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The effect of resting heart rate on the risk of all-cause death in Chinese hypertensive patients: an analysis of Kailuan Follow-up Study

Short title：Heart rate and all-cause mortality

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Key Words: Hypertension; Resting heart rate; All-cause mortality; Chinese population

Trials registry number: ChiCTR-TNC-11001489

Abstract

Objective: Previous studies have demonstrated that elevated heart rate was associated with higher risk of cardiovascular events. However, there remain gaps in our knowledge. The aim of our study was to prospectively explore the relationship between resting heart rate(RHR) and all-cause mortality in Chinese hypertensive patients.

Design and methods: We enrolled 46561 hypertensive patients without receiving beta blockers treatment from the Kailuan cohort study and followed for mean9.25±1.63 years. The subjects of this study were diagnosed as hypertension for the first time during the health examination of employees in Kailuan Group Company in 2006 and 2008. All patients were followed up face-to-face every two years. According to the distribution of RHR in the study population, RHR was categorized into five group based on quintile: Q1(RHR≤68bpm), Q2(69bpm≤RHR≤72bpm), Q3(72bpm<RHR≤76bpm), Q4(76bpm<RHR≤82bpm), Q5(82bpm<RHR).

Results: During a mean follow-up of 9.25±1.63 years, 4751deaths occurred. After adjustment for potential confounders, restricted cubic spline regression showed that the risk of all-cause mortality increased with heart rate. On Multivariate Cox Regression analyses adjusted for age, sex and major covariates, the hazard ratio (HR) for all-cause mortality was 1.31(95%CI, 1.27 ～ 1.33) in the highest quintile group(Q5:82bpm≤RHR) compared to the lowest quintile(Q1:RHR≤68bpm).

Conclusion: An increase of RHR is a long-term risk factor of all-cause mortality in Chinese hypertensive patients.

Trials registry number: ChiCTR-TNC-11001489

Key Words: Heart rate; hypertension; all-cause mortality; resting heart rate

Article summary

Strength and limitation

Strength

1. Our study was based on kailuan study, a large, observational, prospective and population-based cohort study. We enrolled 46561 hypertensive patients and followed for mean 9.25±1.63 years.

2. It is the first prospective study to explore the relationship between RHR and the risk of all-cause mortality in Chinese hypertensive patients.

3. Elevated-heart rate is an independent risk factor of death in Chinese hypertensive patients.

4. 76bpm may be the intervention cut-off point for Hypertensive Patients.

Limitation

1. First, our study was the unbalanced distribution of gender in the Kailuan cohort study, and most of the participants were male coal miners.

2. We did not to include all changes that happened during follow-up. It is possible that the baseline RHR might have changed over the long follow-up duration.

3. Our study was a single center observational study.

Introduction

Cardiovascular and cerebrovascular events have become an important public health problem in China. Cardiovascular death accounts for more than 40% of the total deaths of residents[1], which was the leading cause of death in China. Hypertension is one of the leading causes of cardiovascular and cerebrovascular. At least half of the cardiovascular deaths are associated with hypertension each years[2].Although the control rate of hypertension in China has improved significantly in recent years (the control rate of hypertension has increased from 6.1% in 2002 to 15.3% in 2015[2]), the morbidity and mortality of cardiovascular diseases are still increasing. This implies that other factors may be involved in the increasing mortality in addition to blood pressure.

Sympathetic overactivity is one of the pathogenesis of hypertension. The increase of blood pressure is also closely related to the increase of heart rate[3]. Resting heart rate (RHR) is a non-invasive physiological indicator， which reflects the activity of the autonomic nervous system. Several studies suggested that RHR is an independent risk factor for all-cause mortality in hypertensive patients, and patients with RHR over 80bpm had significantly increased risk of all-cause mortality[4-14]. The 2018 European Society of Cardiology/European Society of Hypertension(ESC/ESH)guidelines for the management of arterial hypertension proposed RHR more than 80 as a factor influencing cardiovascular risk in patients with hypertension [14]. Chinese Expert Consensus on Heart Rate Management of Hypertensive Patients also suggested to set 80bpm as the cut-off point for heart rate intervention in hypertensive patients[15].The

association between RHR and all-cause mortality has been reported in Europe or American population. However, up to now, the effect of elevated RHR on the risk of all-cause mortality has not been studied in Chinese hypertensive patients. Therefore, in order to address this issue, we prospectively investigate the relationship between RHR and all-cause mortality in the Kailuan cohort study (Trial identification: ChiCTR-TNC-11001489).

Methods

Patient and public involvement

patient and public were not involved with the design in this study

Study Design and Participants

Data were derived from the Kailuan cohort study, a large, observational, prospective and population-based cohort study that was carried out from June 2006 to October 2007 with an enrolment of 101,510 men and women (referred to as the "original cohort") in Tangshan city in northern China[16,17]. The design, methods, rationale and examination details of the Kailuan cohort study were previously published elsewhere[18]. Participants were then followed biennially with repeated questionnaires and medical examinations via face-to-face interviews with medical staff and trained research nurses[18,19]. In the current analysis, Participants were eligible if they took part in the medical examination for the first time in either the 2006-2007 or the 2008-2009 examination and were with hypertension (BP≥140/90 mmHg or currently on antihypertensive therapy or physician diagnosis). Patients with arrhythmia(including: atrial fibrillation, atrial flutter, atrial premature beat, ventricular

ectopic beats, atrioventricular block) or taking β-adrenergic blocking agents were excluded.

Data collection and assessment of potential confounding covariates

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[20]. Diabetes mellitus was defined as a fasting blood glucose ≥ 7.0 mmol/L, taking oral hypoglycaemic agents or insulin or having a self-reported physician diagnosis. History of stroke and myocardial infarction was ascertained by self-reported physician diagnosis. Biochemical parameters, including fasting blood glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol were measured using an auto-analyzer (Hitachi747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital[21].

Resting heart rate measurements

RHR was measured via a 12-lead electrocardiogram(ECG9130P, NIHON KOHDEN CORP, Japan) at baseline with participants resting in the supine position for at least 5 minutes. 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-minute interval, on the left arm with participants in seated position after at least 5 minutes of rest, using a mercury

sphygmomanometer. Hypertension was defined as self-reported use of antihypertensive medication, history of hypertension, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

Outcome

The primary outcome of this study was all-cause mortality. Participants were followed from the ending point of the first time examination till the diagnosis of death or end of follow-ups (31 December, 2016), whichever event came first.Participants underwent a clinic examination every two years, and any fatal events were collected through review of death certificates from the provincial vital statistics offices, hospital records, medical insurance data, and interviews with next of kin, relatives, or eyewitnesses, where such undertakings were possible. Vital status was determined by the review committee by December 31, 2016.

Statistical Analysis

Medical data were entered at each participating hospital and was stored in the study database (Oracle 10.2g) hosted in the server at Kailuan Hospital. According to the distribution of RHR in the study population, Participants were categorized into five group based on RHR quintiles: Q1(RHR≤68bpm), Q2(69bpm≤RHR≤72bpm), Q3(72bpm<RHR≤76bpm), Q4(76bpm<RHR≤82bpm), Q5(82bpm<RHR). All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA). Continuous variables were described as mean±SD and categorical variables were presented as percentages. Participants' characteristics among five RHR

groups were compared using the analysis of variance (ANOVA) for continuous variables and Chi-square for categorical variables. The cumulative incidence of the endpoint event among the subgroups was estimated using the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard models were used to analyze the association between the five RHR subgroups and the risk of all-cause death with adjusments for confounding variables. Given that antihypertensive drugs may have additional effects on all-cause death, we performed sensitivity analyses by excluding participants using antihypertensive drugs during 2006–2008. Further analysis to explore the relationships between RHR as a continuous variable and all-cause mortality, we used restricted cubic spline regression (RCS) to calculate the hazard ratios (HRs) and their 95% confidence intervals (CIs).All statistical tests were two-sided and differences were considered statistically significant at $P < 0.05$.

Results

Baseline characteristics of the study population

A total of 126,847 individuals in the original cohort, 55,160 were hypertensive patients. For the remaining participants, 4,554 participants who experienced arrhythmia or started taking beta blockers as well as 4,045 participants with missing information on RHR were excluded, leaving 46,561 participants in the current analysis, (Fig.1). The mean age of 46,561 participants was 54.42±11.41years. The average RHR was 75.19bpm. Of them 39,963 were males(85.8%), 6,598 were females(14.2%). The participants with higher heart rate, were more likely to have Diabetes mellitus(DB), and have higher fasting blood glucose(HBG), total

cholesterol, systolic blood pressure(SBP), diastolic blood pressure (DBP). (Table 1)

	Q1 N=10349	Q2 N=7589	Q3 N=9086	Q4 N=10127	Q5 N=9410	F	*P*
AGE（y）	55.95±11.	52.51±11.	54.29±10.	53.37±11.	53.40±11.	118.39	<0.01
GENDER[(%)	85.58	86.66	84.18	87.14	86.48	39.86	<0.01
RHR(beat/minute)	63.23±4.3	70.07±0.4	73.14±1.3	78.66±1.6	90.73±8.0	53523.5	<0.01
SBP(mmHg)	145.69±1	145.88±1	147.09±1	148.12±1	150.47±1	109.05	<0.01
DBP(mmHg)	90.70±9.5	92.44±9.4	92.91±9.9	93.89±10.	94.75±11.	214.30	<0.01
BMI（kg/m^2）	25.88±3.3	26.09±3.3	26.06±3.4	26.07±3.4	25.79±3.6	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
SMOKE［（%）］	39.72	39.05	42.23	43.66	40.85	49.70	<0.01
DRINK［（%）］	42.06	39.86	42.49	43.79	40.85	31.08	<0.01
ANTIHYPERTENSION	24.60	18.05	22.23	21.77	21.39	98.01	<0.01
History of myocardial	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

Table1. Basline characteristics of the participants according to Resting Heart Rate

Note: BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

Incidence of events

The number of death events and incidence of mortality in each Quintile of RHR was presented in (Table 2). In the mean follow-up period of 9.25±1.63 years, a total of 4,751 all-cause deaths occurred. The all-cause death cases and cumulative incidence in each subgroup were 1048 (10.13%), 638 (8.41%), 875 (9.63%), 1062 (10.49%) and 1128 (11.99%), respectively.（Table2）. The log-rank test revealed that there was a significant difference among 5 pre-specified groups(Fig. 2).

	Q1 N=10349	Q2 N=7589	Q3 N=9086	Q4 N=10127	Q5 N=9410	X^2	*P*
All-cause Death N,(%)	**1048 (10.13)**	**638 (8.41)**	**875 (9.63)**	**1062 (10.49)**	**1128 (11.99)**	**66.459**	**<0.01**
Annual mortality rate(thousand per year)	**10.85**	**9.01**	**10.43**	**11.37**	**13.13**		

Table2. The incidence of all-cause death according to Reasting Heart Rate

RHR and risk of all-cause mortality

In the model 1, subjects in the highest RHR quartile had a higher mortality risk compared with the lowest quartile (unadjusted HR:1.44,95%CI:1.32–1.56). After

accounting for sociodemographic and cardiovascular risk factors (age, sex, low-density lipoprotein, higher-density lipoprotein, triglyceride, physical activity, drinking, smoking, body mass index, systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agents status), similar associations between the RHR categories and all-cause mortality were attenuated but remained statistically significant in model 3 (adjusted HR:1.32,95%CI:1.21–1.45).(Table 3).

The HR (95% CI) for all-cause mortality was estimated by restricted cubic spline regression for RHR. The results were plotted in Figure 3. The RHR ≥76bpm was associated with higher risk of all-cause death and RCS model showed a linear relationship between RHR and outcomes. (Fig.3)

Table3. Hazard ratios (95% CI) for all-cause mortality according to the resting heart rate quintile

	Model1	Model2	Model3
Q1 (RHR<69bpm)	**reference**	**reference**	**reference**
Q2 (69bpm≤RHR<72bpm)	**1.06(0.96～1.17)**	**1.03(0.92～1.10)**	**1.04(0.93～1.15)**
Q3 (72bpm≤RHR<76bpm)	**1.10(1.00～1.20)**	**1.06(0.96～1.16)**	**1.06(0.96～1.17)**
Q4 (76bpm≤RHR<82bpm)	**1.27(1.17～1.38)**	**1.22(1.11～1.33)**	**1.22(1.12～1.34)**

Q5 (82bpm≤RHR)	**1.44(1.32～1.56)**	**1.31(1.20～1.44)**	**1.32(1.21～1.45)**

Model1:adjust for age and sex.

Model2:adjust for age, sex, low-density lipoprotein, higher-density lipoprotein, triglyceride , physical activity, drinking, smoking, body mass index.

Model3: adjust for age, sex, low-density lipoprotein, higher-density lipoprotein, triglyceride , physical activity, drinking, smoking, body mass index, ,systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agents status.

Sensitivity analysis

We found that the results were robust after considering the influence of antihypertensive drugs. In the fully adjusted model, Compared with participants in the lowest quintile, those subjects in the highest quintile of RHR had a 33% (HR,1.33, 95% CI: 1.19–1.48) increased risk of mortality (Table 4).

Table4.Hazard ratios (95% CI) of all-cause mortality excluding the patients withantihypertensive treatment

	Hazard ratio	95% CI	*P*
Q1(RHR<69bpm)	**1.00**		
Q2(69bpm≤RHR<72bpm)	**1.01**	**0.88～1.14**	**0.97**
Q3(72bpm≤RHR<76bpm)	**1.07**	**0.96～1.21**	**0.23**
Q4(76bpm≤RHR<82bpm)	**1.21**	**1.08～1.35**	**<0.01**
Q5(82bpm≤RHR)	**1.33**	**1.19～1.48**	**<0.01**

Adjust for adjust for age, sex, low-density lipoprotein, higher-density lipoprotein, triglyceride , physical activity, drinking, smoking, body mass index,systolic blood pressure, history of stroke, myocardial infarction, diabetes mellitus and antihypertensive agents status.

Discussion

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

Resting heart rate is an easily accessible clinical parameter. It has already demonstrated that elevated RHR was significantly associated with cardiovascular disease (CVD) and all-cause mortality in healthy populations[22], patients with chronic heart failure (CHF)[23] and patients with atrial fibrillation (AF)[24]. In our study, we found that elevated RHR was associated with the increased risk of all-cause mortality and linear shaped relationship has also been established between RHR and all-cause mortality. About the relationship between RHR and all-cause mortality in hypertensive patients, similar findings from Framingham study[8], the Glasgow study[12] and the French study conducted by Benetos[9]were also showed the relationship between increased RHR and all-cause mortality. Morever, we could expect that participants with RHR≥ 76bpm and RHR≥82bpm were associated with 21%、31% increase in the risk of all-cause mortality compared to those at RHR ＜ 69bpm in Chinese hypertensive patients, respectively. Furthermore, restricted cubic spline regression presented a linear-relationship between RHR and the risk of

all-cause mortality and RHR≥76bpm is associated with higher risk for all-cause death. Thus, our findings indicated that 76bpm may be the intervention cut-off point for preventing all-cause mortality in Chinese hypertensive patients. In fact, heart rate management in hypertensive patients is also supported by 2018 ESC/ESH Guidelines for the management of arterial hypertension,which suggested RHR over 80bpm as a factor influencing cardiovascular risk in patients with hypertension [14] . However, the latest Guidelines for Prevention and Treatment of Hypertension in China 2018[25] did not recommend elevated RHR as a prognosis cardiovascular risk factor in hypertensive patients, and the threshold value of RHR intervention was not mentioned. Further studies are needed to explore the threshhold value of RHR for heart rate intervention in Chinese hypertensive patients to reduce all-cause mortality.

The mechanisms of RHR involved in the risk of mortality may associated with sympathetic overactivity. RHR is a noninvasively marker of autonomic nervous system function. Elevated RHR measured in the supine position reflected a heightened sympathetic tone that contribute to vasoconstriction and insulin resistance by stimulating α-adrenergic or β-adrenergic receptors in the long-term, and therefore, lead to increased blood pressure, lipids, and blood sugar[26-30]. On the other hand, elevated RHR is related directly to inflammation, endothelial dysfunction, atherosclerosis progression, myocardial ischaemia and ventricular arrhythmias [31]. In addition, beta blocker intervention slows heart rate, which is conducive to improving cardiovascular disease prognosis in myocardial infarction, sudden death, heart failure, and reducing mortality.[32]

This study has several strengths, including a large sample size with long follow-up of 9.25±1.63 years. In addition, it is the first prospective study to explore the relationship between RHR and the risk of all-cause mortality in chinese hypertensive patients. However, Some limitations must be considered. First, our study was the unbalanced distribution of gender in the Kailuan cohort study, and most of the participants were male coal miners. But, sex distribution in our study was representative of the whole population of Kailuan Company. Second, Our study was a single center observational study. However, we have observed prospectivly over 9 years followed up, and the date was analysed by adjusting for potential CVD risks factors,

Conclusion

An increase of RHR may be an independent risk factor of all-cause mortality in Chinese hypertensive patients. HR measurement should be included in the overall assessment of the hypertensive patient.This study provides a theoretical basis for heart rate management in chinese hypertensive patients. The relationship between repeated measurements of RHR and the risk of all-cause mortality by treating RHR as a time-dependent variable will be investigated in future study. We also need to further explore whether elevated-heart rate is a risk factor to hypertensive patients under 140/90mmHg.

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Figure legend

Fig 1. Flowchart of Kailuan cohort study

Fig 2. Kaplan–Meier survival curve for all-cause mortality stratified by RHR levels.

RHR quintiles are as follows: Q1:RHR<69bpm; Q2:69bpm≤RHR<72bpm; Q3: 72bpm≤RHR<76bpm; Q4: 76bpm≤RHR<82bpm;Q5: 82bpm≤RHR

Key: RHR, resting heat rate

Fig 3. Cubic spline graph of the adjusted HR and 95% CI for the association between RHR and all-cause mortality

Note: The adjust cubic spline model demonstrate the relationship between RHR and all-cause mortality when a resting heart rate of 76bpm is the refernce. The red line represented hazard ratio and blue lines represented the upper and lower 95% confidence limits.

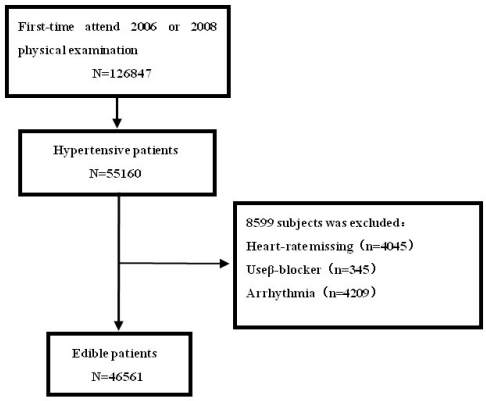

Figure 1 Flowchart of cohort study.

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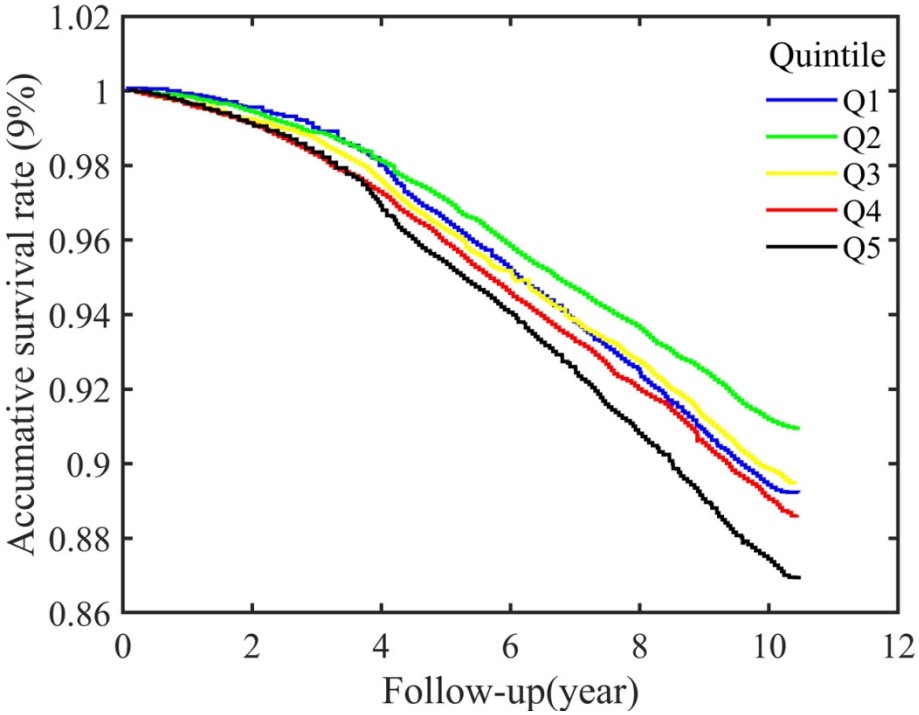

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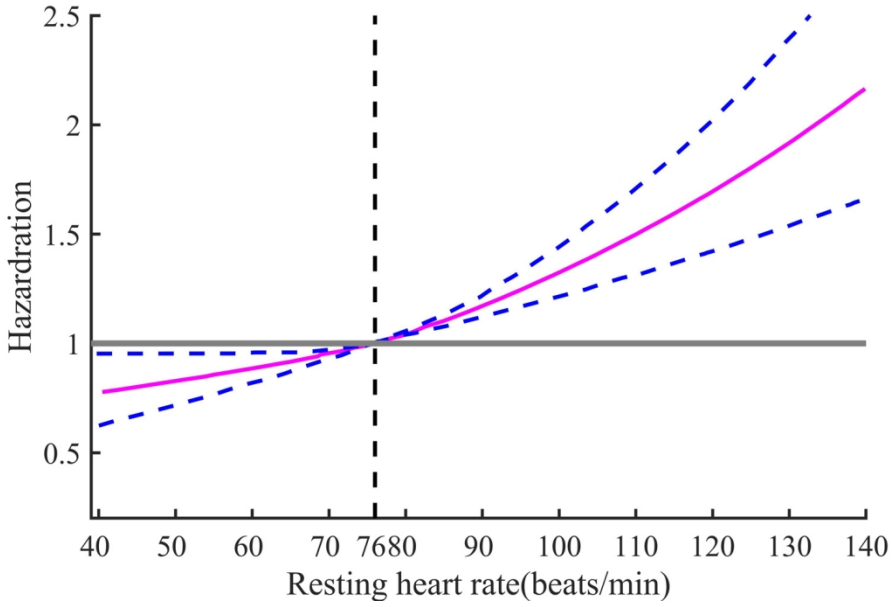

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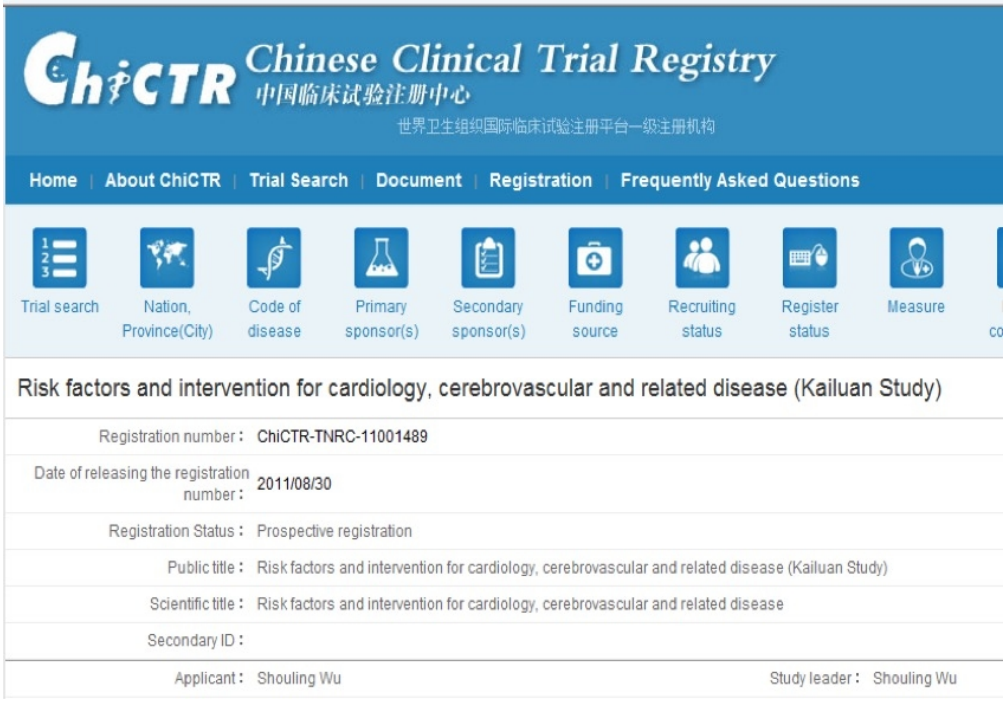

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Effect of resting heart rate on the risk of all-cause death in Chinese hypertensive patients: analysis of the Kailuan follow-up study

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

Short title: Heart rate and all-cause mortality

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Trial registry number: ChiCTR-TNC-11001489

Abstract

Objectives: 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 hypertensive patients.

Methods: We enrolled 46,561 hypertensive patients without receiving beta blocker treatment from the Kailuan cohort study and followed them for a mean of 9.25±1.63 years. The patients in this study were diagnosed with hypertension for the first time during a health examination of employees in Kailuan Group Company in 2006 and 2008. All patients were followed up face-to-face every 2 years. According to the distribution of RHR in the study population, RHR was categorized into five groups on the basis of quintiles: Q1 (RHR ≤68 bpm), Q2 (RHR >68 and ≤72 bpm), Q3 (RHR >72 and ≤76 bpm), Q4 (RHR >76 and ≤82 bpm), and Q5 (RHR >82 bpm). Cox proportional hazards model adjusting for traditional risk factors were 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 hazard ratio (HR) for all-cause mortality was 1.31 (95% confidence interval: 1.27–1.33) 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 hypertensive patients.

Trials registry number: ChiCTR-TNC-11001489

Key Words: Heart rate; hypertension; all-cause mortality; resting heart rate

Article summary

Strengths and limitations of this study

Strengths

1. Our study was based on kailuan study, a prospective and population-based cohort study with large sample size and person-years.

2. It is the first prospective study to explore the relationship between RHR and the risk of all-cause mortality in Chinese hypertensive patients.

3. Elevated-heart rate is an independent risk factor of death in Chinese hypertensive patients.

Limitation

1. First, our study was the unbalanced distribution of gender in the Kailuan cohort study, and most of the participants were male coal miners.

2. We did not to include all changes that happened during follow-up. It is possible that the baseline RHR might have changed over the long follow-up duration.

Introduction

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

Sympathetic overactivity is one of the pathogenesis of hypertension. The increase of blood pressure is also closely related to the increase of heart rate[3]. Resting heart rate (RHR) is a non-invasive physiological indicator， which reflects the activity of the autonomic nervous system. Compared with BMI, smoking and waist circumference, HR is an easy and direct way to reflect health status.[4-6] Several studies suggested that RHR is an independent risk factor for all-cause mortality in hypertensive patients, and patients with RHR over 80bpm had significantly increased risk of all-cause mortality[7-17]. The 2018 European Society of Cardiology/European Society of Hypertension(ESC/ESH)guidelines for the management of arterial hypertension proposed RHR more than 80 as a factor influencing cardiovascular risk in patients with hypertension [17]. Chinese Expert Consensus on Heart Rate Management of Hypertensive Patients also suggested to set 80bpm as the cut-off point for heart rate intervention in hypertensive patients[18].The association between RHR and all-cause mortality has been reported in Europe or American population. However, up to now, the effect of elevated RHR on the risk of all-cause mortality has not been studied in Chinese hypertensive patients. Therefore, in order to address this issue, we

prospectively investigate the relationship between RHR and all-cause mortality in the Kailuan cohort study (Trial identification: ChiCTR-TNC-11001489).

Methods

Patient and public involvement

Patients and the public were not involved with 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[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 mmHg, currently on antihypertensive therapy, or a physician's diagnosis). Patients with arrhythmia (including atrial fibrillation, atrial flutter, atrial premature beat, ventricular ectopic beats, atrioventricular block) or taking beta-adrenergic blocking agents were excluded.

Data collection and assessment of potential confounding covariates

Body mass index 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[23]. Diabetes mellitus was defined as a fasting blood glucose level ≥7.0 mmol/L, taking oral hypoglycemic agents or insulin, or having a self-reported physician diagnosis. A history of stroke and myocardial infarction was determined by a self-reported physician's diagnosis. Biochemical parameters, including fasting blood glucose, triglyceride, total cholesterol, and high-density lipoprotein cholesterol levels, were measured using an auto-analyzer (Hitachi747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital[24].

RHR measurements

RHR was measured via a 12-lead electrocardiogram (ECG9130P; NIHON KOHDEN CORP, Tokyo, Japan) at baseline with participants resting in the supine position for at least 5 minutes. 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-minute interval, on the left arm with participants in a seated position after at least 5 minutes of rest, using a mercury sphygmomanometer. Hypertension was defined as self-reported use of antihypertensive medication, a history of hypertension, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg.

Outcome

The primary outcome of this study was all-cause mortality. Participants were followed from the end point of the first examination until death or the end of follow-up (31 December 2016), whichever event occurred first. Participants underwent a clinic examination every 2 years, and any fatal events were 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 undertakings were possible. Vital status was determined by a review committee by December 31 2016.

Statistical analysis

Medical data were entered at each participating hospital and stored in the study database (Oracle 10.2g) hosted in the server at Kailuan Hospital. According to the distribution of RHR in the study population, participants were categorized into five group based on RHR quintiles as follows: Q1 (RHR ≤68 bpm), Q2 (RHR ≥69 and ≤72 bpm), Q3 (RHR >72 and ≤76 bpm), Q4 (RHR >76 and ≤82 bpm), and Q5 (RHR >82 bpm). All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Continuous variables are shown as mean ± SD and categorical variables are presented as percentages. Participants' characteristics among the five RHR groups were compared using analysis of variance for continuous variables and the chi-square test for categorical variables. The cumulative incidence of end point events among the subgroups was estimated using the Kaplan–Meier method and

compared by the log-rank test. Cox proportional hazard models were used to analyze 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 relationships between RHR as a continuous variable and all-cause mortality, we used restricted cubic spline regression to calculate the hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical tests were two-sided 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 participants with missing information on RHR were excluded. Therefore, a total of 46,561 participants were included in the current analysis (Fig. 1). The mean age of the participants was 54.42±11.41 years. The average RHR was 75.19 bpm. Among the patients, 39,963 were men (85.8%) and 6598 were women (14.2%). 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(Table 1).

Table 1. Baseline characteristics of the participants according to testing heart rate

	Q1 N=10349	Q2 N=7589	Q3 N=9086	Q4 N=10127	Q5 N=9410	F	*P*
AGE（y）	55.95±11.	52.51±11.	54.29±10.	53.37±11.	53.40±11.	118.39	<0.01
GENDER[(%)	85.58	86.66	84.18	87.14	86.48	39.86	<0.01
RHR(beat/minute)	63.23±4.3	70.07±0.4	73.14±1.3	78.66±1.6	90.73±8.0	53523.5	<0.01
SBP(mmHg)	145.69±1	145.88±1	147.09±1	148.12±1	150.47±1	109.05	<0.01
DBP(mmHg)	90.70±9.5	92.44±9.4	92.91±9.9	93.89±10.	94.75±11.	214.30	<0.01
BMI（kg/m^2）	25.88±3.3	26.09±3.3	26.06±3.4	26.07±3.4	25.79±3.6	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
SMOKE［（%）］	39.72	39.05	42.23	43.66	40.85	49.70	<0.01
DRINK［（%）］	42.06	39.86	42.49	43.79	40.85	31.08	<0.01
ANTIHYPERTENSION	24.60	18.05	22.23	21.77	21.39	98.01	<0.01
History of myocardial	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

Note: BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

Incidence of events

The number of death events and 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 were 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) (Fig. 2).

Table 2. Incidence of all-cause death according to resting heart rate

	Q1 N=10349	Q2 N=7589	Q3 N=9086	Q4 N=10127	Q5 N=9410	X^2	*P*
All-cause Death N,(%)	**1048 (10.13)**	**638 (8.41)**	**875 (9.63)**	**1062 (10.49)**	**1128 (11.99)**	**66.459**	**<0.01**
Annual mortality rate(thousand person-years)	**10.85**	**9.01**	**10.43**	**11.37**	**13.13**		

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: 1.32–1.56). After accounting for sociodemographic and cardiovascular risk factors (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 agents 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: 1.21–1.45) (Table 3).

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

Table 3. Hazard ratios (95% confidence intervals) for all-cause mortality according to resting heart rate quintiles

	Model1	Model2	Model3
Q1(RHR≤68bpm)	**reference**	**reference**	**reference**
Q2(68bpm<RHR≤72bpm)	**1.06(0.96～1.17)**	**1.03(0.92～1.10)**	**1.04(0.93～1.15)**
Q3(72bpm<RHR≤76bpm)	**1.10(1.00～1.20)**	**1.06(0.96～1.16)**	**1.06(0.96～1.17)**
Q4(76bpm<RHR≤82bpm)	**1.27(1.17～1.38)**	**1.22(1.11～1.33)**	**1.22(1.12～1.34)**
Q5(RHR>82bpm)	**1.44(1.32～1.56)**	**1.31(1.20～1.44)**	**1.32(1.21～1.45)**

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.

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: 1.19–1.48) compared with those in the lowest quintile (Table 4).

Table 4. Hazard ratios (95% confidence intervals) of all-cause mortality excluding patients with antihypertensive treatment

	Hazard ratio	95% CI	*P*
Q1(RHR≤68bpm)	**1.00**		
Q2(68bpm<RHR≤72bpm)	**1.01**	**0.88～1.14**	**0.97**
Q3(72bpm<RHR≤76bpm)	**1.07**	**0.96～1.21**	**0.23**
Q4(76bpm<RHR≤82bpm)	**1.21**	**1.08～1.35**	**<0.01**
Q5(RHR>82bpm)	**1.33**	**1.19～1.48**	**<0.01**

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 agents status.

Discussion

This study is the first prospective study to investigate the effect of RHR on all-cause mortality in a large-scale, Chinese, hypertensive population. 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 hypertensive patients.

RHR is an easily accessible clinical parameter. An elevated RHR is significantly associated with cardiovascular disease 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. Similar findings from the Framingham study[11], the Glasgow study[15], and a French study [12] also showed a relationship between increased RHR and all-cause mortality. Moreover, we found that participants with 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 those with an RHR <69 bpm in Chinese hypertensive patients, respectively. Furthermore, restricted cubic spline regression showed a linear relationship between RHR and the risk of all-cause mortality, and an RHR ≥76 bpm was associated with a higher risk for all-cause death. Therefore, our findings indicated that 76 bpm may be an intervention cut-off point for preventing all-cause mortality in Chinese hypertensive patients. In fact, management of heart rate in hypertensive patients is also supported by the 2018 ESC/ESH Guidelines for management of arterial hypertension[17]. These guidelines suggest that an RHR >80 bpm is a factor that affects cardiovascular risk in patients with hypertension. However, the latest Guidelines for Prevention and Treatment of Hypertension in China 2018[28] did not recommend elevated RHR as a prognostic cardiovascular risk factor in hypertensive patients, and the threshold value of RHR intervention was not mentioned. Further studies are required to examine the threshold value of RHR for intervention of

heart rate in Chinese hypertensive patients to reduce all-cause mortality.

In addition to European and Japan[29], national guidelines[30-32] from other countries (including United states, Canada, United Kingdom) did not include heart rate as a risk factor of CVD prognosis. Beta blockers are the preferred drug for heart rate control in patients with high blood pressure. However, whether beta blockers can be used as first-line antihypertensive drugs is still controversial in guidelines from different country. The hypertension management guidelines from China and Europe recommend beta blockers as first-line medications, while the hypertension guidelines of the United States, the United Kingdom and Japan did not. One reason for the diversity in different guidelines is that beta blockers (atenolol, mainly) were significantly less effective than other kinds of blood pressure drugs (diuretics, ACE inhibitors, ARBs, CCBs) for prevention of stroke and cardiovascular events[33,34]. However, unlike smoking, drinking, blood lipid and BMI, no results from randomized clinical trials are available making it difficult to provide treatment recommendations for patients with elevated-heart rate. More randomized trial on heart rate intervention in hypertensive patients with high HR is still needed.

The mechanisms of RHR involved in the risk of mortality may associated with sympathetic overactivity. RHR is a noninvasively marker of autonomic nervous system function. Elevated RHR reflects a heightened sympathetic tone that contributes to vasoconstriction and insulin resistance by stimulating alpha-adrenergic or beta-adrenergic receptors, and lead to increased blood pressure, lipids, and blood sugar[35-39]. On the other hand, 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. In addition, Bangalore S[44] provide a strong evidence that beta blocker intervention reduce sympathetic nerve activity, slows heart rate, which is conducive to improving cardiovascular disease prognosis in myocardial infarction, sudden death, heart failure, and reducing mortality.

This study has several strengths, including a 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 the risk of all-cause mortality in Chinese hypertensive patients. However, some limitations must be considered. 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 Company. Second, our study was a single-center, observational study. However, we prospectively observed participants for longer than 9 years of follow-up, and the data were analyzed by adjusting for potential risk factors of cardiovascular disease.

Conclusion

An increase in RHR may be an independent risk factor of all-cause mortality in Chinese hypertensive patients. Measurement of heart rate should be included in overall assessment of hypertensive patients. This study provides a data basis for management of heart rate in Chinese hypertensive patients. The relationship between repeated measurements of RHR and the risk of all-cause mortality by treating RHR as

a time-dependent variable will be investigated in a future study. We also need to further investigate whether elevated heart rate is a risk factor for hypertensive patients with blood pressure <140/90 mmHg.

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Ethical approval

Kailuan cohort study have been ethically approved by the Medical Ethics Committee.

Disclosures: The authors declare that there are no conflicts of interest.

Contributors: Maoxiang Zhao, Quanhui Zhao, Mengyi Zheng, Tong Liu, Yanming Chen, Siyu Yao, Chi Wang , Yao Li, and Miao Wang contributed to the idea. Shouling Wu and Hao Xu led the study. Data analysis was conducted by Maoxiang Zhao, Quanhui Zhao, Mengyi Zheng, and Tong Liu.

Data statement: Our data was based on Kailuan cohort study(Trials registry number: ChiCTR-TNC-11001489). Data of Kailuan cohort study is not publicly available,if you want to use it or learn more about, please contact professor Wu

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Figure legends

Fig. 1. Flowchart of the Kailuan cohort study.

Fig. 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.

Abbreviation: RHR, resting heat rate.

Fig. 3. Cubic spline graph of adjusted HRs and 95% CIs for the association between RHR and all-cause mortality.

Note: The adjusted cubic spline model shows the relationship between RHR and all-cause mortality when a resting heart rate of 76 bpm is the reference. The red line shows the hazard ratio and the blue lines show the upper and lower 95% confidence limits.

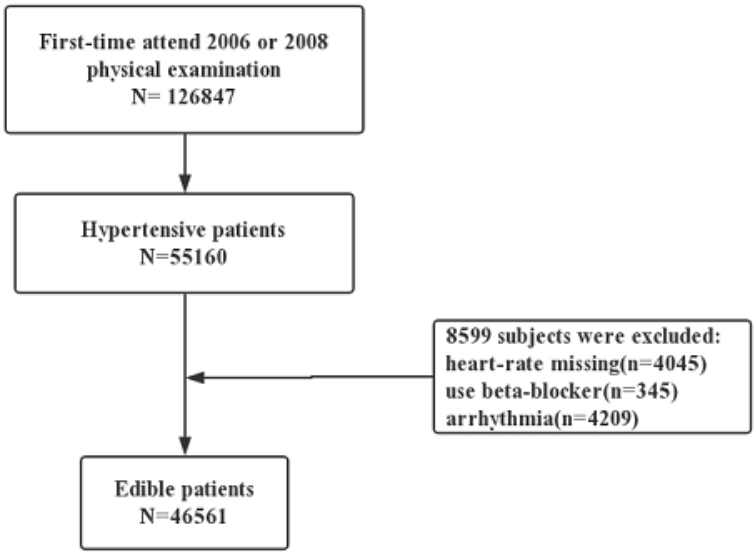
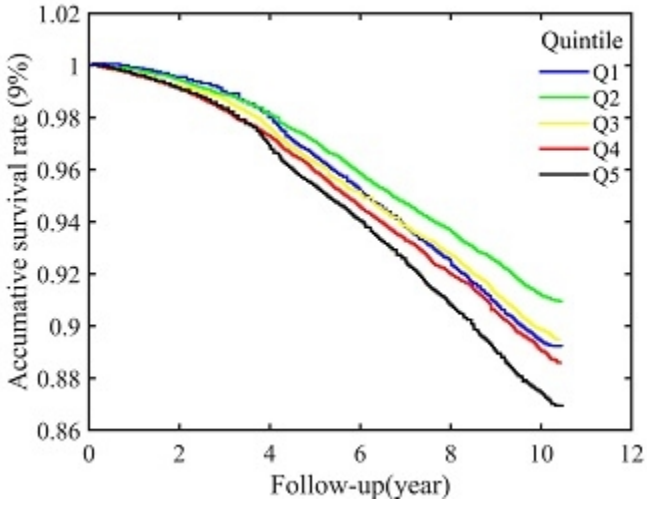


Figure1 Flowchart of cohort study



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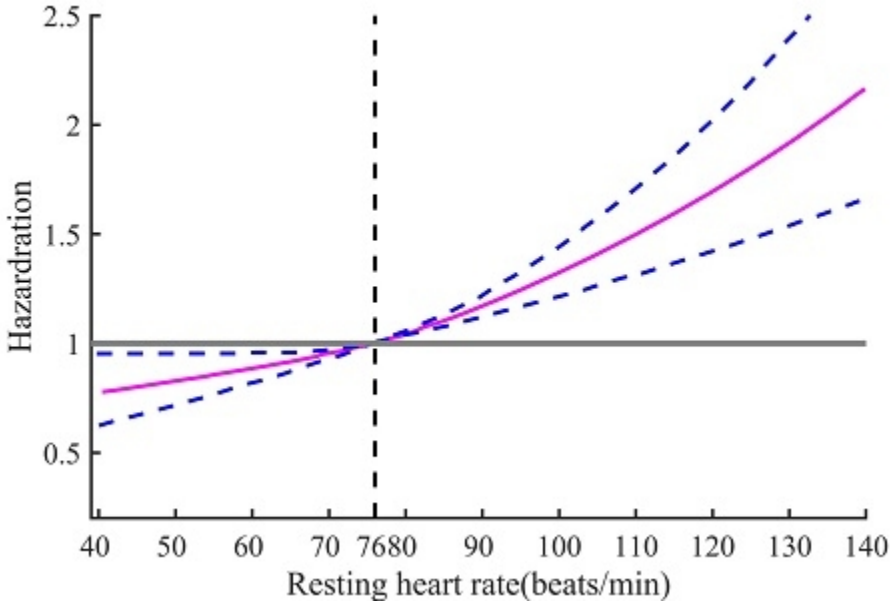

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page3 line6-13
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page3 line14-21
Introduction			
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Page6 line1-19
Objectives	3	State specific objectives, including any prespecified hypotheses	Page6 line19-22 Page7 line1-2
Methods			
Study design	4	Present key elements of study design early in the paper	Page7 line7-20
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page7 line7-20 Page8 line1-20
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page7 line7-20
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page8 line1-20 Page9 line1-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page8 line1-20
Bias	9	Describe any efforts to address potential sources of bias	Page9 line10-21 Page10 line1-9
Study size	10	Explain how the study size was arrived at	Page7 line7-20 Page10 line13-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page9 line10-21 Page10 line1-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page9 line10-21
		(*b*) Describe any methods used to examine subgroups and interactions	Page9 last paragraph line1-6
		(*c*) Explain how missing data were addressed	Page10 last paragraph line1-5
		(*d*) If applicable, explain how loss to follow-up was addressed	Page9 line 10-21 Page10 line1-9

		(*e*) Describe any sensitivity analyses	Page10 line3-9
Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page10 last paragraph line1-5
		(b) Give reasons for non-participation at each stage	Page10 last paragraph line1-5
		(c) Consider use of a flow diagram	Page10 last paragraph line1-5
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page10 last paragraph line5-9
		(b) Indicate number of participants with missing data for each variable of interest	Page10 last paragraph line1-5
		(c) Summarise follow-up time (eg, average and total amount)	Page10 last paragraph line1-9
Outcome data	15 *	Report numbers of outcome events or summary measures over time	Page12 line1-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page12 paragraph2 Page13 line1-9
		(*b*) Report category boundaries when continuous variables were categorized	Page9 paragraph2 line4-5 Page13 table3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page14 line1-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page14 paragraph2 line1-4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page17 last paragraph line4-7 Page18 line1-3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page15 paragraph1 line1-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page17 last paragraph line4-7 Page18 line1-3
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,	Page18 line18-19

	for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

BMJ Open

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

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

Short title: Heart rate and all-cause mortality

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Abstract

Objectives: 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 hypertensive patients.

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

Setting: 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 a health examination of employees in Kailuan Group Company in 2006 and 2008.

Outcomes: 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 categorized into five groups on the basis of quintiles: Q1 (RHR ≤68 bpm), Q2 (RHR >68 and ≤72 bpm), Q3 (RHR >72 and ≤76 bpm), Q4 (RHR >76 and ≤82 bpm), and Q5 (RHR >82 bpm). The 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 hazard ratio for all-cause mortality was 1.31

(95% confidence interval: 1.27–1.33) 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 hypertensive patients.

Trials registry number: ChiCTR-TNC-11001489

Key Words: Heart rate; hypertension; all-cause mortality; resting heart rate

Article summary

Strengths and limitations of this study

Strengths

1. Our study was based on the Kailuan study, which was a prospective, population-based cohort study with a large sample size.

2. This is the first prospective study to examine the relationship between RHR and the risk of all-cause mortality in Chinese hypertensive patients.

3. Given that beta-blockers have effect on RHR, we exclude patients who receive beta-blocker treatment

Limitations

1. Death due to cardiovascular disease was not documented.

2. We did not to include all changes that occurred during follow-up, and therefore, 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 is being paid to control blood pressure in recent years, the mortality of CVD is still increasing[2]. This discrepancy implies that other factors may be involved in the increasing mortality of CVD in addition to blood pressure.

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 activity of the autonomic nervous system. Heart rate is an easier and more direct way to reflect 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 for all-cause mortality in hypertensive patients, and patients with an RHR >80 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 as a factor affecting cardiovascular risk in patients with hypertension [17]. The Chinese Expert Consensus on Heart Rate Management of Hypertensive Patients also suggested to set 80 bpm as the cut-off point for heart rate intervention in hypertensive patients[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 hypertensive patients. 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 with the design of this study.

Study design and participants

Data were derived from the Kailuan cohort study (trial identification: ChiCTR-TNC-11001489), 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 mmHg, 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[19,23-25], 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 hypoglycemic agents or insulin, or having a self-reported physician diagnosis. A history of stroke and myocardial infarction was determined by a self-reported physician's diagnosis. Biochemical parameters, including fasting blood glucose, triglyceride, total cholesterol, and high-density lipoprotein cholesterol levels, were measured using an auto-analyzer (Hitachi747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan General Hospital.

RHR measurements

RHR was measured via a 12-lead electrocardiogram (ECG9130P; Nihon Kohden Corp., Tokyo, Japan) at baseline with participants resting in the supine position for at least 5 minutes. 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-minute interval, on the left arm with participants in a seated position after at least 5 minutes of rest, using a mercury sphygmomanometer. Hypertension was defined as self-reported use of

antihypertensive medication, a history of hypertension, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg.

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 the end of follow-up (31 December 2016), whichever event occurred first. Participants underwent a clinic 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 entered at each participating hospital and stored in the study database (Oracle 10.2g) that is hosted in the server at Kailuan Hospital. According to the distribution of RHR in the study population, participants were categorized into five groups on the basis of RHR quintiles as follows: Q1 (RHR ≤68 bpm), Q2 (RHR ≥69 and ≤72 bpm), Q3 (RHR >72 and ≤76 bpm), Q4 (RHR >76 and ≤82 bpm), and Q5 (RHR >82 bpm). All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Continuous variables are shown as mean ± SD and categorical variables are presented as percentages. Participants' characteristics among the five RHR groups were compared using analysis of variance for continuous

variables and the chi-square test for categorical variables. The cumulative incidence of end point events among the subgroups was estimated using the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard models were used to analyze 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 hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical tests were two-sided 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. Therefore, a total of 46,561 participants were included in the current analysis (Fig. 1). The mean age of the participants was 54.42±11.41 years. 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).

Table1. Baseline characteristics of the participants according to resting heart rate

	Q1 N=10349	Q2 N=7589	Q3 N=9086	Q4 N=10127	Q5 N=9410	F	*P*
AGE（y）	55.95±11.	52.51±11.	54.29±10.	53.37±11.	53.40±11.	118.39	<0.01
GENDER[(%)]	85.58	86.66	84.18	87.14	86.48	39.86	<0.01
RHR(beat/minute)	63.23±4.3	70.07±0.4	73.14±1.3	78.66±1.6	90.73±8.0	53523.5	<0.01
SBP(mmHg)	145.69±1	145.88±1	147.09±1	148.12±1	150.47±1	109.05	<0.01
DBP(mmHg)	90.70±9.5	92.44±9.4	92.91±9.9	93.89±10.	94.75±11.	214.30	<0.01
BMI（kg/m^2）	25.88±3.3	26.09±3.3	26.06±3.4	26.07±3.4	25.79±3.6	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	18.57	16.37	21.56	17.87	14.09	177.32	<0.01
SMOKE［（%）］	39.72	39.05	42.23	43.66	40.85	49.70	<0.01
DRINK［（%）］	42.06	39.86	42.49	43.79	40.85	31.08	<0.01
ANTIHYPERTENSI	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

Note: BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

Incidence of events

The number of death events and 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 were 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) (Fig. 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: 1.32–1.56). 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 agents 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: 1.21–1.45) (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 Fig. 3. An RHR ≥76 bpm was associated with a higher risk of all-cause death. The restricted cubic spline regression model showed a linear relationship between RHR and outcomes (Fig. 3).

Table2. Hazard ratios (95% confidence intervals) for all-cause mortality according to resting heart rate quintiles

Quintile	No. of events	Incidence rate (per 1000 Person-years)	Model1	Model2	Model3
Q1(≤68bpm)	1048	10.85	1	1	1
Q2(68bpm-72bpm)	638	9.01	1.06(0.96-1.17)	1.03(0.92-1.10)	1.04(0.93-1.15)
Q3(72bpm-76bpm)	875	10.43	1.10(1.00-1.20)	1.06(0.96-1.16)	1.06(0.96-1.17)
Q4(76bpm-82bpm)	1062	11.37	1.27(1.17-1.38)	1.22(1.11-1.33)	1.22(1.12-1.34)
Q5(≥82bpm)	1128	13.13	1.44(1.32-1.56)	1.31(1.20-1.44)	1.32(1.21-1.45)
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.

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: 1.19–1.48) compared with those in the lowest quintile (Table 3).

Table3. Hazard ratios (95% confidence intervals) of all-cause mortality excluding patients with antihypertensive treatment

	Hazard ratio	95% CI	*P*
Q1(RHR≤68bpm)	**1.00**		
Q2(68bpm<RHR≤72bpm)	**1.01**	**0.88～1.14**	**0.97**
Q3(72bpm<RHR≤76bpm)	**1.07**	**0.96～1.21**	**0.23**
Q4(76bpm<RHR≤82bpm)	**1.21**	**1.08～1.35**	**<0.01**
Q5(RHR>82bpm)	**1.33**	**1.19～1.48**	**<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.

Discussion

This study is the first prospective study to investigate the effect of RHR on all-cause mortality in a large-scale, Chinese, hypertensive population. 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 hypertensive patients.

RHR is an easily accessible clinical parameter. An elevated RHR is significantly associated with CVD and all-cause mortality in healthy populations[26], in patients with chronic heart failure[27], and in patients with atrial fibrillation [28]. 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. Similar findings from the Framingham study[11], the Glasgow study[15], and a French study [12] also showed a relationship between increased RHR and all-cause mortality. Moreover, we found that participants with 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 those with an RHR <69 bpm in Chinese hypertensive patients, respectively. Furthermore, restricted cubic spline regression showed a linear relationship between RHR and the 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 hypertensive patients 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 Prevention and Treatment of Hypertension in China 2018[29] did not recommend elevated RHR as a prognostic cardiovascular risk factor in hypertensive patients, and the threshold value of RHR intervention was not mentioned. Therefore, further studies are required to examine the threshold value of RHR for intervention of heart rate in Chinese hypertensive patients to reduce all-cause mortality.

In addition to Europe and Japan[30], national guidelines[31-33] from other countries (including USA, Canada, and United Kingdom) did not include heart rate as a risk factor of prognosis of CVD. Beta-blockers are the preferred drug for controlling heart rate in patients with high blood pressure. However, whether beta-blockers can be used as first-line antihypertensive drugs is still controversial in guidelines from different countries. Hypertension management guidelines from China and Europe recommend

beta-blockers as first-line medications, while the hypertension guidelines of the USA[31], the United Kingdom[32], and Japan[33] 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, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, Calcium Channel Blockers) for preventing stroke and cardiovascular events[34,35]. However, unlike smoking, drinking, blood lipids, and BMI, no results of heart rate intervention from randomized, clinical trials are available, which causes difficulty in providing treatment recommendations for patients with an elevated heart rate. Therefore, more randomized trials on heart rate intervention in hypertensive patients 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 noninvasively marker of autonomic nervous system function. Elevated RHR reflects a heightened sympathetic tone that contributes to vasoconstriction and insulin resistance by stimulating alpha-adrenergic or beta-adrenergic receptors. These effects lead to increased blood pressure, lipid levels, and blood sugar levels[36-40]. However, an unbalanced autonomic nervous system is also related to inflammation and endothelial dysfunction[41]. Therefore, elevated RHR could increase the risk of atherosclerosis[42], hyperinsulinemia[43], myocardial ischemia, hypertension[44], and death in the long term. Additionally, Bangalore et al[45] 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 a 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 the risk of all-cause mortality in Chinese hypertensive patients. We also acknowledge several limitations of 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 Company. Second, our study was a single-center, observational study. However, we prospectively observed participants for longer than 9 years of follow-up, and the data were analyzed 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 hypertensive patients. Measurement of heart rate should be included in overall assessment of hypertensive patients. This study provides a basis for management of heart rate in Chinese hypertensive patients. The cutoff point for heart rate interventions on the risk of all-cause mortality in hypertensive patients needs to be further investigated by prospective studies.

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Ethical approval

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

Disclosures: The authors declare that there are no conflicts of interest.

Contributors: Maoxiang Zhao, Quanhui Zhao, Mengyi Zheng, Tong Liu, Yanming Chen, Siyu Yao, Chi Wang, Yao Li, and Miao Wang contributed to the concept of the study. Shouling Wu and Hao Xue supervised the study. Data analysis was conducted by Maoxiang Zhao, Quanhui Zhao, Mengyi Zheng, and Tong Liu.

Data sharing statement: Our data were based on the Kailuan cohort study (trial registry number: ChiCTR-TNC-11001489). Data of the Kailuan cohort study are not publicly available. Please contact Professor Wu (e-mail: drwusl@163.com) for details of the data.

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Figure legends

Fig. 1. Flowchart of the Kailuan cohort study.

Fig. 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), and Q5 (RHR ≥82 bpm).

Abbreviation: RHR, resting heat rate.

Fig. 3. Cubic spline graph of adjusted HRs and 95% CIs for the association between RHR and all-cause mortality.

Note: The adjusted cubic spline model shows the relationship between RHR and all-cause mortality when an RHR of 76 bpm is the reference. The red line shows the HR and the blue lines show the upper and lower 95% confidence limits.

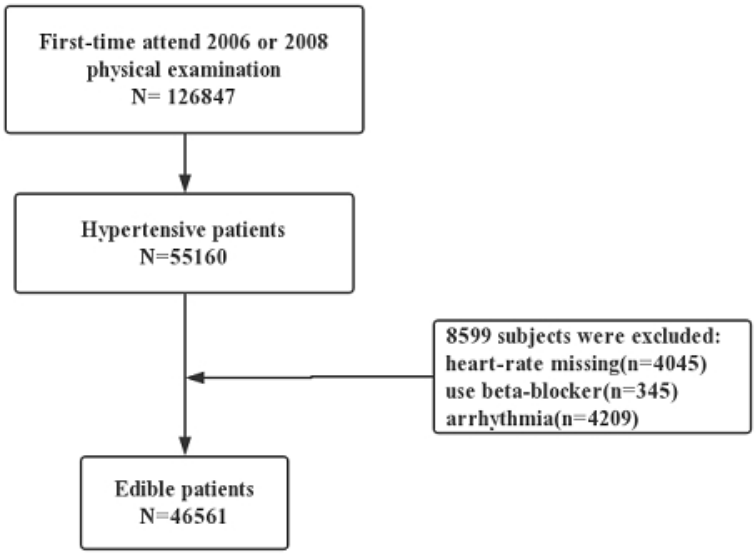
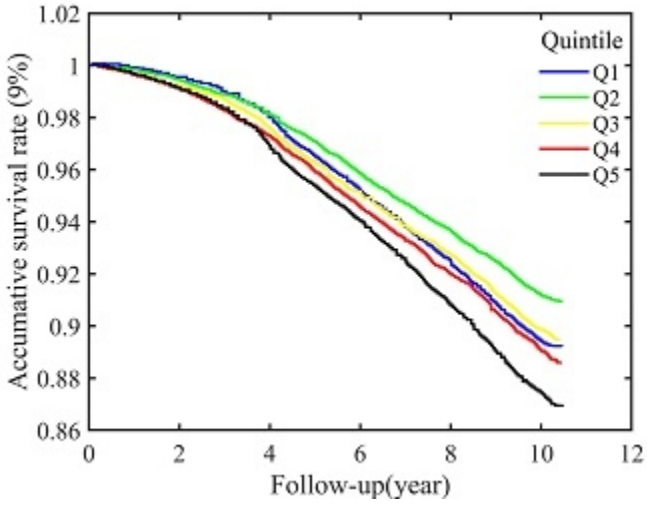


Figure1 Flowchart of cohort study



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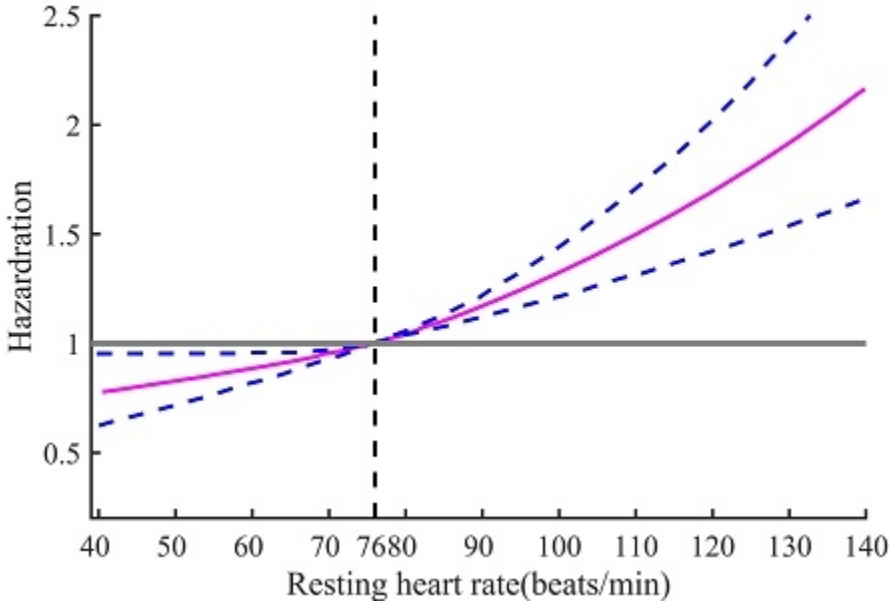

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page3-4
Introduction			
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Page6 line1-19
Objectives	3	State specific objectives, including any prespecified hypotheses	Page6 line19-22 Page7 line1-2
Methods			
Study design	4	Present key elements of study design early in the paper	Page7 line7-20
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page7 line7-20 Page8 line1-20
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page7 line7-20
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page8 line1-20 Page9 line1-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page8 line1-20
Bias	9	Describe any efforts to address potential sources of bias	Page9 line10-21 Page10 line1-9
Study size	10	Explain how the study size was arrived at	Page7 line7-20 Page10 line13-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page9 line10-21 Page10 line1-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page9 line10-21
		(*b*) Describe any methods used to examine subgroups and interactions	Page9 last paragraph line1-6
		(*c*) Explain how missing data were addressed	Page10 last paragraph line1-5
		(*d*) If applicable, explain how loss to follow-up was addressed	Page9 line 10-21 Page10 line1-9

		(*e*) Describe any sensitivity analyses	Page10 line3-9
Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page10 last paragraph line1-5
		(b) Give reasons for non-participation at each stage	Page10 last paragraph line1-5
		(c) Consider use of a flow diagram	Page10 last paragraph line1-5
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page10 last paragraph line5-9
		(b) Indicate number of participants with missing data for each variable of interest	Page10 last paragraph line1-5
		(c) Summarise follow-up time (eg, average and total amount)	Page10 last paragraph line1-9
Outcome data	15 *	Report numbers of outcome events or summary measures over time	Page12 line1-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page12 paragraph2 Page13 line1-9
		(*b*) Report category boundaries when continuous variables were categorized	Page9 paragraph2 line4-5 Page13 table3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page13 last paragraph
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page14 first paragraph
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page16 line1-10 Page17 first paragraph
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page14 last paragraph Page15-16 Page17 first paragraph
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page17 fisrt paragraph
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,	Page18 line18-19

	for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.