

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Sex-based differences in and risk factors for metabolic syndrome in adults aged 40 years and above in Northeast China: Results from the cross-sectional China national stroke screening survey |
| AUTHORS | Li, Feng-e; Zhang, Fu-Liang; Zhang, Peng; Liu, Dong; Liu, Hao-Yuan; Guo, Zhen-Ni; Yang, Yi |

VERSION 1 – REVIEW

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| REVIEWER | JAAKKO TUOMILEHTO National Institute for Health and Welfare, Helsinki, Finland |
| REVIEW RETURNED | 17-Apr-2020 |

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| GENERAL COMMENTS | This cross-sectional study is confirmatory, it does not provide any new knowledge in the field. The study itself is properly done. It is well-known that the different components of the metabolic syndrome are behaving differently by age between men and women. There are linguistic and technical errors in the text. |
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| REVIEWER | Roya Kelishadi Isfahan University of Medical Sciences |
| REVIEW RETURNED | 08-Jun-2020 |

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| GENERAL COMMENTS | he rationale and novelty of the study should be explained. -Actually, the paper is like a report not an original article. -The introduction is too long. The well-known facts should be summarized. -The discussion is weak with a superficial view on items presented. -The interpretation of findings should be expanded in the discussion. -The study limitations should be explained in more detail. -The conclusion should be modified to be more concise and precise. -The English writing should be improved. |
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| REVIEWER | Dug Yeo Han Starship Child Health Auckland District Health Board New Zealand |
| REVIEW RETURNED | 14-Sep-2020 |

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| GENERAL COMMENTS | 1. How to measure physical inactivity? 2. The Authors haven't explained why Mann-Whitney U test was used. |
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| | <p>3. Page 9: In Table 1, z value and chi-square in the heading are confused.</p> <p>4. Page 11: 2. MS prevalence – interpretation results is not clear.</p> <p>5. Page 12 and Page 13: residual P <0.001). – what do you mean by residual?</p> |
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| REVIEWER | Mintu Nath The University of Aberdeen, United Kingdom |
| REVIEW RETURNED | 26-Sep-2020 |

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| GENERAL COMMENTS | <p>The study investigates the prevalence of Metabolic syndrome (MS) in a cross-sectional study from China. Authors employed a multistage stratified cluster sampling method and meticulously planned the sampling strategy with the details of inclusion and exclusion criteria. The presentation of statistical methodologies and modelling scenarios, however, is inadequate in this manuscript. For example, it is not clear why authors used the Mann-Whitney U test and chi-square tests to compare the sex differences, and how the outcomes from these tests informed subsequent statistical modelling decisions. Authors did not elaborate on the model selection strategies for the multivariable logistic regression. The results section included detailed descriptions of single-variable models accompanied by long tables without addressing the issue of multiple comparisons. These tables also do not add values to the main objectives of the study. Tables 2a, 2b and 3 are unnecessary while the text merely presents the data given in these tables. Table 4 is the only useful table in this manuscript. In the context of an observational study, it is important to comment on confounding variables and how the study dealt with the issue. The authors did not explore the possibility of interaction terms between different predictors. A subgroup analysis, as presented in this study, does not provide comparable evidence regarding the effect size in female compared with male. One possible option could be to model the full data and adjust the model incorporating the gender effect along with the interaction terms of gender with other predictors. Finally, the over-emphasising and over-interpretation of the p-values throughout the manuscript is somewhat distracting; a more meaningful approach would be to examine the effect size, confidence intervals, clinical relevance as well as a critical appraisal of the generalisability of the effect. Overall, authors should add further clarity in the statistical methodologies as well as presentation and interpretation of the results.</p> |
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Question:

This cross-sectional study is confirmatory, it does not provide any new knowledge in the field. The study itself is properly done. It is well-known that the different components of the metabolic syndrome are behaving differently by age between men and women.

Answer:

Thank you for your affirmation and professional comments. Just as you said, this study is a cross-

sectional study. But our study has some novelty. In this study, we aimed to seek sex-specific risk factors and preventive measures in Northeast China, a region with cold weather, low incomes, and quite high incidence of MS and cardiovascular disease, especially the highest incidence and mortality of stroke (365 and 159/100 000 person-years) in China. In order to control and prevent the risk of MS and cardiovascular disease more effectively, it is needed to understand modifiable lifestyle determinants of MS in different genders and further identify high risk population according to sex-specific images with risk factors of MS. Appeal to public attention to active lifestyle, preventive interventions in order to reduce fundamentally MS incidence and the cardiovascular diseases burden.

Question:

There are linguistic and technical errors in the text.

Answer:

Thank you for your comments. Language has been embellished and modified by a professional English language editor. The methods part/statistical analyses have been revised by a statistical expert.

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Reviewer 2:

Question:

The rationale and novelty of the study should be explained.

-Actually, the paper is like a report not an original article.

Answer:

Thank you for your professional and transparent comments. This study is a cross-sectional survey. But our study has some novelty. In this study, we aimed to seek sex-specific risk factors and preventive measures in Northeast China, a region with cold weather, low incomes, and quite high incidence of MS and cardiovascular disease, especially the highest incidence and mortality of stroke (365 and 159/100 000 person-years) in China. In order to control and prevent the risk of MS and cardiovascular disease more effectively, it is needed to understand modifiable lifestyle determinants of MS in different genders and further identify high risk population according to sex-specific images with risk factors of MS. Appeal to public attention to active lifestyle, preventive interventions in order to reduce fundamentally MS incidence and the cardiovascular diseases burden.

Question:

The introduction is too long. The well-known facts should be summarized.

Answer:

Thank you for your comment. We have summarized and revised the introduction in the article. (note in page 6, line 4-14)

Question:

The discussion is weak with a superficial view on items presented.

Answer:

Thank you for your comment. We have redone the statistical tabulation and revised the discussion systematically in the article according to your advice and that of the statisticians. (Table 1: note in page 11-12; Table 2: note in page 12-13; Table 3: note in page 15; discussion: note in page 15 line 9-page 20 line 15)

Question:

-The interpretation of findings should be expanded in the discussion.

Answer:

Thank you for your comment. We have analyzed in detail and expanded the interpretation of findings in the discussion. (note in page 15 line 9- page 20 line 15)

Question:

-The study limitations should be explained in more detail.

Answer:

Thank you for your comment. We have explained the study limitations in more detail in the article. "There were also several limitations to this study, such as some self-reported data collected, blood samples measured only once, a lack of consideration of certain lifestyle factors or residual confounders, people sick or too weak excluded. Besides, the conclusion from cross-sectional studies cannot be used for causal inferences, and prospective and randomized studies are needed." (note in page21, line4-9)

Question:

-The conclusion should be modified to be more concise and precise.

Answer:

Thank you for your comment. We have revised the study conclusion more succinctly and accurately in the article. "In our study, the prevalence of MS in women was significantly higher than that in men in Northeast China. It is necessary to accurately identify groups at high risk of MS based on sex-specific factors. We observed that those at the highest risk were elderly women with a low level of education and men with physical inactivity, excessive alcohol consumption, and a lower than college level of education. Abnormal BMI and large neck circumference were risk factors in both sexes. Health management and disease prevention organizations need to actively publicize such information to increase public attention and encourage those at risk to actively change their lifestyle and reduce the impact of preventable risk factors. These changes could fundamentally reduce the growing incidence of MS and the cardiovascular disease burden. There were also several limitations to this study, such as some self-reported data collected, blood samples measured only once, a lack of consideration of certain lifestyle factors or residual confounders, people sick or too weak excluded. Besides, the conclusion from cross-sectional studies cannot be used for causal inferences, and prospective and randomized studies are needed." (note in page 20, line 17 - page 21, line 9)

Question:

-The English writing should be improved.

Answer:

Thank you for your comments. Language has been embellished and modified further by an English language editor. More efforts are needed to improve my English writing.

Reviewer 3:

Question:

1. How to measure physical inactivity?

Answer:

Thank you for your accurate and clear comments. Physical inactivity is defined as insufficient physical activity (attached in the Supplementary table S1), relative to the physical activity, which is defined as the performance of heavy physical labor or regular physical exercise for more than one year, more than 3 times per week, and for at least 30 minutes per session according to the Nutrition and Health

Status of the Chinese People from the journal of China Healthcare & Nutrition 2004.

Question:

2. The Authors haven't explained why Mann-Whitney U test was used.

Answer:

Thank you for your comments. The normality of data was tested by Kolmogorov-Smirnov test. Continuous variables of non-normal distribution were presented as median (IQR). Mann Whitney U test was used to test the difference between the two groups of data with non-normal distribution. Categorical data were presented as number and proportions. The differences between groups were compared using χ^2 -test. Significant variables (those with $P < 0.05$) in univariate analysis were selected for multivariate analyses. Multiple logistic regression analysis was used to explore the independent risk factors of MS in different sexes, and the OR and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using IBM SPSS 23.0 (SPSS, Inc., New York, NY, USA). $P < 0.05$ was considered statistically significant.

Question:

3. Page 9: In Table 1, z value and chi-square in the heading are confused.

Answer:

Thank you for your comments. Yes, we have revised and got rid of the previous table 1, and new table 1 presents the content of sex differences in demographic characteristics and risk factors among participants with MS.

Question:

4. Page 11: 2. MS prevalence – interpretation results are not clear.

Answer:

Thank you for your comments. Yes, we have revised the content of MS prevalence. "Among the 4,100 participants who completed the face-to-face survey, 4,052 were included in the analysis. A total of 2,030 individuals met the criteria for MS, and the prevalence was 50.1% overall (38.4% in males and 57.9% in females; $p < 0.001$)." (note in page 10, line 13-15)

Question:

5. Page 12 and Page 13: residual $P < 0.001$). – what do you mean by residual?

Answer:

Thank you for your comments. We used 'residual' wrongly as 'else '. We have deleted the content and relative table 2a, and change into Table 2 in the article about MS distribution and risk factors according to different demographic characteristics and sex of men and women. (note in page 12-13)

Reviewer: 4

Question:

The presentation of statistical methodologies and modelling scenarios, however, is inadequate in this manuscript. For example, it is not clear why authors used the Mann-Whitney U test and chi-square tests to compare the sex differences, and how the outcomes from these tests informed subsequent statistical modelling decisions. Authors did not elaborate on the model selection strategies for the multivariable logistic regression.

Answer:

Thank you for your professional comment. We totally agree with the reviewer that the statistical analysis part of the manuscript was not fully presented. In the revised manuscript, we explained the

reason for using Mann-Whitney U and chi-square tests. Moreover, we explained that the purpose of univariate analysis was to screen the independent variables included in the multi factor model. "The Mann-Whitney U test was used to assess differences between two groups of data with non-normal distributions. Categorical data are presented as numbers and proportions. The differences between groups were assessed using the χ^2 -test. Significant variables (those with $P < 0.05$) identified in the univariate analysis were selected for the multivariate analyses. Multiple logistic regression analysis was used to explore the independent risk factors of MS in the two sexes, and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated." (note in page 10, line1- 6)

Question:

The results section included detailed descriptions of single-variable models accompanied by long tables without addressing the issue of multiple comparisons. These tables also do not add values to the main objectives of the study. Tables 2a, 2b and 3 are unnecessary while the text merely presents the data given in these tables. Table 4 is the only useful table in this manuscript. In the context of an observational study, it is important to comment on confounding variables and how the study dealt with the issue.

Answer:

Thank you for your comments. We have redone the statistical tabulation and revised the results and discussion systematically in the article according to your advice. The revised table and text highlights sex differences. The results of the manuscript were reanalyzed. Table 1 describes the basic characteristics of the MS population. In Table 2, univariate analysis was conducted in men and women separately, to screen the independent variables that could be included in the multivariate analysis. Table 3 shows the results of multivariate analysis. The results show which factors may be related to the prevalence of metabolic syndrome in male population and which factors may be related to metabolic syndrome in female population. (note in page 10, line 23-page 15 line 4; Table 1: note in page 11-12; Table 2: note in page 12; Table 3: note in page 15)

Question:

The authors did not explore the possibility of interaction terms between different predictors. A subgroup analysis, as presented in this study, does not provide comparable evidence regarding the effect size in female compared with male. One possible option could be to model the full data and adjust the model incorporating the gender effect along with the interaction terms of gender with other predictors.

Answer:

Thank you for your comments and possible option. The revised table and text highlights sex differences. According to our research purposes, the interaction between factors does not seem to have to be included in our research. We got this conclusion based on two similar articles that searched from PubMed (1. Zhang et al. Sex difference in the prevalence of and risk factors for cognitive impairment no dementia among the elderly in a rural area of northern China: A population-based cross-sectional study. *Neuroepidemiology*. 2019;52(1-2):25-31. 2. Qi et al. Sex-specific differences in the prevalence of and risk factors for hyperuricemia among a low-income population in China: a cross-sectional study. *Postgrad Med*. 2020 Aug;132(6):559-567.).

Question:

Finally, the over-emphasising and over-interpretation of the p-values throughout the manuscript is somewhat distracting; a more meaningful approach would be to examine the effect size, confidence intervals, clinical relevance as well as a critical appraisal of the generalisability of the effect. Overall, authors should add further clarity in the statistical methodologies as well as presentation and interpretation of the results.

Answer:

Thanks for your accurate guidance on the discussion. The revised article focuses on the discussion point from the P-value to the OR value after the P-value is meaningful, and further discusses the risk with MS and sex differences. We admire the rigorous attitude of the reviewer and hope that our changes to the manuscript can meet the requirements of the reviewer. (discussion: note in page 15 line 7- page 20 line 15)

VERSION 2 – REVIEW

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| REVIEWER | Roya Kelishadi Isfahan University of Medical Sciences, Iran |
| REVIEW RETURNED | 03-Dec-2020 |

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| GENERAL COMMENTS | Authors have succeeded to make necessary changes. |
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| REVIEWER | Mintu Nath The University of Aberdeen, UK |
| REVIEW RETURNED | 18-Dec-2020 |

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| GENERAL COMMENTS | <p>The revised version contains fewer tables with more focussed results. However, there are still some shortcomings in this version. For Table 1, I feel that the presentation of summary statistics are adequate. Comparison between male and female and the corresponding p-values are not relevant as these do not add any new information to the core objectives of the study. The text on statistical analysis, results and Table 2 suggest that significant variables, identified from the Mann-Whitney and chi-square tests, were subsequently used for the multivariable logistic regression model. It is not a correct approach since the null hypotheses are different in two scenarios. Table 3 presents the outcomes from the multivariable model. The estimate of OR for BMI is exceptionally high, and the authors did not substantiate this further with additional evidence from the literature. The levels of BMI variables are different in Table 2 and 3. The presentation of results is inadequate as it merely repeats the values presented in the table. The statement like "underweight BMI is a protective factor", is also misleading. What is the clinical significance of such a finding? Finally, I expect that authors should provide an insight into the epidemiological interpretation of the identified risk factors. Overall, it is essential to affirm how the overall conclusions from this study provide any new information.</p> |
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VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

Question:

No.

Answer:

Thank you for your comments.

Reviewer: 4

Question:

For Table 1, I feel that the presentation of summary statistics is adequate. Comparison between male

and female and the corresponding p-values are not relevant as these do not add any new information to the core objectives of the study.

Answer:

Thank you for your comment. Comparison between male and female and the corresponding p-values are not necessary, so I deleted the p value from Table 1. (note in page 11-12, Table 1)

Question:

The text on statistical analysis, results and Table 2 suggest that significant variables, identified from the Mann-Whitney and chi-square tests, were subsequently used for the multivariable logistic regression model. It is not a correct approach since the null hypotheses are different in two scenarios.

Answer:

Thank you for your comment. We have adopted the logistics regression model to redo the univariate analysis in Table 2, and obtained OR value and p-values to identify the significant variables subsequently for the multivariable logistic regression model. (note in page 13, Table 2)

Question:

Table 3 presents the outcomes from the multivariable model. The estimate of OR for BMI is exceptionally high, and the authors did not substantiate this further with additional evidence from the literature.

Answer:

Thank you for your comment. We have further cited literature to substantiate that the estimate of OR for BMI is exceptionally high. Compared with that with a normal BMI, the risk of metabolic syndrome with an overweight and obese BMI was 3.11- and 17.18-fold in Korean females and 4.30- and 10.91-fold in Korean males without diabetes mellitus, respectively. (note in page 16, line 20-22)

Question:

The levels of BMI variables are different in Table 2 and 3.

Answer:

Thank you for your comment. One of the levels of BMI variables in Table 3 was lost in the course of revision. Now the levels of BMI variables are same in Table 2 and 3, including underweight BMI, overweight BMI, apparently overweight BMI and obesity BMI. (note in page 13, Table 2 and note in page 14-15, Table 3)

Question:

The presentation of results is inadequate as it merely repeats the values presented in the table.

Answer:

Thank you for your comment. We added the analysis of results to state the values presented mainly in the table 3 (note in page 14-15, Table 3). Multivariate analysis reveals that BMI and hip circumference were significantly associated with MS in both men and women. Age, region, and educational

attainment were associated with MS in females, while physical inactivity was associated with MS in males. Neck circumference, an underweight BMI, smoking, and alcohol consumption were not associated with MS in either sex. (note in page 13, line10- page 14, line 2) For males, BMI, hip circumference, and physical inactivity were associated with MS. (note in page 14, line 3) For females, BMI, hip circumference, and advanced age were associated with MS. Rural residence and junior middle school education or above were negatively associated with MS. The higher the education attainment, the lower the risk of MS. (note in page 14, line 9-11)

Question:

The statement like "underweight BMI is a protective factor", is also misleading. What is the clinical significance of such a finding?

Answer:

Thank you for your comment. The statement "underweight BMI is a protective factor" is indeed misleading. We deleted the sentence. And after redoing the univariate analysis in Table 2, we obtained OR value and p-values to identify the significant variables subsequently for the multivariable logistic regression model. But underweight BMI in Table 3 was not significant. (note in page 14-15, Table 3)

Question:

I expect that authors should provide an insight into the epidemiological interpretation of the identified risk factors. Overall, it is essential to affirm how the overall conclusions from this study provide any new information.

Answer:

Thank you for your comments. Northeast China, with its low income level, has a high incidence of MS and cardiovascular diseases, especially the highest incidence and mortality of stroke (365 and 159/100 000 person-years) in China. This study is a cross-sectional epidemiological study which aim to seek sex-specific risk factors and preventive measures in Northeast China with low income, which has quite high incidence of MS and cardiovascular disease. In order to control and prevent the risk of MS and cardiovascular disease more effectively, it is needed to understand modifiable lifestyle determinants of MS in different genders and further identify high risk population according to sex-specific images with risk factors of MS. (note in page 6, line 3-15)

In our study, we found that in addition to being significantly more prevalent in females than in males, a high BMI and large hip circumference were risk factors for MS in both sexes. In addition, advanced age (≥ 65 years) was a risk factor only for females, whereas physical inactivity was a risk factor only for males. Furthermore, educational attainment and living in a rural region were negatively associated with MS in women but not in men. (note in page 15, line 7-12) The similarities of risk factors of MS are abnormal BMI and large hip circumference in both sexes. BMI combined with hip circumference is an effective indicator of being overweight or obese, and such individuals are more prone to developing MS. Whether obesity or insulin resistance is a cause or consequence of MS is still under debate. Adipokines produced by abnormal adipocytes cause insulin resistance and visceral obesity may be a causal factor of metabolic disease. (note in page 17, line 10-15) The sex-related differences of MS prevalence were shown to be greater in women of advanced age, but remained relatively stable with respect to age in men. As estrogen levels decrease in women after menopause, an increase in insulin resistance and abnormal lipid metabolism result. Thus, the sex differences observed may be related to changes in hormone levels, rather than aging itself. (note in page 16, line 15-18) The specific mechanism by which education affects the prevalence of MS is unclear, although it has been

considered that education influences people's lifestyles and positive attitudes toward health, and increases their access to preventive health services. In addition, it is reported in South Korea that negative correlation between educational level and MS prevalence is largely related to the dietary patterns of Koreans (especially in women). (note in page 18, line 5-10) MS was negatively associated with living in rural regions. The differences may be caused by the degree of economic development, life habits, and dietary patterns; for example, rural women have lower fat intake and more activity than urban women. (note in page 19, line 2-6)

In our study, we found that risk factors of MS have both sex-based similarities and differences; thus, the prevention and treatment of MS should be based on these sex differences. (note in page 20, line 22- page 21, line 1) To prevent the onset of MS, a better understanding of modifiable lifestyle factors is needed in high-risk populations; for example, in men who are physically inactive, further effort should be made to control body weight, especially by focusing on reducing high BMI and hip circumference. Moreover, exercise can result in high brain insulin sensitivity, which can help to lose more body weight and body fat with a lower regain.⁵¹ For women, especially the elderly outside rural regions, efforts should be made to control weight to maintain BMI and hip circumference at normal levels to reduce the risk of MS, and a focus should be directed at changes in hormone levels, especially low concentrations of sex hormone-binding globulin and testosterone, which increase the odds of MS. In the long run, a higher level of educational attainment can reduce the risk of MS. Understanding these factors and the sex differences between them, as well as accurately identifying high-risk groups, could help to develop better public health policies and educational initiatives and reduce the incidence of MS and vascular diseases.(note in page 19 line 19-22- page20, line 1-10) Appeal to public attention to active lifestyle, preventive interventions in order to reduce fundamentally MS incidence and the cardiovascular diseases burden.

VERSION 3 – REVIEW

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| REVIEWER | Mintu Nath University of Aberdeen |
| REVIEW RETURNED | 06-Feb-2021 |

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| GENERAL COMMENTS | <p>I thank the authors for revising the manuscript. I have some minor comments for this version.</p> <p>The authors conducted single variable logistic regression models to identify the significant variables for the multivariable logistic models, however, the Methods section still include the reference to the Mann-Whitney and Chi-squared tests (Page 10: 24-25, Page 11: 1-2). Please edit the text appropriately.</p> <p>Also, mention the statistical test used to test the prevalence of MS in male and female populations.</p> <p>For descriptive statistics presented in Table 1, avoid using the word 'likely' in the text.</p> <p>For Tables 2 and 3, present OR (95% CI) as two decimal places and the p-values as three decimal places (p<0.001 if smaller).</p> <p>An appropriate statistical terminology should be single variable (or simple) and multivariable (or multiple) logistic regression models. Both are technically 'univariate' models. The 'multivariate' is not the correct term for the models explored in this manuscript.</p> |
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VERSION 3 – AUTHOR RESPONSE

Reviewer: 4

Question:

The authors conducted single variable logistic regression models to identify the significant variables for the multivariable logistic models, however, the Methods section still include the reference to the Mann-Whitney and Chi-squared tests (Page 10, line24-25 and Page 11, line 1-2). Please edit the text appropriately.

Also, mention the statistical test used to test the prevalence of MS in male and female populations.

Answer:

Thank you for your comment. I deleted the redundant content about the Mann-Whitney and Chi-squared tests, as well as the related statistical test to test the prevalence of metabolic syndrome. (note in page 9- 10).

Question:

For descriptive statistics presented in Table 1, avoid using the word 'likely' in the text.

Answer:

Thank you for your comment. We have rewritten the inaccurate sentences that contain "likely". (note in page 11, line 2-5)

Question:

For Tables 2 and 3, present OR (95% CI) as two decimal places and the p-values as three decimal places ($p < 0.001$ if smaller).

Answer:

Thank you for your comment. We have further revised Tables 2 and 3 as two decimal places and the p-values as three decimal places. (note in page 13: Table 2; page 14-15: Table 3)

Question:

An appropriate statistical terminology should be single variable (or simple) and multivariable (or multiple) logistic regression models. Both are technically 'univariate' models. The 'multivariate' is not the correct term for the models explored in this manuscript.

Answer:

Thank you for your comment. We have revised the inaccurate words of 'univariate' and 'multivariate'. (note in page 10, line 2; page 12, line 6 and 18; page 13, line 6 and 8; page 14, line 19)

Once again, we appreciate the constructive feedback on our submission.