Author’s response to reviews

Title: Elevated Blood Pressure Level Based on 2017 ACC/AHA Guideline in Relation to Stroke Risk in Rural Areas of Liaoning Province

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Author’s response to reviews:

Dear reviewers and editors,

Thanks for your decisions and advices. We have considered all reviewer’s comments and queries and tried our best to revise the article (No. BCAR-D-18-00404). Now, I will item all changes made, or my explanations, in response to each of the reviewers’ and editors’ comments. Major revised contents had been colored red in revised article.

Response to the reviewers’ and editors’ comments

Manuscript Number: BCAR-D-18-00404

Title: Elevated Blood Pressure Level Based on 2017 ACC/AHA Guideline in Relation to Stroke Risk in Rural Areas of Liaoning Province
Editors’ comments:

1) In the section “Ethics approval and consent to participate” in the Declarations, please give the reference numbers for the ethical approval.

Response: Thanks for your comments. According to your suggestion, we have added the reference numbers for the ethical approval the revised paper. Detail are as follows: The study was approved by Ethics Committee of China Medical University (Shenyang, China) (Num. AF-SOP-07-1. 0-01).

2) Please describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Response: Thanks for your advice. This research was partly supported by funds from National Nature Science Foundation of China (No. 81773510) (design of the study and data collection), Nature Science Foundation of Liaoning Province (No. 20170541048) (design of the study and data collection), National Key R&D Program of China (Grant #2017YFC1307600) (analysis, and interpretation of data and write the manuscript), and Science and Technology Program of Shenyang, China (Grant #17-230-9-06) (analysis, and interpretation of data write the manuscript).

Reviewer 2 (Reviewer 2): "REVISION ASSESSMENT FROM THE ACADEMIC PEER REVIEWER:

Comment 1:

Abstract

* Results section: "However, there was no significant association between stage1 hypertension (SBP:130-139mmHg or DBP:80-89mmHg) and stroke incidence." The authors should add a HR and 95% CI.

Response: Thanks for your comments. we have added a HR and 95% CI in the revision. Detail are as follows: However, there was no significant association between stage1 hypertension (SBP:130-139mmHg or DBP:80-89mmHg) and stroke incidence (HR: 0.985, 95% CI: 0.468 to 2.076, P=0.969).

Comment 2:
* Results section: The last sentence shouldn't begin with 'and' and this sentence does not flow well from the previous sentence.

Response: Thanks for your comments. We have removed 'and' in the revised paper.

Comment 3:
* Conclusion: "The 2017 ACC/AHA stage 2 hypertension definition significant increases the risk of stroke incidence" This sentence is unclear - increases from what?

Response: Thanks for your comments. In the revised paper, we modified this sentence as: Compared with normal BP, the stage 2 hypertension based on 2017 ACC/AHA guideline significantly increases the risk of stroke incidence.

Comment 4:
Introduction

* I think the sentence added to the Background section should read "in order to explore the applicability of the new guidelines" rather than "in order to explaining applicability . . ." 

Response: Thanks for your comments. Combined with the opinions of the two reviewers, we replaced "in order to explaining the applicability of the new guidelines " with "in order to explore the applicability of the new guidelines ".

Comment 5:
Discussion

* The authors state that they cannot adjust for family history of CVD as they don't have this information. Perhaps this could be added to the limitation section of the Discussion.

Response: Thanks for your comments. In revised paper, we have added these to the limitation section of the discussion as follows: Thirdly, our study cannot adjust for family history of CVD as we don't collect these information in the baseline.

Reviewer 3: "STATISTICAL REVIEWER ASSESSMENT:
STATISTICAL REVIEWER COMMENTS:"
The data collection in this study seems very robust and reliable. The authors have chosen appropriate models for the data. However I would recommend an alternate measure for the association between SBP and DBP. Specifically, I do not think it is clinically relevant to measure the association using 1-standard deviation and would recommend a more clinically relevant measure of change, such as 20mmHg or whatever the clinicians seem would be appropriate and generalizable. I also suggest the authors report p-values for the rate difference or rate ratio to compare stroke incidence between sexes rather than the Student's t test. Authors should also report the number of stroke events in their study population and global p-values in their model results.

The data collection and study protocol has a really high standard and robustness. I commend the authors on their work.

Response: Thanks for your evaluation.

Comment 1:

I'm not entirely sure that the purpose of this study is clinically useful in any way. The association are the same as previously, that hypertension is associated with stroke. From an epidemiological perspective, they might be able to show how the new guidelines have changed the prevalence of stroke but that's all I can see for usefulness.

Response: Thanks for your proposal. Although the impact of new stage 1 hypertension in the U.S. population has been summarized in the 2017 ACC/AHA guideline, it is unknown whether this recommendation can be applied to other populations. This is especially true for the Chinese population, in which there is a high risk of stroke mortality and high prevalence of hypertension, as well as a large aging population. The rationale for the application of stage 1 hypertension hinges on the impact of this blood pressure (BP) stratum in a population, including the risk of BP progression, the risk of CVD, and the benefit of treatment and its cost effectiveness. Therefore, this study used the 2017 AHA/ACC hypertension guideline to define BP level and observe the relationship between new BP levels (especially stage 1) and the risk of stroke incidence through a rural community-based prospective cohort study in order to explore the applicability of the new guidelines in rural China.

Comment 2:

Methods section. You mention that people who are pregnant, have malignancies or mental disorders were excluded from the study. It might be useful to outline why they were excluded as this may be a source of selection bias, particularly for women.
Response: Thanks for your comments. What I want to explain is that our cohort excluded people who are pregnant, have malignancies or mental disorders at baseline. This is our exclusion criteria, which are also to avoid competitive risks.

Comment 3:

Is labour strength self-reported by participants or defined by job role?

Response: Thanks for your comments. The labour strength was self-reported by participants. Our questionnaire has questions about labour strength. The specific questions are as follows:

Which type of work or occupation is at or close to the strength of physical activity?

Comment 4:

Methods. I don't understand the section about the participants height and weight. "Keep a decimal when measuring height and weight and with participants in lightweight clothing and without shoes."

Response: Thank you for your question. This may be caused by the problem of my language expression. What I want to express is weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with participants in lightweight clothing and without shoes. According to your question, we have modified this sentence in the revised paper. Details are as follows: Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with participants in lightweight clothing and without shoes. Body mass index (BMI) was calculated as the participant's weight in kilograms divided by their height in meters squared (kg/m²).

Comment 5:

Methods, Statistical analysis. Its unclear to me why they chose to use 1-standard deviation for SBP/DBP. The standard deviation would depend upon this study sample and may not be clinically relevant. I would think it would be more appropriate to use a clinically relevant change, such as 20mmHg change.

Response: Thanks for your critical comments. In the revised paper, we added an independent variable category (an increment of 20mmHg in SBP/DBP) based on the 4 BP categories defined by the 2017 ACC/AHA and an increment of 1-SD in SBP/DBP. The specific results are reflected in Table 2. An increase of the SBP by 20 mmHg increases the risk for stroke by 51% (HR: 1.51,
95% CI: 1.27 to 1.80, \( P<0.001 \). However, no statistical significance was found between 20 mmHg increase of DBP and stroke.

Comment 6:

Methods, statistical analysis. You described the incidence rate, but this is incorrect. The incidence rate is the events divided by the person years and can be represented per 100,000 person-years. I would also not recommend using a student t-test given incidence rate is not normally distributed. It would be more appropriate to test the rate difference or incidence rate ratio between sex.

Response: Thanks for your critical comments. We agree with you that it would be more appropriate to test the rate difference or incidence rate ratio between sex. Therefore, in the revised paper, we have modified the statistical analysis of method. Details are as follows: The incidence rate was denoted by case load/100,000 person-years. \( \chi^2 \) test was used to test the rate difference between sex. We also updated the result as: In addition, no statistical significance was found among sex for incident stroke difference (\( P=0.157 \)).

Comment 7:

Results, Table 2. You should be presenting the p-value for the covariate as a whole, rather than just each category. Without this p-value, we can't ascertain whether BP level is associated with stroke incidence.

Response: Thanks for your critical comments. We have added each p-value of the covariate and BP category in the revision (Table 2).

Comment 8:

Your conclusion should be whether BP level (as defined by the 2017 ACC/AHA) is significantly associated with stroke incidence. This is much more relevant than just looking at one category of BP level.

Response: Thanks for your comments. I agree with you. In the revised paper, we modified the conclusion as follows: In conclusion, the stage 2 hypertension based on 2017 ACC/AHA guideline significantly increases the risk of stroke incidence, but this association was not observed between elevated, stage1 hypertension and stroke incidence.
Comment 9:
Were all the confounding factors that you adjusted for in Model 3 significantly associated with stroke? Since you are only adding the confounders to improve the accuracy of your estimate for BP, then it is probably best to only include confounders that are significantly associated with your outcome or improve the precision of the estimate for BP level.

Response: Thanks for your critical comments. The methods of variable selection in COX regression models is ‘Enter’, according to your comments, we have conducted data analysis through ‘Forward Stepwise’ method again. The response of comment 5 and comment 7 both based on the new analysis results.

Comment 10:
I don't think you've actually reported how many stroke events there were in your population in the results section. This is essential information.

Response: Thanks. We have reported the number of stroke events in "Incidence rate of stroke" of "Results". Details are as follows: During follow-up, 81 (2.5%) non-stroke individuals at baseline developed incident stroke, and the median follow-up year is 4.8.

Comment 11:
I don't think you have a small sample size that would limit your power. In fact, for time-to-event models it is the number of events that define your statistical power rather than the sample size itself.

Response: Thanks for your critical comments. We agree with you that the number of events that define your statistical power rather than the sample size itself. In revised paper, we changed the secondly limitation as follows: Secondly, the relatively small number of incident stroke events meant that we had limited statistical power to detect the weak relationship between BP and stroke.

Comment 13:
Minor comments.
Background, 4th line. The last part of this sentence isn't grammatically correct. It should it revised (making it become the second preventable cause of death after smoking?)
Response: Thanks for your remind. In the revised paper we have modified this sentence as follows: In the United States, hypertension caused more deaths from cardiovascular disease (CVD) than any other CVD risk factor that is changeable, which making it become the second preventable cause of death after smoking 1.

Comment 14:
Background, second paragraph, 1st sentence. Gramatically incorrect. Should read "However, newly issued on November 13, 2017, the American College of Cardiology/American Heart Association guidelines revised the hypertension definition to 130/80, and BP…"
Response: Thanks for your comments. We have revised this sentence in the revised paper as follows: However, newly issued on November 13, 2017, the American College of Cardiology / American Heart Association (ACC/AHA) guidelines revised the hypertension definition to 130/80 mmHg

Comment 15:
Background, second paragraph. The second sentence repeats the same thing written in the first sentence. I suggest you revise to make into one sentence.
Response: Thanks for your critical comments. Based on your suggestion, we have integrated the first two sentences. Details are as follows: However, newly issued on November 13, 2017, the American College of Cardiology / American Heart Association (ACC/AHA) guidelines revised the hypertension definition to 130/80 mmHg and eliminate the category of prehypertension thus increasing the prevalence of hypertension.

Comment 16:
Background, last paragraph, 2nd last line. Grammatically incorrect. It should be "in order to explain."
Hazard ratios are generally presented to 2 decimal places.
Response: Thanks for your comments. Combined with the opinions of the two reviewers, we replaced "in order to explaining" with "in order to explore". In the revised paper, we also presented hazard ratios to 2 decimal places.
Comment 17:

Figure 2. What do the stars represented in Figure 2? Also, I'd rather see the number of stroke events written on top of the bars than the incidence value which is already being represented by the y axis.

Response: Thanks for your comments. First of all, based on your suggestion we replaced the incidence value with the number of stroke events on top of the bars. In addition, the stars in Figure 2 represents significant statistical difference between women and men among different BP level, P <0.05. However, in the revised paper, we cancel the stars symbol because of inaccurate statement.

Thanks for your support. I am expected to receive detailed suggestions if the response might not satisfy you.

Thank you very much.

Yours,

Yanxia Xie, MD

Liqiang Zheng, MD, PhD