Author’s response to reviews

Title: What is the impact of metabolic syndrome and its components on reflux esophagitis? A cross-sectional study

Authors:

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Author’s response to reviews:

Dear Editor:

I am very grateful to your kind letter of “What is the impact of metabolic syndrome and its components on reflux esophagitis? A cross-sectional study” (BMGE-D-18-00399) on October 9, 2018. We revised the manuscript in accordance with the reviewers’ comments and requests, and carefully proof-read the manuscript to minimize typographical, grammatical, and bibliographical errors. We also added acknowledgement to the funding from Changhua Christian Hospital Research Project 106-CCH-IRP-021.

Here below is our description on revision according to the reviewers’ comments.

Part A (Reviewer 1):

Major concerns:

1. Comment: A unusually high prevalence of reflux esophagitis found in this study sample may imply a special study population. Therefore, the author should describe more in details of the study population, such as comorbidities, comediations (e.g. NSAID), social economic status, and life styles etc, which should be listed in Table 1.
Reply: Thank you for providing these insights. We have revised the Table 2 and rewritten the text (Results section, p.11-12, lines 178-183) to provide information about comorbidities of the study population. However, we are unable to provide the details of comediations, social economic status and lifestyles because this is a retrospective cross-sectional study and we did not collect the above information in our health examination questionnaire. Therefore, we include the above arguments in the study limitation (Discussion section, p.18-19, lines 303-311).

2. Comment: Another possible explanation for the high prevalence of reflux esophagitis is the overdiagnosis. Therefore the authors should report the prevalence of reflux symptoms in this population if possible as well as the reliability of the endoscopic diagnosis of reflux esophagitis. Should the authors also report other relevant endoscopic findings such as hiatal hernia, peptic ulcer disease, and H. pylori?

Reply: Thank you for your suggestion. First, we agree with you about the possible explanation of the high prevalence of reflux esophagitis is the overdiagnosis. Therefore, we included the argument in study limitation (Discussion section, p.18, lines 300-301). Second, we provide the other endoscopic findings (including hiatal hernia, peptic ulcer disease, and H. pylori infection) in Table 2 and revised the text (Results section, p.11-12, lines 178-183). After multivariate logistic regression analysis (model 2 & 3), there is a strong correlation between hiatal hernia and reflux esophagitis and peptic ulcer disease and H. pylori infection both showed no significant relationship with reflux esophagitis.

3. Comment: Both smoking and alcohol are associated with reflux esophagitis in this study, however, their definition and prevalence were not reported as the potentially important confounders.

Reply: Thank you for your comments. The definitions and prevalence rates of smoking and alcohol drinking were mainly showed in the revised Table 2. As long as the patient has smoke, he/she was classified as a smoking group. Alcohol drinking and betel nuts chewing were also defined in the same way. We can’t provide further information about pack-year of smoking, alcohol type, and drinking amount (such as c.c. per day) because this is a retrospective study and we didn’t collect the above information in our health examination questionnaire, which may lead to information bias. We also revised the text (Methods section, p.7, lines 114-115) to reflect this comment.

4. Comment: One important finding of this study is the association between the severity of reflux esophagitis and the number of component of metabolic syndrome. However, it would be more clear if the author can report the odds ratios with adjustments to demonstrate a dose-response relation, instead of the trend test analysis alone. Similarly, a dose-response relation can be showed to demonstrate the odds ratios of reflux esophagitis in different number of component of metabolic syndrome, using 0 component as reference.
Reply: Thank you for raising this important point of view. Therefore, we first performed a univariate logistic regression analysis to compare the association between reflux esophagitis and the number of metabolic syndrome components (see in Table 2). A dose-response relation was found between reflux esophagitis and the number of metabolic syndrome components. The positive relation persisted in the multivariate logistic regression analysis after adjusting for age and gender (see in the new Table 3 and Results section, p.13, lines 213-216).

Minor concerns:

1. Comment: Table 1 & Table 2 are considerably overlapping and should be merged.

Reply: Thank you for your kind suggestion. However, we found it is hard to merge Table 1 and Table 2. We will explain the reasons below. Table 1 showed demographic characteristics of the study population, which presented as continuous variables. Several clinical variables in Table 2 are defined by the parameters in Table 1, including (a) elevated blood pressure: defined as elevated SBP, elevated DBP, or hypertension history (b) hyperglycemia: defined as elevated fasting blood glucose, elevated HbA1C or diabetes history (c) abdominal obesity: defined as waist circumference ≥80cm in males and ≥90cm in females, and (d) reduced HDL-C: defined as HDL-C <40mg/dL in males and <50mg/dL in female. We wanted to present the demographic characteristics first and then compared the indicative clinical variables between the groups with and without reflux esophagitis. Due to the above reasons, it's hard to provide so much information in the same table and it’s not confusing. We replaced the title of Table 1 [Baseline characteristics of the study population] with [Demographic characteristics and clinical parameters of the study population (continuous variables)] to use more precise terms. We also add the reference values in Table 2 to establish a clearer focus. Please see Results section (p.11-12, lines 176-183) for the interpretation of Tables.

2. Comment: Table 3 & Table 4 are also overlapping and should be merged if possible. Besides, BMI should be one of the independent factors in the models.

Reply: We agree with you and merge the two tables, as shown in the new Table 3. Three different models of multivariate logistic regression analysis were included in Table 3. Please see Results section (p.12, lines 184-218) for the interpretation of Table 3, and we believed these revisions provide a more thorough discussion.

3. Comment: The text of the results should be avoided to duplicate the content of Tables.

Reply: We agree with you and have rewritten the Results section (p.11-14, lines 173-220) to simplify the description (less description of univariate analysis and more of multivariate analysis).
4. Comment: What is the meaning of "Second, the individuals with RE were not evenly distributed among the groups with LA grade A, B, and C, which may also have led to selection bias and influenced the study results." In the discussion page 17?

Reply: Thank you for your question. We wanted to express that since this is a cross-sectional study rather than a randomized controlled trial, bias may occur in the recruitment of study population. We have reflected this comment by revising the text (Discussion section, p.18, lines 302-303).

5. Comment: The authors should clarify the definitions of elevated TG and reduced HDL-C. Do they include the anti-dyslipidemia medication use?

Reply: You have raised an important question. We did not collect the information about anti-dyslipidemia medication use, so we did not include anti-dyslipidemia medication into the definition of elevated TG and reduced HDL-C. We have rewritten text (Methods section, p.10, lines 150-161) to further clarify the definition and also include the arguments in the study limitation (Discussion section, p.19, lines 310-311).

Part B (Reviewer 2):

1. Comment: The methods of the abstract should include more details about the methods used. How was the variables assessed? Which statistical methods were used?

Reply: Thank you for your kind suggestion. We have revised the abstract (Abstract section, p.3, lines 38-42) to be more in line with your suggestion.

2. Comment: In the introduction, excess gastric acid is included in the list of the multifactorial process of RE. However, this is rare and should probably not be listed here.

Reply: Thank you for your suggestion and we removed “excess gastric acid” (Background section, p.5, lines 71-72) and hope that the deletion clarifies the points we attempted to make.

3. Comment: HP-infections are usually reported as negatively associated with GERD/RE, not positively as stated in the introduction.

Reply: Thank you for pointing out the errors in my article. We reviewed the studies (reference 9-13), and revised the text (Background section, p.5, lines 76-77) to fix mistakes. We added reference 13 as supporting evidence.
4. Comment: In the introduction, the authors refer to a Chinese retrospective case-control study claiming causality (ref 24). This should be corrected to "associations", as causation cannot be claimed in such a study.

Reply: We agreed with you and corrected accordingly.

5. Comment: The methods section should include a description of how the included variables from the questionnaires were assessed. What was the questions and response alternatives?

Reply: Thank you for your suggestion. We have reflected this comment by revising the Methods section (p.7, lines 110-115). Revised Table 2 also showed how the variables been assessed.

6. Comment: The discussion should include that the medical history was self-reported and thus could introduce misclassification.

Reply: Thank you for raising an important question. We acknowledge that self-reported medical history has certain study limitations and revised the text (Discussion section, p.19, lines 310-311) to reflect the comment.

7. Comment: Excellent objective assessment of the anthropometric factors.

Reply: Thank you for your compliments.

8. Comment: I disagree with the use of statistical inference using p-values comparing baseline variables as in Table 1.

Reply: Thank you for your suggestion. We have removed p-values in Table 1 and replaced the title of Table 1 [Baseline characteristics of the study population] with [Demographic characteristics and clinical parameters of the study population (continuous variables)] to use more precise terms. We hope that the revision clarifies the points we attempted to make.

9. Comment: In the text of the results, the focus is on the univariate results, but should be on the adjusted multivariate results. The univariate results could be reduced and the multivariate increased.

Reply: We have merged Table 3 and Table 4, and rewritten the Results sections (p.11-14, lines 178-220) to be more in line with your comments.
10. Comment: I do not understand why the multivariate results are separated in two tables. They should be presented in one table of the main multivariable results, including all the relevant variables.

Reply: Thank you for your comment and please see point 9 above.

11. Comment: Why did the authors adjust for BMI only and not WC only, as WC is probably the stronger risk factor of the two?

Reply: Thank you for your question. I originally misunderstood the meaning of “adjust for” at first and tried to fix the mistakes in the new Table 3. Please see the model 2 in the new Table 3. Because of the strong collinearity between BMI, abdominal obesity, elevated triglycerides, HDL-C and elevated blood pressure, we excluded these variables from model 2. We also excluded betel nuts chewing due to its strong collinearity between smoking and betel nuts chewing. As for the model 3, we excluded BMI rather than WC because WC is one of the MetS components and it is known to be a stronger predictor for cardiovascular disease (see in Discussion section, p.14-15, lines 229-240). Therefore, we thought WC might be the stronger risk factor than BMI.

12. Comment: In the presentation of the results it is not possible to understand which variables are compared to each other. What is the reference value? This should be explained in the methods section, as commented above.

Reply: We agree with your assessment and therefore add the reference values in Table 2 to establish a clearer focus. We also revised a part of Methods section (p.7, lines 110-115 and p.10, lines 150-161) to clarify the definition of each component of metabolic syndrome and other variables. We think these changes now better.

13. Comment: The discussion is a very nice discussion of the different factors involved and the strengths and limitations of the study, except missing a discussion of the problem with self-reported medical history.

Reply: Thank you for your kind suggestion and please see point 6 above.

14. Comment: In the discussion, calcium channel blockers are stated as important "causative factors". I believe this should be "associated factors".

Reply: We agreed with you and corrected accordingly.

15. Comment: In tables 2-4 it is hard to understand what is the outcome and what is the comparison. This would have been easier to understand if the variables where better reported in
the methods section. The tables should also state what the analyses are adjusted for? Adjusted for all the other variables?

Reply: Thank you for your comment and please see point 12 above.

16. Comment: Figure 2 is very nice and illustrative.

Reply: I am very grateful for your compliments.

A revised manuscript with the correction sections red marked was attached as the supplemental material and for editing purpose. All the lines and pages indicated above are in the revised manuscript.

Thank you and all the reviewers again for the kind advice.

Sincerely yours,

I-Ching Lin