Dear reviewers,

Thank you for considering our manuscript for publication in the World Journal of Gastroenterology. We appreciate your time and constructive feedback.

The pages hereunder include comments and answers thereof followed by citations of changes made in the manuscript. All the comments have been read carefully in order to meet your individual requests of modification and deliver thoughtful answers. If an answer is unclear or inadequate, please contact the corresponding author for clarification.

We apologize for the postponement of the first revision and for any inconvenience caused.

Comments from reviewer 00503587, New Zealand

1. *"The title might be revised slightly: the current implication is that this diet was a treatment for IBD (rather than for functional symptoms). The title also suggests that this is beneficial long-term: however, the median follow-up is less than 2 years, which is less than one fortieth of a life-time."*

   The title and subtitle have been revised taking the above points into consideration.

   Page 1, Title page: paragraph 4-5.

2. *"The abstract suggests that patients with functional symptoms on top of underlying IBD had more complete symptom improvement - however the p value listed was above 0.05."*

   The sentence has been corrected to avoid misinterpretations.

   Page 4, Abstract: "Results", 5th line.

3. *"The depiction of the possible disease courses (e.g. continuous (c)) are somewhat confusing to read (particularly with the addition of a letter in brackets)."*

   The sections concerning disease courses have gone through major revision to make them more readable (including removal of the letters in brackets).

   Page 9, Methods: "Questionnaires", 3rd paragraph.

   Page 11, Results: "Disease course and stool type".

4. *"The results comment on adherence. It is not clear (and will be very limited by study design) as to whether or not this means the initial introduction of the low FODMAP diet or subsequent ongoing adherence. The key concept of using this diet is not to stay on complete avoidance forever."*

It is correct that the FARS does not state whether or not the questions concern the initial weeks of dietary treatment or adherence at follow-up. It is our impression that patients still using the diet at follow-up answered the questions based on current dietary adherence, while the responses of the ones not following the LFD anymore were related to initial adherence at introduction.

The FARS would probably be a better tool for assessing adherence in prospective studies for a limited time interval. However, we were interested in evaluating long-term adherence and chose to use the FARS for this purpose.

We agree that the restriction of FODMAPs should not last forever due to the possible long-term side-effects, i.e. alterations of gut microbiota (Halmos *et al* 2015).

5. *"The Abstract concludes that this dietary intervention is efficacious. However, this conclusion does not consider the study design and patient bias, and reports data from patient perspective only. This conclusion should be modified accordingly."*

The conclusion has been adjusted taking the study design into consideration.

Page 5, Abstract: "Conclusion".

6. *"The core tip and the manuscript itself state this works shows how to implement a low FODMAP diet. However, this is not an instructional report. This should be amended accordingly."*

We agree that the statement about implementation was not suitable, thus it has been deleted from the Core tip and the Discussion.

Page 5, Core tip.

Page 13, Discussion, 1st paragraph, 1st line.

7. *"The Methods do not make clear how patients with IBD who had functional symptoms were proven to not have concurrent gut inflammation. Nor do the authors delineate who this was excluded during follow-up as well."*

Forty of the 48 IBD patients had previously participated in eHealth LFD studies at Herlev University Hospital, where patients with moderate to severe disease activity were excluded before study enrolment (Pedersen *et al* 2016 – soon to be published). The small number of patients included in the eHealth study that had relapses during the research period did not experience effect of the LFD suggesting that the LFD should only be recommended for IBD patients with low disease activity or in remission.

The remaining eight patients of our study had been referred to a clinical dietician for LFD consultations by the gastroenterologist due to problems with functional GI symptoms in remission. At follow-up, the IBD patients were not excluded if they had ongoing disease activity.

The above points have been clarified in the Methods section.

Page 7, Methods: "Study population", 3rd paragraph, 2nd line.

Page 7, Methods: "eHealth: a web-program… patients", 1st paragraph, 3rd line.

8. *"The questionnaires section of the Methods comprises a number of one sentence paragraphs."*

The entire section has gone through major revision to ensure a better flow while reading.

Page 8-10, Methods: "Questionnaires.

9. *"There are number of incorrectly used words or English phrases that all need to be corrected. Sat on page 8 of the PDF should be set."*

The manuscript has been corrected thoroughly to improve the language followed by extensive text revision by professional translator Martin McLean, *Riis Burisch & Partner GmbH*, Berlin, Germany.

Corrected words and sentences throughout the text have been marked by yellow.

10. *"The comment about e-Health would be best to be provided in the initial parts of the Methods."*

    The eHealth comment has been moved as suggested and now appears as the third section of the Methods.

    Page 7, Methods: "eHealth: a web-program for IBS and IBD patients".

11. *"The first part of the RESULTS requires a subheading."*

    A subheading has been added.

    Page 10, Results: "Demographic data".

12. *"As above, the first sentence of the DISCUSSION should be amended."*

    The sentence has been deleted as stated in comment 6.

13. *"The first three paragraphs of the Discussion largely restate the Results arising, without discussion thereof."*

    The first paragraph of the Discussion has been shortened to limit repetitions, while text has been added to the second paragraph about disease courses. The third paragraph has been left untouched, as we disagree in this part being restatements without discussion.

    Page 13, Discussion, 1st paragraph.

    Page 13-14, Discussion, 2nd paragraph, 6th line.

14. *"The number of patients who reported full or partial benefits is listed as 87%, but the two subsets are 54% and 32% (which does not add to 87%)."*

    The decimals were excluded to make the text more readable (actual percentages are 86.7, 54.3, and 32.4), however the subsets not adding up don't look good either. In order to avoid decimals in the remaining text, the total percentage of patients with effect has been down regulated to 86% to match the two subsets.

    Page 4, Abstract: "Results", 3rd line.

    Page 11, Results: "Efficacy and symptoms", 1st line.

15. *"The study design and the large number of subjects who were not included (actively or inactively) limits the value of the study, and provides significant bias. This is stated in the Discussion, but should be more clearly stated within study conclusions."*

    The final conclusion has been amended to acknowledge the limitations of the study design and the low response rate.

    Page 15, Conclusion, 1st line.

16. *"Table 2 does not explain what FARSD stands for. This should be more independent from the text of the manuscript. Almost all of the other legends could also be enhanced to be more comprehensive."*

    Table 2 and the table legend are now self-explaining and abbreviations are described. The other legends have been updated likewise.

    Page 21, Table 2: "Dietary adherence at follow-up estimated by the FARS"

    Page 20-27, Tables and figures.

Comments from reviewer 00036328, Italy

1. *"Even though IBD is more prevalent in female gender, the high number of female in IBS and IBD group (82% for both) could be a potential bias for this study."*

   Although both IBS and IBD are more prevalent in females, the number of men participating is lower than desired and could be a potential bias. However, the statistical analysis revealed no association between gender and the response variables.

2. *"Questionnaires were developed to evaluate efficacy of diet, dietary management, compliance, satisfaction, and IBS course prior and after dietary intervention. They seem arbitrarily constructed and not validated even for reliability in previous studies. This make the study results with a lower scientific weight."*

   As described in the Questionnaires section of the Methods we included four self-developed questionnaires in the analysis. Validated questionnaires would have been preferable, but were not available, and therefore we felt necessitated to

construct our own in order to evaluate the relevant outcomes. We are aware of the negative effect on study design as a consequence thereof.

The FARS was inspired by the Medication Adherence Report Scale (MARS), which is a validated tool for measurement of adherence to medicine.

The satisfaction questionnaire was applied in a previous study by Pedersen *et al.*

Page 8-9, Methods: "Questionnaires", paragraph 1-3.

3. *"Table 2: I don't understand a in parenthesis (a)."*

Table 2 has been modified slightly and the letter in brackets (which was a mistake) has been erased.

Page 21, Table 2: "Dietary adherence at follow-up estimated by the FARS"

4. *"Figure legends could be self-explaining. For this reason, the explanation of p values must be added in the legends together with the legend for a, b, c, and d."*

After editing, the figure legends should now be self-explaining.

Page 22-27, Figure 1-5.

Comments from reviewer 00036648, Australia

1. *"It is unclear to me that in a cross-sectional study how the authors can make judgments on the disease course (i.e. as per Figure 1) of IBS. This appears very subjective and unvalidated – there are little data that I am aware of that shows that IBS follows certain courses as described in Figure 1, especially when factors such as stress, holidays, dietary indiscretions or infective exacerbations can easily influence symptoms in IBS?"*

This is a very valid question. We have in our center in three decenniums been dealing with computerized 'pattern recognition of disease courses' in inflammatory bowel disease (see references). These "Copenhagen disease courses" were then adapted to a PRO in Oslo, Norway, where they showed that the IBD patients were as precise as the computer to describe their disease course (Solberg IC et al, Scand J Gastroenterol 2009). All these publications were applied in epidemiological inception cohorts with mild to aggressive disease courses.

This mixed IBS-IBD cohort with LFD follow-up is not an inception cohort followed prospectively. However, they were all in a tertial referral centre after the GPs had given up. We show that IBS patients, as well as IBD patients, are able to use the PRO system to point out their type of disease course, i.e. 10% of the IBS patients in the tertial referral centre had a mild indolent course before the LFD, and that LFD obviously has an impact on long-term follow-up and treatment.

As you suggest these types have to be validated in a larger setting at the GPs office and perhaps even in a large inception cohort followed for 10 years.

Page 9, Methods: "Questionnaires", 2nd paragraph, 3rd line

2. *"I wonder whether it might have been preferable to focus on IBS alone as the condition of interest, given there were relatively small numbers of IBD patients anyway. Moreover, in IBD, there may be even more confounding factors affecting the efficacy of the low FODMAP diet including severity of concurrent inflammation, subtype, disease extent/ distribution and medication factors to name a few. Also comparison of IBD and IBS is rather superfluous in a sense, like comparing apples to oranges – clinical relevance?"*

Given the small number of IBD patients, we decided to omit the sub-analysis of possible confounders in this study. However, investigation of confounding factors (i.e. disease severity/extent, medication) is required in large, prospective studies of IBD and LFD in the future to assess the influences on dietary effect.

It is of clinical relevance to investigate treatment options for functional GI symptoms in IBD as they are present in 30-40% of patients in remission. A recent LFD study of IBD by Pedersen N et al (Inflam Bowel Dis 2016, submitted) found that functional GI symptoms improved significantly after LFD intervention in IBD patients in remission, and, furthermore, there appeared to be no effect if patients had active inflammation.

Off coarse, IBD and IBS patients can not be set side by side as the pathophysiological mechanisms are incompatible, however, some IBD patients in remission and IBS patients share the same clinical symptoms, which in many cases appears to be respondent to the LFD.

3. *"In "Core Tips" section, please change "FOMDAP" to "FODMAP"."*

   The core tip has been rewritten, thus removing the above mentioned error.

   Page 5, Core tip.

4. *"The legend descriptions for Figures 3 and 4 are unclear and should provide more detail as to what the graphs are representing."*

   As to comment 4 of the second reviewer, the figure legends has been edited and should now be self-explainable. In addition, figure 4 has been replaced by a more visual version to help interpretation.

   Page 24-26, Figure 3 and 4.

Additional modifications

- **Title page:** Manuscript number added; Three authors combined under one institution; Details added on academic rules and norms (page 1-2)
- **Abstract**: Modification of aim according to guidelines and requirements (page 5).
- **Core tip**: The entire core tip has undergone major revision (page 5).
- **Methods**: Study design modified (page 7); Statistical statement added (page 10).
- **Comments**: The required fields have been included (page 15-16).
- **References**: Format has been improved to match demands. New references have been added along with PMID and DOI citation numbers if available (page 17-19).
- **Figures**: Figure 4 has been replaced by a new version to improve understanding. Page 25-26.

Thank you very much for your time and comments. We look forward to reading your response.

Best regards,

Louise Maagaard, MD

Denmark