

# BMJ Open Association between blood pressure levels and cardiovascular deaths: a 20-year follow-up study in rural China

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## ABSTRACT

**Objectives** The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guideline recommended 130/80 mm Hg as blood pressure (BP) target goals. However, the generalisability of this recommendation to populations at large with hypertension remains controversial. We assessed the association between BP and cardiovascular diseases (CVDs) mortality using a 20-year follow-up study among Chinese populations.

**Design** Prospective cohort study.

**Participants** 7314 participants were followed up for a median of 20 years in Fangshan District, Beijing, China.

**Methods** The primary outcome variable was death from cardiovascular causes. The adjusted HR for CVDs mortality associated with baseline BP was calculated using Cox regression analysis.

**Results** We identified 350 deaths from CVDs (148 stroke, 113 coronary heart disease and 89 other CVDs) during follow-up. Hypertension (defined by systolic BP (SBP)/diastolic BP (DBP)  $\geq 140/90$  mm Hg) was significantly associated with mortality due to CVDs (HR=2.49, 95% CI=1.77 to 3.50) among people aged 35–59 years rather than people aged  $\geq 60$  years. In addition, there was no significant association between stage 1 hypertension defined by the 2017 ACC/AHA (SBP/DBP of 130–139/80–89 mm Hg) and CVDs mortality when compared with SBP/DBP of  $<120/80$  in neither the participants aged  $<60$  years (HR=0.90, 95% CI=0.54 to 1.50) nor participants aged  $\geq 60$  years (HR=1.47, 95% CI=0.94 to 2.29).

**Conclusion** The study revealed hypertension of SBP/DBP  $\geq 140/90$  mm Hg was an important risk factor of CVDs mortality, especially among people aged 35–59 years. However, stage 1 hypertension under the definition of 2017 ACC/AHA was not associated with an increased risk of CVDs mortality. This study indicated that whether adopting the new hypertension definition needs further consideration in rural Chinese populations.

## INTRODUCTION

Hypertension is the first risk factor of cardiovascular diseases (CVDs), accounted for 7.8 million deaths and 148 million disability life years lost worldwide in 2015.<sup>1</sup> It has been reported that hypertension affected nearly

## Strengths and limitations of this study

- The prospective study had a relatively long follow-up time of 20 years.
- The study examined the association between high blood pressure and mortality from cardiovascular diseases (CVDs), which were hard outcomes.
- Hypertension was defined by systolic blood pressure or diastolic blood pressure at baseline while we failed to acquire blood pressure measurements during follow-up, which may underestimate the strength of the associations we observed.
- Whether the effects of hypertension on CVDs mortality differ by baseline comorbidities including diabetes or chronic kidney disease was not explored due to limited data.
- The information of death was obtained from the Death Surveillance System, the participants lost to follow-up were hard to detect and may cause potential bias.

30% of the adult population in Western countries as well as in China.<sup>2,3</sup>

The management of high blood pressure is a public health priority with implications for the prevention of CVDs.<sup>4,5</sup> However, the optimal blood pressure, particularly for systolic blood pressure (SBP) treatment target is unclear worldwide. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults recommended 130/80 mm Hg as blood pressure target goals.<sup>6</sup> However, the definition of hypertension remains  $\geq 140/90$  mm Hg in the European guideline.<sup>7</sup>

The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated intensive SBP lowering in adults without diabetes or stroke could result in significant decreases in cardiovascular events and all-cause mortality.<sup>8</sup> A network meta-analysis conducted by Bundy *et al* also suggested that a more intensive

treatment target (eg, SBP of 120–124 mm Hg) showed improvement in the prevention of CVD complications and total mortality when compared with a standard SBP target (<140 mm Hg).<sup>9</sup> However, the generalisability of SPRINT findings to populations at large with hypertension remains controversial.<sup>9–13</sup> For example, a recent study showed that the treatment to achieve a target SBP of 110–139 mm Hg did not result in a lower rate of death than standard reduction to a target of 140–179 mm Hg in patients with hypertension with intracerebral haemorrhage.<sup>12</sup>

Here, we aimed to assess the relative risk of CVDs mortality associated with different stages of hypertension according to 2017 ACC/AHA using a 20-year follow-up study in China, to further evaluate the generalisability of SPRINT findings and explore the target blood pressure levels among Chinese populations.

## METHODS

### Study design

The participants for these analyses came from a community-based follow-up study for the prevention and treatment of hypertension, which is being conducted in Fangshan District, Beijing, China. Verbal informed consent was obtained from all participants.

### Inclusion and exclusion of the participants

From January 1997 through June 1999, 8189 participants aged 35–97 years were enrolled. We excluded 669 individuals with CVDs at baseline. In addition, we dropped the participants if any of the key variables required in the analysis (blood pressure, height, weight, demographic variables or potential risk factors including smoking, alcohol consumption or high salt intake) were missing. Finally, a total of 7314 participants (3346 males and 3968 females) were included in the analysis.

### Outcomes variables

The primary outcome variable was death from CVDs. The information on death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. The date of death was ascertained from the record in the system. We determined survival times from the date participants investigated in the baseline survey through 31 December 2017. Participants who were alive at the end of this period contributed with censored observations to the survival analyses of time to death. The causes of death were coded using the International Classification of Diseases, Ninth Revision codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision codes from 2002 to 2017.

### Data collection

The primary exposure variables for these analyses included age at the enrolment and the blood pressure level at baseline. Data on sociodemographic characteristics, lifestyles

and medical history of the participants were collected by questionnaire interviews by trained staff members.

Participants were defined as never smokers, former smokers and current smokers. Information on alcohol consumption was obtained through asking the participants to describe their drinking status: never, light (<two drinks a day) or heavy ( $\geq$ two drinks a day). Furthermore, the salt intake of the participants was assessed according to the question of what kind of taste they liked (salty taste, moderate or light taste).

Physical measurements included height, weight and blood pressure. Blood pressure levels were measured three times using a mercury sphygmomanometer by trained investigators. The mean of the three recorded measurements was included in the analysis.

Hypertension was defined as SBP  $\geq$ 140 mm Hg, diastolic blood pressure (DBP)  $\geq$ 90 mm Hg, self-reported antihypertensive medication in the past 2 weeks or a self-reported history of hypertension.<sup>3</sup> In addition, according to the 2017 ACC/AHA guidelines, the participants were divided into four categories: normal blood pressure (SBP<120 mm Hg and DBP<80 mm Hg), elevated blood pressure (120 mm Hg $\leq$ SBP $\leq$ 129 mm Hg and DBP<80 mm Hg), stage 1 hypertension (130 mm Hg $\leq$ SBP $\leq$ 139 mm Hg or 80 $\leq$ DBP $\leq$ 89 mm Hg), and stage 2 hypertension (SBP $\geq$ 140 mm Hg/DBP $\geq$ 90 mm Hg or taking antihypertensive medications).

### Statistical analysis

Student's t-test and  $\chi^2$  tests were used to test the differences between different baseline hypertensive history groups for continuous variables and categorical variables, respectively.

Person-years for each participant were calculated as the duration from the survey date at baseline through death date or date lost to follow-up, whichever came first. The Cox proportional hazards regression model for CVDs death included baseline blood pressure level, age, sex, education level, body mass index, smoking status, alcohol use, dietary salt intake, antihypertensive medications and family history of hypertension. Participants were classified as two groups according to baseline hypertensive status, and non-hypertension (<140/90 mm Hg) was treated as the reference. To test for possible interactions between age and hypertension, we categorised age with cutoffs of 60 years and hypertension as binary variables, and setting variable cross-product terms of hypertension (yes/no) with age (<60 and  $\geq$ 60 years) in the model. Reference groups were SBP/DBP <140/90 mm Hg and age <60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120–129/<80, 130–139/80–89, 140–159/90–99 and  $\geq$ 160/ $\geq$ 100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.

All analyses were performed using R software (V.3.5.1). All p values for the tests were two-sided and p values <0.05 were considered as statistically significant.

## Patient and public involvement

Patients or the public were not involved in the study.

## RESULTS

Of the 7314 participants (aged  $50.65 \pm 11.8$  years), the prevalence of hypertension was 30.02%. According to the 2017 ACC/AHA guideline, the prevalence of hypertension was 58.96%. The proportion of people aged 60 years and above was higher in patients with hypertension (36.75%) when compared with participants without hypertension (19.05%,  $p < 0.001$ ). In addition, patients with hypertension were less educated than participants without hypertension ( $p < 0.001$ ). Moreover, there were more participants with tobacco smoking (49.27% vs 44.92%) and alcohol consumption (31.74% vs 30.15%) among patients with hypertension when compared with participants without hypertension. Furthermore, the percentage of obesity was higher among patients with hypertension when compared with participants without hypertension ( $p < 0.001$ ) (table 1).

During the median follow-up of 20 years, we have identified 609 deaths, of which 350 deaths were from CVDs (148 stroke, 113 coronary heart disease and 89 other CVDs). In the multivariable model adjusting for age, sex, educational level, smoking, alcohol consumption, dietary salt intake, body mass index (BMI), use of antihypertensive medications and family history of hypertension, we detected statistically significant association between hypertension and mortality from CVDs (HR=1.35; 95% CI 1.08 to 1.69). In the subgroup analysis based on baseline age, we found that, for people aged 35–59 years, patients with hypertension had a higher risk of mortality from CVDs when compared with those without hypertension (HR=2.49; 95% CI 1.77 to 3.50) (table 2). However, there was no significant association between hypertension and mortality due to CVDs among people aged 60 years and over ( $p > 0.05$ ) (table 2). Thus, age may significantly modify the association between hypertension and mortality from CVDs ( $p$  for interaction  $< 0.001$ ). We also assessed the association between hypertension and all-cause, coronary heart disease and stroke mortality (online supplementary table 1).

Stratified analysis according to different baseline blood pressure showed that patients with hypertension with SBP/DBP of 140–159/90–99 and  $\geq 160/100$  mm Hg were more likely to die of CVDs (HR=1.44; 95% CI 1.02 to 2.03; HR=1.74; 95% CI 1.22 to 2.48) when compared with participants with SBP/DBP of  $< 120/80$  mm Hg. However, we failed to detect significant associations between SBP/DBP of 130–139/80–89 mm Hg (HR=1.18; 95% CI 0.85 to 1.64,  $p=0.32$ ) and 120–129/ $< 80$  mm Hg (HR=1.38; 95% CI 0.93 to 2.05,  $p=0.11$ ) and mortality from CVDs, respectively. Furthermore, among participants aged  $< 60$  years at baseline, a similar trend was observed between hypertension and mortality due to CVDs, where HR was 2.32 ( $p < 0.001$ ) for SBP/DBP of 140–159/90–99 mm Hg and 3.25 ( $p < 0.001$ ) for  $\geq 160/100$  mm Hg, respectively.

**Table 1** Characteristics of the participants by hypertensive status at baseline

	Patients with hypertension (n=2196)	Participants without hypertension (n=5118)	P value
Age (years), n (%)			$< 0.001$
<60	1389 (63.25)	4143 (80.95)	
$\geq 60$	807 (36.75)	975 (19.05)	
Sex, n (%)			$< 0.001$
Male	1002 (45.63)	2344 (45.80)	
Female	1194 (54.37)	2774 (54.20)	
Education, n (%)			$< 0.001$
Illiterate	805 (36.65)	1224 (23.91)	
Primary	666 (30.33)	1692 (33.06)	
Middle school	628 (28.60)	1917 (37.46)	
High school and above	97 (4.42)	285 (5.57)	
Tobacco smoking, n (%)			$< 0.001$
Non-smoking	1114 (50.73)	2819 (55.08)	
Ex-smoking	202 (9.20)	234 (4.57)	
Current smoking	880 (40.07)	2065 (40.35)	
Alcohol consumption, n (%)			$< 0.001$
Non-drinking	1499 (68.26)	3575 (69.85)	
Ex-drinking	510 (23.22)	1250 (24.42)	
Current drinking	187 (8.52)	293 (5.73)	
BMI ( $\text{kg/m}^2$ ), n (%)			$< 0.001$
BMI $< 18.5$	48 (2.19)	91 (1.78)	
$18.5 \leq \text{BMI} < 23.9$	956 (43.53)	2930 (57.25)	
$24.0 \leq \text{BMI} < 27.9$	811 (36.93)	1752 (34.23)	
BMI $\geq 28.0$	381 (17.35)	345 (6.74)	
BMI, body mass index			

However, there was no significant association between hypertension and mortality from CVDs with different baseline blood pressure levels for those aged  $\geq 60$  years ( $p$  for interaction  $< 0.001$ ) (table 3).

## DISCUSSION

The present 20-year prospective study filled the gaps for implying the generalisability of the 2017 ACC/AHA hypertension guideline to rural Chinese populations. The results showed there was no significant association between stage 1 hypertension defined by the 2017 ACC/AHA and CVDs mortality when compared with SBP/DBP of  $< 120/80$  mm Hg. In addition, we detected high blood pressure was associated with higher mortality from CVDs among people aged 35–59 years rather than those aged 60 years and over. The findings may contribute to the optimal management of hypertension to address the



**Table 2** Multivariable HRs of mortality from CVDs according to baseline history of hypertension

CVDs mortality				
	N	Deaths	Adjusted HR (95% CI)	P value
Total				
Baseline hypertension status				
No	5118	189	Reference	
Yes	2196	161	1.35 (1.08 to 1.69)	0.01
Age <60 years				
Baseline hypertension status				
No	4143	80	Reference	
Yes	1389	64	2.49 (1.77 to 3.50)	<0.001
Age ≥60 years				
Baseline hypertension status				
No	975	109	Reference	
Yes	807	97	1.01 (0.76 to 1.33)	0.96

CVDs, cardiovascular diseases.

growing burden of CVDs morbidity and mortality among rural Chinese populations, suggesting a large implication both to clinicians and public health practitioners.

In the current study, we first examined the association between hypertension of ≥140/90 mm Hg and mortality from CVDs. The result showed a higher risk of mortality from CVDs in patients with hypertension when compared with participants without hypertension (HR=1.35), which was comparable with previous studies.<sup>4 14–16</sup>

Furthermore, the stratified analysis according to age groups showed that the associations between hypertension and CVDs mortality were stronger among participants aged 35–59 years than those aged 60 years and above. A previous study also showed the association was significant in the age groups of 35–44 and 45–59 years rather than in the group of ≥60 years.<sup>12</sup> Besides, a study based on pooling data from seven diverse US cohort studies showed that individuals who experienced blood pressure increases prior to middle age have associated higher remaining lifetime risk for CVDs when compared with those who had developed hypertension later in age 55 years.<sup>17</sup> Similarly, a previous meta-analysis of 13 prospective cohort studies involving 396 200 participants showed that prehypertension was not associated with CVDs risk among older populations with age ≥60 years.<sup>18</sup> It is reported that the cardiovascular risk for patients with hypertension decreased as the age of onset increased from 40 to 69 years.<sup>19</sup> Possible explanations for the age-specific association between hypertension and mortality from CVDs needs further studies to explore. In addition, it is important to consider the influence of age in the diagnosis of hypertension.

In clinical practice, the staging of hypertension defined by SBP and DBP corresponds with the graded increased risk of cardiovascular disease and events and is in relation

**Table 3** Multivariable HRs of mortality from CVDs according to baseline blood pressure levels

CVDs mortality				
	N	Deaths	Adjusted HR (95% CI)	P value
Total				
<120/80 mm Hg	2132	61	Reference	
120–129/<80 mm Hg	920	43	1.38 (0.93 to 2.05)	0.11
130–139/80–89 mm Hg	2180	91	1.18 (0.85 to 1.64)	0.32
140–159/90–99 mm Hg	1239	80	1.44 (1.02 to 2.03)	0.04
≥160/100 mm Hg	843	75	1.74 (1.22 to 2.48)	<0.01
Age <60 years				
<120/80 mm Hg	1813	32	Reference	
120–129/<80 mm Hg	727	21	1.46 (0.84 to 2.55)	0.18
130–139/80–89 mm Hg	1691	29	0.90 (0.54 to 1.50)	0.70
140–159/90–99 mm Hg	818	34	2.31 (1.41 to 3.79)	<0.001
≥160/100 mm Hg	483	28	3.25 (1.92 to 5.50)	<0.001
Age ≥60 years				
<120/80 mm Hg	319	29	Reference	
120–129/<80 mm Hg	193	22	1.28 (0.74 to 2.24)	0.38
130–139/80–89 mm Hg	489	62	1.47 (0.94 to 2.29)	0.09
140–159/90–99 mm Hg	421	46	1.16 (0.72 to 1.85)	0.55
≥160/100 mm Hg	360	47	1.41 (0.88 to 2.26)	0.16

CVDs, cardiovascular diseases.

to pathophysiological mechanisms, prognostic implications and therapeutic approaches.<sup>20–22</sup> For example, the initiation of pharmacological therapy is recommended for adults with stage 2 hypertension.<sup>22</sup> ACC/AHA Task Force on Clinical Practice Guidelines released the 2017 hypertension guideline, which defined SBP of 130–139 mm Hg or DBP of 80–89 mm Hg as stage 1 hypertension supported by the evidence from SPRINT.<sup>6 8</sup> Based on the new criterion, the prevalence of hypertension would increase substantially in many countries.<sup>23–25</sup> Although intensive blood pressure control was beneficial to cardiovascular events and total mortality, it was associated with an increased number of newly diagnosed patients with hypertension who may not develop CVD events in the future.<sup>23</sup> In particular, with a large ageing population, there was a high prevalence of hypertension in China.<sup>26–28</sup> It is estimated that 2.33 million cardiovascular deaths were attributable to increased blood pressure in China.<sup>14</sup> Furthermore, contrary to western countries that

CVD mortality has decreased significantly during the past years, CVD mortality has increased during the same period in China.<sup>3 15</sup> Thus, whether the results of SPRINT apply to rural Chinese populations is a critical question to answer among Chinese populations.

In the current analysis by different blood pressure levels at baseline, the HR of CVDs mortality related to stage 1 hypertension defined by the 2017 ACC/AHA hypertension guideline (130–139/80–89 mm Hg) was not statistically higher than that related to SBP/DBP of <120/<80 mm Hg. Previous studies have demonstrated diagnosed patients with hypertension tended to prescribe antihypertensive medications despite the lifestyle modifications management suggestions,<sup>18 29</sup> which may increase adverse effects caused by antihypertension treatment among the newly diagnosed patients such as acute kidney injury, acute renal failure, hypotension, syncope or electrolyte abnormality.<sup>13 30</sup> In addition, the higher hypertension diagnosis costs due to treatment is another important issue.<sup>30 31</sup> Since there was a lack of awareness, adherence to hypertension guidelines as well as access to antihypertensive drugs in China, the health and cost-effectiveness of the new diagnostic criteria for hypertension should be evaluated further. The results in our study may help address the current evidence gaps about whether the 2017 ACC/AHA guideline could be applied to populations in rural China.

The 20-year prospective study included a relatively large sample size examining the association between high blood pressure and mortality from CVDs in rural China. The CVDs deaths in the current study were comparable with several previous studies in China.<sup>13 32</sup> A previous study suggested a north-south gradient in the mortality of CVDs due to the difference in the prevalence of hypertension in China.<sup>33</sup> Furthermore, the Sino-Monitoring Trends and Determinants in Cardiovascular Disease (Sino-MONICA) study showed that the number of deaths caused by stroke was larger than that caused by coronary heart disease.<sup>34</sup> In addition, 73% of the stroke burden could be attributed to hypertension in China, and the prevalence of hypertension in stroke survivors in China was relatively high when compared with other countries.<sup>35</sup> Besides, most of the stroke deaths (64.3%) were attributable to ischaemic stroke in the current study. Previous studies indicate that atrial fibrillation is the most common cause of ischaemic stroke and an increased risk of stroke was observed in patients with hypertension with atrial fibrillation,<sup>36–39</sup> which may be another reason for the larger number of stroke deaths compared with coronary heart disease. Further studies are needed to explore the role of atrial fibrillation in the association between hypertension and stroke mortality to confirm our findings. Fangshan District is located in the 'stroke belt' of China.<sup>40</sup> Thus, the study is important to elucidate the association between stage 1 hypertension defined by the 2017 ACC/AHA hypertension guideline and cardiovascular deaths in rural China.

## Limitations of the study

Nevertheless, the study has several limitations. First, we cannot exclude the influence of some potential confounding factors despite the fact that we conducted the analysis with careful adjustment. In particular, the definition of smoking, alcohol consumption, salt intake and the use of antihypertensive drugs was relatively simple due to limited information in the baseline questionnaire. Second, hypertension was defined by SBP/DBP at baseline while we failed to acquire blood pressure measurements during follow-up, which may underestimate the strength of the associations we observed. Next, we had an insufficient sample size to explore whether the effects of hypertension on CVDs mortality differ by baseline comorbidities including diabetes or chronic kidney disease. In addition, information of death was obtained from the Death Surveillance System, the participants lost to follow-up were hard to detect and may cause potential bias. Therefore, further studies with a larger sample size are needed to validate the results in the study. More importantly, our study only included participants in rural China, which might limit the generalisability of the results to other populations with different socioeconomic status, environmental exposures or genetic background.

## CONCLUSION

In conclusion, the current study revealed hypertension of  $\geq 140/90$  mm Hg was an important risk factor of CVDs mortality, especially among people aged 35–59 years. However, stage 1 hypertension under the definition of 2017 ACC/AHA was not associated with an increased risk of CVDs mortality. This study indicated that adopting the new hypertension definition needs further consideration among rural Chinese populations.

**Contributors** MW, TW and Y-HH conceived and designed the paper. L-M, WC, JL, YW, XQ, XT, QZ, SH, SZ, Y-HH, TW and DY coordinated the data acquisition and contributed to critical revision of the manuscript for important intellectual content. MW, PG, WG and CY analysed the data. MW and TW drafted the manuscript. MW, TW, LL and Y-HH were responsible for the overall content of article and data analysis. The manuscript is approved by all authors for publication.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article.

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