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

Authors:

Yanxia Xie (1342660403@qq.com)
Mingfeng Ma (mamingfeng106@sina.com)
Zhao Li (2680481161@qq.com)
Xiaofan Guo (guoxiaofan1986@foxmail.com)
Guozhe Sun (gzhsun66@163.com)
Zhaoqing Sun (sunzhaoqing@vip.163.com)
Jia Zheng (1637643374@qq.com)
Yingxian Sun (sunyingxian12@126.com)
Liqiang Zheng (liqiangzheng@126.com)

Version: 1 Date: 23 Oct 2018

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

Reviewer #1:

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

Submitted to: BMC Cardiovascular Disorders

It is a generally interesting paper whose research question addresses a medical condition of global importance. I have some comments which I think will improve the manuscript.

Response: Thanks for your evaluation.

Major Compulsory Revisions

1. Abstract

   a. L. 25: Please specify type of study and add information on the source population, population size and time-frame of the study.

Response: Thanks for your comments. According to your suggestions, we have added this missing content in revised paper as follows: In total, 3229 participants age ≥35 years and free of stroke at baseline were followed for up to 4.8 years during 2012 to 2017 in a rural community-based prospective cohort study of Xifeng County.

   b. L. 25-31: Based on the information given in the Background paragraph of the Abstract it is not clear whether the authors actually wanted to estimate a measure of disease frequency or a measure of effect or both. While the outcome of interest is clearly mentioned, the levels of exposure respectively health condition stay vague. Because the authors estimated the Hazard Ratio for comparisons among categories I suggest mentioning the levels of exposure and the control level chosen.

Response: Thanks for your comments. I agree with your viewpoints and re-write the Background and make the results clearer than before. The revision is as follows: The new ACC/AHA hypertension guideline lower the definition of hypertension from 140/90 mmHg to 130/80 mmHg and eliminate the category of prehypertension thus increasing the prevalence of hypertension. A purpose of this study is to explore the applicability of the new guidelines in rural China (Background). Compared with normal BP (Systolic BP (SBP)<120mmHg and Diastolic BP (DBP)<80mmHg), stage 2 hypertension (SBP≥140mmHg or DBP≥90mmHg) had approximately 2.2 greater risks for stroke (HR: 2.191, 95% CI: 1.172 to 4.095, P=0.014) after
adjusting for age, sex, race, education level, current drinking and current smoking. However, there was no significant association between stage1 hypertension (SBP:130-139mmHg or DBP:80-89mmHg) and stroke incidence. And an increment of 1-SD in SBP were associated with greater HR of 1.508 (95% CI: 1.126 to 2.020) for stroke after fully adjustment. (Results).

c. L. 42-45: The authors report an incidence rate that was not mentioned as a measure of interest in the Method paragraph of the Abstract.

Response: Thanks for your comments. The content of the incidence of stroke is not the main result of this article, so we delete it in the abstract.

d. Conclusions: The statement in the first sentence of the paragraph is weak because the authors do not relate it to anything or give a comparison. In the second sentence of the paragraph the authors just restate a result.

Response: Thanks for your comments. I agree with your viewpoint that the conclusion is not accurate and highly generalized. We have rewritten this part, the specific changes are as follows: The 2017 ACC/AHA stage 2 hypertension definition significant increases the risk of stroke incidence, but this association was not observed between stage1 hypertension and stroke incidence in Chinese rural adults.

It would be nice to stay with keywords: Does ‘new BP classification’ mean the same as ‘BP level group’?

Response: Yes, thanks very much! In our revise paper, we have modified all similar errors.

2. Background

a. L. 25: ‘The death of cardiac cerebral vascular disease is the first cause of death in China.’ I assume the sentence is wrongly formulated.

Response: Thanks for your remainder. We have replaced the original sentence with “China has one of the highest incidences of stroke worldwide”.

b. L. 36-42: I suggest to mention that the new ACC/AHA High Blood Pressure Guidelines lower the definition of high blood pressure from 140/90 mmHg to 130/80 mmHg and eliminate the category of prehypertension thus increasing the prevalence of high blood pressure.

Response: Thanks for your suggestion. We have supplemented this paragraph in the Background, details are as follows: The new ACC/AHA hypertension guideline lower the definition of hypertension from 140/90 mmHg to 130/80 mmHg and eliminate the category of prehypertension thus increasing the prevalence of hypertension. Similarly, if China follows the guideline of the United States, more people will become hypertensive patients, especially in the
rural population, many previous studies by our team also have shown that the prevalence of hypertension is high in rural populations in Liaoning 9-11.

3. Methods

Study population

a. L. 20-28: Please add information on the procedure used to select participants at baseline of the study in 2012.

Response: Thanks for your suggestion. Based on your suggestions, we have added to the first paragraph of Method with more detailed contents at baseline of the study, such as population size, time, exclusion criteria, etc. Details are as follows: This study was based on a rural community-based prospective cohort study of Xifeng County, which is located in northeast China. From June 2012 to August 2012, 4157 Chinese rural participants aged ≥35 years from 2 of the 19 towns were included by cluster random sampling (2 towns, Anmin and Helong). Individuals who are pregnant, malignancies or mental disorders are excluded from this study. The study was approved by Ethics Committee of China Medical University (Shenyang, China). All procedures are conducted in accordance with the ethical standards of this committee. All participants received written consent after learning the objectives, benefits and medical details of the study and the confidentiality agreement regarding personal information.

Stroke and BP level Assessment

b. L. 12-23: I suggest mentioning that a hemorrhagic stroke or an ischemic stroke is the outcome of interest in the study. The sentence ‘Include patients exhibit…’ confuses the reader because he or she may think the stroke event is a criterion for the inclusion of participants in the study.

Response: Thanks for your remainder. I am sorry that there is an expression error. We reorganized the expression in the revision as follows: The definition included patients presenting with clinical signs and symptoms of subarachnoid hemorrhage, intracerebral hemorrhage, thrombosis.

Statistical analysis

c. L. 45-47: I expect the authors to report the overall mean and the standard error of the mean.

Response: We shall be glad to receive your comments. We have reported the overall mean and the standard error of the mean in the full text, including Table 1.
d. L. 50-53: I think to test whether there is a difference between categories is not meaningful because all participants were systematic categorized in relation to the blood pressure value measured.

Response: Thanks for your great comments. In our revised paper, we have modified Table 1 and divided the population into women and men groups for comparison of baseline characteristics. In addition, we have changed the statement as follows: The difference of baseline characteristics between different sex were evaluated using the student’ t test or the χ²-test, as appropriate.

e. L. 53-56: I think the (Wilcoxon-Mann-Whitney)-U test is not appropriate to compare person-year incidence rates. I wonder why the authors do not report an effect measure based on the incidence rates among the blood pressure categories.

Response: Thanks for your remainder, I agree with your viewpoint that the (Wilcoxon-Mann-Whitney)-U test is not appropriate to compare person-year incidence rates. After studying, we have confirmed that the student’ t test is suitable to compare person-year incidence rates. In addition, we have reported the incidence rates among the blood pressure categories in the paper, but the description of the incidence rates of stroke in different blood pressure categories is based on sex stratification.

4. Results

Baseline characteristics of the study population

a. I suggest presenting the baseline characteristics of the study population in a table which should just be referenced.

Response: Thanks for your remainder. In our revised paper, based on the modification of Table 1, we also have presented the baseline characteristics of the study population in Table 1 and referenced it as “Table 1 shows the baseline characteristics of all participants”.

Incidence rate of stroke

b. I suggest presenting the incidence rates of stroke in a figure which should just be referenced.

Response: Thanks for your remainder. In our revised paper, we have modified Figure 2, which presented the incidence rates of stroke between women and men. The legends of Figure 2 as follows: Incidence rate of stroke (per 100000 person-years) in different BP level between women and men.

Abbreviations: * represents significant statistical difference between women and men among different BP level, P <0.05.
c. L. 58-1: The statement in this sentence is a bold statement because it suggests that there is a steadily increase of the cumulative incidence of stroke events. That is not really true.

Response: Sorry, this is a writing error. We have replaced cumulative incidence of stroke with incidence of stroke.

Multivariate Cox regression analysis for BP and stroke

I think only the results from the Cox regression analysis are pertinent to the question the authors posed in the Background section of the paper. Therefore the authors should report these results first in the Result section of the paper.

Response: Yes, thanks very much! We have changed the order in which the results are described.

d. L. 1-9: The authors estimated Hazard Ratios with 1-SD increase of systolic and diastolic blood pressure in relation to all stroke events. That should be mentioned in the Method section of the paper.

Response: Thanks for your comments. In our revised paper, we have added the relative sentence in the “Statistical analysis (Method)” section as follows: Cox proportional hazards model were used to identify independent associations between different BP category or an increment of 1-standard deviation (SD) in SBP/DBP and stroke incidence in the 3 different models...

The Hazard Ratio describes the change of risk in relation to the change of exposure and the outcome of interest. Therefore it would be nice to get a statement like that: ‘An increase of the systolic blood pressure by 10 mmHg increases the risk for stroke by 50%’.

Response: We are very glad to receive your comments. In our revised paper, we used the same expression as follows: An increase of the SBP by 20 mmHg increases the risk for stroke by 50.8% (HR: 1.508, 95%CI: 1.126 to 2.020, P=0.006) after multivariable adjustment in model 3.

5. Discussion

Unfortunately, in the first two sentences of the Discussion section the authors restate results and do not answer the question they posed in the Background section of the paper.

Response: Thanks for your honesty comments. In our revised paper, we have re-write the first two sentences of the “Discussion” section as follows: The present study, with a relatively successful (>90%) follow-up, revealed that the 2017 ACC/AHA stage 2 hypertension definition significant increases the risk of stroke incidence, but this association was not observed between
stage 1 hypertension and stroke incidence. And increment of 1-SD in SBP is associated with risk of stroke incidence.

a. L. 28-34: The authors revealed an unacceptable low rate of treatment for hypertension among the participants of the study. I fully agree with the authors there because that is a very important result of the study and should have an essential impact on the awareness for the high blood pressure as a global health-threatening condition.

Response: Yes, thanks very much!

b. L. 1-6: The authors mention limitations of their study. The blood pressure of the participants was measured three times in a day and not on three different days thus possibly introducing a misclassification bias in the study. It could then be a differential exposure misclassification bias. In this context I am wondering about the category with normal blood pressure. This is because a tiny fraction of the participants already take antihypertensive medications and the frequency of stroke in this category nearly equals that of the categories with elevated blood pressure and with stage 1 blood pressure in terms of a standardized measure of frequency. If it is still the authors concern, then I would like to recommend a reassessment of the exposure status especially of the participants in this seemingly heterogeneous category.

Response: Thanks for your remainder, the blood pressure of the participants was measured three times in a day and not on three different days is really one of our limitations and we also mentioned it in the limitation. In our revised paper, we added sensitivity analysis excluding those on anti-hypertensive treatments (n=3118).

Minor Essential Revisions

1. Abstract

a. L. 31: ‘were analyzed’ change to ‘were estimated’

Response: Yes, thanks very much!

2. Methods

   Study population

a. One point is unexplained by the authors. Did they collect other data apart from the stroke events at the follow-up of the study? Should a new onset of high blood pressure or an
uncontrolled high blood pressure among the participants during the follow-up be of concern in relation to the data analysis?

Response: Thanks for your comments. We have collected other data apart from the stroke events at the follow-up of the study, but the main purpose of this article is to explain the relationship between blood pressure level and incidence of stroke, so there's no mention of other events. And we did not collect data about high blood pressure or an uncontrolled high blood pressure among the participants during the follow-up, which lead us cannot further analyze.

Statistical analysis

a. L. 1: switch ‘different’ and ‘3 ‘
Response: Yes, thanks very much!

b. L. 3: add ‘current drinking’
Response: Yes, thanks very much!

3. Results

a. L. 6: ‘stage 1 BP’ change to ‘stage 2 BP’
Response: Yes, thanks very much!

b. L. 31: ‘median’ change to ‘mean’
Response: Yes, thanks very much!

c. L. 47: ‘According to the 2015’ change to ‘According to the 2017’
Response: Yes, thanks very much!

d. L. 48: ’64.5’ change to ‘64.3’
Response: Yes, thanks very much!

e. It is not a must. But please add information on the frequency of type of stroke in relation to blood pressure categories.
Response: Thanks for your comments. However, only 81 of our patients had a stroke, and our population was in the northeastern rural China population, which resulted in a stroke subtype of 73 ischemic strokes and 8 hemorrhagic strokes. Due to the main limitation of sample size, we cannot analyze the relationship between stroke subtypes and blood pressure categories.

4. Discussion
a. L. 39: Reference ‘22’ should not be referenced because the subject of that study was stroke recurrence. The authors excluded patients with history of stroke at baseline from the study.

Response: Yes, thanks very much! In our revised paper, we have deleted the citation of this reference.

b. The Discussion section should be shorter. One part of the Discussion section could do for the Background section and another part could do for the Conclusion section.

Response: Yes, thanks very much! In our revised paper, we have deleted a portion of discussion about possible pathogenesis of hypertension to stroke

Annotation

From my point of view the authors do not answer the posed research question satisfactory. That may be because the story they tell seems unfinished. I would like to mention explicitly that this is just my concern and I may be totally wrong.

Therefore I would like to explain.

In 2017 the new ACC/AHA High Blood Pressure Guidelines were published. The new definition of high blood pressure allows for earlier intervention to prevent people from cardiovascular complications thus increasing the prevalence of high blood pressure also. The authors take the new definition of high blood pressure like a template and estimate the risk of stroke based on blood pressure values measured at baseline in 2012. That may be fine. But what would be the risk for stroke among the participants of the study in 2012 based on the definition of hypertension according to the old ACC/AHA High Blood Pressure Guidelines from 2003? Or in other words, does the risk for stroke change only because the definition of high blood pressure did change? It would tell the story to the end if the authors would address those questions also in their research.

Response: Thanks for your comments. I agree with your viewpoint that the individual’s risk of stroke incidence will not change because of the definition of high blood pressure change. But the 2017ACC/AHA lower the definition of hypertension from 140/90 mmHg to 130/80 mmHg, which generated a significant impact on public health. By comparing the risk of stroke in different blood pressure level, our study provides significant evidence of a link between the new BP level and the risk of stroke incidence, and provides foundational data for future related studies, which are indispensable if application of the 2017 ACC/AHA hypertension guideline is to be considered in rural China even in China.

Thanks very much!
Reviewer #2:

REVIEWER COMMENTS

This is an interesting prospective study exploring the associations between the new ACC/AHA blood pressure classification and the incidence of stroke in rural China, over 4.8 years of follow-up. The objective is a little unclear in terms of what the study will add to the literature - it is purely a descriptive study? The study design is fairly well designed but there are some additional statistical analyses and adjustments the authors should make. Also, the conclusions are not supported by the data provided. Lastly, the grammar and language has several errors and is unclear in places.

Response: Thanks for your evaluation.

REQUESTED REVISIONS: The objective is a little unclear in terms of what the study will add to the literature - the authors should add information on whether this is purely a descriptive study or whether it is to be used to inform whether to adopt the new AHA BP guidelines in China.

Response: Thanks for your great comments. Actually, the purpose of our study is unclear description. In our revised paper, we have re-write the content about the objective in “Abstract” and “Background” as follows: The new ACC/AHA hypertension guideline lower the definition of hypertension from 140/90 mmHg to 130/80 mmHg and eliminate the category of prehypertension thus increasing the prevalence of hypertension. The purpose of this study is to explore the applicability of the new guidelines in rural China (Abstract). Therefore, this study used the 2017 AHA/ACC hypertension guideline to define BP and observe the relationship between BP levels and the risk of stroke incidence through a rural community-based prospective cohort study, thus explaining the applicability of the new guidelines in rural China (Background).

Abstract - The results section only mentions the risk of stroke in the old BP classification (stage 2) – it should also mention risk in the new BP classification (stage 1) as this is surely what the study set out to do. Also, the conclusion section is unclear. The first sentence reads: “higher prevalence of hypertension and incidence of stroke were observed” – higher than what? The authors need to clarify. The second sentence doesn’t make sense – “there was an increase in risk of BP level to stroke across the four BP level.” The authors should reword this.

Response: Thanks for your critical comments. We have completely revised the abstract and considering the limit on the number of words, and only the main results are related to the relationship between blood pressure categories and the risk of stroke incidence were saved. We have added the risk information in the stage 1 as follows: However, there was no significant association between stage1 hypertension (SBP:130-139mmHg or DBP:80-89mmHg) and stroke incidence. In addition, we have re-write the first and second sentence thoroughly in revision paper as follows: The 2017 ACC/AHA stage 2 hypertension definition significant increases the
risk of stroke incidence, but this association was not observed between stage 1 hypertension and stroke incidence in Chinese rural adults.

Statistical analysis - there are some additional statistical analyses and adjustments the authors should make:

• Further adjustment for physical activity levels and family history of CVD, as these confounders are major cardiovascular risk factors.

Response: Thanks for your comments. In our revised paper, we have adjusted physical activity levels, which was replaced by labor strength in Model 3. However, it is particularly regrettable that we don't have data on the family history of CVD.

• The authors should test whether there is any effect medication by sex or age group.

Response: Thanks for your comments. In our revised paper, we have analyzed that whether there is any effect medication by sex or age group. The results showed that no interaction occurred in the 3 models.

• The authors should include sensitivity analysis excluding those on anti-hypertensive drugs

Response: Thanks for your critical comments. We have added sensitivity analysis excluding those on anti-hypertensive drugs in revision paper. We have added content about sensitivity analysis in the statistical methods and results, respectively. Details are as follows: After excluding participants who were taking antihypertensive medications, sensitivity analyses were performed (Statistical analysis). Similar results were found after excluding participants on antihypertensive treatments (n=3118) (Results).

• For the Cox models, did the authors test the proportional hazards assumption?

Response: Thanks for your critical comments. This is partly because the article written not clearly enough, but in fact we made the proportional hazards assumption in the process of statistical analysis. In our revised paper, we added a description of this assumption as follows: …after testing for the assumption underlying the use.

Conclusion - The conclusions are not supported by the data provided. The authors have suggested that adopting the new guidelines for BP in China is a good idea but the results of this study do not provide any evidence for this. In fact, the authors state: “the data also showed that there was no significant association between stage 1 group and stroke.”

Response: Thanks for your critical appraisal. I am sorry that I did not summarize the results as conclusion better. We have re-write the “Conclusion” in revised paper as follows: In conclusion, the 2017 ACC/AHA stage 2 hypertension definition significant increases the risk of stroke incidence, but this association was not observed between stage 1 hypertension and stroke incidence. Our study provides significant evidence of a link between the new guidelines' BP
categories and the risk of stroke incidence, and provides foundational data for future related studies, which are indispensable if application of the 2017 ACC/AHA hypertension guideline is to be considered in rural China even in China.

The grammar and language has several errors and is unclear in places. The authors should check throughout. For example: “Many studies have also reported that China is a major stroke country and a major hypertension country”/ May be better phrased as “China has one of the highest incidences of stroke worldwide” or something similar perhaps.

Response: Thanks for your comments. According to your suggestions, the English language of revised paper has been thoroughly edited and reviewed by a native English speaker. In addition, we have changed the sentence “Many studies have also reported that China is a major stroke country and a major hypertension country” to “China has one of the highest incidences of stroke worldwide” in the section of “Background” in revised paper. It is a grammar mistake, sorry.

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

Mingfeng Ma, MD, PhD

Liqiang Zheng, MD, PhD