

Response to Reviewers

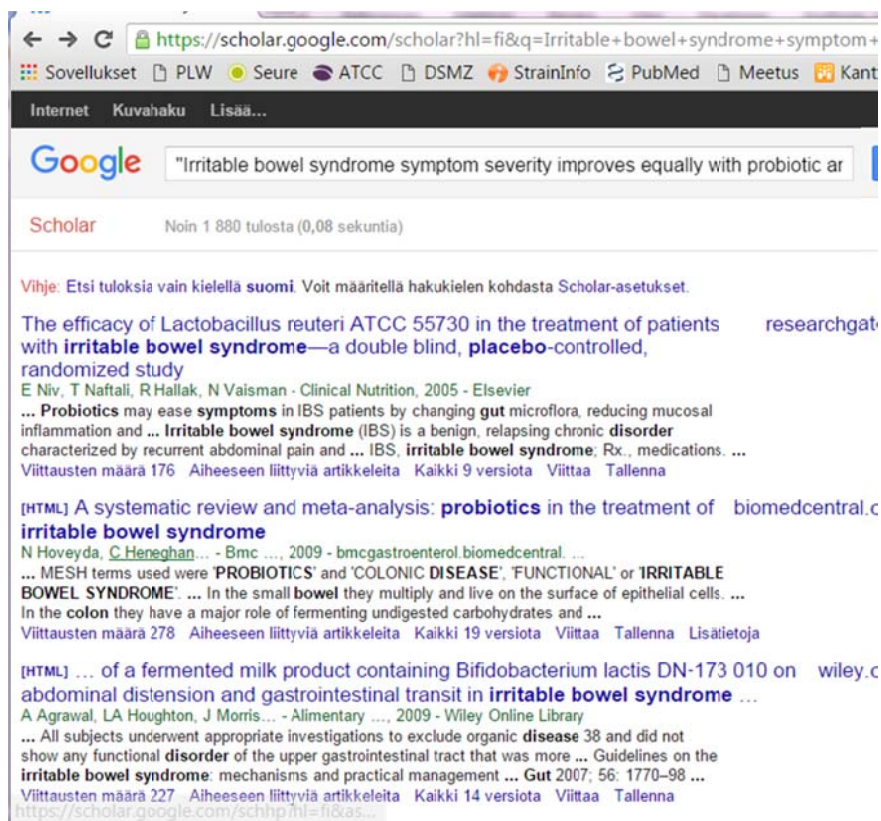
General revisions

All editions in the revised manuscript are indicated with red color font. The revised manuscript has been language edited and a new language editing certificate is provided.

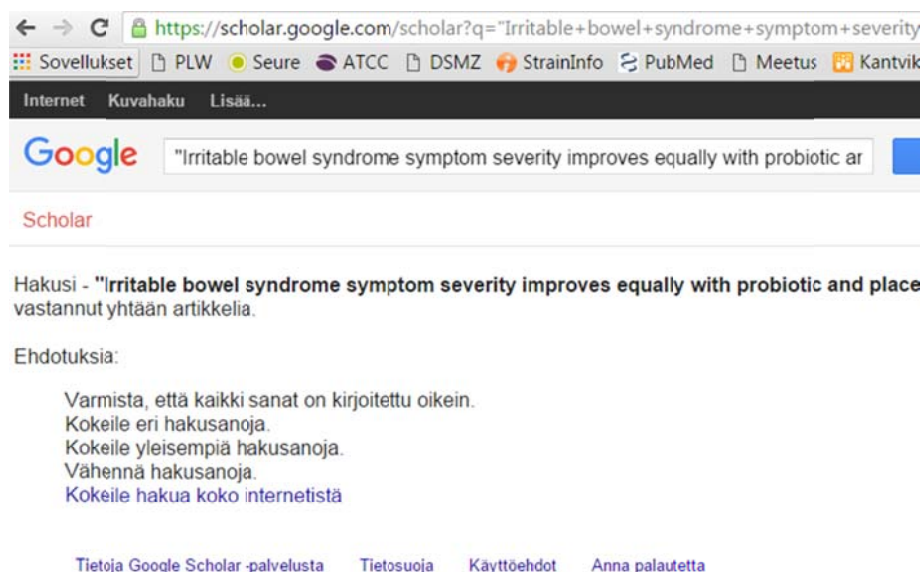
The following revisions have been made according to editor's comments:

1. The Author contribution section has been re-formatted.
2. The phrase "This trial was sponsored by DuPont Nutrition and Health, Global Health & Nutrition Science" was deleted as it does not refer to a grant application or funding agency. DuPont was the sole trial sponsor.
3. The Methods section in Abstract was edited to include at least 80 words.
4. The Audio core tip has been made and is available as a separate file.
5. Terminology was not explained as we did not find any terms to be novel to the majority of readers of World Journal of Gastroenterology.
6. Reference list was checked and no repeated references or missing authors were found. All available DOI and PMID citations have been added (no PMID citation was available for reference 3).
7. Abbreviations were checked to be given in full when introduced and used as abbreviations thereafter.
8. The figures have been provided in formats allowing edition.
9. GoogleScholar search on title:

For words in the title:



For the exact title (requires the exact phrase as in the title)



(=result in Finnish and says there are no hits)

10. CrossCheck was made at www.crossref.org

Response to reviewer 03327970

Thank you for reviewing our manuscript in a thorough manner. We hope we have addressed all comments raised in the revised version. In the revised version we've written numbers as actual numbers unless they begin a sentence. We have revised the use of the word 'per' except in the term "per protocol" where it is commonly applied.

The below revisions were made essentially as requested:

Comment by Reviewer	Revision made
Abstract – Results – 2nd sentence: IBS-SS improved over 12 weeks of treatment in all groups, .. → this should be mentioned already in the beginning of the sentence	The sentence now reads: 'IBS-SSS improved over 12 weeks of treatment in all treatment groups, decreasing by a mean \pm SD of 44.0 ± 80.2 , 50.8 ± 82.4 , and 48.3 ± 72.2 in the placebo, active low-dose, and active high-dose groups, respectively.'
Introduction Page 5, line 10: timely is not the correct word, maybe temporary or over time	'timely' has been revised to 'over time'
Page 5, line 12-13: well-founded is exaggerated, the sentence needs to be rephrased for grammatical	The sentence now reads: 'Thus, manipulation of the GI microbiota with probiotics is a

reasons also	putative therapeutic option for IBS.'
Page 5, line 19-21: not very clear English language, e.g. should be combination of strains	The sentence now reads: 'Moreover, each strain or combination of strains and each dose requires a separate clinical trial to show efficacy.'
Page 5, line 23: you mean statistically adequately?	Yes; wording has been revised to 'statistically adequately'
Page 6, line 1: rephrase "The sensation of functional bowel symptoms" Material and methods	The wording has been revised to 'Participant-reported severity of functional bowel symptoms' and the lengthy sentence divided into two. It now reads: 'Participant-reported severity of functional bowel symptoms, however, has merely been evaluated for a high-concentration combination of <i>L. acidophilus</i> NCFM and <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bi-07 ^[16] , which is significantly less effective in increasing MOR expression than <i>L. acidophilus</i> NCFM alone ^[15] . Therefore, assessment of the clinical effects of <i>L. acidophilus</i> NCFM as a single-strain supplement for functional bowel symptoms, including visceral pain, was of essential.
Page 6, line 16: per is the wrong word	Revised as 'according to'
Page 7, line 7: Crohn's disease	Revised accordingly
Page 7, Line 13: Iron supplements	Revised accordingly
Page 7, Line 22: per is the wrong word	Revised as 'according to'
Page 9, line 24: per is the wrong word	Revised 'per os' as 'orally'
Results Page 12, Line 15: per is the wrong word	Revised as 'according to'
Page 13, Line 3: insignificance	Revised as 'significance'
Page 14, Line 1: explain here already that the > 35 is part of the IBS-SSS, see also results in abstract	The pain score is now explained as "pain score VAS > 35/100 at baseline" throughout the document.
Page 14, Line 4-7: where is this data shown? Any figure or table?	The data is presented in Table 4.
Discussion Page 17, Line 14-15: Sentence is unclear	The sentence now reads "A decrease of >50 in IBS-SSS indicates clinical improvement of symptoms[18]. In the present trial, the IBS-SSS decreased from 44.0 to 50.8 in the 3 different treatment groups suggesting a borderline clinically significant effect."

Page 17, line 23-26: Sentence is unclear	The sentence now reads: “Volunteers had had difficulty comprehending whether the weekly AR question should be referenced to the baseline period, as intended, or to the previous calendar week. Thus some participants compared consecutive intervention weeks rather than treatment to baseline in the AR questionnaire.”
Page 18, line 8-11: please clarify this sentence	The sentence now reads: “Thus recruitment of all IBS symptom subtypes is justifiable.”
Page 19, line 3-6: Should be part of a separate paragraph ‘Conclusion’, which should be a little bit more elaborated than these three lines	The concluding paragraph now reads: “L. acidophilus NCFM can be consumed safely by adult IBS volunteers over a 3-month period but is ineffective against IBS symptoms in general compared to placebo. However, L. acidophilus NCFM treatment alleviated abdominal pain in IBS volunteers with at least moderately severe visceral pain. More frequent—preferably daily—assessment of bowel symptoms with a user-friendly application is recommended for future trials in this area. Moreover, enquiring individual symptoms rather than a composite score sum may be more applicable. Among the recruited IBS participants with moderate symptom severity at baseline bowel movement frequency appeared normal regardless of stool consistency and anxiety and depression levels were not clinically notable.”

Response to Reviewer 00043396

Thank you for reviewing our manuscript. No comments were made and thus none have been addressed.

Response to Reviewer 00036578

Thank you for reviewing our manuscript. According to your request we have revised the original title “*Lactobacillus acidophilus* NCFM alleviates moderate to severe visceral pain in IBS volunteers” to “Irritable bowel syndrome symptom severity improves equally with probiotic and placebo”. We hope the revised title better states the findings related to the primary outcome in the trial as IBS symptom score was significantly reduced in all treatment groups (low and high dose active groups and the placebo group).

Accordingly, the running title “*Lactobacillus acidophilus* alleviates IBS pain” has been revised to “Probiotic intervention on IBS symptoms”.