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Cumulative blood pressure predicts risk of cardiovascular outcomes in middle-aged and older population

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ABSTRACT

Background: Cardiovascular disease (CVD) remains a major health concern globally, contributing to a considerable disease burden. However, few studies have considered long-term cumulative blood pressure (cBP) exposure in middle-aged and older population in China. The aim of this study was to investigate whether long-term cBP was associated with subsequent cardiovascular outcomes among participants without CVD at baseline in Chinese over 45 years old.

Methods: 6435 participants in China of the CHARLS (The China Health and Retirement Longitudinal Study) were included. Cumulative BP was calculated as the area under the curve using measurements from wave 1 (2011) to wave 2 (2013). Outcomes included CVD, heart disease and stroke.

Results: During a median follow-up period of 5 years, 1101 CVD events, 826 heart disease, and 351 stroke were recorded. Each 1-SD increase in cumulative systolic blood pressure (cSBP), cumulative diastolic blood pressure (cDBP), and cumulative mean arterial pressure (cMAP) was associated with increased risk of CVD (HR, 1.12; 95%, 1.05–1.20, HR, 1.14; 95%, 1.07–1.22, HR, 1.14; 95%, 1.07–1.22), heart disease (HR, 1.05; 95%, 0.97–1.13, HR, 1.09; 95%, 1.01–1.17, HR, 1.08; 95%, 1.00–1.16) and stroke (HR, 1.35; 95%, 1.21–1.51, HR, 1.31; 95%, 1.17–1.46, HR, 1.36; 95%, 1.22–1.51). The relationship between cBP and CVD has only been found in people younger than 60 years of age. A significant association was observed for cumulative pulse pressure (cPP) with stroke (HR, 1.23; 95%, 1.10–1.38). None nonlinear relationships were identified (p-nonlinear > .05). For the prediction of cardiovascular outcomes, cBP load outperformed baseline BP in terms of C statistics ($p < .001$).

Conclusions: Long-term cSBP, cDBP and cMAP were associated with subsequent CVD and only found in people younger than 60 years of age, whereas cPP was associated with stroke only across all ages. Cumulative BP may provide a better prediction of cardiovascular outcomes compared with single BP measurement. Efforts are required to control long-term BP in assessing cardiovascular risks.

HIGHLIGHTS

- We used a large national database and a prospective cohort study.
- Long-term cSBP, cDBP and cMAP were associated with subsequent CVD and only found in people younger than 60 years of age.
- Long-term cPP was associated with stroke only across all ages.
- Cumulative BP may provide a better prediction of cardiovascular outcomes compared with single BP measurement.

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Introduction

The global population is experiencing a persistent trend of aging due to enhanced living conditions and declining fertility rates [1]. It is estimated that by 2100, nearly a quarter of the global population will be 65 years of age and older [2]. Meanwhile, the aging process in China is becoming more severe. According to the seventh national census, the proportion of adults aged 60 and over in China has exceeded 18%

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[3]. An aging population will result in an increased burden of disease and many other problems [4], and cardiovascular disease (CVD) is one of the significant burden associated with aging.

CVD continues to be a major worldwide health issue, accounting for considerable disease burden [5]. With the increasing number of elderly people worldwide, mortality attributed to CVD has climbed to 170,000 per year in 2016 [6]. Compelling evidence has demonstrated a correlation between elevated blood pressure (BP) and CVD outcomes [7,8]. Elevation of blood pressure is a long-term process, but it fluctuates due to numerous variables, such as behavioral and psychological factors [9], reliance on single BP measurement may prove inadequate for accurate CVD prediction. Recently, there has been a growing trend to use cumulative BP exposure as a supplementary index, calculating the area under the curve (mmHg × years) of numerous BP examinations. This measure considers the time aspect of blood pressure fluctuations, which could potentially enhancing the predictive accuracy of CVD risk models compared to traditional baseline BP assessment [10]. Additionally, it is reported that cumulative BP could be considered as an independent predictor of CVD [11] and dementia [12].

Recently studies have shown that individuals with higher cumulative BP exposure in early adulthood have heavier left ventricular weights and higher levels of coronary artery calcification [13]. These changes appear to be resistant to remediation through BP medication. Patients with type-2 diabetes who experience a higher cumulative SBP load can lead to increased risk of cardiovascular events and all-cause mortality [14]. In addition, in a CARDIA study, researchers found that cumulative blood pressure was associated with the risk of heart failure, coronary heart disease, stroke, and CVD in young adults [15]. Nevertheless, there is a lack of comprehensive investigation into the relationship between systolic, diastolic, pulse, mean arterial pressure (SBP, DBP, PP, MAP) and cardiovascular outcomes in middle-aged and older population is limited, particularly in the case of PP and MAP, which reflect cardiac ejection fraction and vascular function [16,17] (combining SBP and DBP), implying that more evidence is required to address this gap. This finding suggests that evaluating the cumulative BP exposure may could provide a more insightful evaluation of CVD risk than single-occasion BP assessments.

This study aimed to evaluate the relationship between long-term cumulative blood pressure exposure and the occurrence of composite CVD, heart disease and stroke in China. Additionally, this study aims to investigate whether cumulative BP load is a more accurate predictor of CVD than a single BP assessment. Data were obtained from a population-based cohorts: the China Health and Retirement Longitudinal Study (CHARLS). Our hypothesis is that higher cumulative BP (SBP, DBP, PP, MAP) exposure could be used to predict CVD risk in adults aged 45 years or older in Chinese people.

Methods

Study population

Data were obtained from CHARLS, a prospective and nationally representative cohorts of community-dwelling adults aged 45 years or older in China. Details concerning the cohorts can be found elsewhere [18–20]. In brief, 17,708 participants aged 45 years or older were recruited by multistage probability sampling procedure from 450 communities. The study was performed according to the guidelines of the Declaration of Helsinki. Ethical approval for all the CHARLS waves was granted from the Institutional Review Board at Peking University (IRB00001052-11015). Written informed consent was obtained from all participants. Besides, this study has been approved by the Institutional Review Board at Southern Medical University for exemption from the ethical statement for conducting database research. We used 2-year data from wave 1 (2011) to wave 2 (2013) in CHARLS to evaluate cumulative BP. Wave 1 of CHARLS was considered as the baseline. Cardiovascular outcomes were assessed for a 5-year span from wave 2 (2013) to wave 4 (2018). The study timeline is presented in Figure 1S. Participants were excluded if they met any of the following criteria: (1) diagnosis of cardiovascular-related diseases at baseline; (2) BP data from less than two waves; and (3) lost during follow-up (Figure 2S).

Measurement of blood pressure

CHARLS conducted BP measurements with standardized protocols applied. Automated electronic BP monitoring was used in CHARLS, using a validated oscillometric device (Omron HEM 705CPINT) on the right arm after a 5-min rest in a sitting position in a quiet, temperature-controlled room (20 °C–24 °C). Three measurements were taken at 1-min intervals, and the average of the 2 measurements of SBP and DBP were used [21]. BP used for cumulative exposure included systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP) and mean arterial pressure (MAP). BP measurements from 2 visits (wave 1, wave2) in CHARLS were employed for evaluating cumulative BP.

Measurement of outcomes and follow-up

The primary outcomes in the analysis comprised composite CVD outcomes. Participants who reported heart disease (heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems) or stroke were defined as having CVD. Secondary outcomes included individual components of the composite cardiovascular outcomes, including heart disease and stroke or transient ischemic attack (TIA). The diagnosis of stroke and heart disease was determined by the information self-reported by the participants in the follow-up survey. At each round of follow-up, doctors asked the individuals if they had ever suffered or were currently suffering from stroke and heart disease. If the answer was 'yes', they were considered new cases of the disease. Information on deceased participants was derived from the tracker file of the exit interview, with verification from their spouses or partners. The outcomes were assessed by rigorously trained interviewers through standardized questionnaires. Wave 2 in CHARLS was defined as the beginning of outcomes follow-up, and the time to event was calculated as the time interval between the start of follow-up and age at first diagnosis or age at censoring.

Covariates

Sociodemographic characteristics included age (years), sex (male or female), marital status (on married or not), living place (urban or rural), education (received education or not) and household income (no/yes). The health behaviors included smoking (nonsmoker, former smoker, and current smoker), leisure physical activity (vigorous or not), and alcohol consumption (ever drinks any alcohol before or not). Other potential confounders were body mass index (kg/m^2; continuous), self-reported or regular use of any related medications were defined as dyslipidemia, cancer and diabetes (no/yes). Taking blood pressure medication was defined as taking medication in any wave of w1(2011) to w2(2013).

Statistical analysis

Baseline characteristics were presented according to with/without CVD events. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables are presented as frequencies (%). Differences in characteristics between groups were tested using analysis of variance, the t-test, or the chi-square test. We used area under the curve to estimate cumulative BP exposure, on the basis of the same approach adopted in previous studies [12]. Mean BP between two consecutive visits was calculated, multiplied by the number of years between those two visits, and then summed to determine cumulative BP. Details of the calculation of the area under the curve are presented (Figure 3S).

To evaluate the relationship between cumulative BP and risk of cardiovascular outcomes, multivariable Cox regressions were performed. A proportional hazard assumption was evaluated using weighted Schoenfeld residuals. We used a restricted cubic spline to explore the potential non-linearity relationship, selecting 4 knots (5th, 35th, 65th, and 95th percentiles of cumulative BP) to smooth the curve and further exploring the effect of lower or higher cBP on CVD. The reference point for cumulative BP was the reference group's median value. To minimize the potential for inferential bias and to maximize the statistical power possible, we used multiple imputation with chained equations to assign any missing covariate values. The missing rates for all variables were below 2%. The detail of participants with missing covariates was showed in Table 1S.

We performed subgroup analyses to further explore the interactions between cumulative BP and sex(men or women), age (<60 or ≥60 years) and long-term antihypertensive medication use (yes or no). Receiving antihypertensive medication was defined as reporting the use of medication during waves 1–2. Interactions among subgroups were examined using the likelihood ratio test, comparing models with and without multiplicative interactions. Additionally, receiver operating characteristic (ROC) curve analysis was performed to assess the significance of cumulative BP in predicting cardiovascular outcomes. We used C statistics, integrated discrimination improvement (IDI), and net reclassification index (NRI) to evaluated the incremental predictive value of to determine whether cumulative BP improved the prediction of the outcomes compared with baseline BP.

All statistical analyses were conducted using R version 4.2.0 (R Foundation for Statistical Computing), with a two-sided $p < .05$ was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the study participants stratified by CVD events (participants with CVD vs. without CVD). Out of 6435 participants, 3314 (51.5%) were female, with a mean age of 59.01 years.

Table 1. Baseline characteristics of the study participants stratified by CVD events.

	Total (*n* = 6435)	Participants without CVD (*n* = 5373)	Participants with CVD (*n* = 1062)	*p* value
Age, year (mean (SD))	59.01 (8.81)	58.69 (8.83)	60.63 (8.56)	<.001
Sex (%)				
Male	3121 (48.5)	2668 (49.7)	453 (42.7)	<.001
Female	3314 (51.5)	2705 (50.3)	609 (57.3)	
Married (%)	5446 (84.6)	4563 (84.9)	883 (83.1)	.155
Received education (%)	4566 (71.0)	3835 (71.4)	731 (68.8)	.103
Living place (%)				
Rural	4433 (68.9)	3722 (69.3)	711 (66.9)	.145
Urban	2002 (31.1)	1651 (30.7)	351 (33.1)	
Having household income (%)	4704 (73.1)	3983 (74.1)	721 (67.9)	<.001
Smoke (%)				
Current	2069 (32.2)	1774 (33.0)	295 (27.8)	<.001
Former	505 (7.8)	399 (7.4)	106 (10.0)	
Never	3861 (60.0)	3200 (59.6)	661 (62.2)	
Ever drink (%)	2565 (39.9)	2163 (40.3)	402 (37.9)	.153
BMI, kg/m^2 (mean (SD))	23.36 (7.04)	23.23 (7.47)	24.02 (4.19)	.001
Vigorous exercise (%)	4839 (75.2)	4061 (75.6)	778 (73.3)	.118
Cancer (%)	55 (0.9)	51 (0.9)	4 (0.4)	.095
Using antihypertensive medication (%)	1374 (21.4)	1000 (18.6)	374 (35.2)	<.001
Diabetes (%)	329 (5.1)	236 (4.4)	93 (8.8)	<.001
Dyslipidemia (%)	544 (8.5)	380 (7.1)	164 (15.4)	<.001
SBP, mm Hg (mean (SD))	128.27 (20.53)	127.30 (20.23)	133.14 (21.33)	<.001
DBP, mm Hg (mean (SD))	74.64 (11.95)	74.23 (11.83)	76.70 (12.35)	<.001
PP, mm Hg (mean (SD))	53.62 (14.15)	53.07 (13.87)	56.44 (15.18)	<.001
MAP, mm Hg (mean (SD))	92.52 (13.83)	91.92 (13.67)	95.51 (14.22)	<.001
Cumulative SBP, mm Hg×y (mean (SD))	257.70 (36.43)	255.96 (35.98)	266.54 (37.44)	<.001
Cumulative DBP, mm Hg×y (mean (SD))	149.63 (20.84)	148.92 (20.63)	153.25 (21.50)	<.001
Cumulative PP, mm Hg×y (mean (SD))	108.07 (25.38)	107.04 (24.89)	113.29 (27.11)	<.001
Cumulative MAP, mm Hg×y (mean (SD))	185.66 (24.27)	184.60 (24.03)	191.01 (24.74)	<.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure, PP: pulse pressure; MAP: mean arterial pressure.
Definitions of cancer and other diseases were based on records of self-reported physician diagnosis or any medication used. *P* values are reported for differences using Student's t-test, chi-square test, or Wilcoxon rank test.

Overall, 1062 (16.5%) reported CVD outcomes in the study. Compared with those without CVD, participants with CVD were elder, more likely to be female, not having a household income, not current smokers, having a higher BMI. Mean cumulative exposure to SBP, DBP, PP and MAP were 257.70 ± 36.43, 149.63 ± 20.84, 108.07 ± 25.38 and 185.66 ± 24.27 mmHg × year, respectively.

Association of cumulative BP and outcomes

After adjusting for sociodemographic characteristics, health behaviors, and other potential confounders mentioned in the Method section with the Cox proportional hazards regression models, the HRs (95% CI) of the second to fourth quartiles of cumulative BP for predicting CVD were HR, 1.36; 95%, 1.12–1.66, HR, 1.49; 95%, 1.22–1.81, and HR, 1.56; 95%, 1.27–1.91 for cumulative SBP, HR, 1.17; 95%, 0.97–1.41, HR, 1.29; 95%, 1.07–1.55, and HR, 1.47; 95%, 1.22–1.77 for cumulative DBP, HR, 1.04; 95%, 0.86–1.26, HR, 1.18; 95%, 0.98–1.43, HR, 1.19; 95%, 0.97–1.45 for cumulative PP, HR, 1.16; 95%, 0.95–1.40, HR, 1.43; 95%, 1.19–1.73, HR, 1.51; 95%, 1.25–1.82 for cumulative MAP, compared with the first quartile (Table 2). For heart disease, the HRs (95% CI) of the second to fourth quartiles of cumulative BP for predicting heart disease were HR, 1.27; 95%, 1.02–1.59, HR, 1.30; 95%, 1.04–1.61, and HR, 1.28; 95%, 1.02–1.61 for cumulative SBP, HR, 1.17; 95%, 0.94–1.44, HR, 1.16; 95%, 0.94–1.44, and HR, 1.36; 95%, 1.10–1.68 for cumulative DBP, HR, 0.98; 95%, 0.79–1.22, HR, 1.12; 95%, 0.91–1.39, HR, 1.04; 95%, 0.83–1.31 for cumulative PP, HR, 1.07; 95%, 0.86–1.34, HR, 1.33; 95%, 1.08–1.64, HR, 1.28; 95%, 1.03–1.59 for cumulative MAP, compared with the first quartile. After adjusted Cox models (per 1-SD increase), cumulative SBP, DBP, PP, MAP were positively associated with stroke (SBP, HR, 1.35; 95%, 1.21–1.51); DBP, HR, 1.31; 95%, 1.17–1.46; PP, HR, 1.23; 95%, 1.10–1.38; MAP, HR, 1.36; 95%, 1.22–1.51). Substantial interactions were identified from subgroup analyses (Figure 1). Age significantly modified the relationships of cumulative BP with composite CVD and heart disease; sex and use of antihypertensive medication did not significantly modify the associations of cumulative BP with all the outcomes.

Nonlinear associations between cumulative BP and outcomes

To better explain the observed nonlinear association, we further analyzed SBP, DBP, PP, MAP as a continuous variable using cubic spline regression adjusting for all covariates mentioned in the Methods section. As shown in Figure 2, none significant nonlinear dose-response pattern was observed between

Table 2. Association between cumulative blood pressure exposure and risk for composite CVD, heart disease and stroke.

	CVD			Heart Disease			Stroke		
	Events/Total	HR(95%CI)	*p* value	Events/Total	HR(95%CI)	*p* value	Events/Total	HR(95%CI)	*p* value
Cumulative SBP, mm Hg×y									
Q1	168/1582	reference	/	139/1582	reference	/	35/1582	reference	/
Q2	245/1621	1.36 (1.12, 1.66)	.002	190/1621	1.27 (1.02, 1.59)	.032	69/1621	1.83 (1.22, 2.76)	.004
Q3	296/1620	1.49 (1.22, 1.81)	<.001	216/1620	1.30 (1.04, 1.61)	.021	102/1620	2.41 (1.63, 3.57)	<.001
Q4	353/1612	1.56 (1.27, 1.91)	<.001	249/1612	1.28 (1.02, 1.61)	.034	138/1612	2.91 (1.96, 4.33)	<.001
P for trend	/	/	<.001	/	/	.056	/	/	<.001
Per SD increment	/	1.12 (1.05, 1.20)	<.001	/	1.05 (0.97, 1.13)	.194	/	1.35 (1.21, 1.51)	<.001
Cumulative DBP, mm Hg×y									
Q1	203/1607	reference	/	160/1607	reference	/	54/1607	reference	/
Q2	246/1609	1.17 (0.97, 1.41)	.093	192/1609	1.17 (0.94, 1.44)	.152	68/1609	1.20 (0.84, 1.72)	.315
Q3	278/1568	1.29 (1.07, 1.55)	.007	197/1568	1.16 (0.94, 1.44)	.160	98/1568	1.62 (1.15, 2.27)	.005
Q4	335/1651	1.47 (1.22, 1.77)	<.001	245/1651	1.36 (1.10, 1.68)	.004	124/1651	1.94 (1.39, 2.71)	<.001
P for trend	/	/	<.001	/	/	.006	/	/	<.001
Per SD increment	/	1.14 (1.07, 1.22)	<.001	/	1.09 (1.01, 1.17)	.022	/	1.31 (1.17, 1.46)	<.001
Cumulative PP, mm Hg×y									
Q1	200/1586	reference	/	158/1586	reference	/	50/1586	reference	/
Q2	227/1596	1.04 (0.86, 1.26)	.699	170/1596	0.98 (0.79, 1.22)	.889	68/1596	1.24 (0.86, 1.79)	.258
Q3	290/1619	1.18 (0.98, 1.43)	.078	220/1619	1.12 (0.91, 1.39)	.291	97/1619	1.55 (1.09, 2.21)	.014
Q4	345/1634	1.19 (0.97, 1.45)	.089	246/1634	1.04 (0.83, 1.31)	.712	129/1634	1.79 (1.24, 2.57)	.002
p for trend	/	/	.047	/	/	.501	/	/	.001
Per SD increment	/	1.05 (0.99, 1.13)	.123	/	1.00 (0.92, 1.08)	.947	/	1.23 (1.10, 1.38)	<.001
Cumulative MAP, mm Hg×y									
Q1	186/1600	reference	/	151/1600	reference	/	43/1600	reference	/
Q2	228/1618	1.16 (0.95, 1.40)	.146	172/1618	1.07 (0.86, 1.34)	.535	71/1618	1.54 (1.05, 2.25)	.027
Q3	301/1601	1.43 (1.19, 1.73)	<.001	228/1601	1.33 (1.08, 1.64)	.008	92/1601	1.82 (1.26, 2.63)	.002
Q4	347/1616	1.51 (1.25, 1.82)	<.001	243/1616	1.28 (1.03, 1.59)	.029	138/1616	2.49 (1.73, 3.57)	<.001
P for trend	/	/	<.001	/	/	.009	/	/	<.001
Per SD increment	/	1.14 (1.07, 1.22)	<.001	/	1.08 (1.00, 1.16)	.049	/	1.36 (1.22, 1.51)	<.001

SBP: systolic blood pressure; DBP: diastolic blood pressure, PP: pulse pressure; MAP: mean arterial pressure.
[a]Adjusted covariates included sex, age, marital status, education, living place, household income, smoking, alcohol consumption, body mass index, physical activity, diabetes, hyperlipidemia, cancer and antihypertensive medication use.

cumulative BP and CVD, heart disease and stroke (*p* for non-linear > 0.05). Cumulative SBP, DBP, and MAP showed a linear relationship with the risk of CVD, meaning that as cumulative BP increased, the risk of CVD increased (*p* for linear <.05).

Comparison in the incremental predictive value of BP

We compared the predictive value of cumulative BP with baseline BP in predicting CVD outcomes. When CVD as the outcome of interest, the addition of the cumulative SBP, DBP, and MAP could significantly improve the C statistic, IDI, and NRI (Table 3). We further analyzed ROC curves to evaluate the predictive potentials of the outcomes. With cumulative SBP, DBP and MAP, the area under the ROC curve increased moderately, demonstrating that the combination with cumulative BP elevated prediction efficiency (Figure 4S–6S).

Nonresponse analyses

A total of 11,273 participants were excluded from the analysis. Compared with the excluded participants, the included participants were generally older and living rural. Detailed results for this comparison are summarized in Tables 2S.

Discussion

In our cohort study, which included 6435 Chinese participants with an average age of 59.01 years, we found long-term cSBP, cDBP and cMAP were associated with subsequent CVD and only found in people younger than 60 years of age, whereas cPP was associated with stroke only across all ages. Cumulative BP might offer a more accurate prediction of cardiovascular outcomes compared with single BP measurement. According to our knowledge, this study is the first that measures cumulative BP, with a particular emphasis on cumulative MAP, to estimate the risk of composite CVD, heart disease and stroke in Chinese participants.

Our study aligns with previous findings that there is a connection between long-term BP exposure and all-cause mortality [22,23], cardiac dysfunction [24–26], brain structure [27], cognitive dysfunction [28], and retinal microvasculature [29]. For example, the CARDIA (Coronary Artery Risk Development in Young Adults) trial highlighted that long-term exposure to BP from early adulthood to middle age resulted in increasing left ventricular systolic and diastolic dysfunction [24]. In another similar study, Nwabuo et al. found that cumulative BP in participants at younger ages was associated with risks of heart failure, CHD, stroke, and CVD [15]. A Chinese multi-province cohort study showed that participants with higher levels of

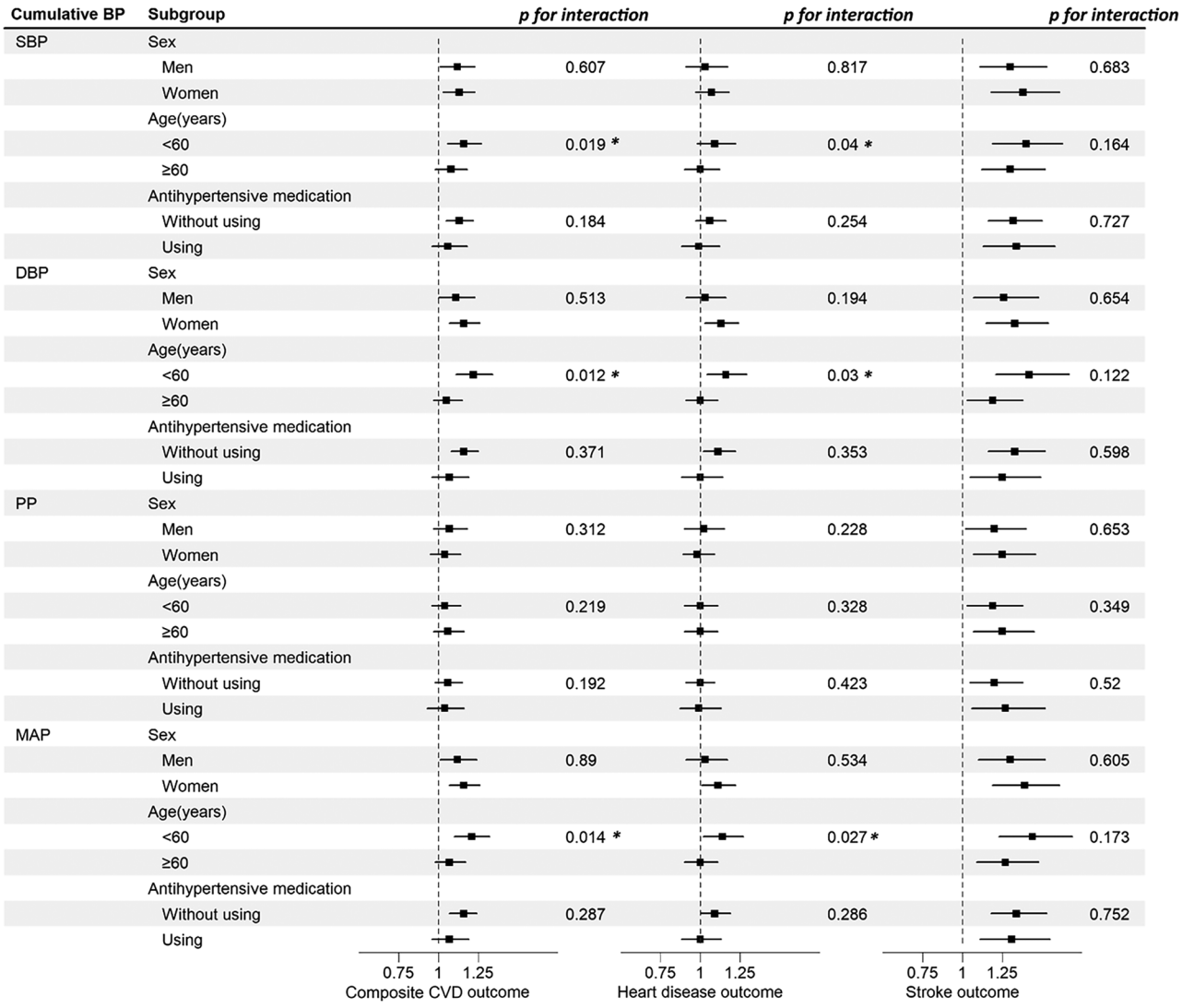

Figure 1. Subgroup analyses for association between each SD increment in cumulative blood pressure and risk of incident CVD (left), heart disease (middle) and stroke (right).

cumulative SBP or DBP had a higher incidence of CVD. In addition, for participants with a 15-year cumulative BP level above the median, the risk of CVD was higher in subsequent years [30]. In another study of the Chinese general population, cumulative SBP and PP were associated with cardiovascular mortality in persons older than 65 years, however, no relationship between cumulative DBP and mortality was observed [31].

Research has linked elevated PP with arterial stiffness [32,33], left ventricular hypertrophy [34,35] and cardiovascular death [36]. However, in our analysis, the association between cumulative PP and outcomes were not observed. One possibility could be the age range of the participants. Previous research concentrated on individuals in early to medium adulthood, whereas our study specifically focused on individuals in middle to late life stages. In the Framingham Heart Study, SBP and DBP increased steadily in early adulthood; in contrast, PP started to rise at around age 40 and rose sharply throughout the remaining life course [37]. Further studies are required to investigate the relevance of cumulative PP in different clinical and research situations.

Our findings suggest that the higher the cumulative blood pressure, the higher the risk of CVD. This suggests that not only the value of blood pressure but also the duration must be considered to assess CVD risk. Specifically, when reclassifying and discriminating statistics for cBP compared with baseline blood pressure, cumulative BP outperformed single measurements in terms of the C-statistic. Thus, the cumulative BP load can be calculated from a series of BP measurements at different time points and considered in future CVD risk projections.

The primary consequence of our discoveries is the potential advantage of extended blood pressure control among middle-aged and older persons. We

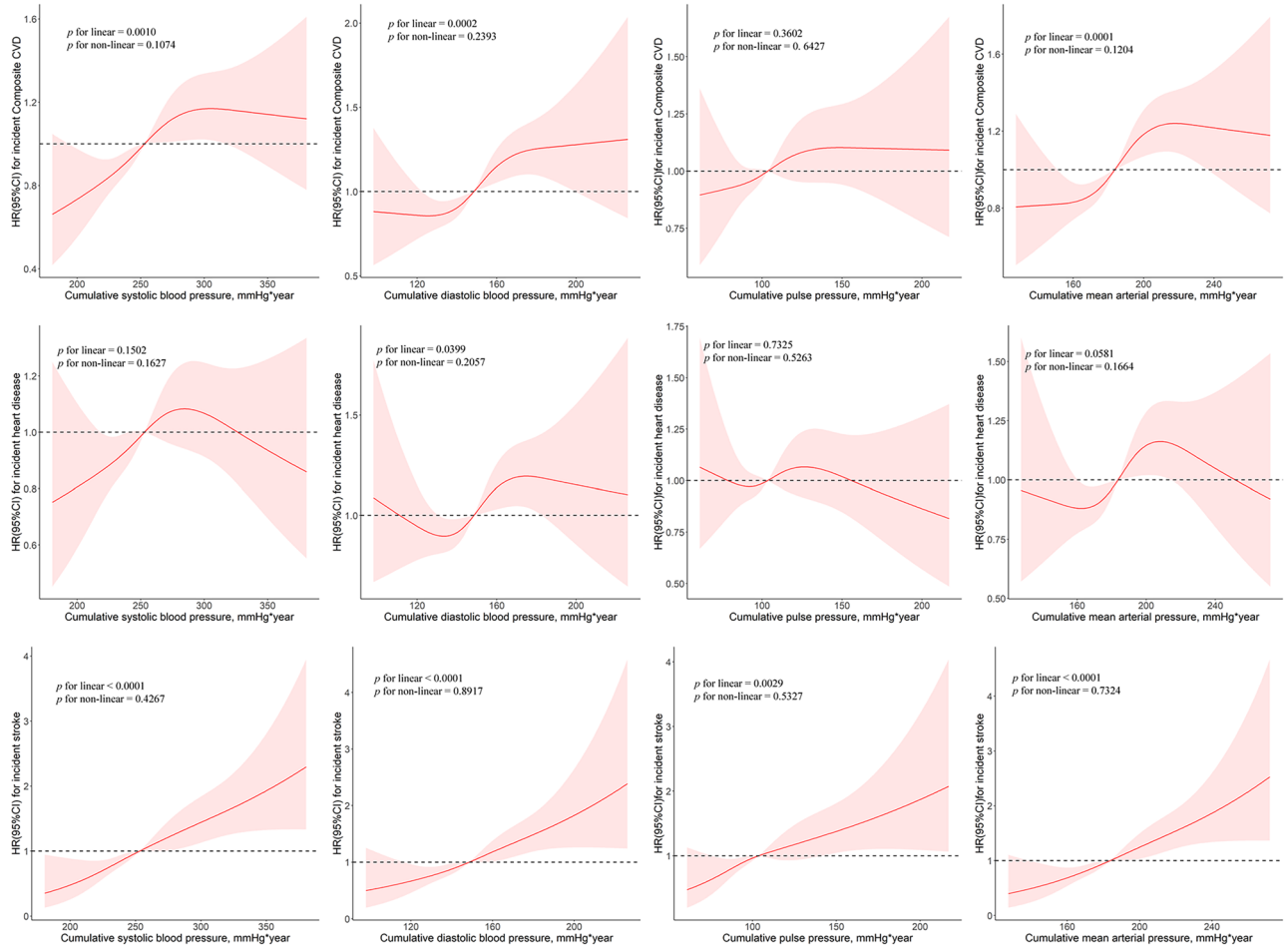

Figure 2. Dose-Response of Cumulative Blood Pressure and CVD (top), Heart Disease (middle) and Stroke (bottom).

discovered that those with higher long-term cumulative SBP, DBP and MAP were associated with elevated risk of CVD and stroke. Besides, cumulative PP was only associated with stroke. Our findings suggest that monitoring MAP could have additional predictive value for cardiovascular outcomes.

Strengths and limitations

Our study had multiple strengths. Initially, we evaluated cumulative BP and its association with composite CVD, heart disease and stroke. In addition, we first noticed connections between cumulative MAP and cardiovascular risks. Finally, our study sample comprised a substantial proportion of individuals residing in the community, the majority of whom were above the age of 45.

There are also some limitations in our study. First, the findings are applicable to individuals aged 45 years or above, and they are specifically restricted to the Chinese population, hence limiting their generalizability. Second, a substantial number of participants were excluded in the analysis. Third, the study is purely observational and does not provide the basis for making causal inferences. Fourth, only two measurements were used as cumulative blood pressure, which may not be sufficient to estimate the risk of CVD associated with long-term blood pressure changes. Fifth, the follow-up time of 5 years is considered limited. Furthermore, another limitation of our study is that we did not focus on lower extremity arterial disease, an important CVD that is greatly influenced by blood pressure [38]. Finally, this study did not examine the specific antihypertensive drugs on the chronic damage to the target organs.

Perspectives and clinical applications

Our study indicates that the surveillance of BP is a highly efficient method to evaluate the risk of CVD. Keeping BP within a specific range can potentially have a beneficial impact on decreasing the risk of CVD, this study provides some insight into prevention strategies.

Table 3. Reclassification and discrimination statistics for cumulative blood pressure compared with baseline blood pressure.

	C statistics		IDI		NRI	
	Estimate (95 % CI)	*p*	Estimate (95 % CI)	*p*	Estimate (95 % CI)	*p*
Cardiovascular disease						
SBP						
Model 1[a]	0.644(0.626, 0.662)		reference		reference	
Model 2[b]	0.645(0.627, 0.663)	<.001	0.80(0.10, 1.50)	.020	48.5(15.7, 59.6)	.040
DBP						
Model 1[a]	0.644(0.626, 0.662)		reference		reference	
Model 2[b]	0.646(0.628, 0.664)	<.001	1.70(0.60, 0.03)	.000	53.8(37.8, 60.9)	<.001
PP						
Model 1[a]	0.641(0.623, 0.659)		reference		reference	
Model 2[b]	0.642(0.624, 0.660)	<.001	−0.10(−1.0, 0.50)	.653	−57.0(−63.4, 57.5)	.673
MAP						
Model 1[a]	0.645(0.627, 0.663)		reference		reference	
Model 2[b]	0.646(0.628, 0.664)	<.001	1.50(0.60, 2.30)	<.001	52.6(27.4, 61.5)	.020
Heart disease						
SBP						
Model 1[a]	0.643(0.623, 0.663)		reference		reference	
Model 2[b]	0.644(0.624, 0.664)	<.001	0.00(−0.90, 0.80)	.950	45.4(−65.8, 69.3)	.990
DBP						
Model 1[a]	0.644(0.624, 0.664)		reference		reference	
Model 2[b]	0.645(0.625, 0.665)	<.001	0.90(0.10, 2.0)	.040	51.7(29.2, 65.1)	<.001
PP						
Model 1[a]	0.642(0.622, 0.661)		reference		reference	
Model 2[b]	0.642(0.622, 0.661)	<.001	−0.40(−0.15, 0.2)	.158	−57.6(−64.1, 57.8)	.178
MAP						
Model 1[a]	0.644(0.624, 0.664)		reference		reference	
Model 2[b]	0.645(0.625, 0.665)	<.001	0.50(−0.2, 1.4)	.218	50.6(−33.1, 68.4)	.079
Stroke						
SBP						
Model 1[a]	0.669(0.640, 0.698)		reference		reference	
Model 2[b]	0.672(0.643,0.701)	<.001	1.00(0.30, 2.10)	<.001	50.5(45.1, 56.2)	<.001
DBP						
Model 1[a]	0.661(0.632, 0.690)		reference		reference	
Model 2[b]	0.667(0.638, 0.696)	<.001	1.1(0.40, 2.4)	<.001	52.4(41.1, 62.8)	<.001
PP						
Model 1[a]	0.662(0.631, 0.672)		reference		reference	
Model 2[b]	0.661(0.630, 0.692)	<.001	0.1(−0.2, 0.5)	.475	44.1(−61.4, 50.3)	.812
MAP						
Model 1[a]	0.666(0.637, 0.695)		reference		reference	
Model 2[b]	0.672(0.643, 0.675)	<.001	1.2(0.5, 2.0)	<.001	51.6(41.7, 60.3)	<.001

[a]Model 1: Adjusted covariates included sex, age, marital status, education, living place, household income, smoking, alcohol consumption, body mass index, physical activity, diabetes, hyperlipidemia, cancer, antihypertensive medication use and baseline blood pressure.
[b]Model 2: Adjusted covariates included sex, age, marital status, education, living place, household income, smoking, alcohol consumption, body mass index, physical activity, diabetes, hyperlipidemia, cancer, antihypertensive medication use and cumulative blood pressure.

Conclusion

Our study revealed that long-term cSBP, cDBP and cMAP were associated with subsequent CVD, and this was only found in those under the age of 60, whereas cPP was associated with stroke only across all ages. For those people, it might be necessary to make efforts to control long-term SBP and DBP, with a particular concentrate on controlling long-term MAP. Additional investigation is required to explore the relationship of cumulative PP to composite CVD and heart disease in a variety of study settings. The results of our study highlight the significance of considering cumulative BP level with high risk of CVD in the future.

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Author contributions

CRediT: **Fang-Fei You**: Data curation, Writing – original draft, Writing – review & editing; **Wen-Fang Zhong**: Data curation, Writing – review & editing; **Yi-Ning Gao**: Data curation, Writing – review & editing; **Zhi-Hao Li**: Data curation, Writing – review & editing; **Jian Gao**: Data curation, Writing – review

& editing; **Dong Shen**: Data curation, Writing – review & editing; **Jiao-Jiao Ren**: Data curation, Writing – review & editing; **Xiao-Meng Wang**: Data curation, Writing – review & editing; **Qi Fu**: Data curation, Writing – review & editing; **Wei-Qi Song**: Data curation, Writing – review & editing; **Chuan Li**: Data curation, Writing – review & editing; **Chen Mao**: Supervision, Writing – review & editing.

Ethical approval

The study was performed according to the guidelines of the Declaration of Helsinki. Ethical approval for all the CHARLS waves was granted from the Institutional Review Board (IRB) at Peking University (IRB00001052-11015). Written informed consent was obtained from all participants. Besides, this study has been approved by the Institutional Review Board at Southern Medical University for exemption from the ethical statement for conducting database research.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author [CM] upon reasonable request

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