

Response to Reviewer Comments

Dear Editors and Reviewers
World Journal of Gastroenterology

Thank you for your kind and thoughtful comments.

We have revised our manuscript taking the comments from the reviewers into consideration. As per editorial request, we have added a brief introductory section at the beginning of the manuscript. We attach a revised version, with changes highlighted in yellow. Below are the specific responses to reviewers:

1. Reviewer 00055194

1.1. "I consider the manuscript publishable in its current form"

Response: Thank you for your review

2. Reviewer 01468021

2.1. "A failure to replicate animal data in man has been so common in microbiome studies that it has really questioned the validity of animal models or, at the very least, exposed their limitations."

Response: We agree with this statement. We have added a sentence alluding to this in the text (second page, paragraph 2).

2.2. "How about impact of microbiome and interventions that modulate same on GI symptoms in MS"

Response: Indeed, in case series, around a third of all patients with MS have GI symptoms, such as constipation, dysphagia and dyspepsia (Mult Scler Int. 2013;2013:319201). Furthermore, the mechanisms involved are unclear, and likely not solely explained by neurological factors. Associations between these and microbiome changes has not been studied in detail, and is certainly an area of future research. We have added a sentence commenting on this issue (first page, paragraph 4).

2.3 "Your statements about probiotics in UC are a bit contradictory; early in the piece you suggest that they do not work but later allude to some positive studies. Of relevance to MS where,

like UC, the phenotype is varied, some very carefully defined UC subgroups do seem to do well on probiotics.”

Response: The reviewer is correct, and we could have been more clear in our statements. The strongest evidence is on UC, and chronic puchitis. We thus modified our early statements (second page, paragraph 4).

2.4 “Confounders, including GI conditions, such as constipation; common in MS, as well as diet which may be altered in MS, have a major impact on the microbiome. These may not have been accounted for in prior studies.”

Response: Indeed, as stated above, this has not been accounted for and is an interesting outstanding issue. See our comments from 2.2 above.

2.5 “The limitations of many studies in terms of methodology - 16S vs metagenomics and metabolomics, choice of primers, DNA isolation etc. deserve mention.”

Response: The reviewer is right. We have added a sentence mentioning technical/methodological limitations. (first page, paragraph 4).

Thank you again for considering our work

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