Published in final edited form as:

J Am Geriatr Soc. 2017 May ; 65(5): 989–994. doi:10.1111/jgs.14714.

Does the impact of resting heart rate on cardiovascular disease and all-cause deaths differ by age?

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Abstract

Objectives—To examine whether the association of resting heart rate (RHR) with all-cause mortality and/or cardiovascular disease (CVD) differs among younger and older subjects.

Design—Prospective cohort.

Setting—Community in Beijing, China.

Participants—Individuals aged 40 and older without CVD at baseline (N=6209).

Measurements—Trained investigators interviewed participants using a standard questionnaire to obtain information on demographic characteristic, medical history and life style risk factors in 1991. RHR was evaluated according to the following quartiles: <72, 72 to 76, 76 to 84, 84 beats/min. Cox regression model was used to assess the association of RHR with all-cause mortality and CVD events.

Results—During a mean follow-up of 8.3 years, 840 subjects died and 676 subjects suffered from CVD. In older subjects (≥60 years old), higher RHR was associated with both all-cause mortality ($P_{\text{trend}} < 0.001$) and CVD events ($P_{\text{trend}} = 0.002$). However, the associations of RHR with all-cause mortality and CVD events in the younger participants (<60 years old) were not significant (both $P_{\text{trend}} > 0.05$). There were significant modifying effects of age on the association of RHR with both all-cause mortality and CVD events ($P_{\text{interaction}} < 0.001$ and $= 0.002$, respectively). After exclusion of individuals who died ($n=100$) or suffered from CVD ($n=45$) during the first 2 years of follow-up, similar results were observed.

Conclusion—Elevated RHR appears to be an independent determinant of both all-cause mortality and CVD events in older subjects but not in younger people.

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Conflict of Interest: The authors declare no financial, personal, or potential conflicts of interest.

Author Contributions: Kuibao Li, Chonghua Yao: study design. Lei Dong, Kuibao Li: interview of study participants, data management. Xinchun Yang: analysis of data, interpreted of data. Kuibao Li, Chonghua Yao: drafting the manuscript. All authors: manuscript revision, approval of final version of manuscript for publication.

Keywords

resting heart rate; death; cohort study; cardiovascular disease; epidemiology

A large number of epidemiological studies suggest that a high resting heart rate (RHR) is an important determinant of all-cause mortality, and cardiovascular morbidity and mortality among healthy subjects,¹⁻⁷ as well as in those who are at elevated risk for cardiovascular diseases (CVD).⁸⁻¹⁴ However, as we know, infants and young children have higher RHR compared to adults, but they are healthy. This suggests age may modify the effect of high RHR on our physical fitness. Also, high RHR has been shown to be associated with markers of endothelial dysfunction and with carotid and aortic arterial stiffness in human,¹⁵⁻¹⁷ which are also more common and serious in aged individuals. Given these facts, we speculated age might modify the association of RHR with CVD incidence and/or all-cause mortality.

A few prior studies have explored the effect modification of age on the association of RHR with CVD incidence or mortality; however, the results are inconsistent. In a previous study,¹⁸ the same associations were observed between RHR and the different cause of mortality in both younger and older subjects. In contrast, in a subgroup analysis of one recent study,⁷ there was a significantly higher risk associated with CVD risk for those aged below, compared with above, 65 years of age and the RHRs for total mortality did not differ between these two groups. In view of the aforementioned findings, the aim of the present study is to investigate the modifying effect of age on the association of RHR with CVD incidence and all-cause mortality in a large prospective cohort study conducted in Beijing, China.

Subjects and Methods

Study participants

In the 1991 China National Hypertension Survey, a multistage random cluster sampling design was used to select a representative sample of the general Chinese population aged 15 years or older from all 30 provinces in mainland China.¹⁹ In this investigation, the participants came from this National Hypertension Survey in Beijing City of China. In detail, stratified random-cluster sampling was performed during the first stage of sampling. Among six counties of Beijing City, two to three urban residential communities or one rural town were sampled in each county. During the second stage of sampling, four villages were randomly sampled in one rural town. Then, all the subjects aged 15 years or older in sampled urban residential communities or villages were surveyed. Of these, 7601 subjects who were 40 years old were scheduled to be followed up two times in 1996 and 1999, respectively, by trained investigators. In this study, we excluded subjects with a history of coronary heart disease (heart infarction, angina pectoris, or revascularization) or stroke (n=326) at baseline. Besides, 1066 individuals who failed to be contacted during follow-up were also excluded. Thus, a total of 6209 individuals were left in this present study. The subjects excluded from the present study and those included in this study were comparable in terms of the baseline characteristics except for the former being younger (54.7 versus 57.4).

This study was approved by the Tulane University Health Sciences Center Institutional Review Board and the Cardiovascular Institute and Fu Wai Hospital Ethics Committee. Written informed consent was obtained from all participants involved in our study.

Baseline examination

Trained investigators interviewed participants in Beijing of China using a standard questionnaire to obtain information on demographic characteristic, medical history and life style risk factors.¹⁹ The methods of collecting these information have been previously reported in detail.²⁰ Briefly, resting heart rates were measured by palpating the radial pulse over a period of 15 seconds with a stop watch and multiplying by 4. If the pulse was irregular or difficult to count, the test was extended to 60 seconds and a stethoscope may be used at the apex of the heart and counted for a 60-second interval if necessary.

Follow-up and endpoints

The follow-up examination, which was conducted in 1996 and 1999 respectively, has also been reported in detail previously.²⁰ Briefly, the follow-up examination included tracking study participants or their proxies to a current address, performing in-depth interviews to ascertain disease status and vital information, and obtaining hospital records and death certificates. An end point assessment committee reviewed and confirmed (or rejected) the hospital discharge diagnosis and the cause of death based on the abstracted information, using preestablished criteria.

The primary outcomes of interest in the present study were CVD events and all-cause mortality. We defined CVD events as a composite of fatal and/or nonfatal events from coronary heart disease (CHD) and/or stroke events. The definition of CHD and acute stroke events was based on the criteria developed by the World Health Organization (WHO) MONICA project.²¹⁻²³ CHD events comprised acute myocardial infarction, sudden death, and other coronary deaths. The events were diagnosed based on symptoms, developments in electrocardiograms over time, serum enzymes, and autopsy findings. Stroke was defined as evidence of an acute disturbance of focal 24 hours and thought to be caused by intracranial hemorrhage or ischemia,²⁴ with exception of transient ischemic attack. Causes of all-cause death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9).

Statistical analyses

Given 60 years and over is generally considered to be a cut point for defining an elderly person, especially for Chinese population,²⁵⁻²⁷ we divided the participants into 2 age categories at the baseline examination (40-60 years old (n=3905) and 60 years old (n=2304)). Continuous variables were shown as means (standard difference) and were compared using one-way analysis of variance. Categorical variables were shown as counts and percentages and were compared using χ^2 tests for association. To explore the relationship between RHR and the primary outcomes of interest, we performed 2 sets of analyses in which RHR was modeled as a categorical or a continuous variable. For analyses of RHR as a categorical variable, RHR was evaluated according to the following quartile: <72, 72 to 76, 76 to 84, 84 beats/min. Survival curves were calculated by the Kaplan-Meier

method. The differences of survival probability among RHR groups were compared using Log-rank test. The analyses were further adjusted for baseline potential confounders including age, sex, smoking, alcohol drinking, blood pressure and BMI by use of Cox proportional hazards models.

The interactions between gender and RHR, as well as age (< 60 years and ≥ 60 years) and RHR, were tested by adding interaction terms to the main effects model. Given an interaction effect between RHR and age categories, instead of gender, on all-cause deaths as well as CVD was identified, we analyzed the data separately by aforementioned age groups, other than sex strata.

In the second set of analyses, we modeled RHR as a continuous variable to assess whether a nonlinear trend existed between RHR and the outcomes of interest among two age categories. We used proportional hazards regression polynomial modeling of RHR to find a best fitting transformation of RHR by comparing model deviances using a χ^2 distribution with 1 degree of freedom.²⁸

To avoid the potential bias resulting from occult disease at baseline, a sensitivity analysis was conducted by excluding the patients who died during the first 2 years of follow-up. Also, in view of the fact that the aforementioned cut point for old age might be somewhat arbitrary and to test the robustness of the results from the above 2 age categories, we performed another sensitivity analysis to further explored different risks of RHR across age tertiles (40~51, 52~61, ≥ 62). We also set a multiplicative interaction term of age tertiles and RHR quartiles in a multivariable COX regression model. All analyses were performed by using STATA 12 (StataCorp LP, College Station, Texas, USA), with two tailed tests at the significance level of 0.05

Results

Subjects characteristics

General characteristics of the study population were presented in Table 1. The mean age of the participants was 57.4 (± 10.7) year, and the average resting heart rate was 76.6 (± 11.2) beats per minute. During a mean follow-up period of 8.3 years, 840 subjects died; The overall death rate was 16.2 (95% CI:15.1-17.3) per 1000 person-years and 676 subjects suffered from CVD with CVD incidence being 13.3 (95% CI: 12.4-14.4) per 1000 person-years.

The modifying effects of age on the association of RHR with both all-cause mortality and CVD incidence

There were significant modifying effects of age on the association of RHR with both all-cause mortality and CVD incidence ($P_{\text{interaction}} < 0.001$ and equal to 0.002, respectively). In contrast, the modifying effects of gender on the relationship between RHR and all-cause mortality or CVD did not reached significant (both $P > 0.05$).

Figure 1 presented survival probability curve according to RHR classes for all-cause mortality and CVD incidence in younger and older participants. In older subjects (≥ 60 years

old), higher RHR was associated with both all-cause mortality (Figure B: $P < 0.001$) and CVD incidence (Figure D: $P = 0.002$). However, the associations of RHR with all-cause mortality and CVD incidence in the younger participants were not significant (Figure A, C: both $P > 0.05$).

Table 2 showed the risk ratios for all-cause mortality and CVD incidence in younger and older subjects after adjustment for age, sex (upper section) and for these two variables and other potential risk factors (lower section). In older group, higher RHR remained independently associated with higher risks for both all-cause mortality and CVD incidence (both $P_{\text{trend}} < 0.05$). In contrast, neither all-cause mortality nor CVD incidence was associated with RHR in younger group (both $P_{\text{trend}} > 0.05$).

No a nonlinear relationship between RHR and the outcomes of interest exists

When RHR was considered as a continuous variable, fractional polynomial regression model revealed that neither fractional polynomial regression model of second-degree (FP2) nor the model of first-degree (FP1) significantly improve a linear model regarding the relationship between RHR and all-cause mortality or CVD incidence among both younger and older participants (all P value > 0.05). This indicated that there was no a nonlinear relationship between RHR and the outcomes of interest.

Sensitivity analyses

After the exclusion of individuals who died ($n=100$) or suffered from CVD ($n=45$) during the first 2 years of follow-up, the results were similar to the total cohort participants. Among these subgroup participants, the modifying effects of age on the association of RHR with both all-cause mortality and CVD incidence remained significant ($P_{\text{interaction}} < 0.001$ and equal to 0.004, respectively).

Figure 2 showed the RRs of all-cause deaths and CVD events in participants with faster RHR were highest in the oldest and lowest in the youngest persons across age tertiles; only in the top tertile of age (≥ 62 years), multivariable adjusted RRs of RHR for all-cause deaths and CVD events reached statistically significant ($P < 0.001$ and $= 0.017$; $P_{\text{interaction}} < 0.001$ and $= 0.001$, respectively).

Discussion

In this community-based prospective cohort study in Beijing City, the capital of China, we found that it was among older subjects (≥ 60 years old), other than younger ones (< 60 years of age), that high RHR was an independent predictor of both all-cause mortality and CVD events; the relative risks of all-cause deaths and CVD events in participants with high RHR were highest in the oldest and lowest in the youngest persons; there were significant modifying effects of age on the association of RHR with both all-cause mortality and CVD events.

Although a lot of studies have demonstrated RHR is an independent predictor of all-cause mortality as well as CVD incidence among general population or high risk patients,^{8-14, 29} only limited studies have focused on age modifying effect on the relationship

between RHR and all-cause mortality or CVD incidence. If a modifying effect of age on their associations was documented, age differences in the utility of RHR for risk stratification might be needed to consider.

In one previous study,¹⁸ 19 386 French subjects aged 40 to 69 years were enrolled and followed up for 20 years. The results indicated that in both younger (40-55 years) and older age (55-69) groups, the same associations were observed between RHR and the different cause of mortality. Recently, data from 112,680 subjects in 12 cohort studies were pooled and analyzed by Woodward M et al.⁷ In their subgroup analysis, the risks of RHR for total mortality were similar for younger and older subjects. In contrast, there was a significantly higher risk associated with CVD for younger subjects compared with older people (P interaction = 0.01). The findings in the present study are inconsistent with these researches. A few discrepancies between the previous studies and ours as follows may partially account for the inconsistent results. First, the patients with CVD at baseline usually took a few drugs, including beta-blocker. Moreover, heart rate is regulated by the automatic nervous system, so can be affected easily by various disease conditions.³⁰ Accordingly, the CVD or other occult disease itself and the drugs taken due to these diseases, which may be imbalance between younger and older participants, could be important confounders. In the present study, we ruled out the patients with CVD at baseline. Nevertheless, two aforementioned studies did not as ours. Thus, they might ignore this potential confounding effect. Second, the latter study⁷ collected data from 12 cohorts. In these cohort studies enrollment criterion and methods of measuring baseline variables and outcomes could be various. Therefore, the pooled data from these studies may suffer from bias, such as measurement bias, of some individual researches. This may result in unconvincing results. Lastly, the previous studies and ours differ in enrolled participants. In the French study, only participants less than 69 years of age were enrolled.

In the present study, we not only dichotomized the participants at a point of 60 years of age, but also grouping them based on tertiles of age. We found that with age increasing the RRs of CVD or all-cause mortality tended to rise, which also suggests age differences in the utility of RHR for risk stratification might be needed to consider.

The major concern in the assessment of the associations between heart rate and mortality or CVD is reverse causal relationship. People with a history of cardiovascular disease or occult disease could have higher RHR; thus, people with a higher RHR might increase the estimated risk of death or CVD. To avoid such potential reverse causal relationship, we excluded the patients with a history of cardiovascular disease at baseline and a sensitivity analyses was conducted by excluding deaths or CVD that occurred during the first 2 years of follow-up in present study. As a result, the modifying effect of age on association between RHR and all-cause mortality or CVD remained unchanged.

The reasons for the discrepant relationship between RHR and mortality or CVD among younger and older subjects are uncertain. It is reported higher RHR is associated with an increase in vascular oxidative stress, endothelial dysfunction, subclinical inflammation, atherosclerosis progression, plaque disruption, ventricular arrhythmias and myocardial ischemia, which contribute to CVD incidence or mortality.³¹⁻³⁶ In fact, these

pathophysiologies more frequently exist in older people than in younger subjects, irrespective of RHR. This may be one of the reasons that age has the modifying effect on the association between RHR and CVD or mortality.

There are several strengths in our study. First, participants were randomly selected and enrolled from Beijing communities, providing a community-based sample of middle-aged and older participants, thus increasing generalizability of our findings. Second, we focused primary endpoints on all-cause mortality as well as CVD incidence and the results showed the modifying effects of age on the association of RHR with these two outcomes were the same in present study, which makes our findings more convincing. Third, all dead cases and CVD incidence were ascertained by reviewing hospital charts or documents at local Administrative Office, supplemented by interviews with local physicians, families or witness of the fatal events. Moreover all endpoints were centrally adjudicated by an end point assessment committee. These increased the accuracy of judging the endpoints of interest. Lastly, we had fully considered potential biases in our analyses.

There are also a few limitations in our investigation worth mentioning. First, although we excluded cardiovascular disease at baseline, we did not remove other potential diseases, which may confound the association between RHR and all-cause mortality or CVD. To eliminate the potential influence of preclinical disease, we excluded those who died or developed CVD during first 2 years of follow-up and found that the results were the same as those derived from the whole cohort population. Second, we only used baseline RHR levels and no repeat RHR levels were provided during follow-up, which might suffer potential bias from a single baseline measurement. Third, a total of 1066 subjects could not be contacted during follow-up and were excluded in the present study. These participants were younger compared with those included in the present study. Excluding these participants might have a possibility of selection bias. Fourth, we have no data regarding the differences of disease characteristic in the 1990s and nowadays. To some extent this may limit the possibility to extrapolate the results to current practice. However, we focused on the association between RHR and all-cause deaths or CVD incidence in present study, thus, the difference of disease characteristics may have less effects on their associations. Lastly, although we adjusted for some potential confounders in present study, other unmeasured residual confounders might exist. Thus future researches are warranted to confirm our findings.

Conclusion

In summary, our findings suggest that elevated RHR is an important risk factor for all-cause mortality as well as CVD in older subjects but not younger people in Chinese population of Beijing City. If this is further verified by future researches, especially in diverse population, it may indicate utility of RHR for risk stratification should depend on age differences.

Acknowledgments

Work for this study was supported by national grant-in-aid 9750612N from the American Heart Association and partially supported by grant U01HL072507 from the National Heart, Lung, and Blood Institute of the National Institutes of Health and grant 1999-272 from the Chinese Ministry of Health and the Chinese Academy of Medical Sciences.

Sponsor's Role: The sponsors had no role in the design, methods, analysis, or preparation of the paper.

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Figure 1.
 Survival probability curve according to RHR classes for all-cause mortality and CVD incidence in younger and older participants.

Figure 2.

Relative risks (RRs) and 95% confidence intervals (CIs; T-shaped bars) of RHR [top quartile (≥ 84 beats/min) vs bottom quartile (< 72 beats/min) of RHR] for all-cause deaths (A) and CVD events (B) according to age tertiles. Adjustment for age, sex, systolic blood pressure, body mass index, smoking, and alcohol drinking. $P_{\text{interaction}} < 0.001$ (A) and $= 0.001$ (B).

Table 1
Characteristics of study population according to heart rate categories

	HR<72 (n=1450)	76<HR 72 (n=1282)	84<HR 76 (n=1875)	HR 84 (n=1602)	P
age,y	57.3±0.3	56.7±0.3	57.2±0.3	58.2±0.3	0.002
male(%)	622(42.9)	540(42.1)	792(42.2)	750(46.8)	0.023
Weight,kg	61.2±11.5	61.3±11.0	62.0±11.3	62.3±12.1	0.016
Height,cm	1.6±0.1	1.6±0.1	1.6±0.1	1.6±0.1	0.532
BMI,kg/m ²	23.7±3.8	23.6±3.7	24.0±3.8	24.1±3.9	0.004
SBP,mmHg	132±24	132±24	132±24	135±24	0.001
DBP,mmHg	78±12	79±12	79±12	80±12	<0.001
Smokers(%)	479(33.0)	455(35.5)	677(36.1)	661(41.3)	<0.001
Drinkers(&percent;)	281(19.4)	262(20.4)	340(18.1)	352(22.0)	0.037
All-cause deaths	149(10.3)	171(13.3)	251(13.4)	269(16.8)	<0.001
CVD	139(9.6)	126(9.8)	204(10.9)	207(12.9)	0.013

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease

Table 2
Relative risks (95% confidence interval) of RHR for all-cause deaths and CVD according to age categories

RHR Group	age <60 years		age ≥ 60 years	
	all-cause deaths	CVD	all-cause deaths	CVD
Adjusted for age and sex				
RHR 72	reference	reference	reference	reference
72<RHR 76	1.48(0.93-2.38)	1.08(0.68-1.71)	1.32(1.03-1.69)	1.09(0.82-1.45)
76<RHR 84	1.15(0.73-1.83)	1.20(0.79-1.83)	1.34(1.07-1.67)	1.15(0.89-1.48)
RHR > 84	1.27(0.79-2.03)	1.29(0.83-1.98)	1.65(1.32-2.06)	1.36(1.06-1.74)
<i>P</i> *	0.6	0.21	< 0.001	0.014
Adjusted for age, sex and other risk factors **				
RHR 72	reference	reference	reference	reference
72<RHR 76	1.48(0.92-2.37)	1.02(0.64-1.63)	1.26(0.99-1.62)	1.03(0.78-1.37)
76<RHR 84	1.16(0.73-1.85)	1.15(0.76-1.76)	1.34(1.07-1.68)	1.17(0.91-1.51)
RHR > 84	1.23(0.76-1.97)	1.17(0.75-1.80)	1.61(1.29-2.01)	1.34(1.04-1.71)
<i>P</i> *	0.68	0.41	< 0.001	0.012

RHR, resting heart rate; CVD, cardiovascular disease.

*
P values for linear trend for RHR categories.

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other risk factors including systolic blood pressure, body mass index, smoking, and alcohol drinking.