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Title: Irritable Bowel Syndrome: Epidemiology, Overlap Disorders, Pathophysiology and Treatment

Authors: Kai-Yue Huang, Feng-Yun Wang, Mi Lv, Xiang-Xue Ma, Xu-Dong Tang , Lin Lv

Dear Editors:

It was a pleasure to get your message from May 12 and to discover that the World Journal of Gastroenterology is likely to publish our manuscript. We carefully updated the manuscript and assembled the necessary materials in accordance with the requirements after carefully reading the remarks of our Editor-in-Chief and peer review. We appreciate the recommendation of the Reference Citation Analysis (RCA), a superb documentation tool that we used to enhance and augment the outcomes of our cutting-edge study. These other sources are listed below:

[96]Keefer L, Ballou SK, Drossman DA, Ringstrom G, Elsenbruch S, Ljótsson B. A Rome Working Team Report on Brain-Gut Behavior Therapies for Disorders of Gut-Brain Interaction. *Gastroenterology* 2022; **162**(1): 300-315 [PMID: 34529986 DOI: 10.1053/j.gastro.2021.09.015]

[84]Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, Agrawal A, Aziz I, Farmer AD, Eugenicos MP, Moss-Morris R, Yiannakou Y, Ford AC. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut* 2021; **70**(7): 1214-1240 [PMID: 33903147 DOI: 10.1136/gutjnl-2021-324598]

[85]Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. *Gut* 2022; **71**(6): 1117-1126 [PMID: 34376515 DOI: 10.1136/gutjnl-2021-325214]

Point-by-point responses to Reviewer comments

Reviewer #1:

Specific Comments to Authors: Dr. Huang and his team's manuscript on the reviewing the results of IBS research on epidemiology, overlap disorders, pathophysiology, and treatment over the past decade and summarizing the latest research frontiers is overall very good prior to the 5th revision of Rome Criteria but it is a quite long. Its epidemiology [Figure 1 is self-exemplary enough], probiotics and FMT could be 1/3 shorten. There is no need Figure 2. I would recommend to add GI food allergy & recent article on post-IBD IBS-D [Dilemma in post-IBD patients with IBS-D: A 2020 overview. Expert Review Gastroenterol & Hepatol, 15: 5-8, 2021] to this nice review.

Comment 1.1: It is a quite long. Its epidemiology [Figure 1 is self-exemplary enough], probiotics and FMT could be 1/3 shorten. There is no need Figure 2.

Reply 1.1: Thank you for your practical comments on our article. Shortening some parts of the article can improve the comfort of reading for the authors, so we made the necessary reductions in the epidemiology section and the probiotics and FMT sections. In the epidemiology section, it was reduced from 466 words at the beginning to 358 words, a reduction of 23.2%; in the probiotics section, only the RCT with a large and representative sample size was left, from 246 words to 152 words, and the FMT was reduced from 183 words to 155 words, for a total of 28.4% reduction and increased readability, with 5003 words in the main text. Since this is a more involved review, we chose to keep Figure 2, which shortens the textual content of the article and allows readers to read the article more quickly.

Comment 1.2: I would recommend to add GI food allergy & recent article on post-IBD IBS-D [Dilemma in post-IBD patients with IBS-D: A 2020 overview. Expert Review Gastroenterol & Hepatol, 15: 5-8, 2021] to this nice review.

Reply 1.2: Thank you very much for recommending such an outstanding article to us. Post-IBD IBS-D is indeed a point of concern, so we have added mucosal eosinophils

as well as intestinal food allergy to the pathogenesis in the original article (Page 10 reference:[69]) and mentioned in the discussion that the role of GI food allergy in IBS should be focused on in the future. The part of the original manuscript where IBD and IBS overlap also mentions IBS after an IBD infection. Thank you very much for your valuable comments on our article and for your contribution to the article's revision.

Reviewer #2:

Specific Comments to Authors: The paper is well written. Few issues. Its repeatedly mentioned that IBS recommendations will need to be reviewed in view of ROME V criteria. But the latter has not even been published. So, it looks like that ROME V terminology is being used unnecessarily. Please mention it just once or twice. Like this line in the Abstract- "With the upcoming Rome V revision, it is necessary to review the results of IBS research in recent years". Please elaborate the scientific basis of this line. Page number not there in manuscript LFD used, full form not there in the text at all Very less mentioned on the role of fiber especially Psyllium husk in IBS. Please see this and include it in discussion properly (<https://pubmed.ncbi.nlm.nih.gov/33893774/>)

Comment2.1: Its repeatedly mentioned that IBS recommendations will need to be reviewed in view of ROME V criteria. But the latter has not even been published. So, it looks like that ROME V terminology is being used unnecessarily. Please mention it just once or twice. Like this line in the Abstract- "With the upcoming Rome V revision, it is necessary to review the results of IBS research in recent years". Please elaborate the scientific basis of this line.

Reply2.1: Thank you very much for your practical comments to us. So that we can see the shortcomings of the article, we appropriately removed the part of the article that unnecessarily mentions the Rome V criteria. In the second paragraph of the conclusion, the findings of the essay are summarized and sorted out, and the essay becomes better after your suggestions are revised (second paragraph of the conclusion). We firmly believe that the revised content can have an enlightening meaning for future research and can allow

the reader to better access the full content. Thank you for your contribution to improving the article.

Comment2.2: Page number not there in manuscript LFD used, full form not there in the text at all Very less mentioned on the role of fiber especially Psyllium husk in IBS. Please see this and include it in discussion properly (<https://pubmed.ncbi.nlm.nih.gov/33893774/>)

Reply2.2: Thank you very much for recommending such an excellent article to me and making up for the shortcomings of the article. In the original article, only LFD was mentioned in the dietary therapy, but the effective fiber dietary therapy for IBS-C was omitted. After reviewing the literature, we added the "FEED" principle of psyllium for IBS-C (page 12,reference:[91]) to make the article more complete. Thank you for your contribution to the revision of our article.