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# Effect of resting heart rate on the risk of all-cause death in Chinese patients with hypertension: analysis of the Kailuan follow-up study

Mao Xiang Zhao ,[1] Quanhui Zhao,[2] Mengyi Zheng,[3] Tong Liu,[3] Yao Li,[1] Miao Wang,[1] Siyu Yao,[1] Chi Wang,[1] Yan-Ming Chen,[1] Hao Xue,[1] Shouling Wu[2]

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[1]Department of Cardiology, Chinese PLA General Hospital, Beijing, China
[2]Department of Cardiology, Kailuan General Hospital, Tangshan, Hebei, China
[3]North China University of Science and Technology, Tangshan, Hebei, China

**Correspondence to**
Dr Hao Xue;
xuehaoxh301@163.com

## ABSTRACT

**Objective** Previous studies have shown that an elevated heart rate is associated with a higher risk of cardiovascular events. This study aimed to prospectively examine the relationship between resting heart rate (RHR) and all-cause mortality in Chinese patients with hypertension.

**Design** An observational, prospective and population-based cohort study.

**Setting** The Kailuan cohort study was conducted in Tangshan City in northern China.

**Participants** We enrolled 46 561 patients who did not receive beta-blocker treatment and were diagnosed with hypertension for the first time during an employee health examination in Kailuan Group in 2006 and 2008.

**Outcome** The primary outcome of this study was all-cause mortality.

**Methods** The patients in this study were followed for 9.25±1.63 years. All patients were followed up face to face every 2 years. According to the distribution of RHR in the study population, RHR was categorised into five groups on the basis of quintiles: Q1: RHR ≤68 beats per minute (bpm); Q2: RHR >68 and ≤72 bpm; Q3: RHR >72 and ≤76 bpm; Q4: RHR >76 and ≤82 bpm; Q5: RHR >82 bpm. Cox proportional hazards model, which was adjusted for traditional risk factors, was used.

**Results** During follow-up, 4751 deaths occurred. After adjustment for potential confounders, restricted cubic spline regression showed that the risk of all-cause mortality increased with heart rate. In multivariate Cox regression analyses adjusted for age, sex and major covariates, the HR for all-cause mortality was 1.31 (95% CI 1.27 to 1.33) in the highest quintile group (Q5) compared with the lowest quintile group (Q1).

**Conclusion** An increase in RHR is a long-term risk factor of all-cause mortality in Chinese patients with hypertension.

**Trial registration number** ChiCTR-TNC-11001489.

## Strengths and limitations of this study

- Our study was based on the Kailuan study, which was a prospective, population-based cohort study with a large sample size.
- This is the first prospective study to examine the relationship between resting heart rate (RHR) and the risk of all-cause mortality in Chinese patients with hypertension.
- Given that beta-blockers have an effect on RHR, we exclude patients who received beta-blocker treatment.
- Death due to cardiovascular disease was not documented.
- We did not include all changes that occurred during follow-up, and baseline RHR might have changed over the long follow-up duration.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in China.[1] At least half of cardiovascular deaths are associated with hypertension each year.[2] Although more attention has been paid to control blood pressure in recent years, CVD mortality continues to increase.[2] This discrepancy implies that, in addition to blood pressure, other factors may be involved in the increasing CVD mortality.

Sympathetic overactivity is involved in the pathogenesis of hypertension. An increase in blood pressure is also closely related to an increase in heart rate.[3] Resting heart rate (RHR) is a non-invasive physiological indicator which reflects the activity of the autonomic nervous system. Heart rate is an easier and more direct way to determine health status compared with body mass index (BMI), smoking and waist circumference.[4–6] Several studies have suggested that RHR is an independent risk factor of all-cause mortality in patients with hypertension, and patients with an RHR >80 beats per minute (bpm) have a significantly increased risk of all-cause mortality.[7–17] The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines for management of arterial hypertension proposed an RHR >80 bpm as a factor affecting cardiovascular risk in patients with hypertension.[17] The

Chinese Expert Consensus on Heart Rate Management for Hypertensive Patients also suggested to set 80 bpm as the cut-off point for heart rate intervention in patients with hypertension.[18] An association between RHR and all-cause mortality has been reported in Europe[17] and the USA.[11] However, the effect of elevated RHR on the risk of all-cause mortality has not been studied in Chinese patients with hypertension. Therefore, to address this issue, we prospectively investigated the relationship between RHR and all-cause mortality in the Kailuan cohort study.

## METHODS

### Patient and public involvement

Patients and the public were not involved in the design of this study.

### Study design and participants

Data were derived from the Kailuan cohort study, which was a large, observational, prospective and population-based cohort study that was carried out from June 2006 to October 2007. A total of 101 510 men and women (referred to as the 'original cohort') were enrolled in Tangshan City in northern China.[19 20] The design, methods, rationale and examination details of the Kailuan cohort study were previously published elsewhere.[19 21] Participants were then followed biennially with repeated questionnaires and medical examinations via face-to-face interviews with medical staff and trained research nurses.[21 22] In the current analysis, participants were eligible if they took part in a medical examination for the first time in either the 2006–2007 or the 2008–2009 examination and had hypertension (blood pressure ≥140/90 mm Hg, currently on antihypertensive therapy or a physician's diagnosis). Patients with arrhythmia (including atrial fibrillation, atrial flutter, atrial premature beat, ventricular ectopic beats and atrioventricular block) or those taking beta-adrenergic blocking agents were excluded.

### Data collection and assessment of potential confounding covariates

As described in detail previously,[19 21 23 24] BMI was calculated as weight divided by height (kg/m$^2$). Data on baseline variables, including age, sex, smoking habits, drinking status and physical activity, were ascertained from a standard questionnaire. Diabetes mellitus was defined as a fasting blood glucose level ≥7.0 mmol/L, taking oral hypoglycaemic agents or insulin, or a self-reported physician diagnosis. A history of stroke and myocardial infarction was determined by a self-reported physician diagnosis. Biochemical parameters, including fasting blood glucose, triglyceride, total cholesterol and high-density lipoprotein cholesterol levels, were measured using an autoanalyser (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital.

### RHR measurements

RHR was measured via a 12-lead ECG (ECG9130P; Nihon Kohden, Tokyo, Japan) at baseline with participants resting in supine position for at least 5 min. The inverse of the interval between R-waves for five consecutive QRS complexes was used to determine heart rate.

### Blood pressure measurements

Blood pressure was measured twice, at a 5 min interval, on the left arm with participants in a seated position after at least 5 min of rest, using a mercury sphygmomanometer. Hypertension was defined as self-reported use of antihypertensive medication, history of hypertension, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

### Outcome

The primary outcome of this study was all-cause mortality. The determination of death was described in detail previously.[19] Participants were followed from the end point of the first examination until death or end of follow-up (31 December 2016), whichever event occurred first. Participants underwent clinical examination biennially, and information on any fatal events was collected through review of death certificates from provincial vital statistics offices, hospital records, medical insurance data, and interviews with next of kin, relatives or eyewitnesses, where such were possible.[19] Vital status was determined by a review committee by 31 December 2016.

### Statistical analysis

Medical data were obtained from each participating hospital and stored in the study database (Oracle 10.2g) that is hosted in the server at Kailuan General Hospital. According to the distribution of RHR in the study population, participants were categorised into five groups on the basis of quintiles: Q1: RHR ≤68 bpm; Q2: RHR ≥69 and ≤72 bpm; Q3: RHR >72 and ≤76 bpm; Q4: RHR >76 and ≤82 bpm; Q5: RHR >82 bpm. All statistical analyses were conducted using SAS V.9.3. Continuous variables are shown as mean±SD and categorical variables are presented as percentages. Characteristics of the participants among the five RHR groups were compared using analysis of variance for continuous variables and the $\chi^2$ test for categorical variables. The cumulative incidence of end point events among the subgroups was estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard models were used to analyse the association between the five RHR subgroups and the risk of all-cause death, with adjustment for confounding variables. Antihypertensive drugs may have additional effects on all-cause death. Therefore, we performed sensitivity analyses by excluding participants using antihypertensive drugs during 2006–2008. For further analysis to investigate the relationship between RHR as a continuous variable and all-cause mortality, we used restricted cubic spline regression to calculate the HRs and their 95% CIs. All statistical tests were two-sided

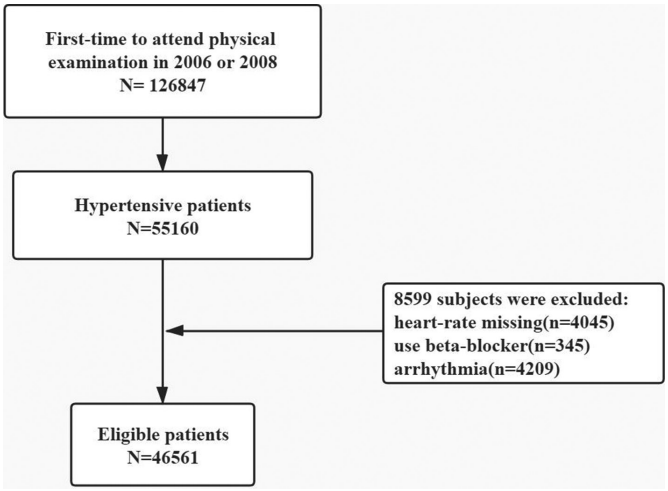


**Figure 1** Flow chart of the Kailuan cohort study.

and differences were considered statistically significant at p<0.05.

## RESULTS

### Baseline characteristics of the study population

Among 126 847 individuals in the original cohort, 55 160 were hypertensive. Among the remaining participants, 4554 who experienced arrhythmia or started taking beta-blockers and 4045 with missing information on RHR were excluded. A total of 46 561 participants were therefore included in the current analysis (figure 1). The mean age of the participants was 54.42±11.41 years and the average RHR was 75.19 bpm. Among the patients, 39 963 (85.8%) were men and 6598 (14.2%) were women. Participants with a higher heart rate were more likely to have diabetes mellitus, higher fasting blood glucose levels, total cholesterol levels, systolic blood pressure and diastolic blood pressure (p<0.01) (table 1).

### Incidence of events

The number of deaths and the incidence of mortality in each quintile of RHR are shown in table 2. In the mean follow-up period of 9.25±1.63 years, a total of 4751 all-cause deaths occurred. The number of all-cause deaths and cumulative incidence in Q1, Q2, Q3, Q4 and Q5 was 1048 (10.13%), 638 (8.41%), 875 (9.63%), 1062 (10.49%) and 1128 (11.99%), respectively (table 2). The log-rank test showed that there was a significant difference among the five subgroups (p<0.05) (figure 2).

### RHR and risk of all-cause mortality

In model 1, patients in the highest RHR quartile had a higher risk of mortality compared with those in the lowest quartile (unadjusted HR: 1.44, 95% CI 1.32 to 1.56). After accounting for sociodemographic and cardiovascular risk factors (age, sex, low-density lipoprotein, high-density lipoprotein, triglycerides, physical activity, drinking, smoking, BMI, systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agent status), similar associations between the RHR categories and all-cause mortality were attenuated, but remained significant in model 3 (adjusted HR: 1.32, 95% CI 1.21 to 1.45) (table 2).

The HR (95% CI) for all-cause mortality was estimated by restricted cubic spline regression for RHR and the results are plotted in figure 3. An RHR ≥76 bpm was associated with a higher risk of all-cause death. The restricted

**Table 1** Baseline characteristics of participants according to RHR

| | Q1 (n=10 349) | Q2 (n=7589) | Q3 (n=9086) | Q4 (n=10 127) | Q5 (n=9410) | $F/\chi^2$ | P value |
|---|---|---|---|---|---|---|---|
| Age (years) | 55.95±11.18 | 52.51±11.25 | 54.29±10.97 | 53.37±11.27 | 53.40±11.72 | 118.39 | <0.01 |
| Sex (male, %) | 85.58 | 86.66 | 84.18 | 87.14 | 86.48 | 39.86 | <0.01 |
| RHR (beats per minute) | 63.23±4.36 | 70.07±0.41 | 73.14±1.35 | 78.66±1.66 | 90.73±8.00 | 53 523.5 | <0.01 |
| SBP (mm Hg) | 145.69±16.86 | 145.88±16.90 | 147.09±17.57 | 148.12±17.58 | 150.47±18.91 | 109.05 | <0.01 |
| DBP (mm Hg) | 90.70±9.53 | 92.44±9.49 | 92.91±9.90 | 93.89±10.54 | 94.75±11.17 | 214.30 | <0.01 |
| BMI (kg/m$^2$) | 25.88±3.31 | 26.09±3.37 | 26.06±3.46 | 26.07±3.47 | 25.79±3.62 | 12.86 | <0.01 |
| TG (mmol/L) | 1.74±1.34 | 1.93±1.53 | 1.84±1.45 | 1.90±1.51 | 2.04±1.69 | 49.19 | <0.01 |
| LDL-C (mmol/L) | 2.38±1.00 | 2.51±0.94 | 2.51±0.99 | 2.58±0.99 | 2.48±0.92 | 53.45 | <0.01 |
| HDL-C (mmol/L) | 1.56±0.44 | 1.58±0.41 | 1.54±0.43 | 1.53±0.40 | 1.58±0.44 | 20.69 | <0.01 |
| FBG (mmol/L) | 5.43±1.47 | 5.55±1.61 | 5.67±1.74 | 5.80±1.86 | 6.15±2.32 | 207.52 | <0.01 |
| Diabetes (%) | 8.67 | 9.53 | 10.32 | 12.63 | 16.25 | 316.85 | <0.01 |
| Physical exercise (%) | 18.57 | 16.37 | 21.56 | 17.87 | 14.09 | 177.32 | <0.01 |
| Smoking (%) | 39.72 | 39.05 | 42.23 | 43.66 | 40.85 | 49.70 | <0.01 |
| Drinking (%) | 42.06 | 39.86 | 42.49 | 43.79 | 40.85 | 31.08 | <0.01 |
| Antihypertensive medication (%) | 24.60 | 18.05 | 22.23 | 21.77 | 21.39 | 98.01 | <0.01 |
| History of myocardial infarction | 1.91 | 1.54 | 1.68 | 1.67 | 1.51 | 5.77 | 0.217 |
| History of stroke | 4.10 | 2.95 | 3.21 | 3.23 | 3.00 | 25.55 | <0.001 |

Q1: RHR ≤68 bpm; Q2: RHR >68 and ≤72 bpm; Q3: RHR >72 and ≤76 bpm; Q4: RHR >76 and ≤82 bpm; Q5: RHR >82 bpm.
BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RHR, resting heart rate; SBP, systolic blood pressure; TG, triglycerides.

Table 2 HR (95% CI) for all-cause mortality according to resting heart rate quintiles

| Quintile | Events (n) | Incidence rate (per 1000 person-years) | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| Q1 (≤68 bpm) | 1048 | 10.85 | 1 | 1 | 1 |
| Q2 (68–72 bpm) | 638 | 9.01 | 1.06 (0.96 to 1.17) | 1.03 (0.92 to 1.10) | 1.04 (0.93 to 1.15) |
| Q3 (72–76 bpm) | 875 | 10.43 | 1.10 (1.00 to 1.20) | 1.06 (0.96 to 1.16) | 1.06 (0.96 to 1.17) |
| Q4 (76–82 bpm) | 1062 | 11.37 | 1.27 (1.17 to 1.38) | 1.22 (1.11 to 1.33) | 1.22 (1.12 to 1.34) |
| Q5 (≥82 bpm) | 1128 | 13.13 | 1.44 (1.32 to 1.56) | 1.31 (1.20 to 1.44) | 1.32 (1.21 to 1.45) |
| Log-rank | <0.05 | | | | |

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, triglycerides, physical activity, drinking, smoking and body mass index.
Model 3: adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, triglycerides, physical activity, drinking, smoking, body mass index, systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agent status.
bpm, beats per minute.

cubic spline regression model showed a linear relationship between RHR and outcomes (figure 3).

### Sensitivity analysis

We found that the results were robust after considering the effect of antihypertensive drugs. In the fully adjusted model, patients in the highest quintile of RHR had a 33% increased risk of mortality (HR: 1.33, 95% CI 1.19 to 1.48) compared with those in the lowest quintile (table 3).

## DISCUSSION

This study is the first prospective study to investigate the effect of RHR on all-cause mortality in a large-scale, Chinese population with hypertension. We found that the risk of all-cause mortality increased with an increase in RHR. Therefore, an increase in RHR is a long-term risk factor of all-cause mortality in Chinese patients with hypertension.

RHR is an easily accessible clinical parameter. An elevated RHR is significantly associated with CVD and all-cause mortality in healthy populations,[25] in patients with chronic heart failure[26] and in patients with atrial fibrillation.[27] In our study, we found that elevated RHR was associated with an increased risk of all-cause mortality, and a linear-shaped relationship was found between RHR and all-cause mortality. The Framingham study,[11] Glasgow study[15] and French study[12] also showed similar findings, where a relationship between increased RHR and all-cause mortality was found. Moreover, we found that an RHR ≥76 bpm and an RHR ≥82 bpm were associated with a 21% and 31% increase in the risk of all-cause mortality compared with an RHR <69 bpm in Chinese patients with hypertension, respectively. Furthermore, restricted cubic

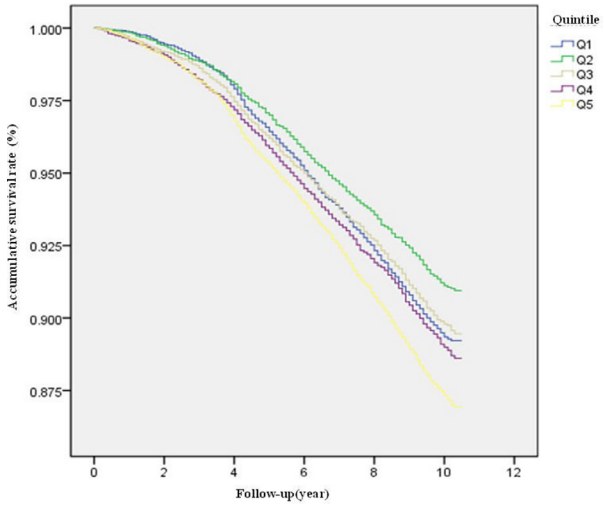


Figure 2 Kaplan-Meier survival curve for all-cause mortality stratified by RHR levels. RHR quintiles are as follows: Q1: RHR <69 bpm; Q2: RHR ≥69 and <72 bpm; Q3: RHR ≥72 and <76 bpm; Q4: RHR ≥76 and <82 bpm; Q5: RHR ≥82 bpm. bpm, beats per minute; RHR, resting heart rate.

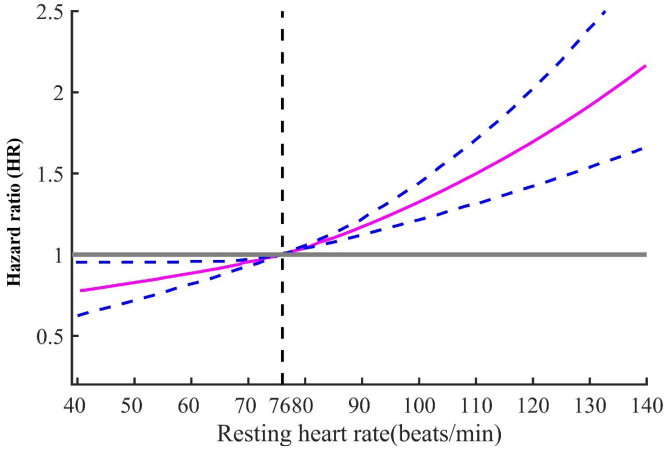


Figure 3 Cubic spline graph of adjusted HR and 95% CI for the association between RHR and all-cause mortality. The adjusted cubic spline model shows the relationship between RHR and all-cause mortality when an RHR of 76 beats per minute is the reference. The pink line shows the HR and the blue lines show the upper and lower 95% confidence limits. RHR, resting heart rate.

Table 3 HR (95% CI) of all-cause mortality excluding patients on antihypertensive treatment

| | HR | 95% CI | P value |
|---|---|---|---|
| Q1 (RHR ≤68 bpm) | 1.00 | | |
| Q2 (RHR >68 and ≤72 bpm) | 1.01 | 0.88 to 1.14 | 0.97 |
| Q3 (RHR >72 and ≤76 bpm) | 1.07 | 0.96 to 1.21 | 0.23 |
| Q4 (RHR >76 and ≤82 bpm) | 1.21 | 1.08 to 1.35 | <0.01 |
| Q5 (RHR >82 bpm) | 1.33 | 1.19 to 1.48 | <0.01 |

The model was adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, triglycerides, physical activity, drinking, smoking, body mass index, systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agent status.
bpm, beats per minute; RHR, resting heart rate.

spline regression showed a linear relationship between RHR and risk of all-cause mortality, and an RHR ≥76 bpm was associated with a higher risk for all-cause death. In fact, management of heart rate in patients with hypertension is also supported by the 2018 ESC/ESH guidelines for management of arterial hypertension.[17] These guidelines suggest that an RHR >80 bpm affects cardiovascular risk in patients with hypertension. However, the latest Guidelines for the Prevention and Treatment of Hypertension in China 2018[28] did not recommend elevated RHR as a prognostic cardiovascular risk factor in patients with hypertension, and the threshold value of RHR intervention was not mentioned. Therefore, further studies are required to examine the threshold value of RHR for heart rate intervention in Chinese patients with hypertension to reduce all-cause mortality.

In addition to Europe and Japan,[29] national guidelines[30–32] from other countries (including USA, Canada and UK) did not include heart rate as a risk factor for prognosis of CVD. Beta-blockers are the preferred drug to control heart rate in patients with high blood pressure. However, whether beta-blockers can be used as first-line antihypertensive drugs remains controversial in the guidelines from different countries. Hypertension management guidelines from China and Europe recommend beta-blockers as first-line medications, while the hypertension guidelines from the USA,[31] UK[31] and Japan[32] do not. One reason for the diversity in different guidelines is that beta-blockers (mainly atenolol) are significantly less effective than other types of blood pressure drugs (diuretics, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers) in preventing stroke and cardiovascular events.[33 34] However, unlike smoking, drinking, blood lipids and BMI, no results of heart rate intervention from randomised, clinical trials are available, which causes difficulty in providing treatment recommendations for patients with an elevated heart rate. Therefore, more randomised trials on heart rate intervention in patients with hypertension with a high heart rate are still required.

The mechanisms of RHR involved in the risk of mortality may be associated with sympathetic overactivity. RHR is a non-invasive marker of autonomic nervous system function. Elevated RHR reflects a heightened sympathetic tone that contributes to vasoconstriction and insulin resistance by stimulating the alpha-adrenergic or beta-adrenergic receptors. These effects lead to increased blood pressure, lipid levels and blood sugar levels.[35–39] However, an unbalanced autonomic nervous system is also related to inflammation and endothelial dysfunction.[40] Therefore, elevated RHR could increase the risk of atherosclerosis,[41] hyperinsulinaemia,[42] myocardial ischaemia, hypertension[43] and death in the long term. Additionally, Bangalore *et al*[44] provided strong evidence that beta-blocker intervention reduced sympathetic nerve activity and slowed heart rate. This condition is conducive to improving prognosis of CVD in myocardial infarction, sudden death and heart failure, and reducing mortality.

This study has several strengths, including its large sample size with a long follow-up of 9.25±1.63 years. Additionally, this is the first prospective study to examine the relationship between RHR and risk of all-cause mortality in Chinese patients with hypertension. We also acknowledge several limitations in our study. First, our study had an unbalanced distribution of sex and most of the participants were male coal miners. However, sex distribution in our study was representative of the whole population of Kailuan Group. Second, our study was a single-centre, observational study. However, we prospectively observed participants for longer than 9 years of follow-up, and the data were analysed by adjusting for potential risk factors of CVD. Third, death due to CVD was not documented.

## CONCLUSION

An increase in RHR may be an independent risk factor of all-cause mortality in Chinese patients with hypertension. Measurement of heart rate should be included in the overall assessment of patients with hypertension. This study provides a basis for management of heart rate in Chinese patients with hypertension. The cut-off point for heart rate interventions to reduce risk of all-cause mortality in patients with hypertension needs to be further investigated in prospective studies.

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**Contributors** MXZ, QZ, MZ, TL, Y-MC, SY, CW, YL and MW contributed to the concept of the study. SW and HX supervised the study. MXZ, QZ, MZ and TL conducted the data analysis.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The Kailuan cohort study protocol was approved by the Medical Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. Our data were based on the Kailuan cohort study and are not publicly available. Please contact SW (email: drwusl@163.com) for details.

**ORCID iD**

Mao Xiang Zhao http://orcid.org/0000-0001-7027-5913

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