

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Interaction of lipid accumulation product and family history of hypertension on hypertension risk: A cross-sectional study in the Southern Chinese population
AUTHORS	Huang, junxuan; Bao, XinYu; Xie, yixian; Zhang, xiaoxia; Peng, xin; Liu, yan; Cheng, mengjiao; Ma, JinXiang; wang, peixi

VERSION 1 – REVIEW

REVIEWER	Dr. Martín-Hidalgo A Hospital Universitario Ramón y Cajal. Madrid. Spain.
REVIEW RETURNED	24-Jan-2019

GENERAL COMMENTS	<p>Reviewer 1. COMMENTS TO THE AUTHORS:</p> <p>Brief Summary: In response to the established association between obesity, especially visceral fat, and family history of hypertension could contribute to hypertension, Huang Junxuan et al. present data from a cross-sectional study in the Southern Chinese population to investigate potentially applicability of lipid accumulation product (LAP) as an indicator on the hypertension risk and its comparison with other obesity indicators on hypertension risk as BMI, WC or WHC; and the interactive effects of LAP and family history of hypertension. Their findings indicate that while in females, high LAP levels had relatively higher risk of hypertension and LAP was a better indicator in indentifying hypertension risk than BMI and WHR; in males, BMI was a better indicator of hypertension risk than LAP. However, the results of this study showed a significant interaction between LAP and family history of hypertension in males but not in females.</p> <p>Opinion: Overall, the results from this study are novel and robust. The authors make a strong case for the association between obesity, especially visceral fat (LAP) and risk of hypertension in females, and family history of hypertension in males. The study does suffer from a small sample size, but this work could spark future research in larger, more diverse populations. I feel this manuscript ranks with a medium level of priority for publication.</p> <p>Recommendation: Given the novelty of these findings and the generation of future research into the effect of visceral obesity measured by LAP on hypertension risk, I recommend that this manuscript be published following revisions.</p>
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	<p>General Comments:</p> <p>A- The clarity of this manuscript is somewhat hindered by issues with language. I have addressed some of the more outstanding examples of this in the specific comments below, but it would be helpful if the authors could review the manuscript as a whole to tighten up the English.</p> <p>B- I have no criticism of the methods or experiments as conducted for this manuscript, but have included a few recommendations or questions in my specific comments that I feel will strengthen the validity of the data and conclusions.</p> <p>Specific Comments:</p> <ol style="list-style-type: none"> 1. To try to understand the differences found in the present study between males and females in the role of LAP as a risk factor of hypertension and familial hypertension; the authors should mention in the conclusion that the differences in the fat distribution between males and females could contribute to explain the differences found between both sexes. 2. In the first sentence of the Introduction paragraph (Line 2), the reference 1 is a study that shows data relating hypertension and cardiovascular risk in a population from China. However, the references 2 and 3 are referred to the world population. Please, change the order, and mention in the first sentence (line 2) the references 2 and 3; and the reference 1 in line 6, when you are written about "hypertension in China". 3. Lines 15-19, page 8: Is the comment noting "Statistically significant differences in age ($P < 0.001$)... and family history of hypertension ($P = 0.005$) were observed between normotension, prehypertension, and hypertension groups". Thus they show that in the hypertension group the media of age is significantly higher than in normotension group. The author should discussed the effect of age and aging in hypertension, 4. Page 10, line 6. Recommend change of "development of the economy" to "development of the economy and sedentary lifestyle". 5. Page 11, line 3. . Recommend change of "dichotomus" to "discontinuous". 6. Page 11, line 5. Add "the" after "based on". 7. Page 11, line 16. Recommend change of "this" by "the"; and "with those in studies by " by " the study of ...". 8. Page 12, line 1. Recommend change of "the" by "this". 9. Page 12, lines 11-12: Is the comment noting "In fact, cardiovascular events occur at a lower rate in females than in males. In our study, the feminine participants who suffered both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in male". I recommend including here that these results are in young and fertile females (36-49 years old). Probably these results change in
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	menopause females (50-60 years old), when they females have lower estrogens and higher androgens . You should comment this point in the discussion. 10. Recommend change of the size of the Figure 1 and Figure 2. Please, amplify the size to read the legend of the different groups.
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REVIEWER	Farhad Hosseinpanah Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	18-May-2019

GENERAL COMMENTS	<p>Comments:</p> <p>Thank you for giving me the opportunity to review this interesting topic. This manuscript presents a cross-sectional study of 2079 community-dwelling adults in Southern China, aimed to compare the applicability of lipid accumulation product (LAP) index with two older obesity indices, BMI and waist-to-hip ratio (WHR), for detection of hypertension in a sex-stratified analysis. Then, the investigators evaluated the interaction of LAP with family history of LAP in both genders. In this study, LAP performed better than BMI and WHR for detection of hypertension in the Southern China female population; while BMI was the superior index in males. On the other hand, LAP had synergism with family history of hypertension in males but not in females.</p> <p>Since the association of LAP with systolic and diastolic blood pressure, and prehypertension in has been previously reported in a number of studies from China, I do first question the need and impact of restatement of this association in southern China. The authors have addressed differences in levels of LAP (possibly triglycerides and waist circumference) and the prevalence of HTN in different parts of China, which is attributed to climate, environmental and lifestyle changes across different regions. First of all, valid reference(s) should be added to provide such differences. Even if this is the case, it still does not support the real need to do similar analyses.</p> <p>The following are also some suggestions and corrections.</p> <p>Major concerns:</p> <ol style="list-style-type: none"> 1) Was this study conducted in the framework of a larger study? If so, reference(s) should be added. 2) The authors must provide more details about the time and the location in which the multistage random sampling took place, and should elucidate if the study population was representative of the southern China. 3) In order to prevent selection bias, the authors have to compare the available characteristics of the excluded participants with that of included participants. 4) The definitions of different categories of physical activity are unclear. The authors should include references regarding validity and reliability of the questionnaire used in the assessment and categorization of physical activity. 5) Since the analyses of this study demonstrate significant differences in males and females, authors are encouraged to reanalyze the baseline characteristics separately among each gender; or devote a separate table to compare the baseline characteristics between males and females. 6) Similarly, it is needed to provide analyzes for the comparing SBP and DBP across LAP quartiles (Table 3) and the association
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	<p>of LAP quartiles with hypertension status (Table 4), separately for males and females.</p> <p>7) I am wondering if ROC curve analysis for waist circumference would be added.</p> <p>8) The discussion does not adequately support and does not provide strong interpretation the study findings and has to be significantly revised. Moreover, discussion is more than half devoted to background information and includes a cluster of redundant sentences.</p> <p>9) The explanation of the main study finding according to differences in fat distribution between males and females is not correct. This section must be revised and rewritten.</p> <p>10) Finally, it is unclear why this study findings are different from the previous reports from other regions of China: https://www.ncbi.nlm.nih.gov/pubmed/29478365 https://www.ncbi.nlm.nih.gov/pubmed/29874254 https://www.ncbi.nlm.nih.gov/pubmed/24306160 https://www.ncbi.nlm.nih.gov/pubmed/30219041</p> <p>From the above mentioned studies, three has shown superiority of LAP over BMI for detection of hypertension and prehypertension in both genders; and one study has shown superiority of LAP over BMI for hypertension only in males. One study has also shown significant interaction between LAP and family history of hypertension in both males and females. The authors should provide clear interpretation about the inconsistencies in their results with previous reports from China.</p> <p>Minor concerns:</p> <p>1) The statement “LAP can be used to distinguish visceral fat from subcutaneous fat” should be revised in different parts of the manuscript. Please note that LAP does not distinguish between subcutaneous and visceral fat, and is just surrogate index for prediction of both subcutaneous and visceral fat metabolism, and thus that can outperform older obesity indexes.</p> <p>2) Page 5 Line 11: Please revise the primary purpose and mention the secondary purpose of the study.</p> <p>3) Please revise the times and the durations in the definition of different physical activity categories.</p> <p>4) The LAP formula in reference 20 has been extracted local males and females of Beijing, and is not applied in the current study. Please mention why this study was cited; otherwise this citation is better being removed.</p> <p>5) Table 1 is better to be omitted due to repetition of data provided in the text.</p> <p>6) Page 8 Line 20: Please revise the sentence, considering that plasma glucose, total cholesterol, SBP and DBP are not anthropometric measures.</p> <p>7) Page 9 Line 13: Change “participants with the fourth LAP quartile” to “participants in the third and fourth LAP quartiles”.</p> <p>8) Page 12 Line 1: In study reference 21, the superiority of LAP over BMI among Mongolian males is suggested to be a result of high TG; please indicate TG levels separately in males and females to confirm this statement.</p> <p>9) Page 12 Line 13: Change feminine to females.</p> <p>10) Page 12 Line 13: Please change the word “suffered”.</p> <p>11) Page 12 Line 15: Explaining the main study finding by a “sampling error” is not acceptable. This section must be revised and rewritten.</p> <p>12) Page 12 Line 6: The first sentence in the conclusion is not supported by the results from this study.</p>
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	13) Page 13 Line 11: Please omit the word “and”; and break the sentence into two statements.
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REVIEWER	Arrigo F.G. Cicero University of Bologna, Italy
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	I've read with attention the paper by Huang et al. that is potentially of interest The methodology applied is overall correct, the results are reliable and adequately discussed. It should however been stressed among limitation the lack of adjustment for renal function, and other risk factors for hypoertension (such as serum uric acid). Moreover, previous link between LAP and arterial stiffness and metabolic syndrome should be cited (Eur J Intern Med. 2018 Jul;53:29-33. Metab Syndr Relat Disord. 2013 Dec;11(6):412-6.)
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REVIEWER	Francesco Paneni University of Zurich, Switzerland
REVIEW RETURNED	22-Jun-2019

GENERAL COMMENTS	<p>Lipid accumulation product (LAP) is emerging as a potential biomarker of cardiovascular risk in cardiometabolic patients. The preset study aims to investigate whether LAP may help in predicting hypertension risk in a cohort of Chinese men and women. Although the study is timely, there remain important issues to be addressed before proceeding further.</p> <p>I have the following comments:</p> <ul style="list-style-type: none"> - The findings that LAP independently associates with hypertension are somehow expected given the strong association of WC and TG with blood pressure. The authors found that LAP may represent a potential indicator of hypertension risk in females, however they failed to confirm this in men, where BMI remained the strongest predictor. How do the authors explain the high performance of BMI among males? - The aim of this study was to investigate the potential use of LAP as a putative indicator of hypertension risk. However, to answer this question the authors should have employed a different study where baseline LAP values were correlated to BP values overtime. Unfortunately, this could not be done here given the retrospective nature of the investigation. Please comment. - The difference in triglyceride levels among the 3 groups (normotensive, prehypertensive, hypertensive) is impressive. What is the predictive value of TG as compared with LAP? WC alone vs. LAP should be also tested. - LAP needs to be better defined in the abstract, this might not be clear to the reader.
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Opinion to Author:

Overall, the results from this study are novel and robust. The authors make a strong case for the association between obesity, especially visceral fat (LAP) and risk of hypertension in females, and family history of hypertension in males. The study does suffer from a small sample size, but this work could spark future research in larger, more diverse populations. I feel this manuscript ranks with a medium level of priority for publication.

Re: Thank you very much for your appreciation and kind advice. We will conduct a larger sample size studies in future studies on these findings.

General Comments to Author:

A- The clarity of this manuscript is somewhat hindered by issues with language. I have addressed some of the more outstanding examples of this in the specific comments below, but it would be helpful if the authors could review the manuscript as a whole to tighten up the English.

RE A-: Thank you for your valuable advice. We have made correction point-by-point according to your suggestion.

B- I have no criticism of the methods or experiments as conducted for this manuscript, but have included a few recommendations or questions in my specific comments that I feel will strengthen the validity of the data and conclusions.

RE B-: Thank you very much for your meticulous work to help us improve the manuscript!

Specific Comments to Author

1. To try to understand the differences found in the present study between males and females in the role of LAP as a risk factor of hypertension and familial hypertension;

the authors should mention in the conclusion that the differences in the fat distribution between males and females could contribute to explain the differences found between both sexes.

Re 1: Thank you very much for your careful work. We have rewritten and revised the explain of the role of LAP as a risk factor of hypertension and familial hypertension between males and females according to the reviewers' comments. (page-12, line-27)

2. In the first sentence of the Introduction paragraph (Line 2), the reference 1 is a study that shows data relating hypertension and cardiovascular risk in a population from China. However, the references 2 and 3 are referred to the world population. Please, change the order, and mention in the first sentence (line 2) the references 2 and 3; and the reference 1 in line 6, when you are written about "hypertension in China".

Re 2: Thank you for your careful work and kind advice. We have changed the sequence according to your comment. (page-4, line-6)

3. Lines 15-19, page 8: Is the comment noting “Statistically significant differences in age ($P < 0.001$)... and family history of hypertension ($P = 0.005$) were observed between normotension, prehypertension, and hypertension groups”. Thus they show that in the hypertension group the media of age is significantly higher than in normotension group. The author should discussed the effect of age and aging in hypertension.

Re 3: We have added the effect of age and aging in hypertension in the discussion.

As follow :

Advancing age is associated with a progressive increase in systolic BP levels and with development and progression of arterial hypertension because of a number of factors, including atherosclerotic changes, large artery stiffening, altered renal function, and arterial baroreflex impairment. That is to say, increase in blood pressure was thought to be an unavoidable consequence of aging. (page-12, line-27)

4. Page 10, line 6. Recommend change of “development of the economy” to “development of the economy and sedentary lifestyle”.

Re 4: We have made correction according to your recommendation. (page-11, line-3)

5. Page 11, line 3. Recommend change of “dichotomus” to “discontinuous”.

Re 5: We have changed “dichotomus” to “discontinuous” according to your recommendation. (page-11, line-26)

6. Page 11, line 5. Add “the” after “based on”.

Re 6: Thank you for your meticulous work. We have added “the” after “based on”. (page-11, line-28)

7. Page 11, line 16. Recommend change of “this” by “the”; and “with those in studies by “ by “ the study of ...”.

Re 7: Thank you for your valuable advice and meticulous work to help us improve the manuscript! We have revised the language of the manuscript carefully according to your kind advice. (page-12, line-11)

8. Page 12, line 1. Recommend change of “the” by “this”.

Re 8: We have made correction according to your recommendation. (page-12, line-21)

9. Page 12, lines 11-12: Is the comment noting “In fact, cardiovascular events occur at a lower rate in females than in males. In our study, the feminine participants who suffered both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in male”. I recommend including here that these results are in young and fertile females (36-49 years old). Probably these results change in menopause females (50-60 years old), when they females have lower estrogens and higher androgens . You should comment this point in the discussion.

Re 9: Thank you for your careful work and kind advice. It is really true as your suggestion that females does have lower estrogens and higher androgens in menopausal status. The relative importance of androgens to female health, especially during reproductive years and menopause, has been a matter of controversy.

However, a 9-year follow-up study conducted by F. Ramezani Tehrani finds that based on menopausal status, there are no significant differences in cardiovascular events after adjustment for age, body mass index and other confounders.⁴⁵ In our study, we have adjusted age, BMI, marital status, educational level, physical activity and so on. So it may be argued that the prevalence rates of hypertension is at a lower rate in females than in male no matter premenopausal status or menopausal status.

45. Ramezani TF, Behboudi-Gandevani S, Ghanbarian A, et al. Effect of menopause on cardiovascular disease and its risk factors: a 9-year follow-up study. *Climacteric*. 2014 Apr;17(2):164-72. doi: 10.3109/13697137.2013.828197.

10. Recommend change of the size of the Figure 1 and Figure 2. Please, amplify the size to read the legend of the different groups.

Re 10: Thank you very much for your kind reminder! The size of legend has been amplified according to your suggestion.

Finally, thank you again for your appreciation and kind advice. Your valuable suggestions are very helpful for modifying this article.

reviewer #2

Comments to the Author

- Thank you for giving me the opportunity to review this interesting topic. This manuscript presents a cross-sectional study of 2079 community-dwelling adults in Southern China, aimed to compare the applicability of lipid accumulation product (LAP) index with two older obesity indices, BMI and waist-to-hip ratio (WHR), for detection of hypertension in a sex-stratified analysis. Then, the investigators evaluated the interaction of LAP with family history of LAP in both genders. In this study, LAP performed better than BMI and WHR for detection of hypertension in the Southern China female population; while BMI was the superior index in males. On the other hand, LAP had synergism with family history of hypertension in males but not in females. Since the association of LAP with systolic and diastolic blood

pressure, and prehypertension in has been previously reported in a number of studies from China, I do first question the need and impact of restatement of this association in southern China. The authors have addressed differences in levels of LAP (possibly triglycerides and waist circumference) and the prevalence of HTN in different parts of China, which is attributed to climate, environmental and lifestyle changes across different regions. First of all, valid reference(s) should be added to provide such differences. Even if this is the case, it still does not support the real need to do similar analyses.

Re : Thank you for your meticulous work and thoughtful question. We have added more valid literature to demonstrate the differences between South and North China.

With a vast territory, China has tremendous difference between South and North. Due to the geographical environment and dietary habits that have formed throughout its long history, there are some dietary and cultural differences between Northern and Southern China.²⁴ The Northern region shows a high intake of wheat, tubers and liquor, etc. While southerner has a high intake of rice, vegetables, meat, poultry, fish etc.²⁴ The Carbohydrate-rich pattern of the northern region is associated with a high risk of hypertriglyceridemia and higher BMI. Studies have found that the northerners were heavier and had higher triglycerides level than southerners.^{25,26} Meanwhile, significant differences are found in SBP/DBP between southern Chinese and northern Chinese due to different climate and dietary habit between southern and northern.²⁷ LAP depends on TG and waist circumference. Differences in dietary habits, or lifestyle, individuals from different regions should lead to different LAP. LAP has a different situation in the north and south. Thus, the applicability of LAP in predicting hypertension in Southern China is worth studying. (page-5, line-1)

We have added references as follow:

24. Song F , Cho M S . Geography of Food Consumption Patterns between South and

North China. *Foods* 2017;6(5). doi:10.3390/foods6050034.

25. Huang Z , Wu X , Stamler J , et al. A north-south comparison of blood pressure and factors related to blood pressure in the People's Republic of China: a report

from the PRC-USA Collaborative Study of Cardiovascular Epidemiology. *Journal of Hypertension* 1994; 12(9):1103-12.

26. Wu Z , Yao C , Zhao D , et al. Cardiovascular disease risk factor levels and their relations to CVD rates in China--results of Sino-MONICA project. *European Journal of Cardiovascular Prevention & Rehabilitation* 2004; 11(4):275-283.

27. Zhao L, Stamler J, Yan L L, et al. Blood Pressure Differences Between Northern and Southern Chinese: Role of Dietary Factors The International Study on Macronutrients and Blood Pressure. *Hypertension* 2004, 43(6):1332-1337.

Major concerns to the Author:

1. Was this study conducted in the framework of a larger study? If so, reference(s) should be added.

Re 1: This study was conducted in the framework of a larger study named Chronic disease risk factor assessment. But this study is the first one to publish, so we are so sorry we can't provide relevant reference.

2. The authors must provide more details about the time and the location in which the multistage random sampling took place, and should elucidate if the study population was representative of the southern China.

Re 2.1: Thank you for your suggestion. We have revised our manuscript according to your advice.

As follow: A cross-sectional survey based on community health was conducted in the FoShan city of Guangdong province in the Southern China. Recruiting the enrollers took place in March 2017. The study samples were selected by a multistage and stratified random sampling method. The stratification according to the economic level and randomly selected street communities at economic levels, then randomly selected communities in street communities according to proportion. Communities residents were then randomly selected from the household lists. (page-6, line-1)

Re 2.2: Thank you for your thoughtful question. Our study had been conducted in a large scale population city in southern China. And the study samples were selected by a multistage and stratified random sampling method. It might partly represent the general population in the Southern China, meanwhile it can provide valuable knowledge of LAP on Southern China population. We also realize that, as your comment, our study population is still not adequately representative of the southern China. Therefore, we have supplemented in the limitations of this manuscript that the study population cannot fully represent the southern China region.

3. In order to prevent selection bias, the authors have to compare the available characteristics of the excluded participants with that of included participants.

Re 3: Thank you for your valuable advice. We have compared the basic characteristics of the excluded participants with that of included participants. There are no statistically significant differences in age ($Z=-1.168$, $P=0.243>0.05$) and sex ($\chi^2 =2.078$, $P=0.149>0.05$) between excluded participants and included participants.

4. The definitions of different categories of physical activity are unclear. The authors should include references regarding validity and reliability of the questionnaire used in the assessment and categorization of physical activity.

Re 4: We have corrected the definitions of physical activity more clearly according to the reference. (Assessment of sedentary behavior with the international physical activity questionnaire. *J Phys Act Health*. 2008;5:S30–44.)

The statement “Physical activities were divided into “seldom or never,” “moderate,” and “high.” Participants with “high” were defined as those who exercised for more than 30 minutes each time, more than 6 times per week.” to “Physical activities were divided into ‘insufficiently active’ and ‘sufficiently active.’ Participants with ‘insufficiently active’ were defined as those who performed activity less than 150min/week. Participants with ‘sufficiently active’ were defined as those who exercised more than 150min/week.” (page-6, line-22)

5. Since the analyses of this study demonstrate significant differences in males and females, authors are encouraged to reanalyze the baseline characteristics separately among each gender; or devote a separate table to compare the baseline characteristics between males and females.

Re 5: Considering the reviewer's suggestion, we have added a new table to the supplementary material

according to your advice.

6. Similarly, it is needed to provide analyzes for the comparing SBP and DBP across LAP quartiles (Table 3) and the association of LAP quartiles with hypertension status (Table 4), separately for males and females.

Re 6: We have revised Tables in our manuscript according to your advice. (page-22, line-4)

7. I am wondering if ROC curve analysis for waist circumference would be added.

Re 7: Thank you for your suggestion. We have added waist circumference in ROC curve analysis. (page-23, line-1)

8. The discussion does not adequately support and does not provide strong interpretation the study findings and has to be significantly revised. Moreover, discussion is more than half devoted to background information and includes a cluster of redundant sentences.

Re 8: Thank you every much for your careful work. We have revised the discussion according to your comments. And deleted the redundant sentences. We have deleted " Nowadays, the prevalence of obesity has increased by 13% in urban areas and by 85% in rural areas in China, and more attention should thus be paid to this issue. " and we also have deleted the sentence " In this present study, we also found that LAP was a better indicator than BMI, WHR and TG for identifying the risk of hypertension in female. Because women are more likely to accumulate adipose tissue around the hips and thighs, we can easily understand why LAP is superior to BMI in identifying the risk of hypertension in females. "

9. The explanation of the main study finding according to differences in fat distribution between males and females is not correct. This section must be revised and rewritten.

Re 9: We are very sorry for our incorrect explanation. The statements of " Because women are more likely to accumulate adipose tissue around the hips and thighs, we can easily understand why LAP is superior to BMI in identifying the risk of hypertension in females. " were corrected as " According to Kahn's study, LAP was greater at older age or remained unchanged for women, while for men, the annual LAP changes were reduced at older age. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. " (page-12, line-26)

10. Finally, it is unclear why this study findings are different from the previous reports from other regions of China:

<https://www.ncbi.nlm.nih.gov/pubmed/29478365>

<https://www.ncbi.nlm.nih.gov/pubmed/29874254>

<https://www.ncbi.nlm.nih.gov/pubmed/24306160>

<https://www.ncbi.nlm.nih.gov/pubmed/30219041>

From the above mentioned studies, three has shown superiority of LAP over BMI for detection of hypertension and prehypertension in both genders; and one study has shown superiority of LAP over BMI for hypertension only in males. One study has also shown significant interaction between LAP and family history of hypertension in both males and females. The authors should provide clear interpretation about the inconsistencies in their results with previous reports from China.

Re 10: Thank you for your careful work. As the reviewer mentioned, three study has shown the superiority of LAP over BMI for detection of hypertension and prehypertension in both genders. However, our study shows that LAP perform better than BMI in female. According to Kahn's study, the annual LAP changes were reduced at older age in male. Thus, the superiority of LAP for predicting hypertension in male may be disturbed by the larger-scale proportion of elder man (23.7%) in our study. The study of Gao, Xin has shown superiority of LAP over BMI for hypertension only in Mongolians males. This finding of Gao Xin may be due to the apparently lower prevalence of high TG in female Mongolians than in male Mongolians (13.20% vs 23.10% , $P < 0.05$), and the facts might disturb the association between LAP and hypertension in female Mongolians. Moreover, the study of Song Jian has shown significant interaction between LAP and family history of hypertension in both males and females. While the interaction analysis in our study indicates the synergistic effect of LAP and family history on the hypertension risk in males, but no statistically significant differences in the interaction effect in females. In our study, the female participants who had both LAP and family history of hypertension were rarely observed and the prevalence rates of hypertension at a lower rate in females than in males. Our study suffer from a small sample size, especially in females. The fewer positive female observers which had higher LAP and family history of hypertension lead to no statistically significant differences in the interaction effect on the hypertension risk in females. The interaction in female was not statistically significant, but their synergistic effect was obvious. (page-12, line-24)

Minor concerns to Author:

1. The statement "LAP can be used to distinguish visceral fat from subcutaneous fat" should be revised in different parts of the manuscript. Please note that LAP does not distinguish between subcutaneous and visceral fat, and is just surrogate index for prediction of both subcutaneous and visceral fat metabolism, and thus that can outperform older obesity indexes.

Re 1: Thank you very much for your kind advice! We have revised in different parts of the manuscript according to your suggestion.

2. Page 5 Line 11: Please revise the primary purpose and mention the secondary purpose of the study.

Re 2: Thank you for your careful work. We have revised this part. (page-5, line-23)

3. Please revise the times and the durations in the definition of different physical activity categories.

Re 3: We have revised the definitions of different physical activity categories according to the reference (Assessment of sedentary behavior with the international physical activity questionnaire. J Phys Act Health. 2008;5:S30–44.). (page-6, line-22)

4. The LAP formula in reference 20 has been extracted local males and females of Beijing, and is not applied in the current study. Please mention why this study was cited; otherwise this citation is better being removed.

Re 4: Thank you for your careful work. The reference 20 is cited to show that Beijing is one of the region in northern China which conducted LAP study. The purpose of citing reference 20 is not to use the LAP's formula of Beijing.

As follow:

A few national studies have investigated the association between LAP and hypertension in China, and all of them were conducted in northern China, including Bengbu, Beijing, and Inner Mongolia.

5. Table 1 is better to be omitted due to repetition of data provided in the text.

Re 5: Thank you for your valuable advice. We have deleted the Table 1.

6. Page 8 Line 20: Please revise the sentence, considering that plasma glucose, total cholesterol, SBP and DBP are not anthropometric measures.

Re 6: Thank you for your suggestion. We have made correction as your suggestion. The statements of " Anthropometric measurements found significant differences in BMI ($P < 0.001$), WHR ($P < 0.001$), LAP ($P < 0.001$), fasting plasma glucose ($P < 0.001$), total cholesterol ($P < 0.001$), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups " were corrected as " Anthropometric measurements found significant differences in BMI ($P < 0.001$), WHR ($P < 0.001$), LAP ($P < 0.001$) between the groups. And significant differences found in laboratory examinations including fasting plasma glucose ($P < 0.001$), total cholesterol ($P < 0.001$), SBP ($P < 0.001$), and DBP ($P < 0.001$) between the groups " (page-9, line-11)

7. Page 9 Line 13: Change "participants with the fourth LAP quartile" to "participants in the third and fourth LAP quartiles".

Re 7: We have changed "participants with the fourth LAP quartile" to "participants in the third and fourth LAP quartiles". (page-9, line-21)

8. Page 12 Line 1: In study reference 21, the superiority of LAP over BMI among Mongolian males is suggested to be a result of high TG; please indicate TG levels separately in males and females to confirm this statement.

Re 8: We have added the TG levels separately in males and females in our manuscript. (page-12, line-22)

9. Page 12 Line 13: Change feminine to females.

Re 9: The statement of "feminine" were corrected as "female". (page-13, line-9)

10. Page 12 Line 13: Please change the word “suffered”.

Re 10: Thank you for your careful work. We have revised as your suggestion.

11. Page 12 Line 15: Explaining the main study finding by a “sampling error” is not acceptable. This section must be revised and rewritten.

Re 11: We have revised this part. The statements of " Fewer positive observers in female might be due to sampling error, but might disturb the interaction effect between LAP and family history of hypertension on the hypertension risk in females. " were corrected as " Our study suffer from a small sample size, especially in females. The fewer positive female observers which had higher LAP and family history of hypertension lead to no statistically significant differences in the interaction effect on the hypertension risk in females. " (page-13, line-19)

12. Page 12 Line 6: The first sentence in the conclusion is not supported by the results from this study.

Re 12: Considering the Review’s suggestion, the first sentence “LAP can be used to distinguish visceral fat from subcutaneous fat in the Southern Chinese population. ” was deleted.

13. Page 13 Line 11: Please omit the word “and”; and break the sentence into two statements.

Re 13: The statements of “The synergistic effect of LAP and family history of hypertension was demonstrated in males, and further studies are needed to investigate the interactive effects between LAP and family history of hypertension in females.” were corrected as “The synergistic effect of LAP and family history of hypertension was demonstrated.”. (page-14, line-16)

Finally, thank you again for your meticulous work. Your valuable suggestions are very helpful for modifying this article.

reviewer #3

Comments to the Author

I've read with attention the paper by Huang et al. that is potentially of interest The methodology applied is overall correct, the results are reliable and adequately discussed. It should however been stressed among limitation the lack of adjustment for renal function, and other risk factors for hypertension (such as serum uric acid). Moreover, previous link between LAP and arterial stiffness and metabolic syndrome should be cited (Eur J Intern Med. 2018 Jul;53:29-33. Metab Syndr Relat Disord. 2013 Dec;11(6):412-6.)

Re1: Thank you very much for your appreciation and suggestion. We will continue to work hard. Because our study is conducted in the general population, but not in patients with hypertension. We are sorry for our negligence of considering the adjustment for renal function, and other risk factors for hypertension (such as serum uric acid) in our study. We have supplemented in the limitations of this manuscript that the study.

Re2: Thank you very much for your kind advice. We have cited the references into our manuscript

according to your suggestion.

Finally, thank you again for your meticulous work. Your valuable suggestions are very helpful for modifying this article.

reviewer #4

Comments to the Author

- The findings that LAP independently associates with hypertension are somehow expected given the strong association of WC and TG with blood pressure. The authors found that LAP may represent a potential indicator of hypertension risk in females, however they failed to confirm this in men, where BMI remained the strongest predictor. How do the authors explain the high performance of BMI among males?

Re: BMI calculation is dependent on height and weight. Since people in southern region is associated with shorter height than the northern Chinese, the southern people with higher weight are more likely to be identified by BMI. Moreover, LAP was greater at older age or remained unchanged for women, while for men, the annual LAP changes were reduced at older age due to men with visceral obesity are also characterized by low testosterone levels.⁴¹ BMI which reflect the degree of overweight overall the body perform better in predicting hypertension than LAP in southern males .

41.Kahn H S, Cheng Y J. Longitudinal changes in BMI and in an index estimating excess lipids among white and black adults in the United States. *Int J Obes* 2008; 32(1):136-143.

- The aim of this study was to investigate the potential use of LAP as a putative indicator of hypertension risk. However, to answer this question the authors should have employed a different study where baseline LAP values were correlated to BP values overtime. Unfortunately, this could not be done here given the retrospective nature of the investigation. Please comment.

Re: Thank you very much for your kind reminder. Owing to our work is a cross-sectional study, we know that our present results are insufficient to indicate causality, and only can provide the clues about the cause of disease. Therefore, we will conducted a prospective studies in future studies on these findings.

- The difference in triglyceride levels among the 3 groups (normotensive, prehypertensive, hypertensive) is impressive. What is the predictive value of TG as compared with LAP? WC alone vs. LAP should be also tested.

Re: We have added TG and WC into the ROC analysis in our manuscript. LAP perform better in predicting the hypertension risk than TG in both sex. Due to low predictive value of TG in southern China, LAP which combines of TG and WC is slightly inferior to WC.

- LAP needs to be better defined in the abstract, this might not be clear to the reader.

Re: Thank you very much for your kind advice! In order to clear the defined of LAP, the statements of “This study aimed to investigate the applicability of lipid accumulation product (LAP) in the Southern Chinese population...” were corrected as “This study aimed to investigate the applicability of **a novel index based on WC and TG, named** lipid accumulation product (LAP) in the Southern Chinese population...” . (page-2, line-1)

Finally, thank you again for your meticulous work. Your valuable suggestions are very helpful for modifying this article.

We tried our best to improve the manuscript by applying some changes. These changes will not influence the framework of the paper. We sincerely appreciate the Editor/Reviewers’ careful work and hope that the corrections will be met with approval.

Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Fardhad Hosseinpanah Research Institute for Endocrine Sciences, Tehran, Iran
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	<p>Thank you once again for giving me the opportunity of reviewing a revised form of this interesting manuscript. The authors should still clarify some concerns and correct some points as listed below:</p> <ol style="list-style-type: none"> 1. The authors have compared the basic characteristics of the excluded participants with that of included participants, and found no statistically significant differences in age and sex between the two population groups. This important part of findings should be added to the manuscript. 2. Gender specific differences are addressed in the supplementary file but not uploaded, at least not provided for review. It should be added to the main manuscript as a very important part of the study results. 3. Please revise the first paragraph of discussion. The authors have added the part “the prevalence of obesity has increased by 13% in urban areas and by 85% in rural areas in China, and more attention should thus be paid to this issue.” but omitted it again. Please be aware to insert this part into the final text. Moreover, the sentence “An increase in body weight is typically followed by enhanced blood pressure.” in this paragraph is redundant and should be omitted. 4. The abbreviation “SBP/DBP” which has been added through revision in page 5, is defined later in page 7. Please define them in at their first appearance. 5. Please rewrite the two first sentences in the second paragraph of introduction in a more decent form (page 4 lines 8-10). 6. Page 10 line 13: please revise “smoker” and “drinker”; for instance, to “smoking” and “alcohol consumption”.
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REVIEWER	Francesco Paneni University of Zurich
REVIEW RETURNED	10-Sep-2019

GENERAL COMMENTS	The authors have addressed all my concerns, I have no further comments on this manuscript
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VERSION 2 – AUTHOR RESPONSE

Reviewer #2

Comments to the Author

1. The authors have compared the basic characteristics of the excluded participants with that of included participants, and found no statistically significant differences in age and sex between the two population groups. This important part of findings should be added to the manuscript.

Re 1 : We have added this part into the manuscript according to your suggestion. (page-6, line-11)

2. Gender specific differences are addressed in the supplementary file but not uploaded, at least not provided for review. It should be added to the main manuscript as a very important part of the study results.

Re 2 : We have added basic characteristics of the participants of different gender into the manuscript. (page-9, line-17)

3. Please revise the first paragraph of discussion. The authors have added the part “the prevalence of obesity has increased by 13% in urban areas and by 85% in rural areas in China, and more attention should thus be paid to this issue.” but omitted it again. Please be aware to insert this part into the final text. Moreover, the sentence “An increase in body weight is typically followed by enhanced blood pressure.” in this paragraph is redundant and should be omitted.

Re 3 : We have added this part into the final text. And we have omitted the sentence “An increase in body weight is typically followed by enhanced blood pressure.” according to your suggestion. (page-11, line-12)

4. The abbreviation “SBP/DBP” which has been added through revision in page 5, is defined later in page 7. Please define them in at their first appearance.

Re 4 : Thank you every much for your careful work. We have revised this part according to your comments. (page-5, line-9)

5. Please rewrite the two first sentences in the second paragraph of introduction in a more decent form. (page 4 lines 8-10)

Re 5 : Thank you for your meticulous work, we have corrected the two first sentences in the second paragraph as “Obesity, especially visceral fat, and family history of hypertension could significantly contribute to hypertension.⁴⁻⁶ Numerous studies have demonstrated that positive family history is an important risk factor for hypertension.⁶⁻⁹” (page 4 lines 8-10)

6. Page 10 line 13: please revise “smoker” and “drinker”; for instance, to “smoking” and “alcohol consumption”.

Re 6 : Thank you for your careful work. We have revised as your suggestion.

Reviewer #4

Comments to the Author

- The authors have addressed all my concerns, I have no further comments on this manuscript

Re : Thank you very much for your meticulous work. We will continue to work hard!

Finally, thank you again for reviewers’ careful work. These valuable suggestions are very helpful for modifying this article.

We tried our best to improve the manuscript by applying some changes. These changes will not influence the framework of the paper. We sincerely appreciate the Editor/Reviewers’ careful work and hope that the corrections will be met with approval.

Once again, thank you very much for your comments and suggestions.

VERSION 3 – REVIEW

REVIEWER	Fardhad Hosseinpanah Research Institute for Endocrine Sciences, Tehran, Iran
REVIEW RETURNED	10-Oct-2019

GENERAL COMMENTS	Thank you once again for giving me the opportunity of reviewing a revised form of this interesting manuscript. The authors should still clarify some concerns and correct some points as listed below: 1. The authors have provided gender-specific baseline characteristics of the study participants and reported no significant difference regarding familial history of hypertension in females. Accordingly, absence of interaction between lipid accumulation product and familial history of hypertension in females should be explained by this important observation. 2. The majority of conclusion sections in the abstract and the manuscript is written based on the ROC curve analysis, which is not the main question of the research. The conclusion sections must be revised according to gender-specific results of interactions between lipid accumulation product and familial history of hypertension.
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VERSION 3 – AUTHOR RESPONSE

Reviewer #2

Comments to the Author

1. The authors have provided gender-specific baseline characteristics of the study participants and reported no significant difference regarding familial history of hypertension in females. Accordingly, absence of interaction between lipid accumulation product and familial history of hypertension in females should be explained by this important observation.

Re 1 : We have added this part into the manuscript according to your suggestion. (page-13, line-21)

2. The majority of conclusion sections in the abstract and the manuscript is written based on the ROC curve analysis, which is not the main question of the research. The conclusion sections must be revised according to gender-specific results of interactions between lipid accumulation product and familial history of hypertension.

Re 2 : Thank you for your meticulous work. The reason why the majority of conclusion sections in the abstract and the manuscript is written based on the ROC curve analysis is as follows. To discuss interaction of lipid accumulation product and family history of hypertension on hypertension risk is one of this manuscript purpose. But since there's still not clear about the applicability of LAP for southern China, and we cannot discuss the interactions without its applicability. Therefore, the ROC curve analysis of LAP is also an important conclusion for this manuscript. Is it better for us to change the title of our manuscript into "The applicability of lipid accumulation product in the Southern Chinese population and its interaction of family history of hypertension on hypertension risk" ? (page-14, line-15 & page-15, line-2)

Finally, thank you again for reviewers' careful work. These valuable suggestions are very helpful for modifying this article.

We tried our best to improve the manuscript by applying some changes. These changes will not influence the framework of the paper. We sincerely appreciate the Editor/Reviewers' careful work and hope that the corrections will be met with approval.

Once again, thank you very much for your comments and suggestions.

VERSION 4 – REVIEW

REVIEWER	Fardhad Hosseinpanah Research Institute for Endocrine Sciences, Tehran, Iran
REVIEW RETURNED	28-Oct-2019
GENERAL COMMENTS	The authors have addressed all my concerns, I have no further comments on this manuscript.

VERSION 4 – AUTHOR RESPONSE

Reviewer #2

The authors have addressed all my concerns, I have no further comments on this manuscript.

Re : Thank you very much for all your valuable comments and suggestions.

Special thanks to Editor and Reviewers for the careful work and kind suggestions. Your valuable suggestions have been very helpful for modifying this article.