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The association between stage 1 hypertension defined by the 2017 ACCAHA Hypertension Guideline and cardiovascular deaths: a 20-year follow-up study in rural China

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Abstract

Objectives: The 2017 ACC/AHA Hypertension Guideline recommended 130/80 mmHg as blood pressure (BP) target goals. However, the generalizability 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 in China.

Design: Prospective cohort study.

Participants: 8,189 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 hazard ratio (HR) for CVDs mortality associated with baseline BP were 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) ≥140/90 mm Hg) was significantly associated with the risk of mortality due to CVDs (HR=2.49, 95% CI=1.77-3.50) among people aged 35-59 years rather than people aged ≥60. 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=0.54-1.50) nor participants aged≥60 years (HR=1.47, 95% CI=0.94-2.29).

Conclusion: The study revealed hypertension of SBP/DBP ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 59 years. However, stage

1 hypertension under the definition of 2017 ACC/AHA was not associated with increased risk of CVDs mortality. This study indicated that whether adopting the new hypertension definition needs further consideration in rural China.

Keywords: hypertension; mortality; cardiovascular diseases; cohort study

Strengths and limitations of this study

1. The prospective study had a relatively long follow-up time of 20 years.
2. The study examined the association between high blood pressure and the risk of mortality from CVDs, which were hard outcomes.
3. 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.
4. 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.
5. 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.

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 [1]. It has been reported that hypertension affected nearly 30% of the adult population in western countries as well as in China [2,3].

The management of high blood pressure is a public health priority with implications for the prevention of CVDs [4,5]. 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 mmHg as blood pressure target goals [6]. However, the definition of hypertension remains ≥140/90 mm Hg in the European guideline [7].

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 [8]. 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) [9]. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial [9,10]. Sun et al found that compared with hypertensive patients with baseline SBP <140mmHg, intensive

SBP lowering could not improve clinical outcomes but generated more treatment-related adverse events among those with higher baseline SBP (≥140mmHg) [11]. In addition, a recent study showed that the treatment to achieve a target SBP of 110 to 139 mm Hg did not result in a lower rate of death than standard reduction to a target of 140 to 179 mmHg in hypertensive patients with intracerebral hemorrhage [12]. Furthermore, a cohort study showed that the hazard ratios (HRs) comparing stage 1 hypertension (130 to 139/80 to 89 mm Hg) to intensive blood pressure control (<120/80 mmHg) for CVDs incidence and mortality were significant among participants aged 35 to 59 years but not in those aged ≥60 years among Chinese populations [13].

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 generalizability of SPRINT findings and explore the target blood pressure levels among Chinese populations.

Methods

Study design and participants

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. From month 1996/1997 through month 1998/1999, 8,189 participants aged 35 to 97 years were enrolled. Informed consent was obtained from all participants. In addition, the study was approved by the Institutional Review Board of Peking University Health

Science Center.

Outcomes variables

The primary outcome variable was death from CVDs. The information of death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017. Among the 8,189 participants, 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) was missing. Finally, a total of 7,314 participants (3,346 males and 3,968 females) were included in the analysis.

Data collection

The primary exposure variables for these analyses included age at the enrollment and the blood pressure level at baseline. Data on sociodemographic characteristics, lifestyles, and medical history of the participants were collected through questionnaire interview 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements were included in the analysis. Hypertension was defined as SBP ≥140 mm Hg, systolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or self -reported history of hypertension [3].

Statistical analysis

Student's t-test and Chi-square test 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 of 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 mmHg) was treated as reference. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.

All analyses were performed using R software (Version 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 7,314 participants (aged 50.65±11.8 years), the prevalence of hypertension was 30.02%. The proportion of people aged 60 years and above was higher in hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, *P*<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants

(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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (P<0.001) (Table 1).

Table1 Characteristics of the participants by hypertensive status at baseline

	Hypertensive patients (n=2,196)	Non-hypertensive participants (n=5,118)	*P*
Age, n (%)			<0.001
<60	1,389 (63.25)	4,143 (80.95)	
≥60	807 (36.75)	975 (19.05)	
Sex, n (%)			<0.001
Male	1,002 (45.63)	2,344 (45.80)	
Female	1,194 (54.37)	2,774 (54.20)	
Education, n (%)			
Illiterate	805 (36.65)	1,224 (23.91)	
Primary	666 (30.33)	1,692 (33.06)	
Middle school	628 (28.60)	1,917 (37.46)	
High school and above	97 (4.42)	285 (5.57)	
Tobacco smoking, n (%)			<0.001
Non-smoking	1,114 (50.73)	2,819 (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	1,499 (68.26)	3575 (69.85)	
Ex-drinking	510 (23.22)	1250 (24.42)	
Current drinking	187 (8.52)	293 (5.73)	
BMI (kg/m^2), n (%)			<0.001
BMI<18.5	48 (2.19)	91 (1.78)	
18.5≤BMI<23.9	956 (43.53)	2930 (57.25)	
24.0≤BMI<27.9	811 (36.93)	1752 (34.23)	
BMI≥28.0	381 (17.35)	345 (6.74)	

BMI: body mass index

During the median follow-up of 20 years, we identified 350 deaths 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 anti-hypertensive medications, and family history of hypertension, we detected statistically significant association between hypertension and the risk of 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, hypertensive patients had a higher risk of mortality from CVDs when compared to those without hypertension (HR=2.49; 95% CI, 1.77 to 3.50) (Table 2). However, there was no significant association between hypertension and the risk of 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 risk of mortality from CVDs (P for interaction<0.001).

Table 2 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline history of hypertension

	CVDs mortality			
	N	Deaths	Adjusted HR (95% CI)	*P*
Total				
Baseline hypertension status				
No	5118	189	Reference	
Yes	2196	161	1.35 (1.08 to1.69)	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; HR: hazard ratio; CI: confidence interval

In the subgroup analysis according to different baseline blood pressure, the results showed that hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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 the risk of mortality from CVDs, respectively. Further, among participants aged<60 years at baseline, similar trend was observed between hypertension and the risk of 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and the risk of mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (*P* for interaction<0.001) (Table 3).

Table 3 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline blood pressure levels

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

CVDs: cardiovascular diseases; HR: hazard ratio; CI: confidence interval

Discussion

The present 20-year prospective study filled the gaps for implying the generalizability of the 2017 ACC/AHA Hypertension Guideline to 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. 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 growing burden of CVDs morbidity and mortality in China, suggesting a large implication both to clinicians and public health practitioners.

ACC/AHA Task Force on Clinical Practice Guidelines released the 2017 hypertension guideline, which defined a SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg as stage 1 hypertension supported by the evidence from SPRINT [6,8]. Based on the new criterion, the prevalence of hypertension would increase substantially in many countries [14-16]. Although intensive blood pressure control was beneficial to cardiovascular events and total mortality, it was associated with an increased number of newly diagnosed hypertensive patients who may not develop CVD events in the future [14]. In particular, with a large aging population, there was a high prevalence of hypertension in China [17-19]. Besides, it is estimated that uncontrolled hypertension was responsible for 750000 CVD deaths in China in 2010 [3]. 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 [3,20]. Thus, whether the results of SPRINT apply to Chinese populations is a critical question to answer. In the current study, we estimated the associations of different blood pressure levels with consequent CVD mortality to provide more evidence among Chinese populations aged 35 years or above.

Firstly, we examined the association between hypertension of ≥140/90 mm Hg and the risk of mortality from CVDs, which showed a higher risk of mortality from CVDs in hypertensive patients when compared with non-hypertensive participants (HR=1.35). The CVDs mortality burden attributable to hypertension has increased in China in recent years [4,20-22], and a previous study found that 2.11 million CVDs deaths were caused by hypertension [21].

In the 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 in our study. Previous studies have demonstrated diagnosed hypertensive patients tended to prescribe antihypertensive medications despite the lifestyle modifications management suggestions [15,23], which may increase adverse effects caused by anti-hypertension treatment among the newly diagnosed patients such as acute kidney injury, acute renal failure, hypotension, syncope, or electrolyte abnormality [13,24]. In addition, the higher hypertension diagnosis costs due to treatment is another important issue [24,25]. 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. Thus, 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.

Further, we conducted a subgroup analysis to explore the association between hypertension and the risk of mortality from CVDs according to different age groups, and the results 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 a significant interaction between age and hypertension for the risk of mortality from CVDs, where the association between hypertension and the risk of CVDs mortality was significant in the age groups of 35 to 44 and 45 to 59 years rather than in the group of ≥60 years [12]. Besides, a study based on pooling data from 7 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 [26]. Similarly, a previous meta-analysis of 13 prospective cohort studies involving 396,200 participants showed that pre-hypertension was not associated with CVDs risk among older populations with age ≥ 60 years [27]. It is reported that the cardiovascular risk for hypertensive patients decreased as age of onset increased from 40 to 69 years [28]. Possible explanations for the age-specific association between hypertension and the risk of mortality from CVDs needs further studies. In addition, it is important to consider the influence of age in the diagnosis of hypertension.

The 20-year prospective study included a relatively large sample size examining the

association between high blood pressure and the risk of mortality from CVDs. A previous study suggested a north-south gradient in the mortality of CVDs due to the difference in prevalence of hypertension in China [29]. Furthermore, the Sino-MONICA study showed that the number of deaths caused by stroke was larger than that caused by coronary heart disease [30]. In addition, 73% of the stroke burden could be attributed to hypertension in China, and prevalence of hypertension in stroke survivors in China was relatively high when compared with other countries [31]. Fangshan District is located in the "stroke belt" of China [32]. Thus, the study is important to elucidate the association between stage 1 hypertension defined by the 2017 ACCAHA Hypertension Guideline and cardiovascular deaths in rural China.

Nevertheless, the study has several limitations. Firstly, we cannot exclude the influence of some potential confounding factors despite we conducted the analysis with careful adjustment. Secondly, 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 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.

Conclusion

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

Competing interests

The authors declare that they have no competing interests.

Founding

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Contributorship statement

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

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Page 1, page 2, and page 3. The study was a prospective cohort study, which was conducted to explore the association between blood pressure and cardiovascular diseases mortality. The title was: The association between stage 1 hypertension defined by the 2017 ACCAHA Hypertension Guideline and cardiovascular deaths: a 20-year follow-up study in rural China
		(*b*) Page 2 and page 3. The abstract gave a brief introduction of the objectives, methods, results, and conclusions of the study.
Introduction		
Background/rationale	2	Page 5 and page 6. In the introduction section, we demonstrated that 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 mmHg as blood pressure target goals. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial.
Objectives	3	Page 6. 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 generalizability of SPRINT findings and explore the target blood pressure levels among Chinese populations.
Methods		
Study design	4	Page 6. As stated it in the Methods section, our study was a prospective cohort study.
Setting	5	Page 6. The study was a community-based follow-up study for the prevention and treatment of hypertension, which is being conducted in Fangshan District, Beijing, China.
Participants	6	Page 6 and page 7. As described in the Methods section about the participants, from month 1996/1997 through month 1998/1999, 8,189 participants aged 35 to 97 years were enrolled. Informed consent was obtained from all participants. In addition, the study was approved by the Institutional Review Board of Peking University Health Science Center.
Variables	7	Page 7. The primary outcome variable was death from CVDs. The information of death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017.
Data sources/	8*	The primary exposure variables for these analyses included age at the enrollment

measurement		and the blood pressure level at baseline. Data on sociodemographic characteristics, lifestyles, and medical history of the participants were collected through questionnaire interview 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements were included in the analysis. Hypertension was defined as SBP ≥140 mm Hg, systolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or self -reported history of hypertension.
Bias	9	Page and page 9. Potential confounders may exist despite careful adjustment for potential confounders in the analysis.
Study size	10	Page 7. A total of 7,314 participants (3,346 males and 3,968 females) were included in the analysis.
Quantitative variables	11	Page 9. Age and BMI were handled as quantitative variables in the models.
Statistical methods	12	(*a*) Page 8 and page 9. Student's t-test and Chi-square test 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 of 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 mmHg) was treated as reference.
		(*b*) Page 9. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.
		(*c*) There was no missing data in the analysis since standard quality control criteria were adopted in our study.
		(*d*) Not applicable
		(*e*) We did not conduct any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Page 7. Our study only had one stage, and all 7,314 participants were included in the analysis.
		(b) Not applicable
		(c) Not applicable
Descriptive data	14*	(a) Page 9 and page 10. Of the 7,314 participants (aged 50.65±11.8 years), the prevalence of hypertension was 30.02%. The proportion of people aged 60 years and above was higher in hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, P<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants (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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (P<0.001).
		(b) Not applicable
Outcome data	15*	Page 10 and page 11. During the median follow-up of 20 years, we identified 350 deaths from CVDs (148 stroke, 113 coronary heart disease, and 89 other CVDs.
Main results	16	(*a*) Page 11 and page 12. We detected statistically significant association between hypertension and the risk of 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, hypertensive patients had a higher risk of mortality from CVDs when compared to those without hypertension (HR=2.49; 95% CI, 1.77 to 3.50).
		(*b*) Page 11 and page 12. There was no significant association between hypertension and the risk of mortality due to CVDs among people aged 60 years and over (P>0.05). Thus, age may significantly modify the association between hypertension and risk of mortality from CVDs (P for interaction<0.001).
		(*c*) Not applicable
Other analyses	17	Page 12 and page 13. Hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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 the risk of mortality from CVDs, respectively. Further, among participants aged<60 years at baseline, similar trend was observed between hypertension and the risk of 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and the risk of mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (P for interaction<0.001).
Discussion		
Key results	18	Page 14, page 15, and page 16. The present 20-year prospective study filled the gaps for implying the generalizability of the 2017 ACC/AHA Hypertension Guideline to 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. 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

		growing burden of CVDs morbidity and mortality in China, suggesting a large implication both to clinicians and public health practitioners.
Limitations	19	Page 17. Firstly, we cannot exclude the influence of some potential confounding factors despite we conducted the analysis with careful adjustment. Secondly, 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 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.
Interpretation	20	Page 14, page 15, and page 16. From an objective perspective, we discussed the results from the aspects recommended in the STROBE Checklist.
Generalisability	21	Page 18. The current study revealed hypertension of ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 59 years. However, stage 1 hypertension under the definition of 2017 ACC/AHA was not associated with increased risk of CVDs mortality. This study indicated that whether adopting the new hypertension definition needs further consideration in rural China.
Other information		
Funding	22	Page 18. All sources of funding were described in the Acknowledgement section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The 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 ACC/AHA Hypertension Guideline recommended 130/80 mmHg as blood pressure (BP) target goals. However, the generalizability 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: 7,314 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 hazard ratio (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) ≥140/90 mm Hg) was significantly associated with mortality due to CVDs (HR=2.49, 95% CI=1.77-3.50) among people aged 35-59 years rather than people aged ≥60. 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=0.54-1.50) nor participants aged≥60 years (HR=1.47, 95% CI=0.94-2.29).

Conclusion: The study revealed hypertension of SBP/DBP ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 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.

Keywords: hypertension; mortality; cardiovascular diseases; cohort study

Strengths and limitations of this study

1. The prospective study had a relatively long follow-up time of 20 years.
2. The study examined the association between high blood pressure and mortality from CVDs, which were hard outcomes.
3. 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.
4. 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.
5. 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.

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 [1]. It has been reported that hypertension affected nearly 30% of the adult population in Western countries as well as in China [2,3].

The management of high blood pressure is a public health priority with implications for the prevention of CVDs [4,5]. 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 mmHg as blood pressure target goals [6]. However, the definition of hypertension remains ≥140/90 mm Hg in the European guideline [7].

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 [8]. 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) [9]. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial [9-13]. For example, a recent study showed that the treatment to achieve a target SBP of 110 to 139 mm

Hg did not result in a lower rate of death than standard reduction to a target of 140 to 179 mmHg in hypertensive patients with intracerebral hemorrhage [12].

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 generalizability 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. In addition, the study was approved by the Institutional Review Board of Peking University Health Science Center.

Inclusion and exclusion of the participants

From January 1997 through June 1999, 8,189 participants aged 35 to 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) was missing. Finally, a total of 7,314 participants (3,346 males and 3,968 females) were included in the analysis.

Outcomes variables

The primary outcome variable was death from CVDs. The information of death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017.

Data collection

The primary exposure variables for these analyses included age at the enrollment and the blood pressure level at baseline. Data on sociodemographic characteristics, lifestyles, and medical history of the participants were collected through questionnaire interview 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements were included in the analysis.

Hypertension was defined as SBP ≥140 mm Hg, systolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or self -reported history of hypertension [3]. 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 ≤ SBP ≤ 129 mm Hg and DBP < 80 mm Hg), stage 1 hypertension (130 mm Hg ≤ SBP ≤ 139 mm Hg or 80 ≤ DBP ≤ 89 mm Hg), and stage 2 hypertension (SBP ≥ 140 mm Hg/DBP ≥ 90 mm Hg or taking antihypertensive medications).

Statistical analysis

Student's t-test and Chi-square test 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 of 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 mmHg) was treated as reference. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.

All analyses were performed using R software (Version 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 7,314 participants (aged 50.65±11.8 years), the prevalence of hypertension was 30.02%. The proportion of people aged 60 years and above was higher in hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, *P*<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants (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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (P<0.001) (Table 1).

Table1 Characteristics of the participants by hypertensive status at baseline

	Hypertensive patients (n=2,196)	Non-hypertensive participants (n=5,118)	*P*
Age, n (%)			<0.001
<60	1,389 (63.25)	4,143 (80.95)	
≥60	807 (36.75)	975 (19.05)	
Sex, n (%)			<0.001
Male	1,002 (45.63)	2,344 (45.80)	
Female	1,194 (54.37)	2,774 (54.20)	
Education, n (%)			<0.001
Illiterate	805 (36.65)	1,224 (23.91)	
Primary	666 (30.33)	1,692 (33.06)	
Middle school	628 (28.60)	1,917 (37.46)	
High school and above	97 (4.42)	285 (5.57)	
Tobacco smoking, n (%)			<0.001
Non-smoking	1,114 (50.73)	2,819 (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	1,499 (68.26)	3575 (69.85)	
Ex-drinking	510 (23.22)	1250 (24.42)	
Current drinking	187 (8.52)	293 (5.73)	
BMI (kg/m^2), n (%)			<0.001
BMI<18.5	48 (2.19)	91 (1.78)	
18.5≤BMI<23.9	956 (43.53)	2930 (57.25)	
24.0≤BMI<27.9	811 (36.93)	1752 (34.23)	
BMI≥28.0	381 (17.35)	345 (6.74)	

BMI: body mass index

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 anti-hypertensive 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, hypertensive patients had a higher risk of mortality from CVDs when compared to 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 (Supplementary Table 1).

Table 2 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline history of hypertension

	CVDs mortality			
	N	Deaths	Adjusted HR (95% CI)	*P*
Total				
Baseline hypertension status				
No	5118	189	Reference	
Yes	2196	161	1.35 (1.08 to1.69)	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; HR: hazard ratio; CI: confidence interval

Stratified analysis according to different baseline blood pressure showed that hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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. Further, among participants aged<60 years at baseline, 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (*P* for interaction<0.001) (Table 3).

Table 3 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline blood pressure levels

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

CVDs: cardiovascular diseases; HR: hazard ratio; CI: confidence interval

Discussion

The present 20-year prospective study filled the gaps for implying the generalizability 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. 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 growing burden of CVDs morbidity and mortality among rural Chinses populations, suggesting a large implication both to clinicians and public health practitioners.

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 with pathophysiological mechanisms, prognostic implications, and therapeutic approaches [14-16]. For example, initiation of pharmacological therapy is recommended for adults with stage 2 hypertension [16]. ACC/AHA Task Force on Clinical Practice Guidelines released the 2017 hypertension guideline, which defined a SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg as stage 1 hypertension supported by the evidence from SPRINT [6,8]. Based on the new criterion, the prevalence of hypertension would increase substantially in many countries [17-19]. Although intensive blood pressure control was beneficial to cardiovascular events and total mortality, it was associated with an increased number of newly diagnosed hypertensive patients who may not develop CVD events in the future [17]. In particular, with a large aging population, there was a high prevalence of hypertension in China [20-22]. Besides, it is estimated that 2.33 million cardiovascular deaths were attributable to increased blood pressure in China [23]. 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 [3,24]. Thus, whether the results of SPRINT apply to rural Chinese populations is a critical question to answer among Chinese populations.

In the current study, we firstly 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 hypertensive patients when compared with non-hypertensive participants (HR=1.35), which was comparable with previous studies [4,23-25].

In the 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 in our study. Previous studies have demonstrated diagnosed hypertensive patients tended to prescribe antihypertensive medications despite the lifestyle modifications management suggestions [18,26], which may increase adverse effects caused by anti-hypertension treatment among the newly diagnosed patients such as acute kidney injury, acute renal failure, hypotension, syncope, or electrolyte abnormality [13,27]. In addition, the higher hypertension diagnosis costs due to treatment is another important issue [27,28]. 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. Thus, 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.

Further, 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 to 44 and 45 to 59 years rather than in the group of ≥60 years [12]. Besides, a study based on pooling data from 7 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 [29]. Similarly, a previous meta-analysis of 13 prospective cohort studies involving 396,200 participants showed that pre-hypertension was not associated with CVDs risk among older populations with age ≥ 60 years [30]. It is reported that the cardiovascular risk for hypertensive patients decreased as age of onset increased from 40 to 69 years [31]. 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.

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 [13,32]. A previous study suggested a north-south gradient in the mortality of CVDs due to the difference in prevalence of hypertension in China [33]. Furthermore, the Sino-MONICA study showed that the number of deaths caused by stroke was larger than that caused by coronary heart disease [34]. In addition, 73% of the stroke burden could be attributed to hypertension in China, and prevalence of hypertension in stroke survivors in China was relatively high when compared with other countries [35]. Besides, most of the stroke deaths (64.3%) were attributable to ischemic stroke in the current study. Previous studies indicate that atrial fibrillation is the most common cause of ischemic stroke and an increased risk of stroke was observed in hypertensive patients with atrial fibrillation [36-39], 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 [40]. 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.

Nevertheless, the study has several limitations. Firstly, we cannot exclude the influence of some potential confounding factors despite we conducted the analysis with careful adjustment. In particular, the definition of smoking, alcohol consumption, salt intake, and the use of antihypertensive drugs was relative simple due to limited information in the baseline questionnaire. Secondly, 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 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 generalizability of the results to other populations with different socioeconomic status, environmental exposures, or genetic background.

Conclusion

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

Competing interests

The authors declare that they have no competing interests.

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Contributorship statement

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

Data availability statement

All data relevant to the study are included in the article.

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Supplementary Table 1 Multivariable hazard ratios (HRs) of all-cause, coronary heart disease, and stroke mortality according to baseline history of hypertension

Cause of mortality	N	Deaths	Adjusted HR (95% CI)	*P*
All-cause				
Baseline hypertension status				
No	5118	358	Reference	
Yes	2196	251	1.18 (0.99 to1.40)	0.06
Coronary heart disease				
Baseline hypertension status				
No	5118	59	Reference	
Yes	2196	54	1.40 (0.95 to 2.07)	0.09
Stroke				
Baseline hypertension status				
No	5118	76	Reference	
Yes	2196	72	1.58 (1.12 to 2.22)	0.009

HR: hazard ratio; CI: confidence interval

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Page 1, page 2, and page 3. The study was a prospective cohort study, which was conducted to explore the association between blood pressure and cardiovascular diseases mortality. The title was: The association between blood pressure levels and cardiovascular deaths: a 20-year follow-up study in rural China.
		(*b*) Page 2 and page 3. The abstract gave a brief introduction of the objectives, methods, results, and conclusions of the study.
Introduction		
Background/rationale	2	Page 5 and page 6. In the introduction section, we demonstrated that 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 mmHg as blood pressure target goals. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial.
Objectives	3	Page 6. 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 generalizability of SPRINT findings and explore the target blood pressure levels among Chinese populations.
Methods		
Study design	4	Page 6. As stated it in the Methods section, our study was a prospective cohort study.
Setting	5	Page 6. The study was a community-based follow-up study for the prevention and treatment of hypertension, which is being conducted in Fangshan District, Beijing, China.
Participants	6	Page 6 and page 7. As described in the Methods section about the participants, from January 1997 through June 1999, 8,189 participants aged 35 to 97 years were enrolled. Informed consent was obtained from all participants. In addition, the study was approved by the Institutional Review Board of Peking University Health Science Center.
Variables	7	Page 7. The primary outcome variable was death from CVDs. The information of death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017.
Data sources/ measurement	8*	The primary exposure variables for these analyses included age at the enrollment and the blood pressure level at baseline. Data on sociodemographic characteristics,

		lifestyles, and medical history of the participants were collected through questionnaire interview 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements were included in the analysis. Hypertension was defined as SBP ≥140 mm Hg, systolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or self -reported history of hypertension.
Bias	9	Page 8 and page 9. Potential bias may exist despite careful adjustment for potential confounders in the analysis.
Study size	10	Page 6 and page 7. A total of 7,314 participants (3,346 males and 3,968 females) were included in the analysis.
Quantitative variables	11	Page 9. Age and BMI were handled as quantitative variables in the models.
Statistical methods	12	(*a*) Page 8 and page 9. Student's t-test and Chi-square test 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 of 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 mmHg) was treated as reference.
		(*b*) Page 9. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.
		(*c*) There was no missing data in the analysis since standard quality control criteria were adopted in our study.
		(*d*) Not applicable
		(*e*) We did not conduct any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Page 6 and page 7. Our study only had one stage, and all 7,314 participants were included in the analysis.
		(b) Not applicable
		(c) Not applicable
Descriptive data	14*	(a) Page 9 and page 10. Of the 7,314 participants (aged 50.65±11.8 years), the prevalence of hypertension was 30.02%. The proportion of people aged 60 years and above was higher in hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, P<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants (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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (P<0.001).
		(b) Not applicable
Outcome data	15*	Page 11. During the median follow-up of 20 years, we identified 350 deaths from CVDs (148 stroke, 113 coronary heart disease, and 89 other CVDs.
Main results	16	(*a*) Page 11 and page 12. We detected statistically significant association between hypertension and the risk of 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, hypertensive patients had a higher risk of mortality from CVDs when compared to those without hypertension (HR=2.49; 95% CI, 1.77 to 3.50).
		(*b*) Page 11 and page 12. There was no significant association between hypertension and the risk of mortality due to CVDs among people aged 60 years and over (P>0.05). Thus, age may significantly modify the association between hypertension and risk of mortality from CVDs (P for interaction<0.001).
		(*c*) Not applicable
Other analyses	17	Page 12 and page 13. Hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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 the risk of mortality from CVDs, respectively. Further, among participants aged<60 years at baseline, similar trend was observed between hypertension and the risk of 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and the risk of mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (P for interaction<0.001).
Discussion		
Key results	18	Page 14, page 15, and page 16. The present 20-year prospective study filled the gaps for implying the generalizability of the 2017 ACC/AHA Hypertension Guideline to 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. 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

		growing burden of CVDs morbidity and mortality in China, suggesting a large implication both to clinicians and public health practitioners.
Limitations	19	Page 17 and page 18. Nevertheless, the study has several limitations. Firstly, we cannot exclude the influence of some potential confounding factors despite we conducted the analysis with careful adjustment. In particular, the definition of smoking, alcohol consumption, salt intake, and the use of antihypertensive drugs was relative simple due to limited information in the baseline questionnaire. Secondly, 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 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 generalizability of the results to other populations with different socioeconomic status, environmental exposures, or genetic background.
Interpretation	20	Page 14, page 15, and page 16. From an objective perspective, we discussed the results from the aspects recommended in the STROBE Checklist.
Generalisability	21	Page 18. The current study revealed hypertension of ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 59 years. However, stage 1 hypertension under the definition of 2017 ACC/AHA was not associated with increased risk of CVDs mortality. This study indicated that whether adopting the new hypertension definition needs further consideration in rural China.
Other information		
Funding	22	Page 18. All sources of funding were described in the Acknowledgement section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The 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 ACC/AHA Hypertension Guideline recommended 130/80 mmHg as blood pressure (BP) target goals. However, the generalizability 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: 7,314 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 hazard ratio (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) ≥140/90 mm Hg) was significantly associated with mortality due to CVDs (HR=2.49, 95% CI=1.77-3.50) among people aged 35-59 years rather than people aged ≥60. 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=0.54-1.50) nor participants aged≥60 years (HR=1.47, 95% CI=0.94-2.29).

Conclusion: The study revealed hypertension of SBP/DBP ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 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.

Keywords: hypertension; mortality; cardiovascular diseases; cohort study

Strengths and limitations of this study

1. The prospective study had a relatively long follow-up time of 20 years.
2. The study examined the association between high blood pressure and mortality from CVDs, which were hard outcomes.
3. 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.
4. 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.
5. 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.

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 [1]. It has been reported that hypertension affected nearly 30% of the adult population in Western countries as well as in China [2,3].

The management of high blood pressure is a public health priority with implications for the prevention of CVDs [4,5]. 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 mmHg as blood pressure target goals [6]. However, the definition of hypertension remains ≥140/90 mm Hg in the European guideline [7].

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 [8]. 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) [9]. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial [9-13]. For example, a recent study showed that the treatment to achieve a target SBP of 110 to 139 mm

Hg did not result in a lower rate of death than standard reduction to a target of 140 to 179 mmHg in hypertensive patients with intracerebral hemorrhage [12].

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 generalizability 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. In addition, the study was approved by the Institutional Review Board of Peking University Health Science Center.

Inclusion and exclusion of the participants

From January 1997 through June 1999, 8,189 participants aged 35 to 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 7,314 participants (3,346 males and 3,968 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017.

Data collection

The primary exposure variables for these analyses included age at the enrollment 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements was included in the analysis.

Hypertension was defined as SBP ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or a self -reported history of hypertension [3]. 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 ≤ SBP ≤ 129 mm Hg and DBP < 80 mm Hg), stage 1 hypertension (130 mm Hg ≤ SBP ≤ 139 mm Hg or 80 ≤ DBP ≤ 89 mm Hg), and stage 2 hypertension (SBP ≥ 140 mm Hg/DBP ≥ 90 mm Hg or taking antihypertensive medications).

Statistical analysis

Student's t-test and Chi-square 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 mmHg) was treated as the reference. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.

All analyses were performed using R software (Version 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 7,314 participants (aged 50.65±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 hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, *P*<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants (*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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (*P*<0.001) (Table 1).

Table1 Characteristics of the participants by hypertensive status at baseline

	Hypertensive patients (n=2,196)	Non-hypertensive participants (n=5,118)	*P*
Age, n (%)			<0.001
<60	1,389 (63.25)	4,143 (80.95)	
≥60	807 (36.75)	975 (19.05)	
Sex, n (%)			<0.001
Male	1,002 (45.63)	2,344 (45.80)	
Female	1,194 (54.37)	2,774 (54.20)	
Education, n (%)			<0.001
Illiterate	805 (36.65)	1,224 (23.91)	
Primary	666 (30.33)	1,692 (33.06)	
Middle school	628 (28.60)	1,917 (37.46)	
High school and above	97 (4.42)	285 (5.57)	
Tobacco smoking, n (%)			<0.001
Non-smoking	1,114 (50.73)	2,819 (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	1,499 (68.26)	3575 (69.85)	
Ex-drinking	510 (23.22)	1250 (24.42)	
Current drinking	187 (8.52)	293 (5.73)	

BMI (kg/m²), n (%)			<0.001
BMI<18.5	48 (2.19)	91 (1.78)	
18.5≤BMI<23.9	956 (43.53)	2930 (57.25)	
24.0≤BMI<27.9	811 (36.93)	1752 (34.23)	
BMI≥28.0	381 (17.35)	345 (6.74)	

BMI: body mass index

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 anti-hypertensive 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, hypertensive patients had a higher risk of mortality from CVDs when compared to 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 (Supplementary Table 1).

Table 2 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline history of hypertension

	CVDs mortality			
	N	Deaths	Adjusted HR (95% CI)	*P*
Total				
Baseline hypertension status				
No	5118	189	Reference	
Yes	2196	161	1.35 (1.08 to1.69)	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; HR: hazard ratio; CI: confidence interval

Stratified analysis according to different baseline blood pressure showed that hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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. Further, 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (*P* for interaction<0.001) (Table 3).

Table 3 Multivariable hazard ratios (HRs) of mortality from cardiovascular diseases according to baseline blood pressure levels

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

CVDs: cardiovascular diseases; HR: hazard ratio; CI: confidence interval

Discussion

The present 20-year prospective study filled the gaps for implying the generalizability 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. 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 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 firstly 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 hypertensive patients when compared with non-hypertensive participants (HR=1.35), which was comparable with previous studies [4,14-16].

Further, 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 to 44 and 45 to 59 years rather than in the group of ≥60 years [12]. Besides, a study based on pooling data from 7 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 [17]. Similarly, a previous meta-analysis of 13 prospective cohort studies involving 396,200 participants showed that pre-hypertension was not associated with CVDs risk among older populations with age ≥ 60 years [18]. It is reported that the cardiovascular risk for hypertensive patients decreased as the age of onset increased from 40 to 69 years [19]. 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 to pathophysiological mechanisms, prognostic implications, and therapeutic approaches [20-22]. For example, the initiation of pharmacological therapy is recommended for adults with stage 2 hypertension [22]. ACC/AHA Task Force on Clinical Practice Guidelines released the 2017 hypertension guideline, which defined SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg as stage 1 hypertension supported by the evidence from SPRINT [6,8]. Based on the new criterion, the prevalence of hypertension would increase substantially in many countries [23-25]. Although intensive blood pressure control was beneficial to cardiovascular events and total mortality, it was associated with an increased number of newly diagnosed hypertensive patients who may not develop CVD events in the future [23]. In particular, with a large aging population, there was a high prevalence of hypertension in China [26-28]. It is estimated that

2.33 million cardiovascular deaths were attributable to increased blood pressure in China [14]. 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 [3,15]. 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 hypertensive patients tended to prescribe antihypertensive medications despite the lifestyle modifications management suggestions [18,29], which may increase adverse effects caused by anti-hypertension treatment among the newly diagnosed patients such as acute kidney injury, acute renal failure, hypotension, syncope, or electrolyte abnormality [13,30]. In addition, the higher hypertension diagnosis costs due to treatment is another important issue [30,31]. 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 [13,32]. A previous study suggested a north-south gradient in the mortality of CVDs due to the difference in the prevalence of hypertension in China [33]. Furthermore, the Sino-MONICA study showed that the number of deaths caused by stroke was larger than that caused by coronary heart disease [34]. 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 [35]. Besides, most of the stroke deaths (64.3%) were attributable to ischemic stroke in the current study. Previous studies indicate that atrial fibrillation is the most common cause of ischemic stroke and an increased risk of stroke was observed in hypertensive patients with atrial fibrillation [36-39], 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 [40]. 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. Firstly, we cannot exclude the influence of some potential confounding factors despite 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. Secondly, 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 generalizability of the results to other populations with different socioeconomic status, environmental exposures, or genetic background.

Conclusion

In conclusion, the current study revealed hypertension of ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 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 among rural Chinese populations.

Competing interests

The authors declare that they have no competing interests.

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Contributorship statement

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

Data availability statement

All data relevant to the study are included in the article.

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Supplementary Table 1 Multivariable hazard ratios (HRs) of all-cause, coronary heart disease, and stroke mortality according to baseline history of hypertension

Cause of mortality	N	Deaths	Adjusted HR (95% CI)	*P*
All-cause				
Baseline hypertension status				
No	5118	358	Reference	
Yes	2196	251	1.18 (0.99 to1.40)	0.06
Coronary heart disease				
Baseline hypertension status				
No	5118	59	Reference	
Yes	2196	54	1.40 (0.95 to 2.07)	0.09
Stroke				
Baseline hypertension status				
No	5118	76	Reference	
Yes	2196	72	1.58 (1.12 to 2.22)	0.009

HR: hazard ratio; CI: confidence interval

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Page 1, page 2, and page 3. The study was a prospective cohort study, which was conducted to explore the association between blood pressure and cardiovascular diseases mortality. The title was: The association between blood pressure levels and cardiovascular deaths: a 20-year follow-up study in rural China.
		(*b*) Page 2 and page 3. The abstract gave a brief introduction of the objectives, methods, results, and conclusions of the study.
Introduction		
Background/rationale	2	Page 5 and page 6. In the introduction section, we demonstrated that 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 mmHg as blood pressure target goals. However, the generalizability of SPRINT findings to populations at large with hypertension remains controversial.
Objectives	3	Page 6. 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 generalizability of SPRINT findings and explore the target blood pressure levels among Chinese populations.
Methods		
Study design	4	Page 6. As stated it in the Methods section, our study was a prospective cohort study.
Setting	5	Page 6. The study was a community-based follow-up study for the prevention and treatment of hypertension, which is being conducted in Fangshan District, Beijing, China.
Participants	6	Page 6 and page 7. As described in the Methods section about the participants, from January 1997 through June 1999, 8,189 participants aged 35 to 97 years were enrolled. Informed consent was obtained from all participants. In addition, the study was approved by the Institutional Review Board of Peking University Health Science Center.
Variables	7	Page 7. The primary outcome variable was death from CVDs. The information of death was continuously obtained from the Death Surveillance System in the Center for Disease Prevention and Control in Fangshan District. 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 December 31, 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 (ICD-9) codes from 1997 to 2001, and International Classification of Diseases, Tenth Revision (ICD-10) codes from 2002-2017.
Data sources/ measurement	8*	The primary exposure variables for these analyses included age at the enrollment and the blood pressure level at baseline. Data on sociodemographic characteristics,

		lifestyles, and medical history of the participants were collected through questionnaire interview 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 (less than 2 drinks a day), or heavy (≥2 drinks a day). Further, 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 3 times using a mercury sphygmomanometer by trained investigators. The mean of the 3 recorded measurements were included in the analysis. Hypertension was defined as SBP ≥140 mm Hg, systolic blood pressure (DBP) ≥90 mm Hg, self-reported antihypertensive medication in the past 2 weeks, or self -reported history of hypertension.
Bias	9	Page 8 and page 9. Potential bias may exist despite careful adjustment for potential confounders in the analysis.
Study size	10	Page 6 and page 7. A total of 7,314 participants (3,346 males and 3,968 females) were included in the analysis.
Quantitative variables	11	Page 9. Age and BMI were handled as quantitative variables in the models.
Statistical methods	12	(*a*) Page 8 and page 9. Student's t-test and Chi-square test 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 of 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 mmHg) was treated as reference.
		(*b*) Page 9. To test for possible interactions between age and hypertension, we categorized 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 ≥60 years) in the model. Reference groups were SBP/DBP of less than 140/90 mm Hg and age of less than 60 years. We also performed a subgroup analysis according to baseline blood pressure levels (SBP/DBP: <120/<80, 120 to 129/<80, 130 to 139/80 to 89, 140 to 159/90 to 99, and ≥160/≥100 mm Hg), where SBP/DBP of <120/<80 was treated as the reference group.
		(*c*) There was no missing data in the analysis since standard quality control criteria were adopted in our study.
		(*d*) Not applicable
		(*e*) We did not conduct any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Page 6 and page 7. Our study only had one stage, and all 7,314 participants were included in the analysis.
		(b) Not applicable
		(c) Not applicable
Descriptive data	14*	(a) Page 9 and page 10. Of the 7,314 participants (aged 50.65±11.8 years), the prevalence of hypertension was 30.02%. The proportion of people aged 60 years and above was higher in hypertensive patients (36.75%) when compared with non-hypertensive participants (19.05%, P<0.001). In addition, hypertensive patients were less educated than non-hypertensive participants (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 hypertensive patients when compared with non-hypertensive participants. Furthermore, the percentage of obesity was higher among hypertensive patients when compared with non-hypertensive participants (P<0.001).
		(b) Not applicable
Outcome data	15*	Page 11. During the median follow-up of 20 years, we identified 350 deaths from CVDs (148 stroke, 113 coronary heart disease, and 89 other CVDs.
Main results	16	(*a*) Page 11 and page 12. We detected statistically significant association between hypertension and the risk of 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, hypertensive patients had a higher risk of mortality from CVDs when compared to those without hypertension (HR=2.49; 95% CI, 1.77 to 3.50).
		(*b*) Page 11 and page 12. There was no significant association between hypertension and the risk of mortality due to CVDs among people aged 60 years and over (P>0.05). Thus, age may significantly modify the association between hypertension and risk of mortality from CVDs (P for interaction<0.001).
		(*c*) Not applicable
Other analyses	17	Page 12 and page 13. Hypertensive patients with SBP/DBP of 140-159/90-99 and ≥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 the risk of mortality from CVDs, respectively. Further, among participants aged<60 years at baseline, similar trend was observed between hypertension and the risk of 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 ≥160/100 mm Hg, respectively. However, there was no significant association between hypertension and the risk of mortality from CVDs with different baseline blood pressure levels for those aged≥60 years (P for interaction<0.001).
Discussion		
Key results	18	Page 14, page 15, and page 16. The present 20-year prospective study filled the gaps for implying the generalizability of the 2017 ACC/AHA Hypertension Guideline to 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. 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

		growing burden of CVDs morbidity and mortality in China, suggesting a large implication both to clinicians and public health practitioners.
Limitations	19	Page 17 and page 18. Nevertheless, the study has several limitations. Firstly, we cannot exclude the influence of some potential confounding factors despite we conducted the analysis with careful adjustment. In particular, the definition of smoking, alcohol consumption, salt intake, and the use of antihypertensive drugs was relative simple due to limited information in the baseline questionnaire. Secondly, 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 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 generalizability of the results to other populations with different socioeconomic status, environmental exposures, or genetic background.
Interpretation	20	Page 14, page 15, and page 16. From an objective perspective, we discussed the results from the aspects recommended in the STROBE Checklist.
Generalisability	21	Page 18. The current study revealed hypertension of ≥140/90 mm Hg was an important risk factor of CVDs mortality, especially among people aged 35 to 59 years. However, stage 1 hypertension under the definition of 2017 ACC/AHA was not associated with increased risk of CVDs mortality. This study indicated that whether adopting the new hypertension definition needs further consideration in rural China.
Other information		
Funding	22	Page 18. All sources of funding were described in the Acknowledgement section.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.