

## Format for ANSWERING REVIEWERS



February 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7202-Review.doc).

**Title:** Association between Helicobacter pylori infection and migraine: A meta-analysis

**Author:** Jing Su, Xiao-ying Zhou, Guo-xin Zhang

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

**ESPS Manuscript NO:** 7202

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

(1) Reviewed by **00058340:**

1) term " migraineurs" should be changed to "patients with migraine"

**Answer:** Thank you very much for your critical comments. We have screened much literature and found that migraineurs are equal to patients with migraine. We apologize for not giving an explanation in our paper and we have added it in the terminology of the comments.

2) "Therefore, H. pylori infection in migraineurs may be less than or equal to that of healthy people". suggest changing to "Therefore, a prevalence of H. pylori infection in patients with migraine may be less than or equal to that of healthy people".

**Answer:** Thank you very much for your critical comments. We have changed the correct expression in our paper.

3) " Gasbarrini [1] studied 225 patients and H. pylori was detected in 40% of the patients with a positive <sup>13</sup>C-urea breath test" . In current version it means that only 40% of patients with positive <sup>13</sup>C-urea breath test have HP infection, which is not true. I suggest to rephrase to "Gasbarrini [1] studied 225 patients and H. pylori was detected in 40% of the patients by <sup>13</sup>C-urea breath test.

**Answer:** Thank you very much for your critical comments. We agree with your suggestion and have corrected it(Gasbarrini [1] studied 225 patients and H. pylori was detected in 40% of the patients by <sup>13</sup>C-urea breath test).

4) In reference #35 the title of journal, year, vol and pages are missing.

**Answer:** Thank you very much for your critical comments. We apologize for this mistake and we have added the missing information.(Epplein M, Cohen SS, Sonderman JS, Zheng W, Williams SM, Blot WJ, Signorello LB. Neighborhood socio-economic characteristics, African ancestry, and Helicobacter pylori sero-prevalence. *Cancer causes & control*: CCC 2012; 23(6): 897-906 [PMID: 22527167 PMID: Pmc3475203 DOI: 10.1007/s10552-012-9960-7])

5)The authors may wish to add another reference: Savi L, Ribaldone DG, Fagoonee S, Pellicano R.Is Helicobacter pylori the Infectious Trigger for Headache?: a Review. Infect Disord Drug Targets. 2013 Dec 1. [Epub ahead of print] and refer to it in an update at the end of the paper clearly spelling out that after completion of our study a recent review paper indicates that the eradication of H. pylori seems efficient at least in a subgroup of patients suffering from migraine.

**Answer:** Thank you again for your good suggestion. This article is published recently and its result is important to our study. We have added it in the end of our paper (After The completion of our study, a recent review paper also indicates that the eradication of H. pylori seems efficient in patients suffering from migraine[40].) .

(2) Reviewed by 01433781

1)Page 8: The following part need to be fixed: Two Studies were included in the positive rate of H. pylori was greater in the migraine Group than that in the control group (OR=3.60, 95% CI: 2.09–6.19, P=0.000). Three Studies were included in the high quality group, and the positive rate was similar between the migraine and control groups (OR=1.23, 95% CI: 0.90–1.69, P=0.190) .

**Answer:** Thank you very much for your critical comments. We apologize for this mistake. We have corrected it in our paper. (Two studies were included in the low quality group, and the pooled data indicated that the positive rate of H.Pylori was greater in the migraine group than that in the control group ).

2) References Number 16 and 30 are the same.

**Answer:** Thank you very much for your critical comments. We apologize for our mistake. The number 16 and 30 references are different studies and we have corrected them in our paper.(16. Ciancarelli I, Di Massimo C, Tozzi-Ciancarelli MG, De Matteis G, Marini C, Carolei A. Helicobacter pylori infection and migraine. Cephalalgia: an international journal of headache 2002; 22(3): 222-225 [PMID: 12047462]; 30. Mavromichalis I. The role of Helicobacter pylori infection in migraine. Cephalalgia: an international journal of headache 2003; 23(3): 240; author reply 240-241 [PMID: 12662197] )

3) Figures are of poor quality especially Figure 1 .There are several typing errors that need to be fixed.

**Answer:** Thank you very much for your critical comments. The figures are not clear in our paper due to the software. We have regenerated the pictures and we could provide clear figures of Tif. We have invited a native English speaker to help us improve our language and we have checked and corrected our spelling carefully.

(3) Reviewed by 02438007

**Answer:** Thank you very much for your appreciation.

(4) Reviewed by 00503535

1)The reviewer's only question is as follows: The levels of H. pylori infection among migraineurs were greater than those in the control group in Asia, but not statistically significant in Europe. It is very interesting. These facts might result from a significantly greater prevalence of H. pylori cagA-positive strains in Asia. Please discuss precisely.

**Answer:** Thank you very much for your critical comments. The problem you asked is worthy of discussing. We have discussed this problem in our paper, but there are few studies focusing on the H. pylori cagA-positive strains infection and migraine. (Furthermore, our subgroup analysis found that the levels of H. pylori infection among migraineurs were greater in Asia, but not statistically significant in Europe. This fact might result from a significantly greater prevalence of H. pylori cagA-positive strains in Asian countries[36]. It has been shown that cagA-positive strains cause greater release of cytokines by gastric epithelial cells[37]. The high persistent inflammatory response to cagA-positive strains of the bacterium induces a hyperreactivity of cerebral vessels to various well-known trigger factors such as psychologic or physical stress, peculiar foods, female hormones and others, which are related with migraine[1])

(5) Reviewed by 02536365

- 1) All included studies were from a particular geographic area: Countries of the Mediterranean except Iran. In my opinion, results of this meta-analysis could not represent worldwide- population of H.pylori infection or migraine. Besides, Turkey, classified with Asia in this meta-analysis, seems to have close relationship with both Italy and Greece in historical or geographic aspects. Therefore, a major conclusion of this analysis, a significantly greater infection rate of H. pylori in migraineurs in Asia, should be seriously reconsidered.

**Answer:** Thank you very much for your critical comments. We have performed a Systematic literature search of PubMed and Embase, which could almost contain all articles. We found the studies about H. pylori infection and migraine were few and only five studies from Italy, Turkey, Greece and Iran could be included in our meta-analysis. Turkey is a contiguous transcontinental country located mostly in Asia. Whether Turkey is an Asian country or Europe country is still controversial. Considering that 97% of Turkey's land area is in Asia and Turks are original from Middle-Asia, we made Turkey as Asian Country in subgroup analysis.

- 2) Although a study of Gasbarrini et al. showed no relationship between H.pylori infection and migraine, they insisted that H.pylori infection was strongly associated with migraine with aura (a subtype of migraine). Meanwhile, other studies showed relationship between H.pylori infection and migraine without aura. As authors described on Information section, there were some differences on pathophysiology between migraine with and without aura. Therefore, analysis for subgroup of migraine would be recommended.

**Answer:** Thank you very much for your critical comments. We agree with your Suggestion. However, considering the five included studies, one study (Gasbarrini et al) could provide the accurate data about the rate of helicobacter pylori infection in migraine with aura, another one(Yiannopoulou KG) could provide information in migraine without aura, the remaining three articles could not provide the data about different type of migraine .we are unable to make subgroup analysis.

- 3) Although the authors used the random effect model for analysis, heterogeneity is too significant to draw certain conclusions. As authors documented, sample size is too small to draw certain conclusions, which might be the most serious limitation of this analysis.

**Answer:** Thank you very much for your critical comments. The heterogeneity in our study is high and we have performed unconditional logistic regression and subgroup analysis to explore the sources of heterogeneity and found that geographic distribution is the most important influencing factor. Meantime, a recent review calculated the similar result that the eradication of H. pylori seems to be efficient in patients suffering from migraine. Therefore, considering obvious heterogeneity, our study suggests a trend of more

frequent *H. pylori* infections in patients and we recommend patients of migraine with *H. Pylori* eradication. More studies including larger sample sizes should be done in the future to further clarify the association between *H. pylori* infection and migraine.

3 References and typesetting were corrected

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

Sincerely yours,

Guoxin Zhang M.D. Ph.D

Department of Gastroenterology

The First Affiliated Hospital of Nanjing Medical University

Nanjing Medical University

No.300 Guangzhou Road, Nanjing 210000, China

Tel: +86 25 68136973

Fax: +86 25 68136973

Email: guoxinz@njmu.edu.cn