

Effect of Blood Pressure on Cardiovascular Outcomes: A 15-Year Prospective Cohort Study

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Research Article

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Abstract

Objective

The association between blood pressure(BP) and cardiovascular outcomes has not been well investigated by large prospective studies on Chinese. We aim to analyze the association of BP with cardiovascular outcomes in Chinese population.

Method

We included a total of 4,569 adults aged 40–90 years from the China Health and Nutrition Survey (CHNS) cohort. Cox proportional hazards regression models were used to estimate hazard ratios and 95% CIs. Restricted cubic spline analyses were used to explore linear and nonlinear relationships of BP with cardiovascular outcomes.

Result

With a mean follow-up of 12.1 years, a total of 4,569 individuals were enrolled in our study, of whom 403 developed cardiovascular outcomes. Multivariable adjusted Cox models showed a strong positive association between BP and cardiovascular outcomes. SBP was significantly associated with composite outcome(HR per 10 mmHg 1.23[1.16–1.29]), myocardial infarction(MI)(HR per 10 mmHg 1.17[1.07–1.27]), and stroke(HR per 10 mmHg 1.29[1.21–1.38]). DBP was significantly associated with composite outcome(HR per 10 mmHg 1.32[1.20–1.44]), MI(HR per 10 mmHg 1.26[1.10–1.44]), and stroke(HR per 10 mmHg 1.39[1.25–1.55]). Restricted cubic spline analyses showed linear relationships of either SBP or DBP with composite outcome, MI and stroke.

Conclusion

Either SBP or DBP is independently and linearly related to the risk of cardiovascular outcomes. These associations are steeper for stroke than for MI, and vary widely by age, use of antihypertensive treatment, and diabetes status.

Introduction

Cardiovascular disease (CVD) has been the leading cause of death in China, accounting for 3.72 million deaths in 2013[1][2][3]. In the past decades, stroke and ischemic heart disease have become the top 2 causes for years of life lost[4]. Hypertension is a highly important risk factor for CVD, with a strong, direct, linear, and continuous relationship between blood pressure(BP) and CVD risk[5][6]. Specifically, the Prospective Studies Collaboration[6] pooled data of 61 cohorts recruited between 1950 and 1990 reported that the risk of CVD increased steadily with progressively higher levels of baseline systolic blood

pressure(SBP) and diastolic blood pressure(DBP), above a usual SBP and DBP of 115 and 75 mmHg, respectively. For a 20 mm Hg higher level of SBP and 10 mm Hg higher level of DBP the risk of CVD was 2-fold higher.

Despite the high burden of CVD in China, previous large prospective studies focused little on the association between BP and adverse cardiovascular outcomes in Chinese population. In order to better prevent adverse cardiovascular outcomes, more evidence on the association between BP and cardiovascular outcomes is needed. Thus, we investigated the association of BP levels with adverse cardiovascular outcomes among 4,569 adults from nine provinces around China.

Method

1.1. Study design

The CHNS was an ongoing open cohort survey of ten waves (1989–2015). The samples of nine provinces in China were obtained by a multistage, random cluster process, and the detailed CHNS samples and cohort profile information were described elsewhere [7][8]. All methods were performed in accordance with the relevant guidelines and regulations[7][8].

1.2. Study population

For this study, data were drawn from the 2000–2015 CHNS cycles. We included Chinese residents with BP data collected at age 40 to 90 years and with subsequent follow-up time available($n = 6,418$). After excluding persons who had a history of stroke or myocardial infarction($n = 141$), persons who were followed up only until 2006 and did not participate in the later follow-up survey in 2015($n = 1,138$), and those without complete BP measure data at baseline($n = 570$). As a result, 2,145 men and 2,424 women were available for analysis.

1.3. Exposure, covariates and outcomes

Participants received detailed physical examinations that included weight, height, arm and head circumference, mid-arm skinfold measurements, and BP. BP was obtained after a 10-minute rest in a seat, and the mean BP values were used. All measures were taken by trained staff using the World Health Organization standard protocol.

Detailed information on history of diseases, sociodemographic and lifestyle factors was collected at each wave using a structured questionnaire. Smoking status was classified into two categories as follows: current smoker or not. Drinking status was divided into two groups: current drinker or not. Diabetes was identified by self-reports of a history of diabetes diagnosis. The biomarker data collected in CHNS 2009 involves the release of 26 fasting blood measures on individuals aged 7 and older. Fasting blood was

taken early in the morning and prepared for further testing in a national central lab in Beijing (medical laboratory accreditation certificate ISO 15189: 2007).

Incident CVD was defined by a self-report history based on a doctor's diagnosis or treatment history for CVD during the follow-up period (2000–2015). The primary outcome in our study was a composite of the first episode of myocardial infarction (MI) or stroke during the observation period. Death was not part of the primary outcome. Cases were censored at the date of diagnosis of MI, stroke or the final visit, whichever came first.

1.4. Statistical analysis

The baseline characteristics of study participants were presented as mean \pm standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables. Mantel-Haenszel χ^2 test was used for categorical variables. T-test was used for continuous variables which were normally distributed and Wilcoxon rank-sum test was used for variables which were not normally distributed.

Cox proportional hazards models were used to explore the relation between BP level and disease incidence. Fully adjusted models were adjusted for potential confounders including age, gender (male or female), body mass index (BMI, kg/m²), current drinker (no or yes), current smoker (no or yes), diabetes (no or yes), taking antihypertensive drugs (no or yes) and site (rural or urban). To examine the independent association of SBP and DBP with disease risk, we further ran a multivariable model including both SBP and DBP. Tests for linear trend were computed by modeling the median values of each category as a continuous variable in regression models. In addition, we also used restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th centiles to flexibly model the association of BP with disease risk[9].

Result

The baseline characteristics of the 4569 participants were shown in Table 1. Within a mean follow-up of 12.1 years, a total of 403 adverse cardiovascular events occurred, including 173 MI and 263 strokes.

Table 1
Baseline clinical characteristics of participants

Characteristics	Total	Gender		P
		Female	Male	
Age(year)	52.00(46.00–61.00)	52.00(46.00–61.00)	52.00(46.00–61.00)	0.620
Gender				
female	2424(53.05%)	NA	NA	
male	2145(46.95%)	NA	NA	
BMI(kg/m ²)	22.91(20.76–25.17)	23.24(21.00–25.49)	22.54(20.55–24.77)	< .001
SBP(mmHg)	120.00(110.00–132.00)	120.00(110.00–132.00)	121.00(112.00–133.00)	< .001
DBP(mmHg)	80.00(71.00–87.00)	79.00(70.00–85.00)	80.00(73.00–88.00)	< .001
Antihypertensive drugs				
no	4204(93.69%)	2216(92.99%)	1988(94.49%)	0.040
yes	283(6.31%)	167(7.01%)	116(5.51%)	
Current smoker				
no	3030(67.54%)	2249(93.94%)	781(37.33%)	< .001
yes	1456(32.46%)	145(6.06%)	1311(62.67%)	
Current drinker				
no	2833(63.79%)	2088(89.23%)	745(35.46%)	< .001
yes	1608(36.21%)	252(10.77%)	1356(64.54%)	
Diabetes				
no	4267(98.18%)	2272(97.80%)	1995(98.62%)	0.046
yes	79(1.82%)	51(2.20%)	28(1.38%)	
Site				
urban	1516(33.18%)	807(33.29%)	709(33.05%)	0.864
rural	3053(66.82%)	1617(66.71%)	1436(66.95%)	
Composite outcome				
no	4166(91.18%)	2242(92.49%)	1924(89.70%)	< .001

Characteristics	Total	Gender		
		Female	Male	P
yes	403(8.82%)	182(7.51%)	221(10.30%)	

2.1. Association of BP level with composite outcome

Table 2 displays the association of BP level with composite outcome. In multivariable adjusted models(model 2), SBP and DBP showed a linear association with composite outcome, respectively. Compared with participants with SBP 0-130 mmHg, the multivariable adjusted HRs[95% CIs] (model 2) were 1.48[1.09-2.00], 2.26[1.69–3.02], 3.15[2.15–4.62], and 3.90[2.25–6.75] for composite outcome in participants with SBP 130–140, 140–160, 160–180, and ≥ 180 mmHg, respectively; a significant positive trend in categorized SBP for incident composite outcome (P for trend < 0.001) was observed; each additional 10 mmHg of SBP was associated with a 23% higher probability of developing composite outcome(1.23[1.16–1.29]). However, in a mutually adjusted model(model 3) including both SBP and DBP, the association with the risk of composite outcome was positive for SBP, but not significant for DBP.

Multivariable adjusted restricted cubic spline analyses showed a linear association of SBP (P for linearity < 0.001 , model 2; P for linearity < 0.001 , model 1) and DBP (P for linearity < 0.001 , model 2; P for linearity < 0.001 , model 1) with composite outcome, respectively (Fig. 1; Figure s1 in appendix). Multivariable adjusted restricted cubic spline analyses (model 3) showed a linear association of SBP with composite outcome; no significant linear or nonlinear relationships of DBP with composite outcome were observed (Figure s2 in appendix).

In subgroup analysis, SBP and DBP were more strongly associated with composite outcome in 40–65 age group, non-use of antihypertensive drugs group, and non-history of diabetes group(Fig. 2 and Fig. 3).

Table 2
Associations of BP with composite outcome

	Model 1		Model 2		Model 3	
	HR[95%CI]	P	HR[95%CI]	P	HR[95%CI]	P
SBP(mmHg)						
0-130	1.00		1.00		1.00	
130-140	1.58[1.20-2.09]	0.001	1.48[1.09-2.00]	0.011	1.34[0.97-1.84]	0.072
140-160	2.69[2.07-3.48]	< .001	2.26[1.69-3.02]	< .001	1.92[1.38-2.67]	< .001
160-180	3.84[2.71-5.43]	< .001	3.15[2.15-4.62]	< .001	2.46[1.57-3.87]	< .001
>=180	5.51[3.32-9.15]	< .001	3.90[2.25-6.75]	< .001	2.78[1.46-5.28]	0.002
P for trend		< .001		< .001		< .001
10mmHg increase	1.28[1.23-1.34]	< .001	1.23[1.16-1.29]	< .001	1.18[1.10-1.27]	< .001
DBP(mmHg)						
0-80	1.00		1.00		1.00	
80-90	1.89[1.48-2.43]	< .001	1.71[1.30-2.25]	< .001	1.40[1.06-1.86]	0.019
90-100	2.57[1.94-3.39]	< .001	2.24[1.66-3.04]	< .001	1.53[1.09-2.15]	0.014
100-110	3.59[2.46-5.23]	< .001	2.58[1.68-3.95]	< .001	1.36[0.82-2.24]	0.230
>=110	4.80[2.80-8.25]	< .001	2.97[1.64-5.37]	< .001	1.17[0.58-2.36]	0.667
P for trend		< .001		< .001		0.162
10mmHg increase	1.45[1.34-1.56]	< .001	1.32[1.20-1.44]	< .001	1.09[0.96-1.23]	0.167
Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site. Model 3 based on model 2, mutually adjusted for SBP and DBP.						

2.2. Association of BP level with MI

Table 3 displays the association of BP level with MI. In multivariable adjusted models(model 2), SBP and DBP showed a linear association with MI, respectively. Compared with participants with SBP 0-130 mmHg, the multivariable adjusted HRs[95% CIs] were 1.42[0.91–2.21], 1.84[1.18–2.87], 2.75[1.53–4.92], and 2.13[0.81–5.64] for MI in participants with SBP 130–140, 140–160, 160–180, and \geq 180 mmHg, respectively; a significant positive trend in categorized SBP for incident MI (P for trend < 0.001) was observed; each additional 10 mmHg of SBP was associated with a 17% higher probability of developing MI(1.17[1.07–1.27]). However, in a mutually adjusted model(model 3) including both SBP and DBP, the association with the risk of MI was positive for SBP, but not significant for DBP.

Multivariable adjusted restricted cubic spline analyses showed a linear association of SBP (P for linearity < 0.001, model 2; P for linearity < 0.001, model 1) and DBP (P for linearity 0.001, model 2; P for linearity < 0.001, model 1) with MI, respectively (Fig. 1; Figure s1 in appendix). The risk of MI might be higher in low DBP level group(model 2, Fig. 1). Multivariable adjusted restricted cubic spline analyses (model 3) showed a linear association of SBP with MI; no significant linear or nonlinear relationships of DBP with MI were observed (Figure s2 in appendix).

In subgroup analysis, SBP was more strongly associated with MI in 40–65 age group, non-use of antihypertensive drugs group, non-history of diabetes group, non-current smoker, non-current drinker, and rural site group. DBP was more strongly associated with MI in male group, non-use of antihypertensive drugs group, non-history of diabetes group, non-current smoker, and non-current drinker (Figure s3 and Figure s4).

Table 3
Associations of BP with MI

	Model 1		Model 2		Model 3	
	HR[95%CI]	P	HR[95%CI]	P	HR[95%CI]	P
SBP(mmHg)						
0-130	1.00		1.00		1.00	
130-140	1.50[0.99-2.28]	0.056	1.42[0.91-2.21]	0.122	1.27[0.80-2.03]	0.310
140-160	2.21[1.47-3.31]	< .001	1.84[1.18-2.87]	0.007	1.54[0.93-2.55]	0.093
160-180	3.55[2.09-6.02]	< .001	2.75[1.53-4.92]	0.001	2.09[1.05-4.19]	0.037
>=180	3.41[1.37-8.48]	0.008	2.13[0.81-5.64]	0.126	1.47[0.49-4.43]	0.490
P for trend		< .001		< .001		0.062
10mmHg increase	1.23[1.15-1.32]	< .001	1.17[1.07-1.27]	< .001	1.12[0.99-1.25]	0.062
DBP(mmHg)						
0-80	1.00		1.00		1.00	
80-90	1.36[0.94-1.98]	0.106	1.29[0.86-1.94]	0.211	1.12[0.73-1.70]	0.610
90-100	2.39[1.60-3.55]	< .001	2.10[1.36-3.24]	0.001	1.58[0.97-2.59]	0.067
100-110	3.01[1.70-5.33]	< .001	2.41[1.29-4.50]	0.006	1.47[0.70-3.12]	0.311
>=110	1.84[0.57-5.87]	0.305	1.14[0.34-3.82]	0.826	0.58[0.15-2.19]	0.417
P for trend		< .001		0.004		0.468
10mmHg increase	1.36[1.21-1.53]	< .001	1.26[1.10-1.44]	0.001	1.11[0.92-1.34]	0.274
Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site. Model 3 based on model 2, mutually adjusted for SBP and DBP.						

2.3. Association of BP level with stroke

Table 4 displays the association of BP level with stroke. In multivariable adjusted models(model 2), SBP and DBP showed a linear association with stroke, respectively. Compared with participants with SBP 0-130 mmHg, the multivariable adjusted HRs[95% CIs](model 2) were 1.44[0.97–2.14], 2.55[1.78–3.65], 4.21[2.69–6.60], and 6.14[3.34–11.29] for stroke in participants with SBP 130–140, 140–160, 160–180, and \geq 180 mmHg, respectively; a significant positive trend in categorized SBP for incident stroke (P for trend < 0.001) was observed; each additional 10 mmHg of SBP was associated with a 29% higher probability of developing stroke(1.29[1.21–1.38]). However, in a mutually adjusted model(model 3) including both SBP and DBP, the association with the risk of stroke was positive for SBP, but not significant for DBP.

Multivariable adjusted restricted cubic spline analyses showed a linear association of SBP (P for linearity < 0.001, model 2; P for linearity < 0.001, model 1) and DBP (P for linearity < 0.001, model 2; P for linearity < 0.001, model 1) with stroke, respectively (Fig. 1; Figure s1 in appendix). Multivariable adjusted restricted cubic spline analyses (model 3) showed a linear association of SBP with stroke; no significant linear or nonlinear relationships of DBP with stroke were observed (Figure s2 in appendix).

In subgroup analysis, SBP and DBP were more strongly associated with stroke in 40–65 age group, non-use of antihypertensive drugs group, and non-history of diabetes group(Figure s5 and Figure s6).

Table 4
Associations of BP with stroke

	Model 1		Model 2		Model 3	
	HR[95%CI]	P	HR[95%CI]	P	HR[95%CI]	P
SBP(mmHg)						
0-130	1.00		1.00		1.00	
130-140	1.58[1.10-2.26]	0.013	1.44[0.97-2.14]	0.068	1.31[0.87-1.97]	0.200
140-160	3.04[2.20-4.19]	< .001	2.55[1.78-3.65]	< .001	2.18[1.45-3.28]	< .001
160-180	5.00[3.34-7.50]	< .001	4.21[2.69-6.60]	< .001	3.32[1.94-5.67]	< .001
>=180	8.36[4.80-14.54]	< .001	6.14[3.34-11.29]	< .001	4.44[2.14-9.22]	< .001
P for trend		< .001		< .001		< .001
10mmHg increase	1.34[1.27-1.42]	< .001	1.29[1.21-1.38]	< .001	1.25[1.15-1.37]	< .001
DBP(mmHg)						
0-80	1.00		1.00		1.00	
80-90	2.54[1.83-3.52]	< .001	2.20[1.55-3.13]	< .001	1.71[1.19-2.46]	0.004
90-100	3.01[2.09-4.34]	< .001	2.51[1.68-3.74]	< .001	1.54[0.99-2.39]	0.055
100-110	4.99[3.16-7.88]	< .001	3.41[2.02-5.73]	< .001	1.51[0.82-2.77]	0.188
>=110	8.12[4.43-14.88]	< .001	4.94[2.53-9.65]	< .001	1.48[0.65-3.35]	0.347
P for trend		< .001		< .001		0.189
10mmHg increase	1.55[1.41-1.70]	< .001	1.39[1.25-1.55]	< .001	1.08[0.93-1.25]	0.333
Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site. Model 3 based on model 2, mutually adjusted for SBP and DBP.						

Discussion

In this study of 4569 patients accruing 403 cardiovascular events during 12.1 years mean follow-up, either SBP or DBP was positively associated with the adverse cardiovascular outcome with adjustment for cardiovascular risk factors, and this association was steeper for stroke than for MI (Table 2, Table 3 and Table 4).

Previous prospective cohort study showed that either SBP or DBP levels were positively associated with the risk of CVD [10]. Higher SBP levels are positively associated with increased risk of CVD with adjustment or stratification for DBP [11]. By contrast, another study demonstrated that DBP was not consistently associated with the risk of CVD, after adjusting or stratification for SBP [12][13]. Our study confirmed the association of either SBP or DBP with the risk of adverse cardiovascular outcomes in the multivariate model (model 2, Fig. 1; model 1, Figure s1 in appendix). However, in a mutually adjusted model (model 3, Figure s2 in appendix) including both SBP and DBP, the association with the risk of adverse cardiovascular outcomes was positive for SBP, but not significant for DBP.

In our study, we noted a significant linear association of either SBP or DBP with the risk of different outcomes (Fig. 1). These linear associations were similar to those from most previous observational studies including the Prospective Studies Collaboration [6] and the Framingham study (in which J-shape associations with DBP occurred only when accompanied by SBP > 140 mm Hg) [14], and is supported by trial evidence in elderly people that shows significant and sustained risk reduction for cardiovascular endpoints with lowering of BP [15].

In our result, association with BP level was more steep for stroke than for MI (Fig. 1), which has also been suggested by the Prospective Studies Collaboration [6] and another observational study [16]. Further, in a meta-analysis that included 147 RCTs, Law et al [17] calculated the CVD risk reduction for the average active treatment versus control trial difference in SBP (10 mm Hg). The reductions in stroke and coronary heart disease (CHD) incidence rates were similar to the benefits expected on the basis of a 10 mm Hg difference in SBP in the Prospective Studies Collaboration meta-analysis of observational studies. Benefit for the same difference in BP was greater for stroke, reflecting the higher risk of elevated BP for cerebral vessels compared with the coronary circulation. In addition, our result also showed that the risk of MI might be higher in low DBP level group (Fig. 1). This result was similar to a previous observational study [18], which reported that low DBP was associated with subclinical myocardial damage and CHD events among adults with SBP \geq 120 mmHg, and thus elevated pulse-pressure.

For subgroup analysis (Fig. 2, Fig. 3), either SBP or DBP was more strongly associated with the risk of adverse cardiovascular outcome in individuals aged 40–65 years than in those aged 65–95 years, except for the association between DBP and MI. Other observational studies demonstrated that the proportional associations of blood pressure with all major cardiovascular diseases become less steep with age, although they remain strong and direct even in the oldest age groups [16][19].

Further, the association was consistently weaker in people who received antihypertensive drugs at baseline than in those who did not. Similar to our result, high-quality meta-analyses have demonstrated the effectiveness of BP lowering for prevention of CVD [18][22][23]. In addition, the association was

consistently weaker in person who with history of diabetes than who without it. The reasons for this difference may due to the participants who reported diabetes at baseline survey may change their lifestyle including dietary patterns or taking blood pressure-lowering treatment due to disease management.

Our study has several limitations. First, we only screen residents older than 40 and younger than 90 years old from nine provinces of China. Therefore, our current results cannot be generalized to all populations in China. Second, we have not accounted for changes in BP and other risk factors over time. A more detailed analysis of lifetime risks would take repeated measures into consideration to account for potential changes and would adjust for the time-dependent effect of medications taken long term. Finally, some other risk factors (such as cholesterol values, air pollutants and dietary patterns) are shown to contribute to CVD risk, we were unable to involve them in present analyses due to lack of these information in this survey.

Conclusion

In conclusion, our study found the relationship between BP and cardiovascular outcomes in the Chinese population. Either SBP or DBP is strongly and positively related to the risk of cardiovascular outcomes, and this positive association was more steep for stroke than for MI. These results provide more evidence for guidelines or health policies of primary prevention of CVD with the management of BP level. Individual-level and population-level interventions to control BP level are needed to reduce the burden of CVD in China.

List Of Abbreviations

BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CHNS	China Health and Nutrition Survey
CVD	cardiovascular disease
DBP	diastolic blood pressure
MI	myocardial infarction
SBP	systolic blood pressure

Declarations

Ethics approval and consent to participate

This research uses data from the China Health and Nutrition Survey (CHNS). The institutional review committees from the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Food Safety, China Centre for Disease Control and Prevention, approved the survey protocols and instruments and the process for obtaining informed consent for the survey. All participants and/or their parents/guardians provided written informed consents for their participation in the survey.

Consent for publication

Not applicable.

Availability of data and materials

Data from China Health and Nutrition Survey was used in this study, which can be downloaded at <http://www.cpc.unc.edu/projects/china/data/datasets>.

Competing interests

The authors declare that there is no conflict of interest.

Funding

Not applicable.

Author contributions statement

QY and QDJ conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

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Figures

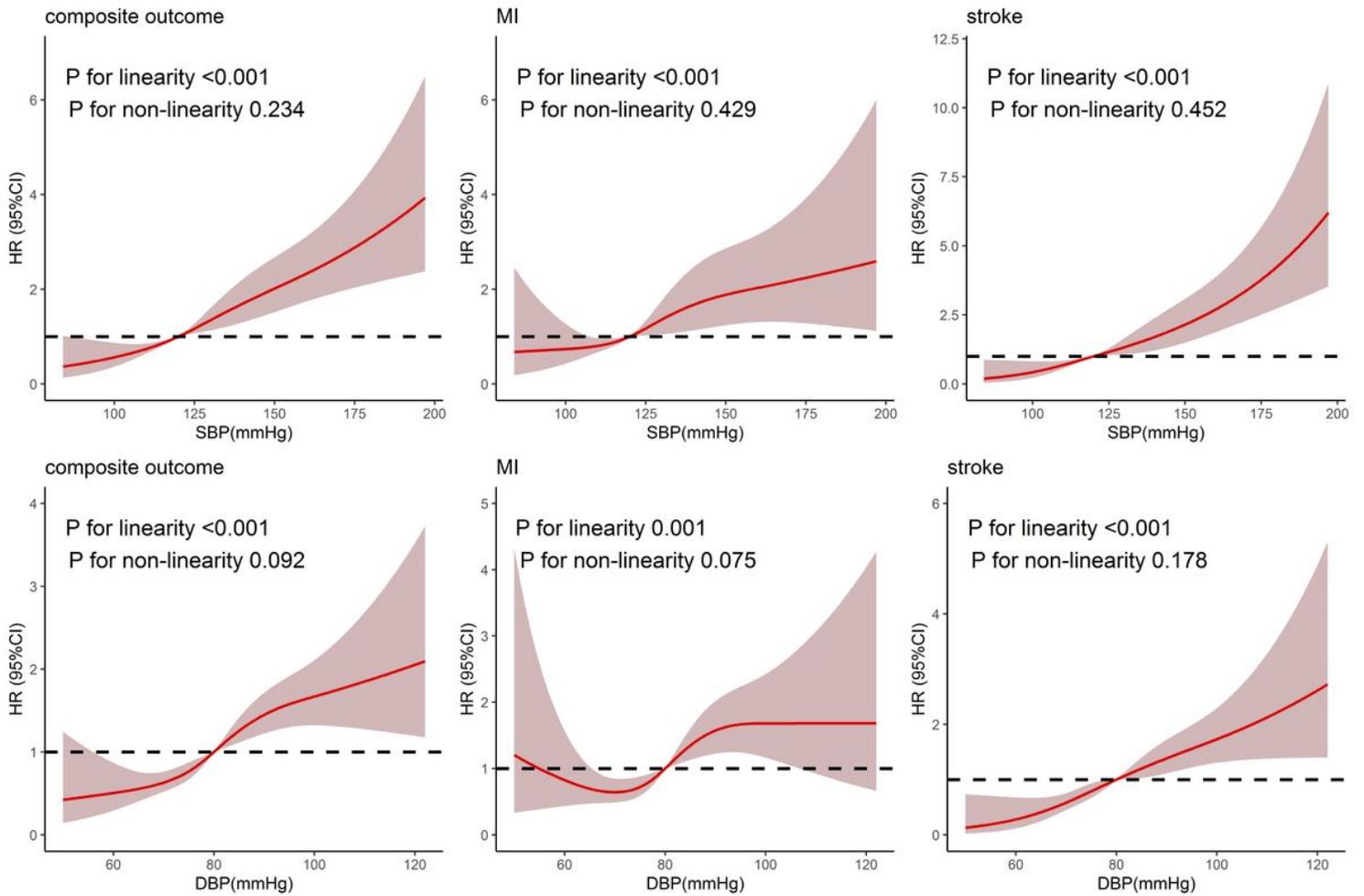


Figure 1

Association of BP with composite outcome, MI and stroke(model 2) Hazard ratios are indicated by solid lines and 95% CI by shaded areas. The reference point is median value for each SBP and DBP, with knots placed at 5th, 35th, 65th, and 95th centiles of each SBP and DBP. All models were adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site.

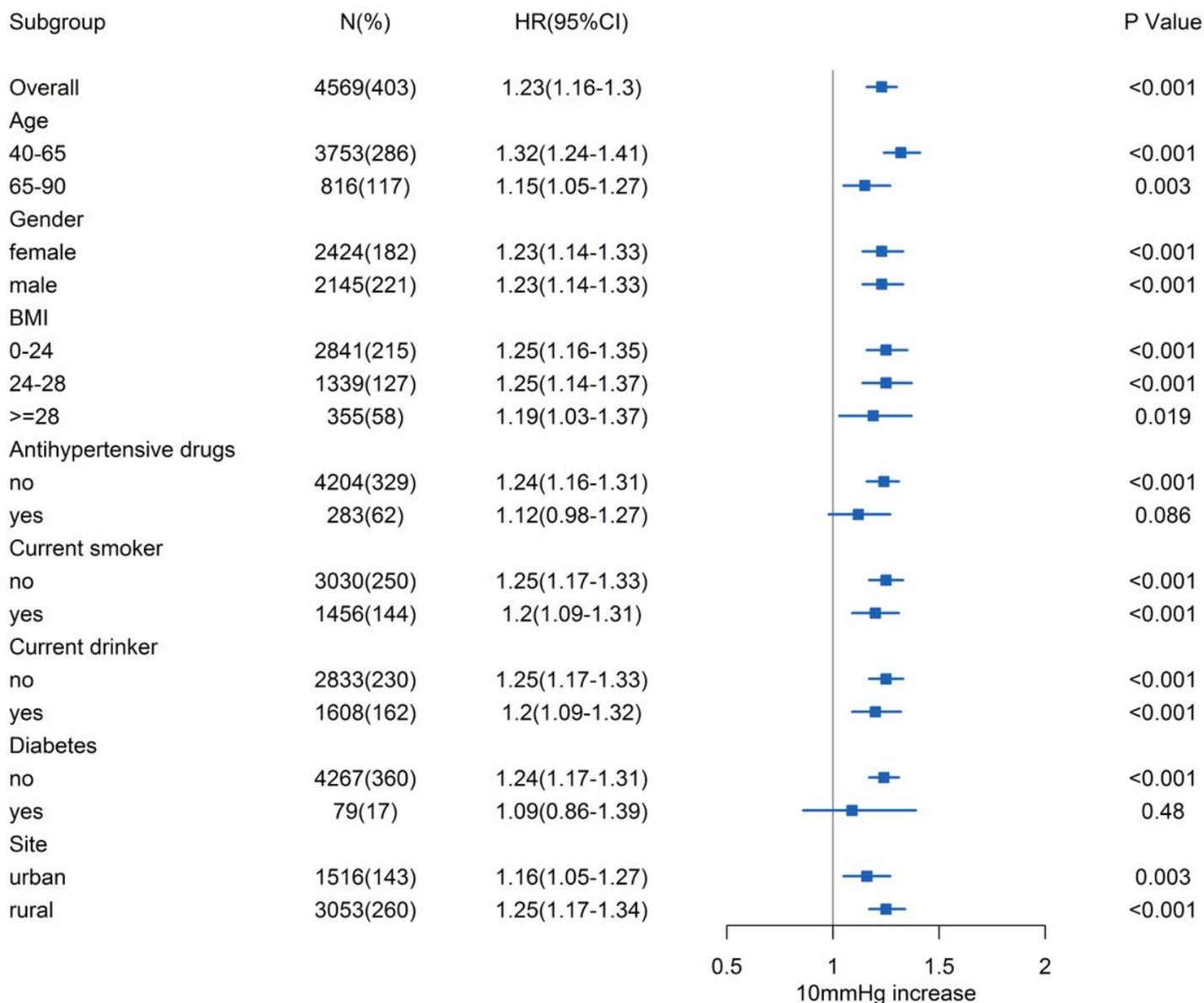


Figure 2

Subgroup analysis for the association of SBP(10 mm Hg changes) with composite outcome All models were adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site.

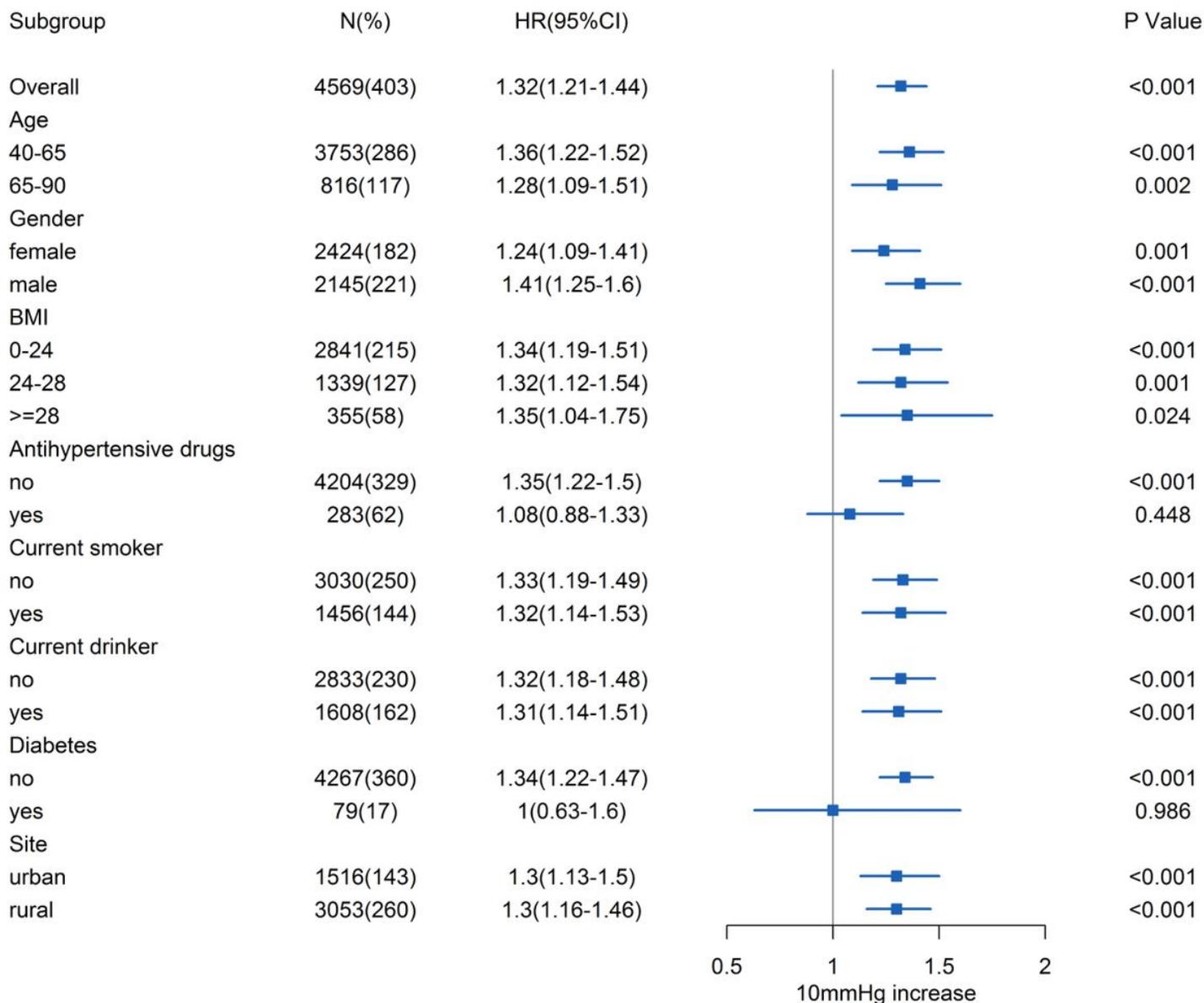


Figure 3

Subgroup analysis for the association of DBP(10 mm Hg changes) with composite outcome All models were adjusted for age, gender, BMI, Antihypertensive drugs, smoking status, drinking status, diabetes, and site.

Supplementary Files

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