

## Peer Review File

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### **Replies to Reviewer A**

**Comment 1:** Reduced physical activity level may be contributing to these results.

**Reply 1:** We agree with this point. In our study, physical activity was assessed using the International Physical Activity Questionnaire during baseline interview, categorizing based on the metabolic equivalent of task (MET) per min per week into low, moderate, and high levels (see Page 8, line 132-136). And we found that with an increase of baseline heart rate, the proportion of low-level physical activity (<600 MET min per week) increased (see Page 12, line 221-222). To correct the confounding effects of physical activity, we adjusted for this factor in the second adjusted model (see Page 10, line 177). After adjusting, an increase of heart rate by 10 beats per minute was still associated with cardiovascular mortality in normotensive and hypertensive subjects (see Page 12-13, line 230-254).

**Changes in the text:** Several sentences have been added in the Results (see Page 12, line 221-222) in the revised version to describe subjects' level of physical activity.

**Comment 2:** The Framingham Heart Study (Gillman MW et al. Am Heart J 1993; 125: 1148-1154) reported in 4530 persons aged 35 to 74 with hypertension at 36-month follow-up that heart rate may be an independent risk factor for cardiovascular death in

persons with hypertension.

**Reply 2:** Similar studies indeed suggest that heart rate may be an independent risk factor for cardiovascular death in persons with hypertension. But prior to our study, little was known whether present or absent hypertension could further influence heart rate-cardiovascular outcome associations. Our research had both normotensive and hypertensive arms to compare the difference. And this question has not been studied in China at the national level. Therefore, our study may fill the gap.

**Changes in the text:** To clarify the implication of our study explicitly, we have revised several sentences in the Introduction (see Page 5, line 65-77), Discussions (see Page 16, line 305-317), and Conclusions (see Page 20, line 394-399) in the revised version.

### **Replies to Reviewer B**

**Comment 1:** In the assessment of the associations between heart rate and risk of CVD, the present study did not provide any new knowledge in the current medicine, even for Chinese population.

**Reply 1:** Indeed, as an observational epidemiological study, we can't confirm whether using heart rate lowering medications could alter CVD and mortality outcomes in normotensive and hypertensive subjects. But we observed a significant interaction between baseline heart rate and present or absent hypertension. Our finding suggested that elevated heart rate is associated with cardiovascular mortality in Chinese normotensive population, and the magnitude of association was even stronger than that in hypertension patients. Thus, high heart rate is supposed to be considered as an early

indicator of CVD or mortality, and heart rate monitoring in normotensive people should also be given equal attention as it in hypertensive patients.

**Changes in the text:** To illustrate our findings more clearly, we have added some sentences in the Introduction (see Page 5, line 71-77), Results (see Page 13, line 242-243), Discussions (see Page 16, line 305-317), and Conclusions (see Page 20, line 394-399) in the revised version.

**Comment 2:** The statistical analyses for comparing the association of heart rate and risk of CVD between the hypertensive and normotensive population seemed inappropriate, even if the authors used the propensity score matching. Comparing the obtained coefficients in the different cohort was meaningless. Instead, the authors could assess the interaction between heart rate and risk of CVD among hypertensive and normotensive patients. Therefore, I recommend interaction analyses.

**Reply 2:** We are very thankful for your valuable recommendation. We have added several sentences to state the interaction in Discussion (see Page 16, line 305-317) and Results (see Page 13, line 242-243). We assessed the interaction before propensity score matching in preliminary analysis and observed a significant interaction between heart rate and present or absent hypertension for cardiovascular death ( $P=0.016$  for interaction in a fully adjusted model). Based on the above, we implemented propensity score matching, to adjust for confounding factors between the normotensive and hypertensive groups, which both derived from the same cohort of PURE-China study (Detailed flow chart of population matching was presented in Figure 1). After propensity

score matching, the interaction was still significant ( $P=0.004$  for interaction in a fully adjusted model), and the magnitude of heart rate-mortality association among normotensive and hypertensive patients was different. Compared with hypertensive subjects, normotensive people had a stronger correlation (heart rate  $\geq 82.5$  bpm group:  $HR_{\text{normotensive}} 3.30$  vs.  $HR_{\text{hypertensive}} 1.04$ ).

**Changes in the text:** Several sentences have been added in the Results (see Page 13, line 242-243), Discussions (see Page 16, line 305-317), and Conclusions (see Page 20, line 394-399) in the revised version to state the interaction between heart rate and present or absent hypertension.

### **Replies to Reviewer C**

**Comment 1 :** In reviewing this article, I found it difficult to follow the background information, protocol and the results due to many grammatical errors. I have included below some specific edits that should be addressed, but the overall paper should be addressed to allow for better understanding of the material. Of the comments below, some show up multiple times throughout the article.

**Reply 1 :** We apologize for the grammar error in our article, and we have revised the manuscript carefully and fixed all the grammar mistakes and typos.

**Changes in the text:** We have revised several sentences in the Introduction, Methods, Results, Discussions, and Conclusions in the revised version thoroughly.

**Comment 2 :** Line 30 – only included one group number

**Reply 2 :** We are sorry for the mistakes and we have revised the sentence in the new version.

**Changes in the text:** See Page 3, line 34-35.

**Comment 3 :** Lines 29-34 methods in abstract need to be made more clear.

**Reply 3:** We have revised the sentence in the new version.

**Changes in the text:** See Page 3, line 37-40.

**Comment 4 :** Line 35 – define person-years?

**Reply 4:** Person-year means the product of the number of observational years times the number of members in a cohort study, which accounts for the length of follow-up time in a dynamic cohort.

**Comment 5 :** Line 40 – include source for optimal HR

**Reply 5:** We have added the reference in the Methods of the revised version.

**Changes in the text:** See Page 10, line 169.

**Comment 6 :** Line 43 - What is a cubic spline?

**Reply 6:** Restricted cubic spline can be used to realize the correlation analysis between continuous exposure and outcomes. It provides a way to represent nonlinear or linear relationships in epidemiological multivariate analysis.

**Comment 7 :** Line 55 – CVD was or is the leading cause of death?

**Reply 7:** We are sorry for the mistakes and we have revised the sentence in the new version.

**Changes in the text:** See Page 5, line 60.

**Comment 8 :** Line 58 – replace “more and more”

**Reply 8:** We have revised the sentence in the new version.

**Changes in the text:** See Page 5, line 65-66.

**Comment 9 :** Lines 59-61 – make more clear

**Reply 9:** We have revised the sentence in the new version.

**Changes in the text:** See Page 5, line 68-71.

**Comment 10 :** Lines 72-73 – what one population? If a singular, what one?

**Reply 10:** We are sorry for the mistakes and we have revised the sentence in the new version.

**Changes in the text:** See Page 6, line 87-88.

**Comment 11 :** Lines 81-85 – these lines were confusing

**Reply 11:** We have revised the sentence in the new version.

**Changes in the text:** See Page 6, line 95-100.

**Comment 12 :** Line 92 – missing period

**Reply 12:** We are sorry for the mistakes and we have revised it in the new version.

**Changes in the text:** See Page 7, line 109.

**Comment 13 :** Line 193 – use the term “sex” instead of “gender”

**Reply 13:** We have revised the sentence in the new version.

**Changes in the text:** See Page 10, line 175, and elsewhere in the text.

**Comment 14:** Line 258 – clarify the insignificant results

**Reply 14:** We have added the hazard ratio and 95% CI and discussed the reasons in the revised version.

**Changes in the text:** See Page 16, line 304-315.

### **Replies to Reviewer D**

**Comment 1 :** Firstly, I would have liked to see the term resting heart rate or baseline heart rate used throughout the manuscript. I constantly found myself putting this in every time I read the word heart rate.

**Reply 1 :** We are very thankful for your recommendation, and we have used the term baseline heart rate throughout the manuscript.

**Changes in the text:** We have revised the term in the Introduction, Methods, Results, Discussions, and Conclusions throughout the manuscript.

**Comment 2 :** Line 191 - p value should be noted.

**Reply 2:** We have added the *P* value in the revised version.

**Changes in the text:** See Page 12, line 215.

**Comment 3 :** Line 211 - I was a little bit confused by this sentence. Were the authors trying to say "cardiovascular mortality increased with an increase in heart rate in normotensives"

**Reply 3:** We are sorry for the ambiguous sentence and we have revised the sentence in the new version.

**Changes in the text:** See Page 13, line 244-246.

**Comment 4 :** Line 113 - There is mention of the patients medication use being recorded however I could not find any further reference to this. Was any adjustment made for those on heart rate lowering medications (Beta-blockers, non-pyridine calcium channel blockers, Ivabradine etc) This would obviously make a huge difference to the resting heart rate.

**Reply 4:** We are very thankful for your valuable recommendation. In our study, antihypertensive medication use was recorded to estimate whether the subject had hypertension. And we further adjusted for use of heart rate lowering medications (beta-blockers, calcium antagonist) and antihypertension medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, and other types of antihypertensive drugs) in hypertensive patients in the revised version. And the

associations for hypertensive subjects almost did not alter (Supplementary material, Appendix Table S1).

**Changes in the text:** We have added some sentences in the Methods (see Page 10, line 177-181), Results (see Page 13, line 237-242) and Supplementary material (Table S1) in the revised version.

**Comment 5 :** Line 510 - "mission values" should be missing values.

**Reply 5:** We are sorry for the mistake and we have revised the word in the new version.

**Changes in the text:** See footnotes of table 1.

### **Replies to Reviewer E**

**Comment 1 :** Abstract, lines 29-30: the construction of the text "including 14,777 participants in hypertensive or normotensive group, respectively" seems strange to me, since the word "respectively" involves assigning multiple characteristics/values to multiple categories/subjects, however only one value is displayed (14,777). I suggest something that can cause less confusion, such as: "including 14,777 participants in each group (hypertensive or normotensive)" or "A total of 29,554 individuals were involved in our analysis, distributed equally between groups of normotensive and hypertensive".

**Reply 1 :** We are very thankful for your informative recommendation, and we have revised the sentence in the new version.

**Changes in the text:** See Page 3, line 34-35.

**Comment 2 :** Background, Lines 84-85: I believe that the phrase "This article is presented following the STROBE reporting checklist" would be better positioned in the Methods section and not in the Background. In addition, I suggest adding the STROBE reference.

**Reply 2 :** We have added the reference in the revised version. We appreciate your opinion, but the phrase "This article is presented following the STROBE reporting checklist" was requested by " Submission Checklist for Authors " to be placed in the Introduction.

**Changes in the text:** See Page 6, line 102.

**Comment 3 :** Methods, Line 92: Apparently some punctuation or connective is missing before "China".

**Reply 3:** We are sorry for the mistakes and we have revised it in the new version.

**Changes in the text:** See Page 7, line 109.

**Comment 4 :** Results, Line 182: I believe that there should not be an end point before the parentheses defining hypertension, since it is a complement to the previous sentence.

**Reply 4:** We are sorry for the mistakes and we have revised it in the new version.

**Changes in the text:** See Page 11, line 204.

**Comment 5 :** Discussion, Lines 265-300: This paragraph seemed to me excessively long (35 lines), I recommend dividing it in 2 in order to facilitate the reading and

understanding of the arguments presented in it.

**Reply 5:** We are very thankful for your valuable recommendation, and we have revised the content in the Discussion in the new version, to state opinions more logically.

**Changes in the text:** See Page 15-18, line 295-364.