

March 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6214-review.doc).

**Title:** Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and gastric cancer susceptibility: A meta-analysis

**Author:** Lei-Zhou Xia, Yi Liu, Xiao-Zhou Xu, Peng-Cheng Jiang, Gui Ma, Xue-Feng Bu, Yong-Jun Zhang, Feng Yu, Ke-Sen Xu, Hua Li

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6214

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Response to Reviewer #2:

There are multiple formatting errors and typos within the manuscript that need to be checked.

1. We have tried our best to correct grammatical errors and our revised manuscript has been polished by native scientific English editor.

The authors should present the results of this meta-analysis using the Forrest plots

1. First, we agree with your perspective that forest plots make the article far more comprehensible and illustrative compared to the cumulative tables. However, we analyzed the association between MTHFR C677T and A1298C polymorphisms and with GC under four genetic models respectively, and then performed subgroup analysis according to ethnicity, tumor site and Lauren's classification; finally we analyzed the correlation between cardia GC and non-cardia GC, intestinal GC and diffuse GC. After all these analysis, we obtained 40 forest plots. We think the forest plots were too many, and avoid occupying too much space; we therefore put all results in Tables.

Discussion part of the manuscript should be restructured to outline the major findings of this study. The authors should clearly state the advantages of their meta-analyses in relation to previously published 6 meta-analyses.

2. Discussion part has been recomposed to make major findings highlighted following your comments (Page 8 line 18-31 and Page 9 line 1-9). Moreover, we emphasized the advantage of our current study and addressed it in the manuscript (Page 9 line 10-14).

Conclusions part of the paper should be revised. It should clearly state the major findings of the study, and also briefly state their findings regarding GC location and histological subtype.

3. According to your comments, we restructured the conclusion section, and made a briefly station on findings of overall and subgroup analysis (Page 10 line 7-10).

The last sentence of conclusion section "studies with larger sample size should be performed to assess the function of MTHFR gene in different ethnic groups" is not correct.

4. Sorry for this mistake, we revised this sentence in the manuscript (Page 10 line 11-13).

Page 2, Line 5, Abstract section: the sentence "A total of 35 studies from 26 eligible publications were included in this meta-analysis" is confusing and needs to be checked. The same applies to the result section page 5, line 23.

5. We made modification on the two sections respectively in the manuscript in order to make it easier to understand (Page 3 line 6 and Page 6 line 18-19).

Page 2, Line 15: GCC and NCGC abbreviation explanation missing.

6. The explanation of GCC and NCGC were addressed in the manuscript (Page 3 line 15).

What is meant by "further clinical trials" in the abstract (Page 2 line 23)? The authors should be more careful about such conclusions.

7. Thank you for your comments, we amended this section in the manuscript (Page 3 line 21-22).

SNP "rs" numbers should be included in the paper for the polymorphisms that have been analyzed.

8. We added "rs" numbers for MTHFR C677T and A1298C in the manuscript following your comments (Page 4 line 16-18).

Page 7, line 27: Our data were consistent with four previously published meta-analyses [38-40] – only three meta-analysis are cited here? Besides, there are at least three additional meta-analyses on the topic that the authors did not cite.

9. All related references were inserted in corresponding sections of manuscript (Page 4 line 24 and Page 9 line 10).

Page 8, line 12: Citation is missing to support the statement "To our knowledge, the distributions of the MTHFR polymorphism were different between various ethnic populations.

10. A reference was cited in the end of the sentence (Page 9 line 9).

Page 10, line 2: The statement "The authors of this study indicate no financial conflict of interest" has nothing to do with the acknowledgement section.

11. We have deleted acknowledgement section in the manuscript.

Response to Reviewer #3:

I recommend the exhibition of the data of the tables 4 and 5 in Forest Plot form.

1. First, we agree with your perspective that forest plots make the article far more comprehensible and illustrative compared to the cumulative tables. However, we analyzed the association between MTHFR C677T and A1298C polymorphisms and with GC under four genetic models respectively, and then performed subgroup analysis according to ethnicity, tumor site and Lauren's classification; finally we analyzed the correlation between cardia GC and non-cardia GC, intestinal GC and diffuse GC. After all these analysis, we obtained 40 forest plots. We think the forest plots were too many, and avoid occupying too much space; we therefore put all results in Tables.

In discussion, in third paragraph, authors said that "In regard to the A1298C polymorphism, we found CC genotype conferred susceptibility to GC in western". This affirmative is not correct

2. Following your comments, we revised this sentence in the manuscript (Page 9 line 1-2).

In Results, in "Subgroup analysis", second paragraph, it was written (TT vs. CT+CC: OR = 1.36 [1.15, 1.67], P = 0.0006). According to the table 4, the correct number is OR = 1.38.

3. Sorry for this mistake, we corrected it in the manuscript (Page 7 line 20).

Table 3 and 5 change intestinal by intestinal

4. We corrected these sections completely in our manuscript (Table 3 and 5).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Lj H

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