Author’s response to reviews

Title: Prevalence and clinical profile of metabolic syndrome in longevity: study from Guangxi Zhuang Autonomous Region, China.

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Author’s response to reviews:
Dear Editor Danan Gu,

Thank you very much for your comments and suggestions.
We have studied the valuable comments from you, and tried our best to revise the manuscript. The point to point responds to the reviewer’s comments are listed as follows.
I would like to re-submit this revised manuscript to your prestigious journal “BMC Geriatrics”, and hope it is acceptable for publication in the journal.

Looking forward to hearing from you soon.

With kindest regards,
Yours sincerely,
Caiyou Hu,
Ze Yang
Response to Reviewer 1:

Major critiques

Question 1. The major problem of this study is cross sectional study.
Response: Thank you for your critical but constructive comment. We agree with the idea for this study that the major problem is cross sectional study. Our next step of the study was to carry out prospective studies on longevity and metabolic syndrome.

Introduction:

Question 2. Authors should describe more new concepts about this study in Introduction.
Response: Thank you for your constructive suggestion. We have rewritten the first and second paragraph of the introduction (see the revised version of page 4 and 5) to make the new concepts (nonagenarians, centenarians and metabolic syndrome) clear.

Materials and Methods:

Question 3. What kind of reason did this study participants consult for?
Response: Thank you for your constructive suggestion. We constructed the study within the framework of the “Longevity and Health of Aging Population in Guangxi China (LHAPGC)” (See the revised version of page 6).

Question 4. Did authors exclude chronic disease such as malnutrition, hepatic disease, and cancer et al., which could effect on various parameters? They must explain the categories of disease of those subjects.
Response: Thank you for your useful suggestion. We have added the above mentioned information to the Study Population part: All participants were examined by a neurologist and underwent extensive neuropsychological test as well as taking instrumental examination such as electrocardiogram and ultrasound examination. Individuals with longevity were excluded if they had chronic diseases such as malnutrition, hepatic disease, kidney disease and cancer. All controls were excluded from taking any drugs or history of cardiovascular diseases. (See the revised version of page 7).
Question 5. On the issue of recruitment, I did not see any mention of ethics/IRB review, approval, or exemption.
Response: Thank you for your kindly suggestion. We have mentioned the IRB review in the Study Population part: The study was conducted according to the principles expressed in the Declaration of Helsinki. The Ethics Committee of Beijing Hospital, Ministry of Health approved the study protocol. Written informed consent was obtained from each of the participants. (See the revised version of page 7).

Question 6. Authors should mention prevalence of antidyslipidemic, antihypertensive, and antidiabetic medication.
Response: Thank you for your constructive comment. We have added the information in Table 1 in the Results part of the manuscript (See the revised version of page 10).

Question 7. Authors should show the daily alcohol consumption and smoking status which could effect on lipids and hematological parameters.
Response: Thank you for your suggestion. We have supplemented the data in Table 1 in the Results part of the manuscript (See the revised version of page 10).

Question 8. Authors should mention prevalence of cardiovascular disease which was included in this study.
Response: Thank you for your advice. We have supplemented the data in Table 1 in the Results part of the manuscript (See the revised version of page 10).

Question 9. The author's policy for selection of confounding factors in the multivariate analysis is not well described.
Response: Thank you very much for the suggestion. We have added the explanation to the Prevalence of metabolic profile in longevity section at the revised version of page 15: Since numbers of male and female in longevity group are not equal, we compared the prevalence of clinical metabolic data among male and female participants. We are sorry that we did not make it clear before.
Question 10. Also in all analyses, parameters with non-normal distributions (e.g., FPG, TG, glucose) were used after log-transformation and then the data are shown as median (interquartile range).

Response: According to your comment, we have revised the data and they were shown as median (interquartile range) in Table 1. Thank you for your suggestion.

Question 11. Author should show LDL-cholesterol.

Response: Thank you for your precise suggestion. We have made statistics about LDL-cholesterol before. Considering that we discuss question about metabolic syndrome (obesity, raised blood pressure, raised triglycerides, lowered high-density lipoprotein cholesterol, and raised fasting glucose) in the manuscript, we thought it might be confusing if we show LDL-cholesterol. Statistic data about LDL-cholesterol was as follows: the serum LDL-C levels in longevity individuals were much higher than that of the controls in our population (P<0.001) (Table 1).

Table 1 Demographic and metabolic characteristics of the study samples between longevity and controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>longevity(N=307)</th>
<th>control(N=486)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>2.76(2.20-3.31)</td>
<td>2.26(1.91-2.51)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

(Median(INR))

Results

Question 12. Author should also describe medication

Response: Thank you for your comment. We have supplemented the data in Table 1 in the Results part of the manuscript (See the revised version of page 10).

Discussion

Question 13. Some limitations of this study must be considered. First, since some of the study population had several risk factors including hyperlipidemia, the authors could not eliminate the possible effect of underlying diseases and medications used for these diseases on the present
findings. Second, the prevalence of various lipid and hematological parameters is based on a single assessment of blood, which may introduce a misclassification bias. Further prospective population-based studies are needed to investigate the mechanisms in order to answer these questions.

Response: Thank for your valuable advice. The limitations mentioned above have been added to the last but one paragraph in the manuscript: However, our study has some limitations. Firstly, this was a cross-sectional study. Many variables were measured at a single time point and may be subject to conditions at the time of measurement. Since some of the study population had several risk factors including hyperlipidemia, we could not eliminate the possible effect of underlying diseases and medications used for these diseases. Secondly, the data came from a single region, which may limit generalizability. Thirdly, the sample size was not big enough in our study. Fourthly, the prevalence of various lipid and hematological parameters was based on a single assessment of blood, which may introduce a misclassification bias. Multicenter collaboration in prospective research of prevalence for MetS in longevity group is needed to address these questions (See the revised version of page 24).

Response to Reviewer 2:

Abstract:

Question 1. "Local healthy control" was used to refer to controls. If they really are healthy, it is not useful to use this control group. I suspect the controls are simply different in age with the study group.

Response: We thank the reviewer to raise the important issue. In the Study population part, we have supplemented the information as follows: The survey was conducted using a uniform standardized protocol. All participants were examined by a neurologist and underwent extensive neuropsychological test as well as taking instrumental examination such as electrocardiogram and ultrasound examination. Individuals with longevity were excluded if they had chronic disease such as malnutrition, hepatic disease, kidney disease and cancer. All controls were excluded from taking any drugs or history of cardiovascular diseases.
For further analyzing the question, we made statistics about the trend for frequency of metabolic abnormalities in two groups, which was described in the manuscript as follows: For further analyzing the trend of MetS, we researched the prevalence of having zero, one, two, three, four, and five MetS components in the two groups. Table 4 showed that compared with controls, long-lived individuals were more likely to have two or more components of MetS (for longevity: 36.2% and 28.0% respectively; for controls: 21.2% and 5.1% respectively; Prange<0.001), and less likely to have zero or one components of MetS (for longevity: 6.2% and 29.6% respectively; for controls: 32.1% and 41.6% respectively; Prange<0.001-0.020) (Table 4) (See the revised version of page 17).

Question 2. Clarify what "dyslipidemia" means. Isn't low-HDL part of it? This term was used in other sections of the paper as well. Need to clarify.
Response: Thank you for your advice. We have clarified the word “dyslipidemia” in the second paragraph of Introduction part as follows: Metabolic syndrome (MetS), a constellation of metabolic disorders including obesity, raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), and raised fasting glucose, may be of special interest because of the increased prevalence with age (See the revised version of page 5).

Introduction:

Question 3. There is interesting information in Introduction, however, as it is written now, it is confusing and hard to follow, and doesn't indicate how this study adds to the literature.
Response: Thank you for your positive and encouraging comment. We have revised the Introduction part according to your suggestion as follows:

Introduction

Individuals who live the longest are of broad interest to researchers in recent years. In 2010, there were 1,948,286 nonagenarians (people aged 90-99) and 35,934 centenarians (people aged 100 and more) in China[1]. As the population of China aging, the number of people aged 90 or more is expected to grow. Since persons who live into their 90s and over 100 are a testament to longevity, studies about their unique characteristics will expand our knowledge on how to extend life expectancy.
Metabolic syndrome (MetS), a constellation of metabolic disorders including obesity, raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), and raised fasting glucose, may be of special interest because of the increased prevalence with age [2, 3]. Studies about longevity population also revealed different types of metabolic disturbances [4-10], but that the results varied across different countries and ethnics. Study from Croatia suggesting that nonagenarians and centenarians had lower prevalence of overweight, obesity and lower blood pressure [4]. Instead, centenarians from Poland showed that mildly elevated blood pressure is a marker for better health status [5]. Recent study of familial longevity from China revealed decreased diastolic blood pressure but increased systolic blood pressure in centenarians [6]. Similar discrepancy can also be found among studies of lipid profile and longevity. Biological study for longevity demonstrated that centenarians and their offspring have significantly larger high-density lipoprotein (HDL) levels and particle sizes and low-density lipoprotein (LDL) levels compared with controls [7, 8]. However, other studies did not find significant association of HDL-C levels with centenarians [9,10].

All of these studies indicated that individuals with longevity might have different metabolic phenotypes from those general individuals under different ethnic background. But no reports on these metabolic items research integrated were seen now yet. Furthermore, the prevalence of MetS increased in Chinese population aged 60-95 [11]. Thus we perform the study to investigate the prevalence and clinical profile of MetS in longevity in Guangxi Zhuang Autonomous Region, China. (See the revised version of page 4-6).

Question 4. It might worth mentioning the population as it is one of the longest live populations in the world.
Response: Thank you for your constructive suggestion. We have added information of longevity population in the first paragraph of the revised manuscript: In 2010, there were 1,948,286 nonagenarians (people aged 90-99) and 35,934 centenarians (people aged 100 and more) in China [1] (See the revised version of page 4).
Methods:

Question 5. Need to separate the definition of metabolic syndrome from waist measurement and BMI. Response: According to your comment, we have separated the definition of metabolic syndrome from waist measurement and BMI.

Question 6. The word "expiration" just before "Laboratory measurements" needs to be clarified, replaced, or removed. Response: Thank you for your careful work. We have removed the word “expiration” in the revised manuscript.

Question 7. Why is genomic DNA mentioned? Is it ever used in the paper? Response: We are sorry for this mistake. We have removed this sentence from the manuscript.

Results:

Question 8. Suggest re-structure Tables 1, 3, 4 to make clear what each row/column is. Add units to where is applicable in tables. Response: Thank you for your constructive advice. We have revised Table 1, Table 3 and Table 4. We hope it is acceptable in the revised version (See the revised version of page 10 for Table 1, page 16 for Table 4 and supplementary data for Table 3).

Question 9. Table 1 results, TG was different between groups, but was not mentioned in the text. This result is quite interesting, but was not discussed anywhere in the paper. Response: Thank you for your advice. We are sorry for the mistake. This data has been supplemented to the “Demographic and metabolic characteristics in two groups” section: Generally, subjects in the long-lived individuals cohort had significantly lower levels of height, body mass index (BMI), weight, waist circumference (WC), and TG than controls (Prange<.001-0.002) (See the revised version of page 10). In the discussion part, we mentioned that TG was a marker for longevity population as follows: Another possible explanation is that MetS components are associated with better health status among the oldest old [5,7,24]. Specifically, low prevalence of highTG might contribute a lot to
longevity in our study, as low TG level has been identified as a marker for human longevity [24,25] (See the revised version of page 23).

Question 10. When data are stratified by gender/age, data are presented very confusing, in the text and in tables. How was age used to stratify data?
Response: Thank you for your constructive suggestion. We are sorry it is confusing. We have revised the data in the text and in tables. We have deleted the part of data stratified by age. Data was stratified by gender in the revised manuscript (See the revised version of page 16 for Table 4 and supplementary data for Table 3).

Question 11. should add analysis to compare the study group with controls with adjustment for age and sex.
Response: Thank you for the important question. We revised the associated information in the Statistical analysis part of the manuscript as follows: Age- and sex- adjusted were applied according to the 2010 population census of the people's republic of China from National Bureau of Statistics [1] (See the revised version of page 9).

Discussion
Question 12. Why is women having longer life expectancy than men a reason for women having higher prevalence of metabolic syndrome? The discussion regarding menopause needs reconsideration.
Response: Thank you for your suggestions. Indeed, the explanation for that women having longer life expectancy than men a reason for women having higher prevalence of metabolic syndrome was not suitable. We have revised this part as follows: It is interesting that women had higher prevalence rates of MetS compared with men. According to the National Bureau of Statistics of China, the female/male ratio of longevity population were 2.02:1 (648,588 male nonagenarians, 1,299,698 female nonagenarians, 8852 male centenarians and 27082 female centenarians in 2010) [1]. In our study, females also occupied a larger proportion (female/male: 2.79/1) in the longevity population. Thus, this group may be more representative of an ordinary group for longevious people, and they may be more sensitive to the risk factors from MetS than
men. More research is needed to determine sex differences between men and women among the oldest old (See the revised version of page 21).

The discussion regarding menopause has been revised as shown below: In addition, women who become postmenopausal had a significantly increased visceral abdominal fat [18, 19], accompanied by insulin resistance and hypertriglyceridemia, ultimately meeting the diagnosis of metabolic syndrome[20]. However, for females aged 90+ years and for who had menopause for more than 40 years, it is hard to say hormonal regulation had an effect on their metabolic state. Additional consideration is required for sex differences between men and women among the oldest old (See the revised version of page 20-21).

Question 13.The discussion regarding population differences relating to hormonal regulation is hard to believe.
Response: Thank you for your excellent suggestion. The discussion regarding population differences relating to hormonal regulation has been revised as follows: The difference among different countries may be due to different ethnics and sample size. Multicenter Collaboration across different countries is needed to address the question (See the revised version of page 22).

Question 14. The discussion "metabolic syndrome was a protective factor" needs more evidence to support.
Response: Thank you for your suggestion very much. The discussion "metabolic syndrome was a protective factor" has been revised as follows: Thus, it seemed that MetS was not a risk factor for the oldest old. However, it is well established that MetS is strongly related to increased incidence of cardiovascular events in people aged 60-95 [11,23] (See the revised version of page 23).

Question 15. No data need to be repeated in discussion.
Response: Thank you for your advice very much. We have deleted the repeated data in the Discussion part.