMI	body mass index
BP	blood pressure
CVD	cardiovascular disease
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
HA	Hospital Authority
HR	hazard ratios
ICPC-2	*International Classification of Primary Care-2*
JNC 8	Eighth Joint National Committee
RCT	randomized controlled trial
SBP	systolic blood pressure
SHEP	Systolic Hypertension in the Elderly Program
SPRINT	Systolic Blood Pressure Intervention Trial
UKPDS	United Kingdom Prospective Diabetes Study

international guidelines and has become one of the main goals of DM care.[5–7] Nevertheless, there is no consensus agreement on optimal SBP, with recommendations ranging from 130 to 140 mm Hg.[8–11] Findings from randomized controlled trials (RCTs) suggest that there may be advantages to more intensive SBP control[12]; however, other studies argue for a patient-centered SBP target to improve adaptability and practicability.[8] Aside from the controversy about SBP targets,[13,14] there have been inconsistent findings on the association between SBP and risk of CVD or mortality, with studies demonstrating linear, J-shaped, or U-shaped relationships.[4,15–17] Nonetheless, most of these did not take regression dilution bias into account, in which variation in SBP measurements captured at baseline may lead to underestimated associations between SBP and outcomes. More important, several large population-based studies in the general population have demonstrated varying intensities of these relationships in different age groups, but it is unclear whether these findings can be generalized to DM populations.[18–21] There have been no studies to date evaluating age-specific associations between SBP and outcomes. Considering the burden of DM, it is important to have a better understanding of how SBP affects the risks of CVD and mortality in patients with DM in different age groups, with different characteristics.

The aim of this study was to investigate the age-specific association between SBP and incidence of CVD and CVD-related mortality among patients with type 2 DM without previous clinically diagnosed CVD, and to examine the pattern variations among patients with different baseline characteristics.

METHODS

Data Availability

Because of the confidentiality of the data used for this study and the strict privacy policy of the data holder stating the data be kept among the designated research personnel only, the data cannot be provided for research purposes.

Data, Materials, and Code Disclosure Statement

The data for this study are hosted by the Hong Kong Hospital Authority (HA). Subject to local law and regulation regarding the use and distribution personal data, the database used in the present study cannot be deposited in public data repositories. Data can be applied through the Data Sharing Portal of the Hong Kong HA (https://www3.ha.org.hk/data/DCL/Index/). Access to the computer code used in this research is available by request to the corresponding author.

Study Design

A population-based retrospective cohort study was conducted. All of the patients were aged 18 to 79 years and clinically diagnosed with type 2 DM and managed

in public primary care clinics in Hong Kong during the period from January 1, 2008, to December 31, 2010. Patients with a prior diagnosis of CVD at baseline were excluded. Diagnosis of type 2 DM was made by the clinic doctors who coded the diagnosis using the *International Classification of Primary Care-2* (*ICPC-2*) code of T90. The source of all of the baseline and outcome measures were from the electronic health database in the clinical management system in the Hong Kong HA, which is the only statutory body administering all 42 public-sector hospitals, 47 specialist outpatient clinics, and 73 primary care clinics in Hong Kong. The HA services are heavily subsidized by public funding and are available to all Hong Kong citizens. More than 90% of the local citizens who have diagnoses of chronic diseases are using HA services.[22] Clinicians and other related healthcare professionals utilize the clinical management system to directly record various clinical information and patient demographics including diagnoses, prescriptions, laboratory tests, emergency department visits, hospitalizations, and specialist and primary care outpatient clinic visits. The current electronic health database has high coding accuracy for diagnosis for myocardial infarction and stroke, with positive predictive values of 85.4% (95% CI, 78.8–90.6%) and 91.1% (95% CI, 83.2%–96.1%), respectively.[23] Data from the clinical management system have been previously adopted for other population-based epidemiological studies.[23–26] Baseline was defined as the date of the first SBP value recorded between January 1, 2008, and December 31, 2010. All patients were continuously followed up until the date of an outcome event, death, or last follow-up as of the censoring date of December 31, 2017, whichever occurred first.

Outcome Measures

The primary outcome was the incidence of the composite of CVD and CVD-related mortality. Secondary outcomes were the independent CVD including the subtype of coronary heart disease, stroke, heart failure, and CVD-related mortality. Mortality records were extracted from the database of Hong Kong Government Death Registry. CVD-related mortality was defined as mortality with a history of CVD or the main cause of death record by the *International Classification of Diseases, Tenth Edition* (*ICD-10*), codes of I20–I25, I50, and I60–I69. Details of other outcomes were defined and identified as per the relevant clinical parameter or diagnostic codes, *ICPC-2* or the *International Classification of Diseases, Ninth Edition, Clinical Modification* (*ICD-9-CM*), as presented in Table S1.

Ethical Approval

Informed consent of participants was not necessary as all data were anonymous and extracted through the computerized administrative system of the HA. Ethics approval was granted by the institutional review boards of the Hong Kong HA. The reported investigations were performed in accordance with the principles of the Declaration of Helsinki as revised in 2008.

SBP Measurement

A standardized guideline is provided for obtaining and documenting SBP readings in patients during the consultations among all clinics.[27] After patients rest for 5 minutes without any distractions in a seated position, SBP is measured several times, and patients are required to rest a minimum of 1 minute between measurements. Nurses or trained patient care assistants are mainly responsible for all measurements using a standardized automated sphygmomanometer (UA-853, Lifesource; EDAN M3A; or other equivalent measurements). Additional measurements are performed if the gap between the 2 readings exceeds 5 mm Hg. The recorded SBP measurement is calculated based on the average of 3 SBP readings. Patients without 3 SBP readings were excluded in this study. Usual SBP was defined as the average of all SBP measurements in the past 2 years. Multiple measurements can minimize the measurement error or short-term variations of SBP. This approach has been shown in previous studies focusing on improving the accuracy of CVD risk prediction.[28,29] The noted average number of SBP readings was 5.5 for the calculation of usual SBP. To deal with random errors in the SBP measurements, a regression dilution ratio was applied to all analyses based on Rosner regression method, employing the SBP readings about 1 year after baseline.[18–21,30,31]

Baseline Covariates

Baseline covariates included sex, age, smoking status, body mass index (BMI), glycated hemoglobin, low-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), Charlson Comorbidity Index,[32,33] and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, others antihypertensive drugs (hydralazine, methyldopa, and prazosin), oral antidiabetic drugs, insulin, or lipid-lowering agents. eGFR was computed based on the creatinine level from blood testing along with the abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese patients (eGFR in mL/min per 1.73 m^2=186×[(serum creatinine in μmol/L)×0.011]–1.154×(age)$^{-0.203}$×(0.742 if women)×1.233, where 1.233 is the adjusted coefficient for Chinese.[34] All laboratory assays were performed in accredited laboratories by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

Data Analysis

This study used multiple imputation to manage missing data in baseline covariates.[35] Each missing value was imputed 20 times by the chained equation method amended with the outcomes. For each of the 20 imputed data sets, the same analysis was implemented with the 20 sets of results joint based on Rubin's rules.[36]

The patients' usual SBP was the criterion for categorizing themselves into 1 of the 7 groups (<120, 120–129, 130–139, 140–149, 150–159 160–169, and ≥170 mm Hg). After multiple imputation for each subgroup of SBP, patients' characteristics were summarized in descriptive statistics. Estimation of incidence rate was conducted by an exact 95% CI hinged on a Poisson distribution.[37] It was examined by multivariable Cox proportional hazards regressions on the association between usual SBP and the incidence of CVD or chronic kidney disease, which was adjusted by all baseline covariates and corrected with regression dilution ratio.[38] The 95% CIs of the hazard ratios (HRs) were assessed with the floating absolute risk based on the Plummer method, without the requirement of selecting a reference group for displaying the standard error.[39] This method was widely applied in several similar studies.[18–21] Furthermore, the nonlinear association between SBP as a continuous variable and the outcomes was assessed by the restricted cubic splines with 3 knots in Cox models.[40] To inspect the proportional hazards assumption, the examination was performed on the plots of the scaled Schoenfeld residuals against time for the covariates. Variance inflation factor was evaluated for the purpose of confirming the existence of multicollinearity, and analysis of the data disclosed that the proportional hazards assumption was fulfilled among all models and multicollinearity was not presented. To estimate the age-specific associations of SBP with outcomes, patients were categorized into 4 age groups (<50, 50–59, 60–69, and 70–79 years). Age-specific HRs were attained using the previous Cox regression approach, corrected by age-specific regression dilution ratios.

Four sensitivity analyses were performed: (1) completed data analysis, which excluded patients with missing data; (2) patients with <1-year follow-up after baseline were also excluded to minimize the effect of reverse causality; (3) considering the variability of SBP, the SD of the usual SBP was counted in the analysis; and (4) the use of aspirin on or before baseline was included in the regression model as an additional adjustment. Subgroup analyses based on the categorization of usual SBP presented as a continuous variable was conducted to evaluate the risks of each outcome by stratifying sex (men, women), age (<50, 50–59, 60–69, and 70–79 years), smoking status (nonsmoker, smoker), BMI (<25, ≥25 kg/m^2), low-density lipoprotein cholesterol (<2.6, ≥2.6 mmol/L), glycated hemoglobin (<7, >7%), eGFR (<90, ≥90 mL/min per 1.73 m^2), with prescribed antihypertensive drugs (yes, no), use of different antihypertensive drugs, and Charlson Comorbidity Index (<4, ≥4) at baseline.

All significance tests were 2-tailed and the statistical significance level was defined as 0.05 presented by *P* value. Stata version 13.0 (StataCorp LLC) was the statistical software for all the analyses.

RESULTS

A total of 180 492 patients with type 2 DM satisfying the inclusion criteria were included. Among those excluded, 19 259 had a history of CVD and 656 patients failed to complete any follow-up visit after baseline. Data completion rates exceeded 80% for all of the baseline covariates except for low-density lipoprotein cholesterol (72.3%) and BMI (71.4%), as shown in Table S2. Table 1 summarizes the baseline characteristics for each subgroup categorized on the basis of SBP by multiple imputation. Overall, men accounted for 47.3% of the patients, and the mean age was 61.5 years (SD, 10.3). The average of baseline and mean SBP values were 137.0 mm Hg (SD, 17.7) and 136.5 mm Hg (SD, 13.9), respectively. Regarding regression dilution ratio, 160 709 (89%) among 180 492 patients had a valid SBP measurement at 1 year after baseline. The overall and 4 age-specific regression dilution ratios were 0.65 (overall), 0.69 (<50 years), 0.66 (50–59 years), 0.62 (60–49 years), and 0.59 (70–79 years).

During over 1.5 million person-years of follow-up (median 9.3 years), 32 545 incident CVD events occurred, compromising 15 620 cases of coronary heart disease, 16 019 cases of stroke, and 8286 cases of heart failure, as well as 11 066 events of CVD mortality, which indicated 23.8 per 1000 person-years for the incidence rate of the composite of CVD (23.4 and 7.4 per 1000 person-years for the incidence rate of CVD and CVD mortality, respectively). Cases and incidence rates of the CVD and CVD mortality events separately for each SBP group were also calculated and are presented in Table 2 and Figure S1. Generally, for all of the age groups, there was a positive and log-linear association between SBP and the risk of CVD, including coronary heart disease, stroke, heart failure, CVD mortality, and their composite events, as shown in Figure 1, with no evidence of a threshold down to 120 mm Hg. Figure S2 shows Cox regression with a restricted cubic spline that exhibited a similar pattern. Sensitivity analyses excluding patients with missing data, less than the 1-year follow-up, including the variability of SBP, and the use of aspirin as the additional adjustment by

Table 1. Baseline Characteristics Among Patients, Stratified by SBP

	Baseline SBP							
	<120 mm Hg (n=20 509)	120 to 129 mm Hg (n=35 615)	130 to 139 mm Hg (n=52 704)	140 to 149 mm Hg (n=44 201)	150 to 159 mm Hg (n=19 469)	160 to 169 mm Hg (n=5679)	≥170 mm Hg (n=2315)	Overall (N=180 492)
Men, %	48.9	49.0	47.7	45.8	45.3	45.2	44.4	47.3
Age, y	56.1 (10.3)	59.7 (10.3)	61.7 (10.1)	63.3 (9.9)	64.2 (9.6)	64.2 (9.6)	64.1 (9.7)	61.5 (10.3)
Current smoker, %	16.4	13.3%	11.2	10.3	9.8	10.2	8.3	11.8
SBP, mm Hg	114.2 (10.2)	126.5 (11.0)	135.7 (11.9)	144.7 (12.5)	153.6 (13.4)	162.8 (14.9)	177.6 (18.0)	137.0 (17.7)
Mean SBP, mm Hg	113.2 (5.5)	125.4 (2.8)	135.0 (2.9)	144.4 (2.8)	153.9 (2.8)	163.8 (2.8)	178.9 (9.4)	136.5 (13.9)
DBP, mm Hg	69.1 (7.7)	73.5 (8.8)	76.1 (9.5)	78.1 (10.1)	80.0 (10.5)	82.7 (11.3)	87.6 (12.6)	76.0 (10.2)
HbA_{1c}, %	7.4 (1.6)	7.4 (1.4)	7.4 (1.4)	7.5 (1.5)	7.6 (1.5)	7.7 (1.7)	7.8 (1.8)	7.5 (1.5)
BMI, kg/m^2	24.4 (4.0)	25.4 (4.1)	25.8 (4.8)	26.0 (4.8)	26.1 (4.3)	26.1 (5.4)	26.2 (5.3)	25.7 (4.9)
LDL-C, mmol/L	3.1 (1.0)	3.1 (1.0)	3.1 (0.9)	3.2 (1.0)	3.2 (1.0)	3.2 (1.0)	3.2 (1.0)	3.1 (0.9)
eGFR, mL/min per 1.73 m^2	112.6 (41.3)	107.5 (80.9)	104.0 (45.2)	101.8 (66.4)	100.2 (126.1)	98.5 (41.4)	96.9 (34.0)	104.5 (66.2)
Charlson Comorbidity Index	2.3 (1.3)	2.6 (1.3)	2.8 (1.3)	3.0 (1.3)	3.1 (1.3)	3.2 (1.3)	3.2 (1.4)	2.8 (1.3)
Medication use, %								
Oral antidiabetic drugs	85.4	82.6	81.6	82.5	83.3	83.7	84.8	82.7
Iinsulin	3.0	2.0	2.0	2.0	2.7	3.0	5.3	2.3
ACEIs/ARBs	12.6	21.4	30.1	40.6	49.3	54.3	56.1	32.1
β-Blockers	12.9	22.9	27.8	31.6	35.7	39.3	42.1	27.5
CCBs	13.6	28.6	36.8	42.3	48.1	53.0	60.0	35.9
Diuretics	4.6	9.6	12.2	13.5	14.8	14.0	13.8	11.5
Other antihypertensive drugs	4.7	7.1	9.1	11.1	13.3	13.5	13.9	9.4
Lipid-lowering agents	9.6	11.6	12.2	11.8	12.3	13.7	16.4	11.8

All parameters are expressed in mean (SD) unless otherwise indicated. ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

Cox regression also obtained the log-linear association between SBP and outcomes, are found in Figures S3 through S6.

Summarized adjusted HRs for the marginal effect of SBP on each outcome in the main and subgroup analyses are shown in Figure 2. From the forest plot, each 10-mm Hg higher SBP was associated with 12% (HR, 1.12; 95% CI, 1.10–1.13), 11% (HR, 1.11; 95% CI, 1.10–1.13), and 20% (HR, 1.20; 95% CI, 1.17–1.22) higher risk of composite of all CVD events, individual CVD, and CVD mortality, respectively. The interaction between SBP and age on CVD risk was significant ($P<0.001$). Considering the age-specific association, the strength of associations between SBP and CVD or CVD mortality decreased with increasing age, where HRs were constantly greater in the younger groups than the older groups. The risk in the age group of those <50 years was ≈22% larger than in the age group of those 70 to 79 years for CVD (HR, 1.33 [95% CI, 1.26–1.41] versus HR, 1.09 [95% CI, 1.07–1.11]), CVD mortality (HR, 1.45 [95% CI, 1.29–1.63] versus HR, 1.15 [95% CI, 1.11–1.18]), and all of the composite events (HR, 1.33 [95% CI, 1.26–1.40] versus HR, 1.09 [95% CI, 1.07–1.12]). This was most apparent for the risk of stroke, where each 10-mm Hg increase was accompanied by a 52% (HR, 1.52 [95% CI, 1.40–1.66]) higher risk in the group of patients <50 years, and only 6% (HR, 1.06 [95% CI, 1.03–1.09]) higher risk in the age group of 70 to 79 years. For CVD mortality, the difference between the groups was even larger (HR, 1.45 [95% CI, 1.29–1.63] versus HR, 1.15 [95% CI, 1.11–1.18]). Smokers had a 10% higher risk compared with nonsmokers for CVD (HR, 1.21 [95% CI, 1.17–1.26] versus HR, 1.10 [95% CI, 1.08–1.12]), CVD mortality (HR, 1.32 [95% CI, 1.24–1.40] versus HR, 1.18 [95% CI, 1.15–1.21]), and their composite (HR, 1.21 [95% CI, 1.17–1.26] versus HR, 1.10 [95% CI, 1.09–1.12]). Meanwhile, comparable effects were observed when stratified by sex, BMI, low-density lipoprotein cholesterol, fasting glucose, eGFR, use of diverse antihypertensive drugs, and Charlson Comorbidity Index.

Table 2. Number, Incidence Rate, and HR of CVD, CHD, Stroke, HF, CVD Mortality, and Their Composite Stratified by SD of SBP

	Baseline SBP						
	<120 mm Hg (n=20 509)	120 to 129 mm Hg (n=35 615)	130 to 139 mm Hg (n=52 704)	140 to 149 mm Hg (n=44 201)	150 to 159 mm Hg (n=19 469)	160 to 169 mm Hg (n=5679)	≥170 mm Hg (n=2315)
CVD							
Cumulative cases with event, No.	2166	5294	9379	9113	4451	1480	662
Cumulative incidence rate, %	10.6	14.9	17.8	20.6	22.9	26.1	28.6
Incidence rate (95% CI)*	13.2 (12.6–13.7)	18.7 (18.2–19.2)	22.6 (22.2–23.1)	26.8 (26.3–27.4)	30.8 (29.9–31.8)	37.1 (35.3–39.1)	43.3 (40.1–46.7)
HR (95% CI)†	1.00 (0.94, 1.07) 1	.15 (1.11, 1.20)	1.25 (1.21, 1.29)	1.36 (1.32, 1.40)	1.45 (1.39, 1.52)	1.85 (1.71, 2.00)	2.22 (1.97, 2.49)
CHD							
Cumulative cases with event, No.	1108	2628	4562	4275	2074	674	299
Cumulative incidence rate, %	5.4	7.4	8.7	9.7	10.7	11.9	12.9
Incidence rate (95% CI)*	6.6 (6.2–7.0)	9.0 (8.6–9.3)	10.6 (10.3–10.9)	11.9 (11.6–12.3)	13.5 (13.0–14.1)	15.7 (14.6–17.0)	18.1 (16.1–20.2)
HR (95% CI)†	1.00 (0.91–1.10)	1.18 (1.11–1.25)	1.29 (1.23–1.34)	1.35 (1.29–1.42)	1.44 (1.35–1.54)	1.70 (1.52–1.92)	1.95 (1.64–2.33)
Stroke							
Cumulative cases with event, No.	1043	2588	4566	4515	2233	728	346
Cumulative incidence rate, %	5.1	7.3	8.7	10.2	11.5	12.8	14.9
Incidence rate (95% CI)*	6.2 (5.8–6.6)	8.8 (8.5–9.2)	10.5 (10.2–10.9)	12.7 (12.3–13.0)	14.7 (14.1–15.3)	17.1 (15.9–18.4)	21.2 (19.1–23.6)
HR (95% CI)†	1.00 (0.91–1.10)	1.13 (1.06–1.20)	1.19 (1.14–1.25)	1.31 (1.25–1.37)	1.42 (1.33–1.51)	1.73 (1.55–1.94)	2.35 (2.00–2.77)
HF							
Cumulative cases with event, No.	368	1108	2251	2484	1348	494	233
Cumulative incidence rate, %	1.8	3.1	4.3	5.6	6.9	8.7	10.1
Incidence rate (95% CI)*	2.1 (1.9–2.4)	3.7 (3.5–3.9)	5.1 (4.9–5.3)	6.8 (6.5–7.1)	8.6 (8.2–9.1)	11.3 (10.4–12.4)	13.8 (12.2–15.7)
HR (95% CI)†	1.00 (0.85–1.17)	1.21 (1.10–1.33)	1.42 (1.33–1.51)	1.68 (1.58–1.78)	1.91 (1.76–2.07)	2.71 (2.37–3.11)	3.25 (2.66–3.97)
CVD mortality							
Cumulative cases with event, No.	613	1567	2947	3230	1747	651	311
Cumulative incidence rate,%	3.0	4.4	5.6	7.3	9.0	11.5	13.4
Incidence rate (95% CI)*	3.6 (3.3–3.9)	5.2 (4.9–5.4)	6.6 (6.3–6.8)	8.7 (8.4–9.0)	10.9 (10.4–11.4)	14.5 (13.4–15.6)	17.9 (16.0–20.0)
HR (95% CI)†	1.00 (0.88–1.13)	0.99 (0.91–1.07)	1.05 (0.99–1.11)	1.29 (1.23–1.36)	1.52 (1.41–1.64)	2.13 (1.89–2.40)	3.07 (2.58–3.65)

(*Continued*)

Table 2. Continued

	Baseline SBP						
	<120 mm Hg (n=20 509)	120 to 129 mm Hg (n=35 615)	130 to 139 mm Hg (n=52 704)	140 to 149 mm Hg (n=44 201)	150 to 159 mm Hg (n=19 469)	160 to 169 mm Hg (n=5679)	≥170 mm Hg (n=2315)
All composite events							
Cumulative cases with event, No.	2208	5373	9521	9260	4528	1516	668
Cumulative incidence rate, %	10.8	15.1	18.1	20.9	23.3	26.7	28.9
Incidence rate (95% CI)*	13.4 (12.9–14.0)	19.0 (18.5–19.5)	23.0 (22.5–23.4)	27.3 (26.7–27.8)	31.4 (30.5–32.3)	38.0 (36.2–40.0)	43.7 (40.5–47.2)
HR (95% CI)†	1.00 (0.94– 1.07)	1.15 (1.10–1.20)	1.24 (1.20–1.28)	1.35 (1.31–1.40)	1.45 (1.39–1.52)	1.87 (1.73–2.02)	2.19 (1.95–2.46)

CHD indicates coronary heart disease; CVD, cardiovascular disease; HF, heart failure; and SBP, systolic blood pressure.

*Incidence rate (cases/1000 person-years) with 95% CIs based on Poisson distribution.

†Hazard ratios (HRs) were generated by Cox proportional hazards regression adjusted with age; sex; smoking status; body mass index; glycated hemoglobin; low-density lipoprotein cholesterol; estimated glomerular filtration rate; use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, other antihypertensive drugs, oral antidiabetic drugs, insulin, or lipid-lowering agents; Charlson Comorbidity Index at baseline; and regression dilatation ratio. CIs are displayed as floating absolute risks.

DISCUSSION

This population-based cohort study is the first to identify the positive and log-linear age-specific association between SBP and risk of CVD, coronary heart disease, stroke, heart failure, and CVD-related mortality among Chinese patients with DM, with no evidence of a threshold down to 120 mm Hg, regardless of patient characteristics. The strength of these associations was enhanced with younger age and smoking but remained consistent among most of the different subpopulations.

There has been no previous study evaluating the age-specific effect of SBP on CVD among a diabetic population. Our findings reveal a log-linear relationship between SBP and risk of CVD in patients with DM, irrespective of sex or age, which concurs with evidence from previous large cohort studies in general populations, including the Prospective Studies Collaboration, the China Kadoorie Biobank, the Asia Pacific Cohort Studies Collaboration, and Clinical Practice Research Datalink.[18–21] Of interest, the strength of the effect for each 10 mm Hg of SBP on CVD among the diabetic population was ≈10% in this study, which was smaller than the effect (≈40%) observed in the general population. Indeed, a landmark observational cohort study from the UKPDS (United Kingdom Prospective Diabetes Study) identified increases of ≈10% and ≈20% risk of myocardial infarction and stroke for each 10 mm Hg of SBP, respectively.[4] This supports our hypothesis that the presence of DM influences the impact of SBP on outcome events. One potential biological explanation is that patients with DM who have relatively higher CVD risks because of irreversible vascular damage, may be less susceptible to the impact of SBP on adverse events.

Conversely, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) RCT showed a greater reduction in the risk of stroke but not in overall cardiovascular events for an SBP treatment target <120 mm Hg compared with <140 mm Hg.[41] However, they claimed this result was attributable to being underpowered as the rate of events was only half of the expected rate as per the planned sample size. Another RCT from SPRINT (Systolic Blood Pressure Intervention Trial), with a similar study design as the ACCORD trial but with over double the total number of patients without DM, demonstrated that patients with an SBP treatment target <120 mm Hg were at lower risk for CVD than those with a target <140 mm Hg.[42] Although several observational studies have found J- or U-shaped associations between SBP and risk of CVD,[15,16,43–46] there is no consensus on such a phenomenon.[44,45] One possible reason may be reverse causality because of low incident event rates, short follow-up periods,

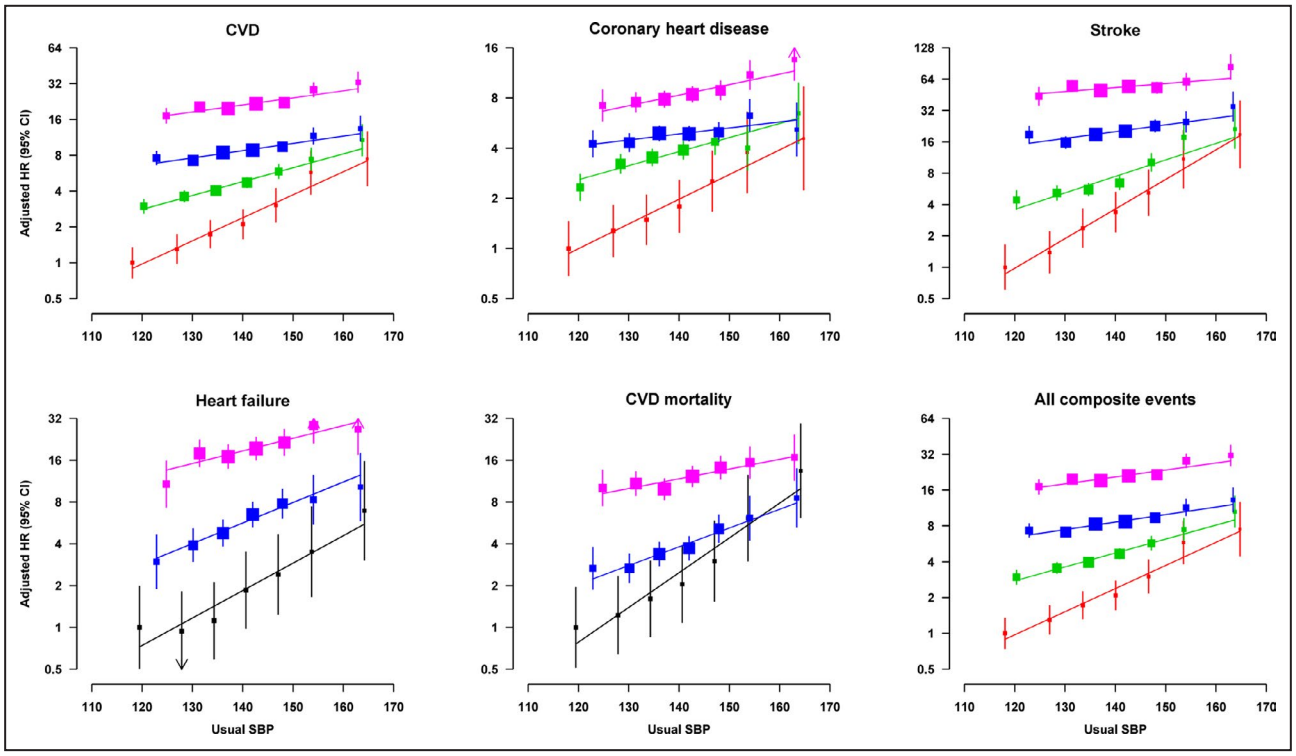

Figure 1. Age-specific adjusted hazard ratios (HRs) for the risk of cardiovascular disease (CVD), coronary heart disease, stroke, heart failure, CVD mortality, and their composite with increasing usual systolic blood pressure (SBP) by multivariable Cox regressions.

HR was adjusted by age; sex; smoking status; body mass index; glycated hemoglobin; low-density lipoprotein cholesterol; estimated glomerular filtration rate; the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, other antihypertensive drugs, oral antidiabetic drugs, insulin, or lipid-lowering agents; Charlson Comorbidity Index; and age-specific regression dilatation ratio. The red, green, blue, and pink lines represent the age groups <50, 50 to 59, 60 to 69, and 70 to 79 years, respectively. As a result of a low incidence of heart failure and CVD mortality in the age groups <50 and 50 to 59 years, these age groups were combined as <60 years (black line). The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks.

and single-point measurement of SBP. A previous study on BP trajectories initiated 20 years before the mortality of patients >60 years identified a declining trend in SBP in the last decade of life, with steeper decreases from 2 years before death.[47] Our present study minimizes the likelihood of reverse causality since it included patients without a history of CVD at baseline, a large number of events over a 10-year follow-up period, and multiple measurements of SBP.

It is worth noting that the results from our subgroup analyses illustrated the magnitude of the effect of SBP on CVD attenuated with increased age, yet the positive and log-linear associations from 120 mm Hg of SBP still held for patients <79 years. Several international guidelines including the JNC 8 (Eighth Joint National Committee) report and the International Diabetes Federation recommended a less stringent SBP treatment target (<150 mm Hg) for elderly patients (eg, patients ≥60 years in JNC 8).[6,9] Nevertheless, a previous RCT from SHEP (Systolic Hypertension in the Elderly Program) for people ≥60 years displayed a 32% risk reduction on CVD from treating SBP to ≈140 mm Hg compared with ≈150 mm Hg.[48] SPRINT also demonstrated that for patients ≥75 years, an SBP treatment target of <120 mm Hg resulted in a 34% lower risk of CVD compared with the target of <140 mm Hg.[49] Several observational population-based cohorts conducted in the general population also obtained a weakened pattern with increased age,[18–20] which were similar to the current results. Previous studies demonstrated that older patients have higher white-coat effect compared with younger patients,[50–52] so this may result in the lower effect of BP on risk of outcome events in older patients. On the other hand, SPRINT revealed no significant differences in serious adverse events between an SBP treatment target of <120 mm Hg and <140 mm Hg even in patients with hypertension ≥75 years without DM.[42,49] Moreover, several RCTs concluded that the efficacy of antihypertensive drugs were not attenuated with age,[53–55] and an RCT even showed a significantly greater relative risk reduction with increasing age.[56] However, the ACCORD trial concluded that the serious adverse events attributed to an SBP treatment target of <120 mm Hg was significantly

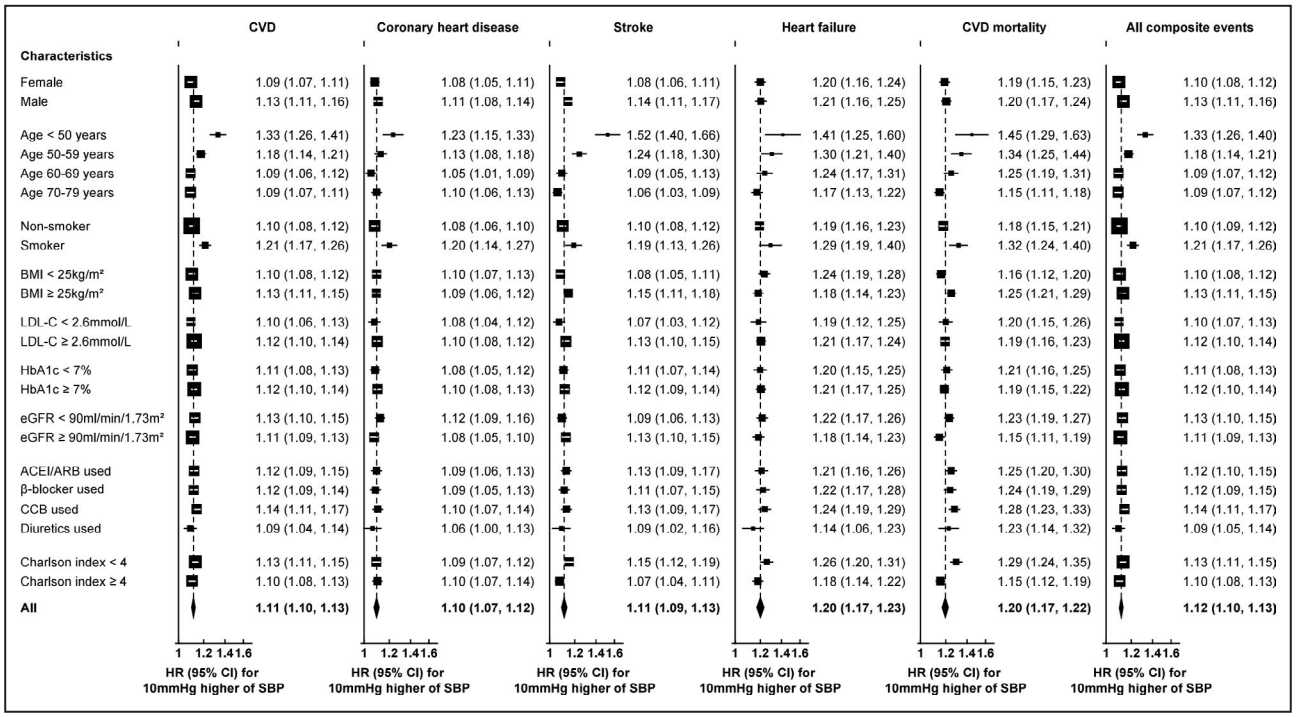

Figure 2. Adjusted hazard ratios (HRs) for the risk of cardiovascular disease (CVD), coronary heart disease, stroke, heart failure, CVD mortality, and their composite events with each 10-mm Hg increasing in SBP by stratifying patient characteristics at baseline using multivariable Cox regressions.

HR was adjusted by age; sex; smoking status; body mass index (BMI); low-density lipoprotein cholesterol (LDL-C); glycated hemoglobin (HbA_{1c}); estimated glomerular filtration rate (eGFR); use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), β-blockers, calcium channel blockers (CCBs), diuretics, other antihypertensive drugs, oral antidiabetic drugs, insulin, or lipid-lowering agents; Charlson index; and age-specific regression dilatation ratio. The area of the square is inversely proportional to the variance log HR.

higher than that from the target of <140 mm Hg.[41] Hence, a lower SBP target may be suitable for younger patients as they might be able to achieve a lower SBP target with fewer adverse effects.

Study Strengths and Limitations

There were number of strengths in this study. A large number of patients with DM were included in this study; hence, the estimation on the intensity of association would be more accurate as a result of a larger number of events. Various statistical analysis methods used, comprising multiple repeated measurement for SBP, regression, and stratified analyses, and sensitivity analyses allowed a comparably comprehensive evaluation on the association between SBP and outcome events. Relevant baseline covariates were collected precisely and conveniently since HA's computerized administrative database made it accessible to patients' clinical characteristics, eg, laboratory results, disease attributes, and treatment modalities. To prevent selection bias, multiple imputations were used to substitute for missing data.

There were also several limitations in this study. First, as a retrospective cohort study, it evaluated only associations and not causation. Other study designs such as RCTs are needed to validate the association between BP and CVD among patients with DM in the Chinese context. Nonetheless, a low probability of reverse causation was observed in the current study as all patients were without a history of CVD at baseline, and the results were highly parallel according to sensitivity analysis when only including patients with a follow-up period of >1 year. Second, other drug therapies and lifestyle interventions (such as regular exercise habit and diet modification) were not taken into consideration, leading to the decrease of CVD. However, the disease markers have been included such as severity of chronic kidney disease together with some key clinical parameters incorporating BMI, glycated hemoglobin, and lipids, to a certain extent, indicating the intensity of disease severity and lifestyle modification. Lastly, individual variation could result in different patterns of association between BP and CVD risk in different Chinese diabetic populations or populations in other regions. Therefore, our findings may not be generalizable to other populations. Further study is warranted to evaluate the effect of BP in these patients.

CONCLUSIONS

This population-based cohort study found that the association between SBP and CVD among Chinese patients with DM without CVD was positive and log-linear, with no evidence of any threshold down to 120 mm Hg. The strength of these associations was greater with younger age and smoking habit, with a consistent pattern observed with most of the different patients' characteristics. The findings from this study suggest that younger patients and smokers may receive the most benefit from a lower BP target, and thus individual SBP target in patients with DM without CVD may be appropriate. An RCT is necessary to validate our findings.

ARTICLE INFORMATION

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Wan and Lam contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis and interpretation of the results, and wrote the article. Yu, Chin, Wong, Chan, and Chen contributed to the interpretation of the results and wrote the article. All authors reviewed and edited the article. Wan is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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Supplementary Materials

Tables S1–S2
Figures S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Definition of the diseases.

Event	ICPC-2 codes	ICD-9-CM codes
CHD	K74-K76	410-414
Heart Failure	K77	428
Stroke	K89-K91	430-438

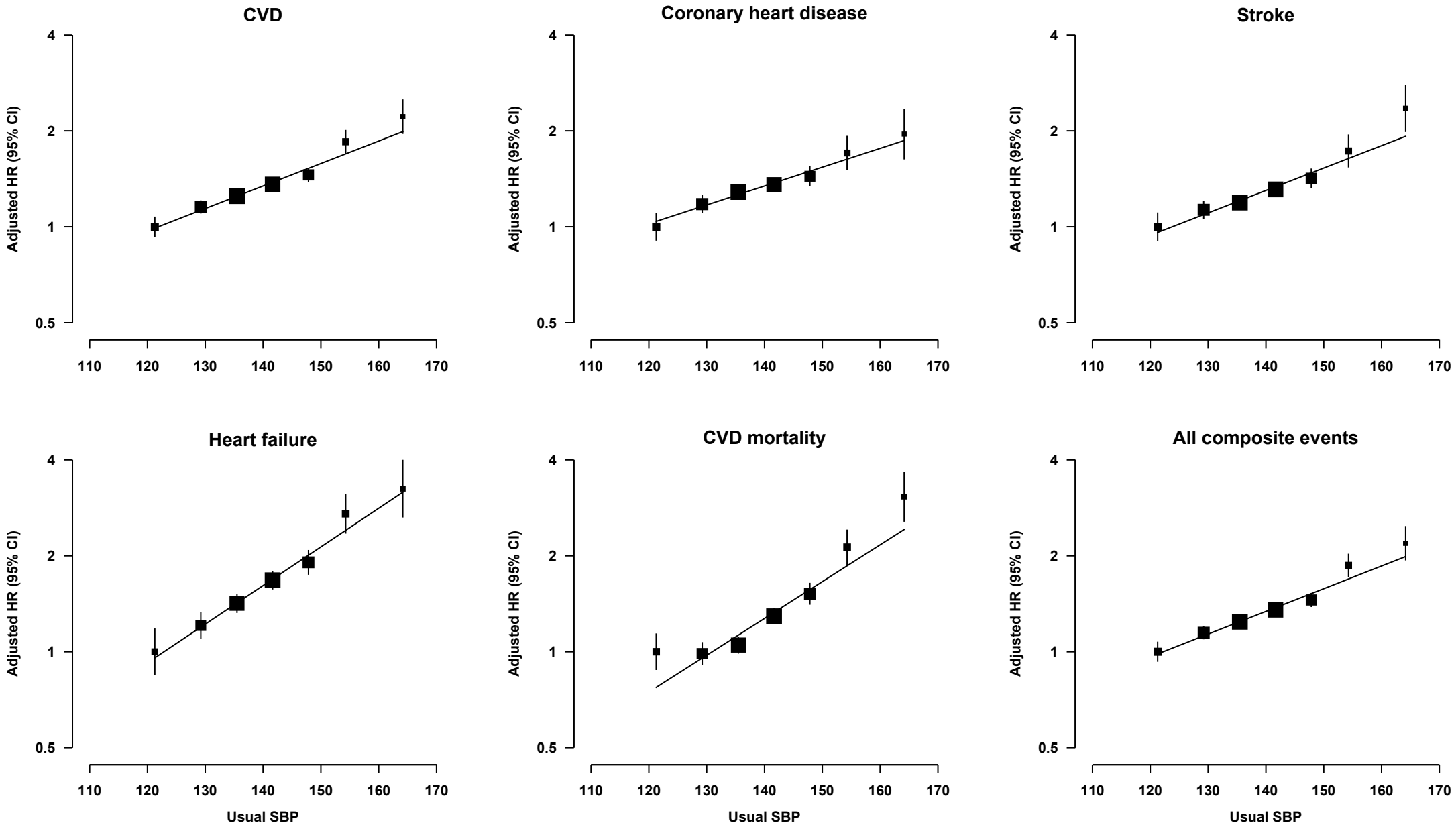
ICPC-2 = the International Classification of Primary Care-2; ICD-9-CM = the International Classification of Diseases, Ninth Edition, Clinical Modification; DM = Diabetes Mellitus; CHD = Coronary heart disease; NA = Not applicable

Table S2. Data completion rate of the information among subjects.

	Total (N = 180,492)
Age	100.0% (180,492)
Sex	100.0% (180,492)
Smoking status	98.4% (177,534)
BMI	71.4% (128,815)
SBP	100.0% (180,492)
DBP	100.0% (180,492)
HbA1c	93.0% (167,945)
LDL-C	72.3% (130,459)
eGFR	82.9% (149,643)
Charlson Index	100.0% (180,492)
Use of oral anti-diabetic drugs	100.0% (180,492)
Use of Insulin	100.0% (180,492)
Use of ACEI/ARB	100.0% (180,492)
Use of β-blocker	100.0% (180,492)
Use of CCB	100.0% (180,492)
Use of Diuretic	100.0% (180,492)
Use of other anti-hypertensive drugs	100.0% (180,492)
Use of lipid-lowering agents	100.0% (180,492)

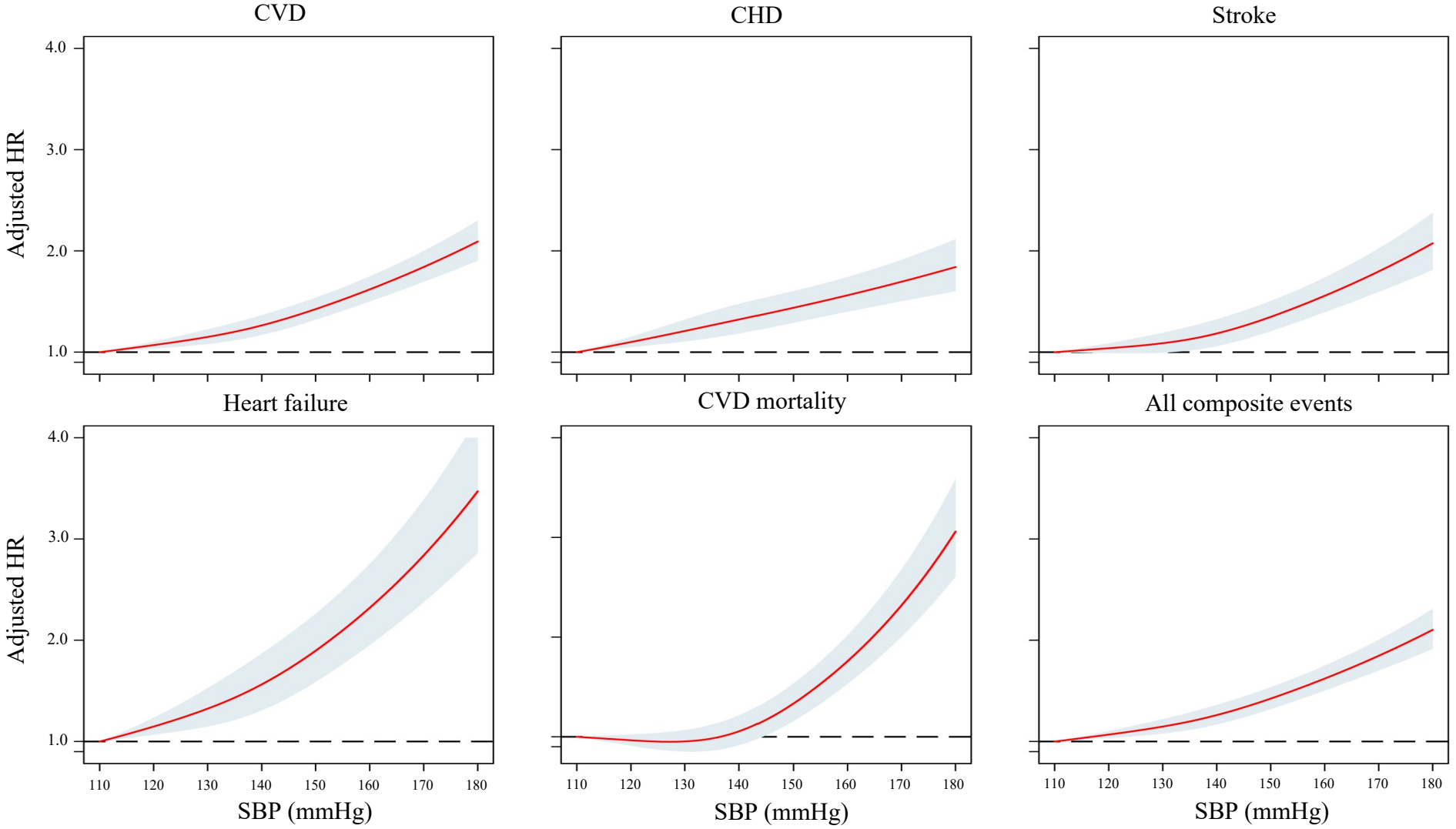
BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HbA1c = Haemoglobin A1c; LDL-C = Low-density Lipoprotein-Cholesterol; eGFR = estimated glomerular filtration rate; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker.

Figure S1. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and their composite with with increasing usual SBP by multivariable Cox regressions.



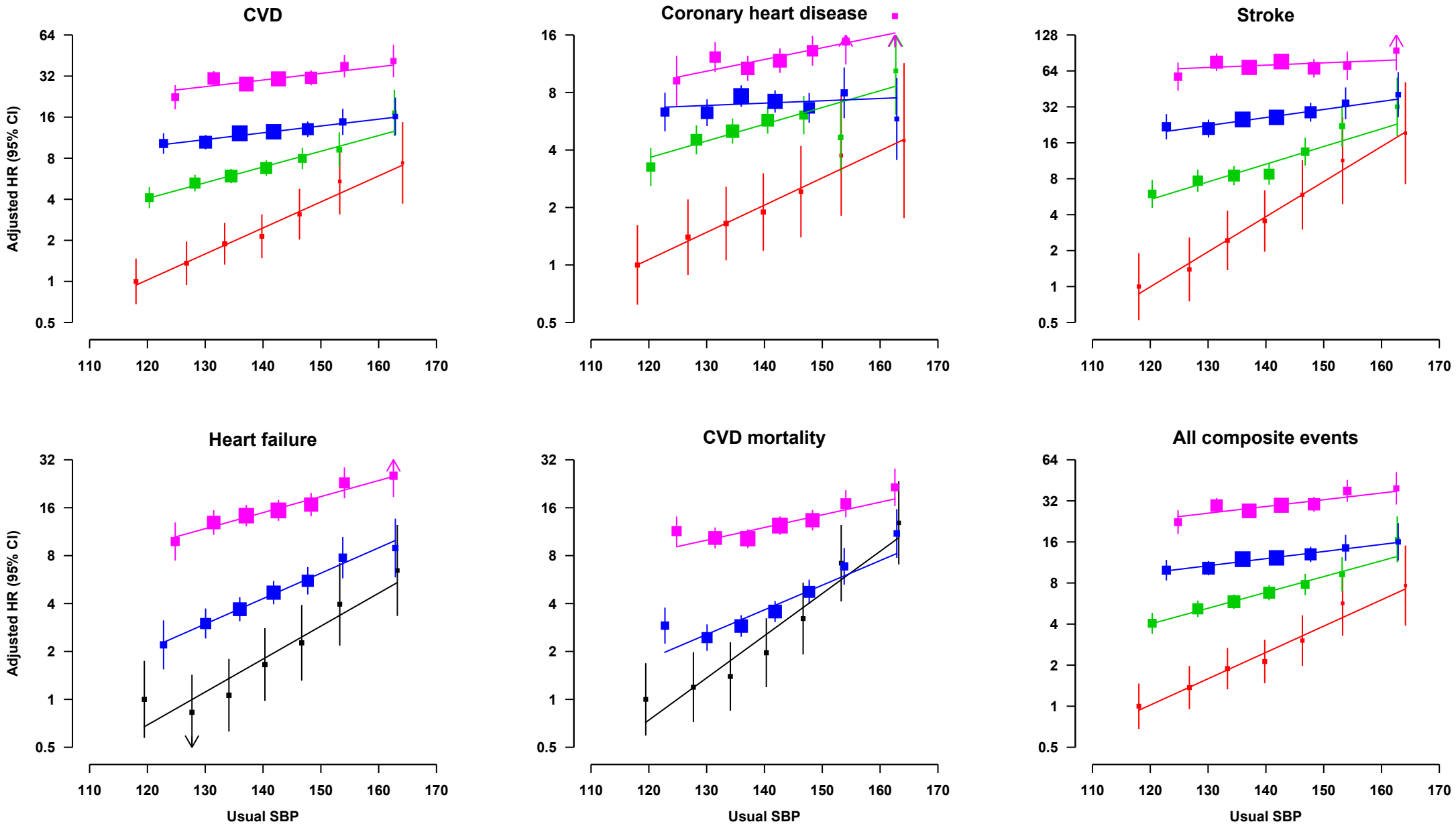
HR was adjusted by age, sex, smoking status, body mass index, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, Charlson's index and regression dilatation ratio. The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.

Figure S2. Adjusted hazard ratios for incidence of CVD, CHD, stroke, heart failure, CVD mortality and their composite with increasing SD of SBP by multivariable Cox regressions with restricted cubic spline.



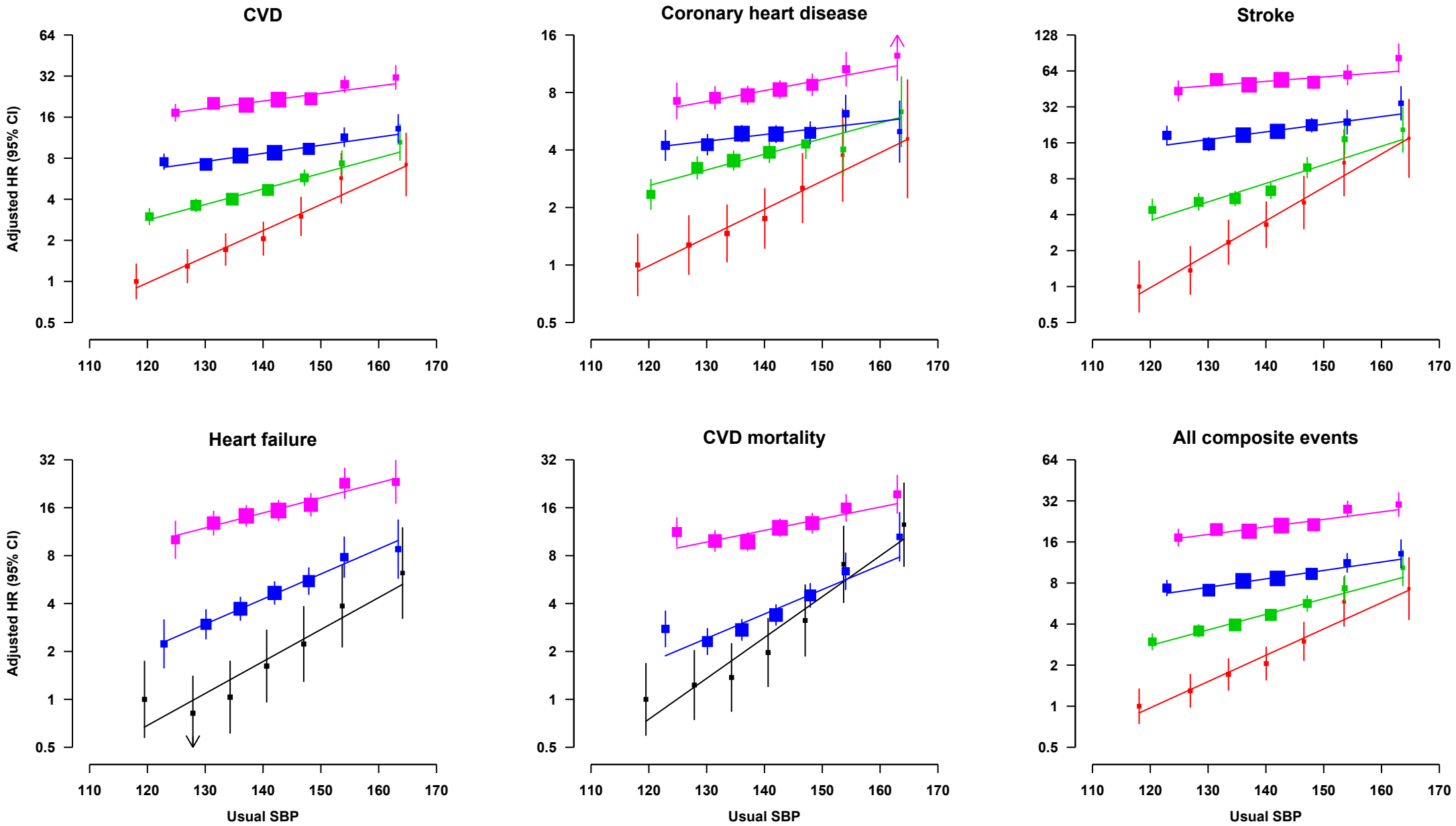
Hazard ratios were adjusted by age, sex, smoking status, body mass index, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, Charlson's Index and regression dilatation ratio. Shaded region represents 95% confidence intervals. SBP=Systolic blood pressure; CVD=Cardiovascular disease; CHD=Coronary heart disease;

Figure S3. After excluding patients with missing data, age-specific adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and their composite with with increasing usual SBP by multivariable Cox regressions.



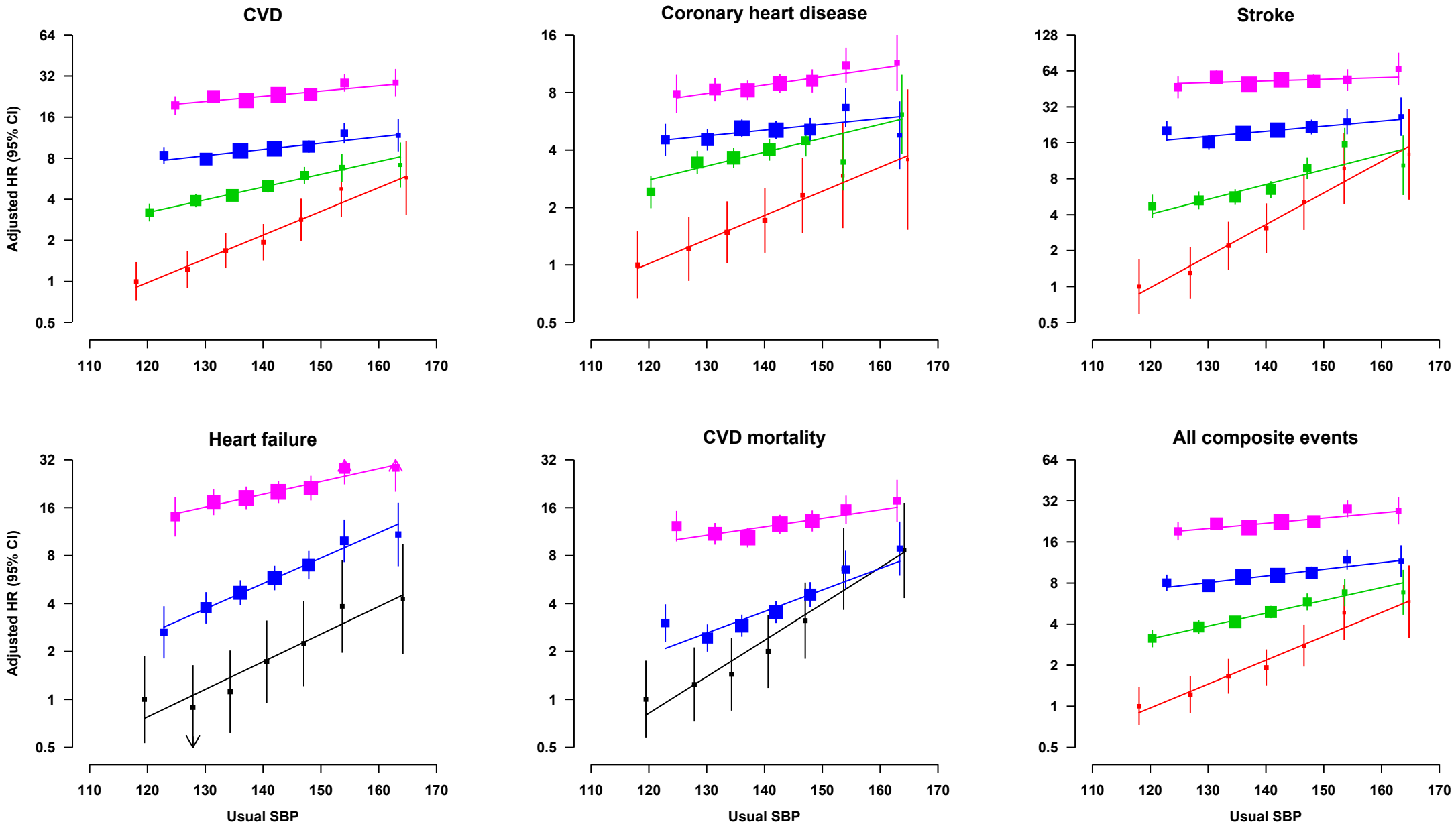
HR was adjusted by age, sex, smoking status, body mass index, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, Charlson's index and age-specific regression regression dilatation ratio. Red, green, blue and pink line were <50, 50-59, 60-69 and 70-79 age group. Due to low incidence heart failure and CVD mortality in <50 and 50-59 age group, these age groups were combined as < 60 age group (black line). The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.

Figure S4. After excluding patients with less than 1 year follow-up, age-specific adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and their composite with with increasing usual SBP by multivariable Cox regressions.



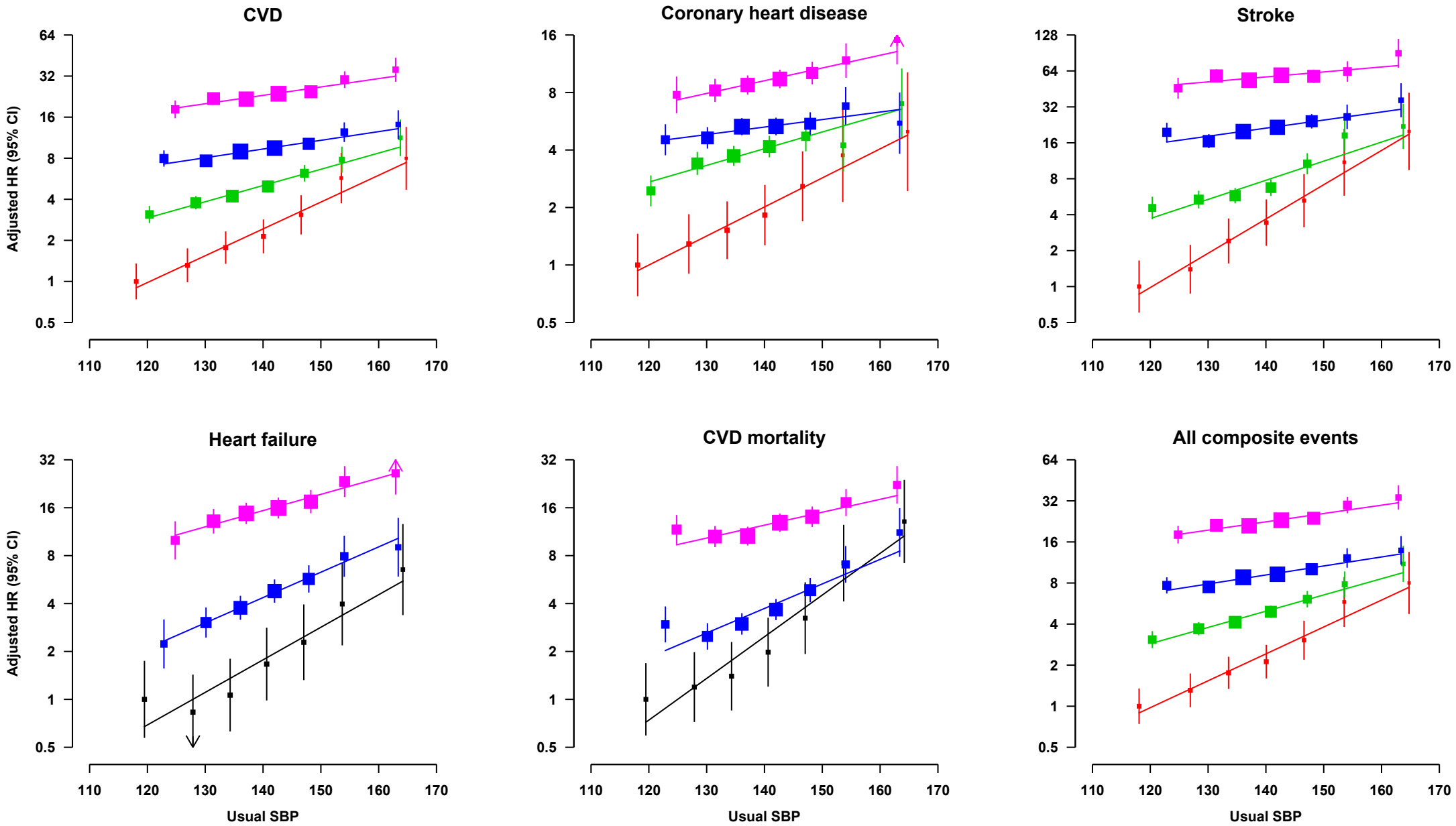
HR was adjusted by age, sex, smoking status, body mass index, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, Charlson's index and age-specific regression regression dilatation ratio. Red, green, blue and pink line were <50, 50-59, 60-69 and 70-79 age group. Due to low incidence heart failure and CVD mortality in <50 and 50-59 age group, these age groups were combined as < 60 age group (black line). The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.

Figure S5. After including the variability of SBP (Standard deviation of SBP), age-specific adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and their composite with with increasing usual SBP by multivariable Cox regressions.



HR was adjusted by age, sex, smoking status, body mass index, Standard deviation of SBP, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, Charlson's index and age-specific regression regression dilatation ratio. Red, green, blue and pink line were <50, 50-59, 60-69 and 70-79 age group. Due to low incidence heart failure and CVD mortality in <50 and 50-59 age group, these age groups were combined as < 60 age group (black line). The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.

Figure S6. After including the additional confounding variable for the usage of aspirin on or before baseline, the variability of SBP (Standard deviation of SBP), age-specific adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and their composite with with increasing usual SBP by multivariable Cox regressions.



HR was adjusted by age, sex, smoking status, body mass index, Standard deviation of SBP, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral anti-diabetic drugs, insulin, lipid-lowering agent, aspirin, Charlson's index and age-specific regression regression dilatation ratio. Red, green, blue and pink line were <50, 50-59, 60-69 and 70-79 age group. Due to low incidence heart failure and CVD mortality in <50 and 50-59 age group, these age groups were combined as < 60 age group (black line). The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.