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)	The relationship between obesity indices and hypertension among middle-aged and elderly populations in Taiwan: a community-based, cross-sectional study
AUTHORS	Lin, Yen-An; Chen, Ying-Jen; Tsao, Yu-Chung; Yeh, Wei-Chung; Li, Wen-Cheng; Tzeng, I-Shiang; Chen, Jau-Yuan

VERSION 1 – REVIEW

REVIEWER	Lingzhong Xu School of Public health,Shandong University, Jinan 250012, China
REVIEW RETURNED	15-Jun-2019

GENERAL COMMENTS	Comments and Suggestions for Authors: This study attempt to explore the relationship between obesity indices and hypertension in Taiwan elderly and find out the best obesity index for predicting HTN. General comments: -Provide more information on the novelty of your study. -The sample size is relatively small. Did you calculate the sample size before the investigation and what the minimum sample size needed in this study? Besides, the samples were all come from a community hospital, could they represent the elderly population in Taiwan? -You should provide a detail explanation of all the variables (how you get them and the criteria you classified them) included in the study. For example, did you assess stages of smoking and drinking rather than yes/no, because moderate drinking may be protective? Current smoking means what? Regular exercise means how often they exercise a week/month? Please explain them in detail. -What were the distributions of the Continuous Variables (such as anthropometric indices)? You used t-test for all comparisons which is only valid if each variable is normally distributed; this was not presented. You fit your models with multiple anthropometric indices, so there is great concern for collinearity among these variables; did you assess or account for this? -The introduction and discussion sections need improvement. Please cite more references to support your result. I recommend to accept the paper for publication after major review. Sincerely Yours.

REVIEWER	Mark Lown University of Southampton, UK
REVIEW RETURNED	10-Jul-2019

GENERAL COMMENTS	Overall I have concerns regarding the research question and methods. Regarding the effect of sarcopenia on anthropoetic measurements, it would be useful to select a population with a high expected prevalence of sarcopenia eg > 65 or at least to perform subgroup analysis. Sarcopenia could also have been assessed (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4269139/) Did you exclude those with secondary hypertension or medications which increase BP? Did you measure several BP readings per patient and average 2nd and 3rd? Which meter was used - and is it accurate when arrhythmias are present eg AF? The discussion refers to many gender differences but you did not perform gender subgroup analysis. Was the SBP analysis corrected for anti-hypertensive medication use? Suggestions for further work / clinical utility of the results would be useful

VERSION 1 – AUTHOR RESPONSE

Responses to Comments from Reviewer #1
Major Comment 1:
Provide more information on the novelty of your study.
Response:
We thank the reviewer for reminding us this important issue. In response to this comment, we have added statements, which read as: “However, these previous observations were mainly from the general population. Thus, the novel findings of this study are the association between various obesity indices and HTN in middle-aged and elderly population, an age group that has high risk of HTN” (Lines 228-230).

Major Comment 2:
The sample size is relatively small. Did you calculate the sample size before the investigation and what the minimum sample size needed in this study? Besides, the samples were all come from a community hospital, could they represent the elderly population in Taiwan?
Response:
We thank the reviewer for reminding us this important issue. We did calculate the minimum sample size before this study. We have added statements to explain this calculation. These statements read as: “The minimum sample size for this study was calculated at the initial stage of the study. After previewing a relative smaller population, we found that the Non-HTN to HTN ratio was approximately 1:1. Considering 90% power, 95% confidence level, 0.30 as the exposure (obesity) rate among the Non-HTN, and a Non-HTN to HTN ratio of 1:1, we calculated that 308 participants were required to detect at least 2 odds ratio differences between these two study groups” (Lines 126-131).
We fully agree with the reviewer regarding the fact that our findings were obtained from community-based subjects and cannot be generalized to the whole middle-aged and elderly population in Taiwan. To response to the reviewer’s comment, this limitation has been acknowledged in the discussion section (Lines 255-257).

Major Comment 3:

You should provide a detail explanation of all the variables (how you get them and the criteria you classified them) included in the study. For example, did you assess stages of smoking and drinking rather than yes/no, because moderate drinking may be protective? Current smoking means what? Regular exercise means how often they exercise a week/month? Please explain them in detail.
Response:
We think the reviewer for allowing us to further explain this issue. The detailed explanations for major variables and obesity indices were mentioned in the method section (Lines 104-124). We have added a statement (Lines 110-112) to explain the definition of hypertension, which was based upon the 2015 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension.
Unfortunately, we were not able to well define variables such as the stages of smoking or drinking. However, we have defined regular exercise as exercising for 30 minutes three or more times a week. This is because these items were included in the questionnaire used in our study. The questionnaire was designed for community participants during health examination. A questionnaire with too complicate questions would largely decrease the willingness of the participation. We have also acknowledged this limitation in the discussion section (Lines 257-260). We sincerely hope that the reviewer could understand our obstacle.

Major Comment 4:
What were the distributions of the Continuous Variables (such as anthropometric indices)? You used t-test for all comparisons which is only valid if each variable is normally distributed; this was not presented. You fit your models with multiple anthropometric indices, so there is great concern for collinearity among these variables; did you assess or account for this?
Response:
We thank the reviewer for reminding us this important issue. We did check the normality of the data using the Kolmogorov-Smirnov test. This description has been provided in the method section (Lines 132-133).
The reviewer is correct about the collinearity. We did assess the collinearity among multiple anthropometric indices and found that the correlation between any two indices was high (Please see the supplemental file, Table S1). This high correlation has been previously reported in other studies. For this reason, we did not put these anthropometric indices into one regression analysis. Instead, we separately put each anthropometric index alongside with other confounders (e.g., DM and hyperlipidemia) into one regression analysis to avoid collinearity (Tables 3 and 4). We sincerely hope that the reviewer could approve our explanations.

Major Comment 5:
The introduction and discussion sections need improvement. Please cite more references to support your result.
Response:
In response to the reviewer's suggestion, we have cited more references in the introduction and discussion section. The additional references are in number 5, 11, 12, 15. Accordingly, we have changed the sequence of citations in the text.

Responses to Reviewer #2
Comment 1:
Overall I have concerns regarding the research question and methods. Regarding the effect of sarcopenia on anthropoetic measurements, it would be useful to select a population with a high expected prevalence of sarcopenia eg > 65 or at least to perform subgroup analysis. Sarcopenia could also have been assessed
Response:
The suggestion from the reviewer is excellent. In response to this suggestion, we have performed a subgroup analysis of participants with an age ≧ 65 years old. The results are shown in table 4(a). As

shown, these obesity indices remained independent risk factors in the subgroup of participants with an age ≧ 65 years old (Table 4a). We have reported these data in the result section (Lines 162-173) and discussed in the discussion section (Lines 220-222).
This study was conducted in a community setting and we collected data during health examination when we carried out a community health promotion project. Therefore, we did not assess the status of sarcopenia in our participants because the project did not include this item. We sincerely hope that the reviewer could understand our obstacle.

Comment 2:
Did you exclude those with secondary hypertension or medications which increase BP?

Response:
We thank the reviewer for reminding us this important issue. We did exclude subjects with secondary hypertension or medications which increase BP. This exclusion criterion has been added to the method section (Lines 97).

Comment 3:
Did you measure several BP readings per patient and average 2nd and 3rd? Which meter was used - and is it accurate when arrhythmias are present eg AF?

Response:
We thank the reviewer for reminding us this important issue. We measured blood pressure in each subject for 3 times separated by an interval of 10 minutes, and calculated the mean value of these three readings. A standardized electronic sphygmomanometer (OMRON, model HEM-7130) was used for this purpose. In response to the reviewer's comments, we have added statements in the method section to clarify this issue (Lines 115-120).
This study was conducted in a community setting and we collected data during health examination when we carried out a community health promotion project. Therefore, the supportive equipments were minimal and were not able to define the presentation of arrhythmia. We sincerely hope that the reviewer could understand our obstacle.

Comment 4:
The discussion refers to many gender differences but you did not perform gender subgroup analysis.

Response:
The suggestion from the reviewer is excellent. In response to this suggestion, we have performed a subgroup analysis of participants according to gender. The results are shown in table 4(b) and 4(c). As shown, these obesity indices remained independent risk factors in the subgroup of male (Table 4b) or female participants (Table 4c).We have reported these data in the result section (Lines 162-173) and discussed in the discussion section (Lines 220-222).

Comment 5:
Was the SBP analysis corrected for anti-hypertensive medication use?

Response:
We thank the reviewer for allowing us to explain this issue. In our record, most (> 95%) of our participants were treated with anti-hypertensive medication. Thus, we were unable to correct this medical condition when performing the SBP analysis. We sincerely hope that the reviewer could approve our explanation.

Comment 6:
Suggestions for further work / clinical utility of the results would be useful

Response:
We thank the reviewer for this comment. We have added statements in the discussion section for suggestions for further work/clinical utility of the results. These statements read as: “Thus, our findings may provide valuable information for clinicians to alert subjects in this age group regarding the increased risk of HTN” (Lines 265-266).

VERSION 2 – REVIEW

REVIEWER	lingzhong xu School of Public Health, Shandong University, Jinan 250012, China
REVIEW RETURNED	15-Aug-2019

GENERAL COMMENTS	The authors aimed to evaluate the best obesity index for predicting HTN in middle-aged and elderly populations in Taiwan. I am interested in this topic, however, the data mainly came from a specific community hospital which can not represent the whole population in Taiwan. I am sorry that i think sample's representation is qiute important for a study like this, so i don't think it is qualified enough for publication.

REVIEWER	Mark Lown Southampton University
REVIEW RETURNED	14-Aug-2019

GENERAL COMMENTS	Thanks for this revision which I believes still requires major changes: Major points: 1. It would be useful to list the medications associated with HTN that you used to esclude patients 2. Why did you take 3 readings 10 mins apart – did some participants refuse to participate based on 30 mins required to measure blood pressure. What were the participnats asked to do during the 10 minute breaks ? 3. Please justify method of BP measurement ie average of 3 readings. 4. It’s not completely clear where the recruitment poster was placed – at the hospital or in the community – please clarify that all participants were recruited in the community. 5. Were arrhythmias checked for either from the warning light on the BP machine or manual auscultation regarding excluding inaccurate results? 6. What was the missing data – please clarify 7. Justify why sarcopenia was not assessed – could also suggest this as an area for future work. 8. Results section – 200 had HTN (not clear this was based upon just BP readings or the previous definition including taking Antihypertensive medication and history of hypertension). Following on from this – were patients taking AHT meds included in the hypertensive group SBP results? 9. In the discussion you mention previous work using both WC & BMI – was the ROC improved with combined models? 10. Strengths and Limitations – you mention some of the conclusions in this section which are not S&L Minor points:

	There are too many typos / grammatical errors to mention specifically: 1. Abstract: 'best obesity index' – perhaps several anthropometric measurements 2. 'measured by the annual health exam' at the annual health exam 3. Obesity indices were … 4. Introduction: The utility of different types of obesity indices has been discussed in the past. If the BF percentage by Dual-energy X-ray absorptiometry (DXA) is regarded as a gold standard, it would be hard to assess as the sensitivity and specificity of BMI vary with gender. Grammar ? if BMI. Etc, etc, etc.

VERSION 2 – AUTHOR RESPONSE

Responses to Comments from Reviewer #1

Comment:

The authors aimed to evaluate the best obesity index for predicting HTN in middle-aged and elderly populations in Taiwan. I am interested in this topic, however, the data mainly came from a specific community hospital which cannot represent the whole population in Taiwan. I am sorry that I think sample's representation is quite important for a study like this, so I don't think it is qualified enough for publication.

Response:

We agree with the reviewer regarding the fact that our findings were obtained from community-based subjects and cannot be generalized to the whole middle-aged and elderly population in Taiwan. However, it is very difficult to perform a project conducting measurements of anthropometrics and blood pressure, collecting blood lab data, and survey by questionnaires from subjects through all the regions in Taiwan. We sincerely hope that the reviewer could understand our obstacle.

To response to the reviewer's comment, this limitation has been acknowledged in the discussion section (Lines 265-267). We have also mentioned the limitation that our findings were obtained from community-based subjects and cannot be generalized to the whole middle-aged and elderly population in Taiwan (Lines 35-36).

Responses to Reviewer #2

Major Comment 1:

It would be useful to list the medications associated with HTN that you used to exclude patients.

Response:

We thank the reviewer for the suggestion. We have listed the medication which could induced secondary hypertension according to 2015 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension as below: licorice, oral contraceptives, steroids, NSAIDs, cocaine, amphetamines, erythropoietin, cyclosporin, tacrolimus, and anti-VEGF (Lines 98-100).

Major Comment 2:

Why did you take 3 readings 10 mins apart – did some participants refuse to participate based on 30 mins required to measure blood pressure. What were the participants asked to do during the 10 minute breaks?

Response:

We thank the reviewer for allowing us to further explain this issue. In our project, no participants refused to participate based on 30 mins required to measure blood pressure. We asked the participants to sit and rest on the chair during the 10 minutes breaks.

Major Comment 3:

Please justify method of BP measurement ie average of 3 readings.

Response:

We thank the reviewer for allowing us to further explain this issue. According to the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, 2 to 3 separate occasional blood pressure measurements would minimize random error and provide a more accurate basis for the estimation of blood pressure. (Lines 121-124)

Major Comment 4:

It's not completely clear where the recruitment poster was placed – at the hospital or in the community – please clarify that all participants were recruited in the community.

Response:

We thank the reviewer for reminding us this important issue. We had mentioned the recruitment poster placement in the method section. These statements read as:" The recruitment posters were all placed in the community and all participants were recruited in the community." (Lines 89-90).

Major Comment 5:

Were arrhythmias checked for either from the warning light on the BP machine or manual auscultation regarding excluding inaccurate results?

Response:

We thank the reviewer for allowing us to further explain this issue. There was a warning light on our electronic sphygmomanometer (OMRON, model HEM-7130) for irregular heart beat detection. In addition, we performed physical examination for every participant including manual auscultation, and there was no participant with an irregular heart beat detected by the warning light or manual auscultation (Lines 125-127).

Major Comment 6:

What was the missing data – please clarify

Response:

We thank the reviewer for allowing us to further explain this issue. We have mentioned the missing data in the method section. The statements read as: “Four participants were excluded because they had pacemaker implantations.” (Lines 91-92)

Major Comment 7:

Justify why sarcopenia was not assessed – could also suggest this as an area for future work.

Response:

The suggestion from the reviewer is excellent. We have not assessed sarcopenia because hand grip and walking speed were not measured from our subjects in this project. In response to this suggestion, we have added statements in the discussion section to justify this and suggest this as an area for future work (Lines 270-272). This statement read as: “Fifth, sarcopenia was not assessed in our study because hand grip and walking speed were not measured in our subjects in this project. The potential impact of sarcopenia may be an area for future work.

Major Comment 8:

Results section – 200 had HTN (not clear this was based upon just BP readings or the previous definition including taking Antihypertensive medication and history of hypertension). Following on from this – were patients taking AHT meds included in the hypertensive group SBP results?

Response:

We thank the reviewer for allowing us to further explain this issue. In 200 participants with hypertension, there were 192 people with history of hypertension or using antihypertensive medications, and 8 people without history of hypertension or using antihypertensive medications had elevated mean BP after 3 readings of BP measurements. We had mentioned the definition of hypertension in the method section. These statements read as:” HTN was defined as SBP ≧ 140 mmHg or DBP ≧ 90 mmHg, or current use of antihypertensive medications, or history of HTN.” (Lines 112-113).

Major Comment 9:

In the discussion you mention previous work using both WC & BMI – was the ROC improved with combined models?

Response:

We thank the reviewer for allowing us to further explain this issue. In that study, the association analysis between WC & BMI combination and hypertension had better odds ratio than WC in man. But there was no ROC curve analysis in that study.

Major Comment 10:

Strengths and Limitations – you mention some of the conclusions in this section which are not S&L

Response:

We fully agree with the reviewer's comment. In response to the reviewer's suggestion, we have revised the Strengths and Limitations section (Lines 29-36). These statements read as:

- We conducted a community-based study and comprehensively collected various data from a health promotion project, that may have clinical implications.
- This is a first study to explore the association between different obesity indices and hypertension in middle-aged and elderly Taiwanese population.
- A cross-sectional study cannot effectively determine the causal relationship between obesity indices and hypertension.
- Our findings were obtained from community-based subjects and cannot be generalized to the whole middle-aged and elderly population in Taiwan.

Minor Comment 1:

There are too many typos / grammatical errors to mention specifically:

Abstract: 'best obesity index' – perhaps several anthropometric measurements

Response:

We thank the reviewer for reminding us this suggestion. In response to the reviewer's suggestion, we have revised the abstract section. The statement read as: " In this study, we evaluated several anthropometric measurements for the prediction of HTN in middle-aged and elderly populations in Taiwan." (Lines 3-5)

In response to the reviewer's comments, the revised manuscript has been professional edited for improvement of language.

Minor Comment 2:

'measured by the annual health exam' at the annual health exam

Response:

We thank the reviewer for reminding us this suggestion. In response to the reviewer's suggestion, we have revised the abstract section. The statement read as: "Anthropometrics and blood pressure were measured at the annual health exam." (Lines 9-10)

Minor Comment 3:

Obesity indices were …

Response:

We thank the reviewer for reminding us this suggestion. In response to the reviewer's suggestion, we have revised the abstract section. The statement read as: "Statistical analyses, including Pearson's correlation, multiple logistic regression, and the area under ROC curves (AUCs) between HTN and anthropometric measurements, were used in this study." (Lines 11-13)

Minor Comment 4:

Introduction: The utility of different types of obesity indices has been discussed in the past. If the BF percentage by Dual-energy X-ray absorptiometry (DXA) is regarded as a gold standard, it would be hard to assess as the sensitivity and specificity of BMI vary with gender. Grammar ? if BMI.

Response:

We thank the reviewer for reminding us this suggestion. In response to the reviewer's suggestion, we have revised the introduction section. The statement read as: "If the BF percentage determined by dual-energy X-ray absorptiometry (DXA) is regarded as a gold standard, it would be difficult to assess as the sensitivity and specificity of BMI vary by sex." (Lines 47-50)

VERSION 3 – REVIEW

REVIEWER	Mark Lown University of Southampton
REVIEW RETURNED	16-Sep-2019

GENERAL COMMENTS	Major comments now addressed