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ORIGINAL ARTICLE

The association of resting heart rate and mortality by gender in a rural adult Chinese population: a cohort study with a 6-year follow-up

Chengyi Han[1] · **Ming Zhang**[2] · **Xinping Luo**[2] · **Chongjian Wang**[1] · **Junmei Zhou**[2] · **Lu Zhang**[1,2] · **Yongcheng Ren**[1,2] · **Bingyuan Wang**[1,2] · **Xiangyu Yang**[1] · **Hongyan Zhang**[1] · **Yang Zhao**[1] · **Yanxia Shen**[3] · **Dongting Wu**[3] · **Chao Pang**[4] · **Lei Yin**[4] · **Tianping Feng**[4] · **Dongsheng Hu**[1,2] · **Jingzhi Zhao**[4]

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Abstract

Aim Although previous studies have reported an association between resting heart rate (RHR) and cancer mortality, the association is contradictory. The relationship between RHR and disease-specific mortality has not been explored in the Chinese population. We examined this relationship in a rural adult Chinese population from a cohort study with a 6-year follow-up.

Subjects and methods The RHR of a cohort of 20,069 participants was measured between July–August of 2007 and July–August of 2008, and 17,151 participants (85.5 %) were followed up between July–August of 2013 and July – October of 2014. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) for deaths due to all causes, cardiovascular disease (CVD), stroke, cancer, and other causes in RHR groups.

Results Males and females with RHR ≥ 90 showed the highest all-cause mortality (33,27 and 1,226/100,000 person-years) and adjusted HR for all-cause deaths—2.20 (95 % CI 1.64–2.93) and 1.99 (1.43–2.77). A similar association was observed for deaths due to CVD, stroke and cancer (except for females), and other causes of mortality.

Conclusions Elevated RHR may be an independent marker of all-cause, CVD and other causes of death for both sexes and stroke and cancer deaths for males.

Keywords Cancer · Cardiovascular disease · Mortality · Resting heart rate · Stroke

Chengyi Han and Ming Zhang contributed equally to this work.

✉ Dongsheng Hu
hud@szu.edu.cn

✉ Jingzhi Zhao
zhao_jingzhi@126.com

1 Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, 100 Kexue Avenue, High-tech Development Zone, Zhengzhou, Henan 450001, China

2 Department of Preventive Medicine, Shenzhen University Health Sciences Center, 3688 Nanhai Avenue, Nanshan District, Shenzhen, Guangdong 518060, China

3 Department of Clinical Medicine, Shenzhen University Health Sciences Center, 3688 Nanhai Avenue, Nanshan District, Shenzhen, Guangdong 518060, China

4 Department of Prevention and Health Care, Military Hospital of Henan Province, 18 Jinshui Road, Jinshui District, Zhengzhou, Henan 450003, China

Introduction

Of the 56 million global deaths in 2012, 38 million were due to non-communicable diseases, principally cardiovascular disease (CVD; 17.5 million deaths), cancer (8.2 million) and chronic respiratory disease (World Health Organization 2014). Identifying and managing associated risk factors is crucial. As a noninvasive and inexpensive-to-measure but important indicator of cardiac function (Honda et al. 2010; Tanaka et al. 2011), resting heart rate (RHR) has caused wide concern in recent years. A meta-analysis of 46 studies demonstrated elevated RHR independently associated with increased risk of all-cause and CVD mortality for both sexes (Zhang et al. 2016). A 22-year follow-up of a Chicago study of men and women suggested a significant association between RHR and subsequent cancer mortality in middle-aged men and women (Greenland et al. 1999); however, previous studies excluding females found no association of high RHR and cancer mortality (Batty et al. 2010; Kristal-Boneh et al. 2000).

Only three prospective studies have explored the relationship between RHR and all-cause mortality in the Chinese population and concluded that elevated RHR might be an independent risk factor of all-cause mortality (Mai et al. 2009; Wang et al. 2014), with a greater association in males than females (Chen et al. 2013). Here, we examined the association between RHR and all-cause and cause-specific mortality by gender in a rural adult Chinese cohort.

Materials and methods

Study design and participants

Study participants were selected by cluster random sampling among people ≥ 18 years old who had lived for at least 10 years in a rural area of Henan Province in China. We excluded participants for whom RHR or questionnaire information was not available and those with severe psychological disorders, physical disabilities, Alzheimer's disease, dementia, tuberculosis, acquired immune deficiency syndrome, or other infectious diseases. Ultimately, a cohort of 20,069 adult participants was established between July–August of 2007 and July–August of 2008; 17,151 (85.5 %) were followed up between July–August of 2013 and July–October of 2014. All participants gave their informed consent for inclusion before they participated in the study. The study protocol was approved by the Ethics Committee of Zhengzhou University.

Baseline examination

Trained staff collected data on demographics (gender and age), socioeconomic status (education level, income, and marital status), behavioral variables (smoking and drinking), physical activity, and medical history by face-to-face interview with a specially designed questionnaire. A smoker was defined as a person who had smoked 100 or more cigarettes during their lifetime. An alcohol drinker was defined as having consumed alcohol 12 or more times in the past year. The physical activity level was classified as low, moderate, or high according to the International Physical Activity Questionnaire (IPAQ) scoring protocol. Details regarding variables and the questionnaire have been reported previously (Wang et al. 2012). Body weight and height were measured twice by use of a metric scale and a vertical height scale to the nearest 0.1 kg and 0.1 cm, respectively, in participants wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. With the participant standing, two waist circumference measurements were obtained 1 cm above the navel by using a metric tape measure. After participants had sat quietly for about 5 min, an electronic sphygmomanometer (HEM-770AFuzzy, Omron, Japan) was used to record blood pressure and pulse rate three times at 30-s intervals. Hypertension was defined as mean systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or self-reported current use of antihypertension medication (Weber et al. 2014). RHR was divided into five categories (<60, 60–69, 70–79, 80–89, and ≥ 90 beats per min [bpm]; Fujiura et al. 2001; Seccareccia et al. 2001), with RHR 60–69 bpm as a reference.

An overnight fasting venous blood sample was taken by physicians and sent in vacuum tubes containing sodium fluoride to the Centers for Disease Control and Prevention. After centrifugation at 4 °C and 3,000 rpm for 10 min, plasma was stored in a low-temperature freezer. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and plasma glucose were measured by use of a Hitachi 7060 automatic biochemical analyzer (Tokyo). Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula (LDL-C = TC − HDL-C − TG/2.2). Dyslipidemia was defined as TC ≥ 6.22 mmol/L, TG ≥ 2.26 mmol/L, HDL-C < 1.04 mmol/L, LDL-C ≥ 2.26 mmol/L, or use of lipid-lowering medication according to the China Adult Dyslipidemia Prevention Guide (2007 edition) criteria (China Adult Dyslipidemia Prevention Committee 2007). Diabetes mellitus was diagnosed by fasting plasma glucose ≥ 7.0 mmol/L or current treatment with antidiabetes medication (International Diabetes Federation Clinical Guidelines Task Force 2005).

Follow-up data collection

If death occurred during follow-up, the time and cause of death were collected by dedicated survey staff who used a specially designed questionnaire with face-to-face interviews with relatives, local village physicians, or other healthcare providers. The death information was checked with vital registration data in the local Center for Disease Control and Prevention. If data were inconsistent, we went to the participant's residence to confirm with relatives or local village physicians. Cause-related mortality was assigned by using the International Classification of Diseases, 10th Revision (all-cause: A00-Z99; CVD: I00-I99; stroke: I60-I69; cancer: C00-D48; other: A00-B99, D50-H93, and J00-Z99).

Statistical analysis

Person-years of follow-up were computed as the date of death or follow-up minus the date of baseline

Table 1 Baseline characteristics of study participants by gender

Variables	Male ($n = 6767$)	Female ($n = 10\ 384$)	P-value
Age (years), median (IQR)	54.0 (43.0–63.0)	51.0 (41.0–59.0)	<0.01
Education, *n* (%)			<0.01
≤ Primary school	2,460 (36.4)	6,035 (58.1)	
≥ Middle school	4,307 (63.7)	4,349 (41.9)	
Married/cohabiting, *n* (%)	6,004 (88.8)	9,379 (90.3)	<0.01
Mean individual income (monthly), *n* (%)			0.01
< 500 CNY	6,200 (91.8)	9,762 (94.3)	
500–1,000 CNY	442 (6.55)	465 (4.49)	
≥ 1,000 CNY	111 (1.64)	126 (1.22)	
Tobacco consumption, *n* (%)	4,605 (68.1)	30 (0.29)	<0.01
Alcohol consumption, *n* (%)	1,862 (27.5)	68 (0.65)	<0.01
Physical activity, *n* (%)			<0.01
Low	3,653 (54.0)	4,223 (40.7)	
Moderate	1,242 (18.4)	2,377 (22.9)	
High	1,873 (27.7)	3,784 (36.4)	
Body mass index, (kg/m^2), median (IQR)	23.3 (21.1–25.7)	24.5 (22.1–27.2)	<0.01
Waist circumference (cm), median (IQR)	82.0 (75.1–90.3)	82.0 (74.7–89.3)	<0.01
SBP (mmHg), median (IQR)	123 (113–136)	122 (110–139)	<0.01
DBP (mmHg), median (IQR)	77.3 (70.7–85.0)	77.7 (70.7–86.3)	<0.01
RHR (bpm), *n* (%)			<0.01
< 60	694 (10.3)	319 (3.07)	
60–69	2,127 (31.4)	2,266 (21.8)	
70–79	2,301 (34.0)	4,057 (39.1)	
80–89	1,203 (17.8)	2,638 (25.4)	
≥ 90	442 (6.53)	1,104 (10.6)	
Total cholesterol (mmol/L), median (IQR)	4.28 (3.75–4.89)	4.49 (3.90–5.14)	<0.01
Triglycerides (mmol/L), median (IQR)	1.32 (0.95–1.92)	1.40 (0.98–2.02)	<0.01
HDL-C (mmol/L), median (IQR)	1.09 (0.94–1.26)	1.17 (1.02–1.36)	<0.01
LDL-C (mmol/L), median (IQR)	2.50 (2.00–3.00)	2.60 (2.10–3.10)	<0.01
Fasting glucose (mmol/L), median (IQR)	5.33 (4.97–5.76)	5.38 (5.03–5.84)	<0.01

Abbreviations: *bpm* beats per minute; *CNY* Chinese Yuan; *DBP* diastolic blood pressure; *HDL-C* high-density lipoprotein cholesterol; *IQR* interquartile range; *LDL-C* low-density lipoprotein cholesterol; *RHR* resting heart rate; *SBP* systolic blood pressure

examination for each participant. Wilcoxon rank sum and chi-square tests were used to evaluate differences in continuous and categorical variables, respectively. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) for death in RHR groups with two models: unadjusted and adjusted for age, education, marital status, mean individual monthly income, tobacco and alcohol consumption, physical activity, BMI, waist circumference, SBP, DBP, TC, TG, HDL-C, LDL-C, fasting glucose, history of disease (hypertension, dyslipidemia, diabetes mellitus, myocardial infarction, heart failure, stroke, and cancer) and medication use (antihypertensive, lipid-lowering, and antidiabetic drugs). All analyses involved use of IBM SPSS 21.0. Statistical significance was set at two-tailed $P < 0.05$.

Results

Baseline characteristics of participants by gender are shown in Table 1. Data for 17,151 participants (6,767 males) were analyzed. We found 1,099 deaths during follow-up (CVD, $n = 479$; stroke, $n = 302$; cancer, $n = 265$; and other causes, $n = 355$). Deaths due to other causes ($n = 355$) involved disease related to the respiratory ($n = 44$), urinary and reproductive ($n = 32$), digestive ($n = 21$), nervous ($n = 4$) and hematological systems ($n = 5$); accidental death ($n = 66$); and unknown causes ($n = 183$). Data for age, education, mean individual income (by month), smoking and drinking rate, high physical activity, waist circumference, and SBP were higher for males than females, whereas data for marital status, BMI, DBP, high RHR and levels of TC, TG, HDL-C, LDL-C, and fasting glucose were lower ($P < 0.05$).

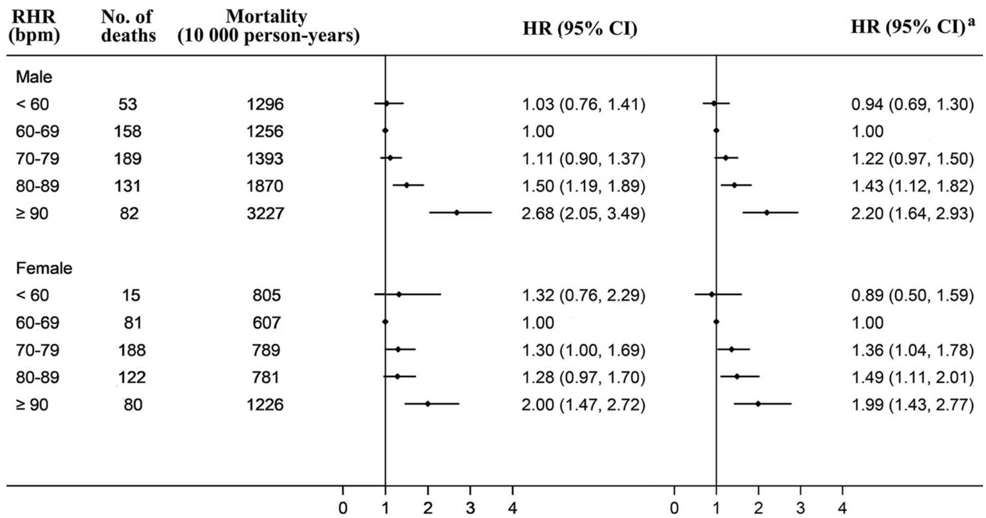

Fig. 1 All-cause mortality and HRs (95 % CIs) by RHR category. Abbreviations: *bpm* beats per minute; *CI* confidence Interval; *HR* hazard ratio; *RHR* resting heart rate. The *superscripted a* means: adjusted for age, education, marital status, mean individual income (monthly), tobacco and alcohol consumption, physical activity, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting glucose, history of disease (hypertension, dyslipidemia, diabetes mellitus, myocardial infarction, heart failure, stroke, and cancer) and medication use (antihypertensive, lipid-lowering, and antidiabetic drugs)

Figure 1 summarizes data for all-cause mortality and HRs (95 % CIs) by RHR category. Males and females with RHR ≥ 90 showed the highest all-cause mortality (3,327 and 1,226/100,000 person-years) and adjusted HR for all-cause deaths—2.20 (95 % CI 1.64–2.93) and 1.99 (1.43–2.77). Males and females with RHR ≥ 60 bpm showed a significant

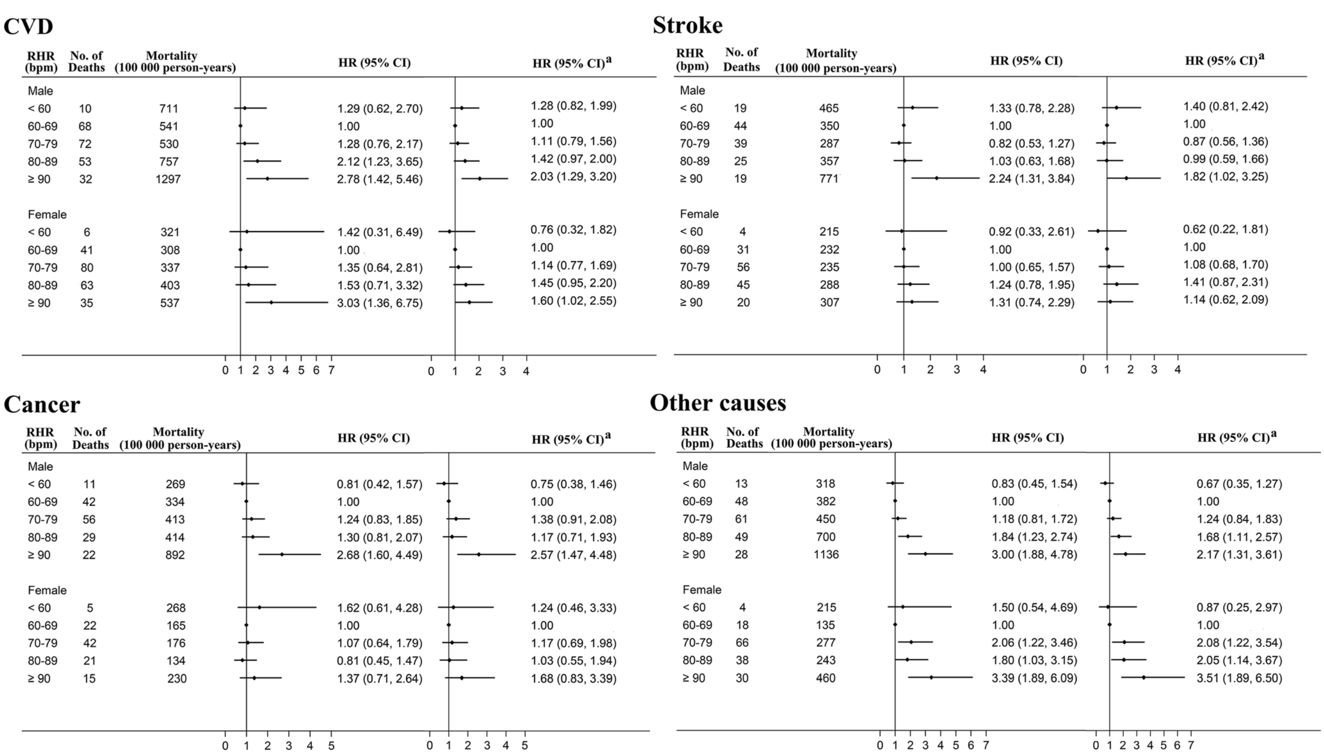

Fig. 2 Mortality and HRs (95 % CIs) for CVD, stroke, cancer, and other causes by RHR category. Abbreviations: *bpm* beats per minute; *CI* confidence Interval; *CVD* cardiovascular disease; *HR* hazard ratio; *RHR* resting heart rate. The *superscripted a* means: adjusted for age, education, marital status, mean individual income (monthly), tobacco and alcohol consumption, physical activity, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting glucose, history of disease (hypertension, dyslipidemia, diabetes mellitus, myocardial infarction, heart failure, stroke, and cancer) and medication use (antihypertensive, lipid-lowering, and antidiabetic drugs)

upward trend of HRs for all-cause death with increased RHR after adjustment for demographic and other covariates.

The relationships of RHR categories and CVD, stroke, cancer, and other causes of deaths are shown in Fig. 2. For males, RHR ≥ 90 bpm was associated with CVD, stroke, cancer, and other causes of death: adjusted HR 2.03 (95 % CI 1.29–3.20), 1.82 (1.02–3.25), 2.57 (1.47–4.48), and 2.17 (1.31–3.61). RHR 80–89 bpm was also significantly associated with other causes of death: adjusted HR 1.68 (1.11–2.57). For females, RHR ≥ 90 bpm was associated with CVD and other causes of death: adjusted HR 1.60 (1.02–2.55) and 3.51 (1.89–6.50). RHR 70–79 and 80–89 bpm were still significantly associated with other causes of death: adjusted HR 2.08 (1.22–3.54) and 2.05 (1.14–3.67).

Discussion

In a rural adult Chinese population, we confirmed by meta-analysis that the risk of both all-cause and CVD deaths was elevated in males and females with high RHR (Zhang et al. 2016). We found RHR, especially RHR ≥ 90 bpm, positively associated with stroke and cancer deaths for males and with deaths due to other causes for both sexes during 6 years of follow-up.

Previous cohort studies have demonstrated that elevated RHR is not significantly associated with stroke mortality in Western populations (Benetos et al. 1999; DiFrancesco and Camm 2004; Tverdal et al. 2008); however, we found that elevated RHR could be a risk factor for stroke deaths in rural Chinese males. The contradictory findings may be due to the widespread availability of high-quality medical services in Western as compared with Eastern populations because advanced medical treatment can extend life and reduce deaths.

We found a weak but significant association between RHR and cancer mortality for males. This finding agrees with results of an 8-year follow-up study that found a graded relationship between heart rate and cancer mortality in a large group of middle-aged males (Thomas et al. 2001). A more recent and comprehensive study also found consistent, graded and highly significant associations of RHR and exercise heart rate with subsequent cancer mortality in males (Jouven et al. 2011). Kristal-Boneh et al. reported a lack of association between RHR and cancer mortality, but their study only involved 45 cancer-related deaths in a group of 3,527 young and middle-aged male industrial employees (Kristal-Boneh et al. 2000).

The mechanisms for the association of RHR and cancer mortality are unclear, but one possibility is that elevated RHR might be a marker of chronic stress and anxiety, which may increase the risk of cancer (Cohen and Herbert 1996). Frequent or regular exercise can reduce RHR and improve monocyte function (Peters et al. 1995), which could protect against the development or metastasis of various cancers by enhancing cancer phagocytosis and cell apoptosis. In a dose–response meta-analysis of prospective studies (Wu et al. 2013), risk of breast cancer was gradually decreased with increasing exercise, which could be related to suppressing endogenous estrogen secretion (Friedenreich 2011). Because exercise training can also lower RHR, risk of breast cancer could be reduced with regular exercise via reduced RHR; thus, associations between RHR and cancer may be worthy of further exploration, including the relation of RHR to specific cancers.

For the sex differences in the association of RHR and stroke and cancer, a likely explanation might be a higher normal RHR for females than males (Valentini and Parati 2009). Another explanation is that males might have greater stress from daily life and work than females in rural China, which may play a central role in the pathogenesis of numerous adverse health conditions. As well, differing physiological factors (Ouyang et al. 2006) and health awareness (Greenland et al. 1999) may be explanations.

We found a significant association between RHR and other causes of death, which agrees with the results of a 12-year follow-up study of 379,843 participants 40–45 years old: the HRs for males and females with an increase of 10 bpm RHR were 1.16 (95 % CI 1.13–1.19) and 1.10 (1.07–1.13), respectively (Tverdal et al. 2008). Similarly, for males ≥ 60 and females 30–59 years old, RHR was robustly associated with non-CVD and non-cancer deaths in a 16.5-year Japanese cohort (Okamura et al. 2004).

A meta-regression of 25 randomized clinical trials strongly suggests that RHR reduction could be a major determinant of clinical benefits for cardiac deaths, all-cause deaths, sudden deaths and non-fatal myocardial infarction recurrence (Cucherat 2007). Regular exercise could decrease RHR, which may be a mechanism of exercise training, and lower CVD, cancer, and all-cause mortality (Gremeaux et al. 2012). Regular exercise can improve health status and prevent adverse conditions; therefore, intensive interventions should be targeted to rural Chinese people with elevated RHR.

A major advantage of our study is its novel evaluation of the association of RHR with cause-specific mortality by gender in a rural adult Chinese population from a cohort study; moreover, because of the large sample size and all participants being from communities, the results may be suitable for extrapolation to the general population. In addition, we used face-to-face interviews and stringent quality control by dedicated study staff.

Our findings are for rural participants, so the representativeness might be limited. RHR was assessed by baseline measurement, and we did not obtain information on possible changes in RHR over time for death cases, which might affect the relation because of regression dilution bias (MacMahon et al. 1990). Some people died at home and not in hospitals, and autopsies were not conducted to ascertain the cause of death. Therefore, the cause of death was unknown for 183 of 355 deaths, which might imply information bias. In addition, considering the relatively large rate of lost to follow-up (14.5 %), a statistical analysis was performed on baseline characteristics by response status. The results showed significant differences in sociodemographic characteristics (except for gender and income level) by response status, which might imply follow-up bias; therefore, caution is warranted when interpreting and comparing the findings.

In conclusion, this study demonstrated that elevated RHR in rural Chinese participants is an independent predictor of all-cause, CVD and other causes of death for both sexes, and stroke and cancer deaths for males. Intensive interventions should be targeted to rural Chinese participants with elevated RHR to reduce deaths due to non-communicable disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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