Format for ANSWERING REVIEWERS

26, June 2015

Dear Editor,

We would like to thank you for the peer-review of our manuscript. For your convenience you can find at the bottom of this letter a point-by-point reply to the reviewer's comments. After taking the reviewers' comments into consideration, we have revised the manuscript aiming to provide accurate and high-impact information to your readers. Please find enclosed the edited manuscript in Word format. (file name: 18193_review.doc).

Title:
Author: Vasilios Papastergiou, Stylianos Karatapanis, Sotirios D Georgopoulos

Name of Journal: *World Journal of Gastroenterology.*

ESPS Manuscript NO: 18193

The manuscript has been improved according to the suggestions of reviewers:
(Reviewer 1) **Comment:** The manuscript is quite well written It represents a comprehensive topic of the field It would be useful for the readers to include the discussion of PMID 23054412.
Reply: We thank the reviewer for his/her valuable comments. Accordingly, a comment was added quoting this relevant study by Amedei et al (Page 13, last sentence).

(Reviewer 2) **Comment:** Language needs only minor polishing, and apart from minor errors (eg. heading of table 2 is missing), structure and presentation of the manuscript is adequate
Reply: The article was extensively revised for minor grammar/use of English issues, and several parts were rewritten in order to guarantee an adequate level of English.
Comment: A description of the exact methods of the review process is missing. How did the authors search which databases, and which were inclusion or exclusion criteria for selection of references
Reply: A detailed description of the review process is now given at the last paragraph of the introduction. (Pages 4-5)
Comment: The authors use solely the Odds Ratio (OR) in order to describe correlations between H. pylori infection or gastritis and CRC. I doubt that all cited references indeed provided OR for their data. Did the authors calculate the OR, or did the authors only select references that provided OR?
Reply: We thank the reviewer for this constructive comment. Indeed, some of the ORs shown in Table 1 were calculated as many relevant articles did not provided ORs. To make this clear for the reader, this information was added as footnote to Table 1.
Comment: The authors nicely discussed factors causing potential bias in the section "H. pylori infection status and colorectal neoplasia". However, a similar critical discussion of the other parts of the review (cross sectional studies, meta analyses) is completely missing. And there are definitively aspects that should be addressed in order to allow proper interpretation of the data. For example, with regards to the presented meta analyses, the authors should provide information about: a. How many patients have been included in total in the different meta analyses to generate the respective data? b. How many original studies were used in more than just one of the meta analyses to generate data? How big is the overlap of underlying studies between the meta analyses? Are the meta analyses only showing similar results because the cited references are the same? c. What are the inclusion and exclusion criteria of the different meta analyses? Why do some meta analyses include only 9 studies, and others 28 studies? d. Information on quality and

relevance of the different meta analyses are missing. For example, the second graphs states that some meta analyses contain "*only case-control studies", and others "included only data based on East-Asian population". This does not allow proper comparison of the respective results. Similarily, there are no details or critical discussion at all on the selected cross sectional studies provided.

Reply: In lien with these suggestions, we have now extensively discussed on the limitations and possible bias of cross-sectional studies and relevant meta-analyses. Differences regarding the number of included studies among the meta-analyses may be largely explained by different outcomes (eg some meta-analyses pooled data for colorectal polyps, whilst other for adenomas or cancer). After revising the article, we believe that these critical details are now straightforward to the reader. Moreover, we now provide more details (eg; total nr of studies, nr of patients), as well as a comment on the degree of overlap of underlying studies between the meta-analyses (Pages 7-8 of the revised manuscipt).

Comment: The section "H. pylori-related chronic gastritis and colorectal neoplasia" contains only data from a single study. The results from this study are poorly presented (eg: "large national database of 156000 patients (mean age: 58.7 years, 41% males) who had undergone bidirectional endoscopy with biopsy results available from both procedures" => what nation? Why did the patients undergo bidirectional endoscopy? etc Furthermore, limitations of this study were only very briefly discussed.

Reply: We thank the reviewer for these valuable comments. The study by Sonenberg and Gienta is indeed a landmark study. We have now provided a detailed description of the study's methods and results. Moreover, we have critically commented on the limitations of this study (Pages 8-9).

Comment: From the data presented in the section "H. pylori-related gastric premalignant lesions and colorectal neoplasia" the authors conclude that "Progression to H. pylori-related gastric precancerous lesions, namely chronic atrophic gastritis and gastric intestinal metaplasia, appears to enhance by somewhat this risk". This conclusion is in my opinion not supported by the presented data: 4 out of 6 studies show no correlation between atrophic gastritis and neoplasia, one study that shows a positive correlation includes only 99 patients, and the only larger study that supports this statement is the national study that was mentioned earlier, and information about the quality and relevance of this study is missing.

Reply: Indeed, the only histological data to date confirming an association between gastric precancerous lesions and colorectal neoplasia comes from the large-scale study by Sonenberg and Gienta. In accordance with the reviewer's comments, we have now revised our conclusions, including the following amendments (Page 10):

"The only evidence to date supporting a positive association between gastric intestinal metaplasia and the risk of colonic neoplasms comes from the large case-control study by Sonnenberg and Gienta".

"In summary, no solid conclusions can be drawn as yet on whether progression to gastric precancerous conditions (ie; chronic atrophic gastritis and gastric intestinal metaplasia) could enhance the risk of neoplastic transformation in the colon".

Comment: In my opinion, the manuscript would profit from a brief summary of the relevant findings at the end of each paragraph, as results are ofte

Reply: Once again, we are grateful for this valuable suggestion. A brief summary of relevant findings/conclusions was now added at the end of most of the paragraphs/sections.

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

Sincerely yours,

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