

January 17, 2016

Re: "Helicobacter Pylori Eradication for Functional Dyspepsia: Systematic Review and Meta-Analysis" (ESPS manuscript NO: 23556)

Dear Editor Yu:

Thank you very much for your email of December 22, 2015 regarding this manuscript. We have revised the manuscript to address the comments of the reviewers. Our point-by-point responses are listed below. In the revised manuscript we have highlighted the changes that were made from the original manuscript in "track changes" and also provided a separate clean version of the revised manuscript.

We eagerly look forward to your response.

Sincerely,

Ning Dai, M.D.

**Reviewer 3 (Reviewer's code 00199523):**

**1. In the abstract, Line 4 of the Methodology section should be corrected (Cochrane Library for those from inception). When was inception. Same for the Methodology section of the full paper.**

The inception year for the oldest electronic database (PubMed) used to search the studies was 1988. We have now revised the Abstract section and added the inception year to the Methods section.

"Randomized controlled trials investigating the efficacy and safety of *H. pylori* eradication for patients with functional dyspepsia published in English (up to May 2015) were identified by searching PubMed, EMBASE, and The Cochrane Library." (Page 3, Line 6)

"PubMed, EMBASE, and The Cochrane Library were searched for published randomized controlled trials (RCTs) in English from 1988 to 2015." (Page 6, Line 10)

**2. The P in Helicobacter should be changed to small letter p everywhere it appeared in the text.**

We have now used the terms "*Helicobacter pylori*" or "*H. pylori*" throughout the manuscript.

**3. Page 12, Line 5- relief should be changed to relieve.**

We have now revised the statement.

"Cognitive-behavioral therapy (CBT), psychotherapy, anxiolytics, and antidepressants can also be taken into consideration to relieve dyspeptic symptoms" (Page 13, Line 14)

**In Line 12, design should be changed to designs.**

We have now revised the statement.

"Secondly, the random effect model was chosen to evaluate the short-term symptom improvement and development of adverse events in the presence of significant study heterogeneity resulting from different study designs and methods." (Page 14, Line 4)

**4. Unqualified use of the word ulceration should be changed to peptic ulceration in the whole text**

We have now used the words “peptic ulceration” or “peptic ulcer” throughout the manuscript.

**5. Reference: The word screen appeared after some references eg refs 25, 26, 30, 31, 32, 33 etc, I wonder the import of this, It should be removed.**

We have now deleted the word “screen” and revised the Reference section according to the journal guidelines.

**Also first letter of words in Journal Title should be capitalized.**

We have capitalized the first letter of words in the Journal Title in reference.

**Reviewer 4 (Reviewer’s code 00068583):**

**The only question for the authors is about the evidence on their suggestion "Eradication therapy is advocated for people with ulcer or gastric cancer family history". This suggestion is not provided in the results neither in discussion, but only in abstract as a core tip.**

We agree with Reviewer that our study did not provide any direct evidence supporting our initial recommendation for *H. pylori* eradication in patients with peptic ulcers or family history of gastric cancer. We have now provided additional analysis that evaluating the proportion of patients who had histological resolution of chronic gastritis comparing eradication to control. Ten studies reported histological outcomes following intervention. Our analysis demonstrated that a higher proportion of patients achieved histologic resolution of chronic gastritis after *H. pylori* eradication compared to control (RR=7.13; 95% CI 3.68-13.81,  $P<0.00001$ ).

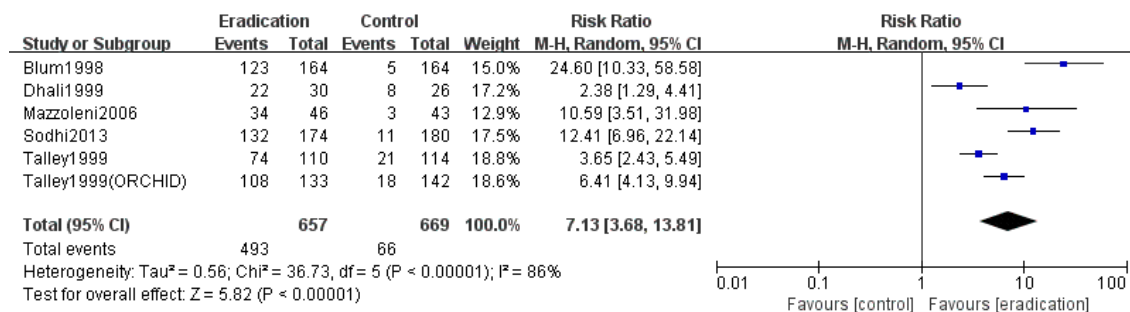
We have now added the results of the additional analysis in the Abstract, Method, Result and Figure sections.

“Ten studies demonstrated that patients who received *H. pylori* eradication were more likely to obtain histologic resolution of chronic gastritis compared to no eradication therapy (RR=7.13; 95% CI 3.68-13.81,  $P<0.00001$ ).” (Page 4, Line 2)

“The secondary outcomes were the pooled RR of improvement of dyspepsia at short-term (<1 year) and long-term (>1 year) follow-up, standard mean difference (SMD) of improvement in life’s quality (SF-36), pooled RR of incidence of peptic ulceration during follow-up, pooled RR of development of treatment-related adverse events, and pooled RR of histologic resolution of chronic gastritis.” (Page 7, Line 17)

“Ten studies that reported histological outcomes following intervention (Figure 10). Patients who received *H. pylori* eradication were more likely to obtain histologic resolution of chronic gastritis compared to control (RR=7.13; 95% CI 3.68-13.81,  $P<0.00001$ ).” (Page 10, Line 18)

**Figure 10. Forest plot of the effects comparing *H. pylori* eradication vs. control on histologic resolution of chronic gastritis.**



Furthermore, we have now deemphasized our initial point by deleting the statements advocating eradication for people with peptic ulcers or family history of gastric cancer in the Abstract and the Core Tip sections. We have also modified the statement in the Discussion section to deemphasize this point given that no direct evidence to support our recommendation was provided in the Result section.

“Firstly, eradication therapy may be preferable among patients with risk factors for peptic ulcer or gastric cancer. Our meta-analysis showed benefit for other long-term outcomes such as reduction in incidence of future peptic ulcer disease and resolution of gastritis, which are associated with gastric cancer.<sup>[50, 51]” (Page 12, Line 18)</sup>

#### **Additional Main Corrections:**

1. We have made grammatical revisions to improve the clarity of the manuscript in the manuscript with tracking changes.
2. We have changed the order of third (JJK) and fourth (SK) authors.
3. We have changed “summary RR” to “pooled RR” throughout the manuscript.
4. In the Abstract, Methods, and Result sections, we have revised the following sentences to clarify the definition of long-term (>1 year) and short-term (<1 year) improvement in dyspepsia.

“Twenty-three of these studies were used to evaluate the benefits of *H. pylori* eradication on symptom improvement; the pooled RR was 1.23

(95% CI, 1.12-1.36,  $P<0.0001$ ). *H. pylori* eradication demonstrated symptom improvement during long-term follow-up at  $>1$  year (RR=1.24; 95% CI 1.12-1.37,  $P<0.0001$ ), but not during short-term follow-up at  $<1$  year (RR=1.26; 95% CI 0.83-1.92,  $P=0.27$ ).” (Page 3, Line 12)

“The secondary outcomes were the pooled RR of improvement of dyspepsia at short-term ( $<1$  year) and long-term ( $>1$  year) follow-up, standard mean difference (SMD) of improvement in life’s quality (SF-36), pooled RR of incidence of peptic ulceration during follow-up, and pooled RR of development of treatment-related adverse events.” (Page 7, Line 17)

“*H. pylori* eradication demonstrated symptom improvement during long-term follow-up at  $>1$  year (RR=1.24; 95% CI 1.12-1.37,  $P<0.0001$ ) but not during short-term at  $<1$  year (RR=1.26; 95% CI 0.83-1.92,  $P=0.27$ ).” (Page 9, Line 8)

5. In the Abstract and Results sections, we have now clarified the three statements that contain the RR of *H. pylori* eradication.

“Six studies demonstrated that *H. pylori* eradication therapy reduced the development of peptic ulcer disease compared to no eradication therapy (RR=0.35; 95% CI, 0.18-0.68,  $P=0.002$ ). Eight studies showed that *H. pylori* eradication increased the likelihood of treatment-related side effects compared to no eradication therapy (RR=2.02; 95% CI 1.12-3.65,  $P=0.02$ ).” (Page 3, Line 18)

“Ten studies demonstrated that patients who received *H. pylori* eradication were more likely to obtain histologic resolution of chronic gastritis compared to no eradication therapy (RR=7.13; 95% CI 3.68-13.81,  $P<0.00001$ ).” (Page 4, Line 2)

“*H. pylori* eradication therapy reduced the development of peptic ulcer disease compared to no eradication therapy (RR=0.35; 95% CI, 0.18-0.68,  $P=0.002$ ).” (Page 10, Line 2)

6. We have revised and referenced the statement that provided our systematic review on cost of interventions.

“One study that provided outcome data on the cost of intervention that included medication, diagnostic tests, and physician consultation did not demonstrate a difference between eradication therapy vs. control<sup>[38]</sup>. However, the cost of intervention from this study was estimated from utilization of healthcare rather than the actual cost.” (Page 10, Line 14)

7. The comments were added in the manuscript. (Page15)

8. The supportive foundations, data sharing statement, and acknowledgment sections were added in the manuscript.