

## 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

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| <b>TITLE (PROVISIONAL)</b> | Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in Chinese Population |
| <b>AUTHORS</b>             | Yu, Peng; huang, teng; hu, senlin; Yu, Xuefeng  |

### VERSION 1 – REVIEW

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| <b>REVIEWER</b>        | Dongsheng Hu<br>Shenzhen University School of Medicine<br>3688 Nanhai Avenue<br>Shenzhen, Guangdong<br>CHINA |
| <b>REVIEW RETURNED</b> | 27-Mar-2020  |

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| <b>GENERAL COMMENTS</b> | <p>My comments and suggestions for the manuscript are as follows:</p> <ol style="list-style-type: none"><li>1. The optimal cut-off value for RFM in male and female population should be described. (p. 4, line 50)</li><li>2. Introduction : The authors should provide information about existing models for predicting hypertension in the Introduction, and provide a clearer justification for using RFM. What do they believe is missing from existing studies? Why start by explore the prediction value of RFM?</li><li>3. Method<ol style="list-style-type: none"><li>a) How many participants completed the questionnaire interview? How many research staff were involved in this massive data collection? How many institutions were involved in data collection?</li><li>b) Missing data were excluded. How lowered bias?</li><li>c) Why was age examined categorically and not as a continuous variable?</li><li>d) How was smoking and alcohol drinking determined?</li><li>e)The description of statistical analysis was not right. Single-factor logistic regression was used in unadjusted logistic regression model. Multiple logistic regression was used in model 1, model 2, model 3. (p. 7, line 26-27)</li><li>f) Why did not use Cox regression model?</li><li>g)The association of cardiometabolic risk factors and RFM are compared for or Linear tendency<math>\chi^2</math>-test or not<math>\chi^2</math>-test. (p. 7, line 23-25) (Table 2)</li></ol></li><li>4. Discussion :<ol style="list-style-type: none"><li>a)The authors write that their findings “RFM algorithm gives a less accurate estimation of body fat percentage in Chinese population than in Western population”(p. 9, line 31-34). I think such a conclusion is impertinent only according this study. More discussion should be provided.</li><li>b)“we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction</li></ol></li></ol> |
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|  | and compare it predicting power with traditional obesityrelated indices". but are not there any indeed?<br>c) The models did not validated internally. The paper could be strengthened by more discussion of this point. |
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| <b>REVIEWER</b>        | Renata Kuciene<br>Lithuanian University of Health Sciences; Lithuania |
| <b>REVIEW RETURNED</b> | 06-Apr-2020   |

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| <b>GENERAL COMMENTS</b> | <p>I have reviewed the manuscript titled "Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in a Chinese Population". I consider that the study hypothesis is interesting. The manuscript in question is consistent on it's relevance, timeliness and appropriateness of the theme for the field of Cardiovascular Epidemiology and Public Health. I just have a few points for the authors to clarify.</p> <p>In the abstract, remove the words "sensitive analysis", because logistic regression analysis was performed to investigate the association between RFM and incident hypertension.</p> <p>Authors must include a statement on ethics approval (the name of the ethics committee that approved the study) and consent to participate.</p> <p>Authors should describe the justification for calculation of sample size.</p> <p>In results, (Page 8, lines 35-36, table 3), check the ORs. What the intra- and inter-observer errors were accepted in the measurements (blood pressure and anthropometric)?</p> <p>Are there any differences in characteristics between those included and excluded from the study (762 were excluded)?</p> |
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer: 1

Reviewer Name: Dongsheng Hu

Institution and Country:

Shenzhen University School of Medicine

3688 Nanhai Avenue

Shenzhen, Guangdong

CHINA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

My comments and suggestions for the manuscript are as followings:

1. The optimal cut-off value for RFM in male and female population should be described. (p. 4, line 50)

**Answer:** Thank you for your suggestion. We added the optimal cut-off value for RFM in our revised manuscript.

2. Introduction: The authors should provide information about existing models for predicting hypertension in the Introduction, and provide a clearer justification for using RFM. What do they believe is missing from existing studies? Why start by explore the prediction value of RFM?

**Answer:** Thank you for pointing this out. We rewrite the third paragraph of the introduction.

### 3. Method

a) How many participants completed the questionnaire interview? How many research staff were involved in this massive data collection? How many institutions were involved in data collection?

**Answer:** Thank you for your comment. This survey was co-launched by Carolina Population Center at the University of North Carolina at Chapel Hill, the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention and China-Japan Friendship Hospital. According to the cohort file, the response rates were 88% at individual level and 90% at household level.

b) Missing data were excluded. How lowered bias?

**Answer:** We optimized the flow chart of sample selection from the China Health and Nutrition Survey in our revised manuscript. After excluding those that did not meet our inclusion criteria, there were 717 individuals with missing information. Compared to those who were included in the study, those who were excluded owing to missing data were slightly younger and higher percentage of males, there were no statistically significant differences in BMI, WC, biochemical parameters at baseline and the incidence of hypertension at 2015.

These individuals (n=443) lacking serum biomarker data, but they had anthropometric data, when taken these individuals into account (n=3849), the conclusion from ROC analysis remained stable.

AUCs for each anthropometric index in predicting hypertension (n=3849)

|     | Men                 |         | Women              |         |
|-----|---------------------|---------|--------------------|---------|
|     | AUC(95%CI)          | p value | AUC(95%CI)         | p value |
| RFM | 0.601 (0.578-0.624) | < 0.001 | 0.643(0.621-0.663) | < 0.001 |

|      |                     |         |                    |         |
|------|---------------------|---------|--------------------|---------|
| BMI  | 0.596 (0.573-0.619) | < 0.001 | 0.611(0.589-0.632) | < 0.001 |
| WC   | 0.590 (0.567-0.613) | < 0.001 | 0.639(0.617-0.659) | < 0.001 |
| WHtR | 0.601 (0.578-0.624) | < 0.001 | 0.643(0.621-0.663) | < 0.001 |

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AUC, area under the curve; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass

In male, there were no significant differences in AUC value of RFM as compared to other obesity indices (Bonferroni-adjusted p-value > 0.05). In female, RFM only had higher AUC value than that of BMI (Bonferroni-adjusted p-value = 0.036) (ROC curves were compared using the method developed by DeLong et al)

c) Why was age examined categorically and not as a continuous variable?

**Answer:** Thank you for your comment. Age entered into the models as a continuous variable in our study.

d) How was smoking and alcohol drinking determined?

**Answer:** Thank you for your comment. Smokers were defined as more than 100 cigarettes lifelong. Current smoking was defined as a positive answer to the question “do you still smoke cigarettes or a pipe?”. Then the smoker would be asked about the number of cigarettes smoked per day. Alcohol drinking was defined as a positive answer to the question “during the past year, what was your consumption of beer, liquor and wine?”. Then the drinker would be asked about how much do they drink each week.

e) The description of statistical analysis was not right. Single-factor logistic regression was used in unadjusted logistic regression model. Multiple logistic regression was used in model 1, model 2, model 3. (p. 7, line 26-27)

**Answer:** Thank you for pointing this out. We had corrected this mistake in our revised manuscript.

f) Why did not use Cox regression model?

**Answer:** Thank you for your comment. Logistic regression ignores the timing of events. However, as these participants were not yearly follow-up, we only obtain information about the incidence of hypertension at 2015.

g) The association of cardiometabolic risk factors and RFM are compared for or Linear tendency  $\chi^2$ -test or not  $\chi^2$ -test. (p. 7, line 23-25) (Table 2)

**Answer:** Thank you for your comment. In our revised manuscript, linear-by-linear association  $\chi^2$ -test was used for trend analysis between the quartiles.

#### 4. Discussion :

a) The authors write that their findings “RFM algorithm gives a less accurate estimation of body fat percentage in Chinese population than in Western population”(p. 9, line 31-34). I think such a conclusion is impertinent only according this study. More discussion should be provided.

**Answer:** Thank you for your comment. We are very sorry for our inappropriate writing. We had changed this sentence into “The efficiency of the RFM algorithm for estimating body fat percentage in Chinese population is unknown and needs further validation study” in our revised manuscript.

b) “we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction and compare it predicting power with traditional obesity related indices”. but are not there any indeed?

**Answer:** Thank you for your comment. We done literature retrieval again and found the paper named “Relative fat mass is a better predictor of dyslipidemia and metabolic syndrome than body mass index” examined the association of RFM and hypertension in Israel. However, they only use univariate logistic regression model to explore this association, meanwhile, they only compare the OR of RFM with that of BMI. In order to express this point more rationally, we revised the sentence into “we were the first longitudinal study to investigate whether the current RFM algorithm can be applied in hypertension prediction in Chinese population and compare it predicting power with traditional obesity related indices”.

c) The models did not validated internally. The paper could be strengthened by more discussion of this point.

**Answer:** Thank you for your suggestion. In order to give more validation to our results, AUC was calculated for the regression models. The effect of each index of obesity plus other risk factors including age, smoking, alcohol drinking, uric acid, eGFR, ALT, TG, TC, HDL-C, LDL-C, and FPG in predicting hypertension were evaluated. For both male and female population, there were no statistical differences among the AUC values of the four models when compared in a pairwise manner

(all Bonferroni-adjusted p-value > 0.05). (Table 6). This revealed that RFM did not show superiority when compared to BMI, WC and WHtR in assessing hypertension risk from another prospective.

**Reviewer: 2**

Reviewer Name: Renata Kuciene

Institution and Country: Lithuanian University of Health Sciences; Lithuania

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I have reviewed the manuscript titled "Predictive Value of Relative Fat Mass Algorithm for Incident Hypertension: a 6-year Prospective Study in a Chinese Population". I consider that the study hypothesis is interesting. The manuscript in question is consistent on its relevance, timeliness and appropriateness of the theme for the field of Cardiovascular Epidemiology and Public Health. I just have a few points for the authors to clarify.

In the abstract, remove the words "sensitive analysis", because logistic regression analysis was performed to investigate the association between RFM and incident hypertension.

**Answer:** Thank you for pointing this out. We had corrected this mistake in our revised manuscript.

Authors must include a statement on ethics approval (the name of the ethics committee that approved the study) and consent to participate.

**Answer:** Thank you for your comment. The survey was approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety and Chinese Center for Disease Control and Prevention. All participants had signed the informed consent forms during the CHNS survey. We provided this information in the footnotes.

Authors should describe the justification for calculation of sample size.

**Answer:** Thank you for your comment. In our revised manuscript, we provided the calculation of sample size. Appropriate sample size was calculated using the OpenEpi software program (<http://www.openepi.com/SampleSize/SSCohort.htm>) before initiate the study. Considering 5% level of significance for a two-sided test, 80% power; unexposed/exposed ratio of 1.3, percent of unexposed with outcome = 15 and percent of exposed with outcome = 33 according to the results from the China hypertension survey. Based on these settings, the estimated sample size required

was at least 198 subjects. A total of 3406 participants were included in our study, thus the sample of this study was sufficient.

In results, (Page 8, lines 35-36, table 3), check the ORs.

**Answer:** Thank you for pointing this out. We are sorry for our mistake. In our revised manuscript, we had checked the results.

What the intra- and inter-observer errors were accepted in the measurements (blood pressure and anthropometric)?

**Answer:** Thank you for your comment. Each individual's height and weight were measured by the investigators according to the standard of protocol, height was measured without shoes to the nearest 0.1 cm using a portable stadiometer, body weight was measured with subjects wearing light clothing without shoes, to the nearest 0.1 kg on a calibrated digital scale. For blood pressure measurements, a difference of less than 10mmHg between two measurements were accepted. Meanwhile, the quality control officers would check the measurements in a randomly selected manner.

Are there any differences in characteristics between those included and excluded from the study (762 were excluded)?

**Answer:** Thank you for your comment. We optimized the flow chart of sample selection from the China Health and Nutrition Survey in our revised manuscript. After excluding those that did not meet our inclusion criteria and those with missing information about smoking, drinking, outcome, anthropometric measurement, biomarker data (n=717), there were 3406 participants included. Compared to those who were included in the study, those who were excluded owing to missing data were slightly younger and higher percentage of males, there were no statistically significant differences in BMI, WC, biochemical parameters at baseline and the incidence of hypertension at 2015.

#### VERSION 2 – REVIEW

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| <b>REVIEWER</b>         | Dongsheng Hu<br>Shenzhen University School of Medicine<br>3688 Nanhai Avenue<br>Shenzhen, Guangdong<br>CHINA |
| <b>REVIEW RETURNED</b>  | 28-Apr-2020  |
| <b>GENERAL COMMENTS</b> | I have no further comments.  |

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| <b>REVIEWER</b>        | Renata Kuciene<br>Lithuanian University of Health Sciences; Lithuania |
| <b>REVIEW RETURNED</b> | 04-May-2020   |

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| <b>GENERAL COMMENTS</b> | This revised manuscript has been improved. However, the authors need to specify the methods. In the methods section, please to write the definitions of smoking and alcohol use. |
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## VERSION 2 – AUTHOR RESPONSE

### Reviewer: 1

Reviewer Name: Dongsheng Hu

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Shenzhen, Guangdong

CHINA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I have no further comments.

**Answer:** We feel great thanks for your professional review work on our manuscript.

### Reviewer: 2

Reviewer Name: Renata Kuciene

Institution and Country: Lithuanian University of Health Sciences; Lithuania

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This revised manuscript has been improved. However, the authors need to specify the methods. In the methods section, please to write the definitions of smoking and alcohol use.



**Answer:** We feel great thanks for your professional review work on our manuscript. We added these details in our revised manuscript.