

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 02531403

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-11 22:30

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Dear authors, I read with interest the manuscript written by Pedersen and coworkers, about the use of a low foodmap diet compared to LGG and natural western/danish diet in IBS. This is an excellent work, providing new and interesting insights for the management of IBS patients. I would like to suggest to the authors to highlight the results of the analysis of covariance, in particular suggesting how the counselling (about smoking habits, the diet adherence, etc) may drive the attention of the clinicians towards the importance of both the diet and the lifestyle in the management of IBS. Please mention the role of the "classical" medication in this setting: the authors in the introduction define them as "a mild palliation", however how they could explain the positive correlation in their statistical analysis with the resolution of IBS SSS? I have no further remarks and I congratulate with the authors.

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**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 02861597

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-12 00:15

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Interesting study. 1. The non-blinded nature of the study design is obviously a problem. While I acknowledge the challenges that dietary studies pose, a placebo for the probiotic could have been included. 2. How was the study powered? 3. How were corrections for multiple comparisons made? 4. The references to FODMAPs trials are not up to date. 5. Some of the references are duplicates e.g. Hungin et al. 6. I am not impressed that the correlations with QOL etc, add much to the paper.

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**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 00008491

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-16 00:13

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

**GENERAL COMMENT** This could be an innovative paper which seems to demonstrate that a self-managed web application could potentially improve the management of the IBS population. However, its major weakness is the lacking of a control group. Perhaps, the Authors could compare the studied population with a historical one, followed for the same period length, in which no WEB assistance was (or will be) provided. Other conclusions, about the interventional groups (LFD and LGG), are very hard to reach. In fact, in these cases also - but in my opinion much more than for the "pure web" group -, the lack of the controls does not permit to reach any conclusions.

**SPECIFIC POINTS** A detailed list of the foods which were avoided by the patients included in the LFD group would be useful. It could be submitted as supplementary file. The Authors stated that all patients included in the study "had negative outcome of colonoscopy". In this way, I think that it is not useful (also expensive) to perform fecal calprotectin assay. I would suggest to take off this paragraph (page 7). The Authors reported that "eight patients from LFD group drop out due to difficulty with the diet; 8 of 42 patients is 19%: this is a quite high percentage and this should be evaluated in an intention to treat analysis and discussed. Furthermore, the Authors reported that "There were a higher number of consultations in the LFD group (45 %), mostly due to the questions regarding the diet". This is indicative of the difficulty to adhere to this kind of the diet. This difficulty should be underlined and the likelihood that this diet can be accepted for a long time should be



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discussed.

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 00159517

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-18 13:49

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

The manuscript addresses an important issue in regards to the influence of diet on IBS symptoms. The authors compare a low FODMAP diet with a probiotic strain against a standard diet. They address the limitations of a non-blinded study which would require further investigation and likely a different study design. The innovative use of an online survey/diary is an interesting approach. A few things that should be considered: careful review of the diction and grammar - some sentences are not clear when describing the population and the process of randomization. In the discussion, the authors state that the diet should be followed for at least 6 weeks. Is there any data on maintaining the lower symptom scores if the diet is discontinued after that period? It would be likely that patients may have to stay on the diet for a much longer period of time if not for the rest of their life. Some statements about effectiveness of both LFD and LGG in IBS-D and IBS-A should be revised as this is not supported by the presented data and results section. Further explanation about the web-based approach should be given in the methods section especially in regards to patient privacy and data protection.

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 00036578

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

This is a well-written paper about the efficacy of FODMAP diet in IBS patients. The originality of the paper is the development for assessing the effect of the treatment of an IBS website application. But unfortunately, this was an unblinded study involving a rather low number of patients. Therefore this paper does not provide any substantial additional evidence about the symptomatic effect of a low FODMAP diet in IBS patients

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 01557050

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-23 21:19

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

1) General comments Pedersen et al. described Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome. The article is informative and well-presented. The reviewer has some comments. Comments The reviewer would like to know a correlation coefficient in Figure 4 and 5. Please insert a correlation coefficient in Figure 4 and 5.

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 11898

**Title:** Ehealth: Low Fermentable Oligo-, Di-, Mono-saccharides And Polyols vs. Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome

**Reviewer code:** 02721496

**Science editor:** Su-Xin Gou

**Date sent for review:** 2014-06-11 14:17

**Date reviewed:** 2014-06-24 18:27

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

Review low FODMap diet IBS.

This paper by Pedersen et. Al examines the effect of a low FODMAP diet and a probiotic LGG on symptoms of irritable bowel syndrome (IBS) as measured by questionnaires answered on a web-app. The effect in the two treatment groups is compared to symptom reporting in a non-intervention control group (also using the app). The authors find an effect on symptoms in all three groups including the control group. The authors conclude that low FODMAP diet and LGG is efficacious for patients with IBS.

Comments/questions for the authors considerations:

#### General:

The authors are addressing interesting treatments for IBS. But in general the results are over interpreted and there is a lack of addressing regression towards the mean in the patients. Also a more realistic conclusion of the results of the study as the effect of both LGG and LFD was non impressive compared to a non-interventional treatment group

#### Specific comments:

##### Abstract:

The abstract does not describe the study adequately. One should be able to read the abstract independently and



get an overview of the manuscript.

-First of all in the “aim” it is not stated what the effect of low FODMAP diet and LGG are evaluated for?? It should be stated that it is evaluated for IBS.

-The conclusion should reflect/be an answer to the aim. The self-managed web app is not mentioned in the aim, so it is confusing that 2/3 of the conclusion is regarding the web app. Furthermore the conclusion does not really reflect the findings of the study. The web app is a minor finding compared to some of the other findings.

#### **Introduction:**

-Should start with a brief introduction to what IBS is.

-It could be relevant to mention the high placebo effect in this patient group when addressing the lack of effective treatments.

- It is stated that poorly absorbed short-chain carbohydrates can cause gas production and increase intestinal permeability (ref 12-15). To my knowledge it is not proved that they can cause increase in intestinal permeability. The references do not support this either.

-There is lacking a reference after the sentence: “ The FODMAPs component comprise... fermented bacteria (Ref)

-In the same sentence: I’m not sure make sense to state “ they have the property of being small and therefore osmotically active”. They are not diffusing freely over the mucosa even though they are small? Some of the FODMAPs are thought to pull water into the lumen, but is this just because it is small molecules? There are many other small molecules in the intestine, which do not necessarily cause water diffusion.

#### **Materials and method**

-The first reference (26) does not support the sentence:” .... prior to study enrollment.”

- In the second sentence where reference 26 is used a better reference could be used.

#### **Study design**

-When writing RCT it should not be repeated subsequently that it is a randomized controlled trial.

-The sentence “One of three groups”: it sounds better with “one” instead of “that” when mentioning the group.

-The study group should not be described as “receiving ND”, but just as a non-intervention control group.

-Spelling mistake: “1:1:1 based on”

-When describing the primary endpoint it should be described that the reduction in the treatment group is compared to a non-intervention control group.

#### **Treatment conditions**

-What happened in the control group? Were they seen by a doctor once or?

#### **Additional measures:**

-It should be included in the introduction why HADS and FC is measured. What was the purpose? Was it thought to interfere with effect of treatment? And why FC when colonoscopy were performed?

-How was the study subjects educated in the web-app and IBS generally? By a doctor? In a group? Or?

#### **Statistics**

-Non parametric continuous variables should be described by median (IQR) and not by mean (SD). Difference in IBS-SSS and IBS-QoL is tested by a non parametric test, this must be because it is not normally distributed.

-SSCAI is mentioned. Why? Seems like copy paste from a text on IBD. There is 9 co-authors on the manuscript

whom should all have critically read the manuscript. How come none of them have seen this obvious mistake?

#### Ethics

Was the study reported to the data protection agency? Was the study performed as recommended by the Helsinki declaration?

#### Results

Table 1: Why is there a p-value for difference in group size? Have never seen it before. Im not sure it really makes any sense.

General: Instead of reporting  $p > 0.05$ . Report the exact number.

-Is there significant difference in drop-out between the groups?

-The reported results of differences in IBS-SSS have very large standard deviations e.g.: mean 77 SD 104. Intuitively it seems as a not very relevant result when the SD is so much bigger than the mean. Is it because it is not normally distributed and it should have been reported as median (IQR)? Do you really get a mean (SD) as a result when doing Man Whitney? Seems unlikely.

-The reason for not finding a significant difference in IBS-SS in the IBS-C group could simply be because these subgroups contains of much less subjects 5 and 7 in each group compared to the other subtypes groups. Therefore the effect on specific subtypes should not be over interpreted. It should be mentioned in the discussion that no effect on subtype-C could be because of lack of power.

-It is stated that: "The analysis of covariance showed that patients taking IBS medication, having higher IBS-SSS at baseline and treated with LFD, significantly improved IBS-SSS". But from table 2 it seems as the LFD group does not experience any significant difference when compared to the LGG group. So it is an over interpretation of results.

- It is also later on stated that: "Adjusted linear regression....showed statistically significant improvement in LFD vs. ND but not in LGG vs ND. It should also be stated that there is no difference in LFD vs LGG.

Table 2: It is not clear which group is the reference group. Stating IBS-A vs. IBS-D DIFF SSS: 46.1096 p-value 0.04. I read this as IBS-D having difference of 46.1096 larger than the IBS-A group and that it is a significant difference. But Im not sure that the right way to read it? It could be the IBS-A group having a larger difference than the IBS-D group? And why is IBS-A and IBS-C not compared?

#### IBS-QoL

-It is stated that: "The analysis of covariance showed that patient with a higher IBS-QoL at baseline, experienced a significantly improved quality of life by the end of the study". I read the result of table 3 as the exact opposite. As per baseline QoL point the patient's experience -0.2972 DIFF in QoL. That is the higher QOL at baseline, the less the difference. Either you have misinterpreted the results or table 3 should be more clear.

-How did the patients score on HADS?

-FC results should be mentioned?

Table 3: Same as table 2. It is not clear which group is the reference group.

#### Feasibility of web- application

-It is stated that there was a higher number of consultations in the LFD group. It could be stated in a more relevant part of the result section. It should be included in the discussion what the possible effect of multiple consultations could be on the effect on IBS-SSS. (Placebo response?)

## Discussion

-As commented on in the result I believe you over interpret data when stating the effect of the LFD is dependent on subtypes. It is more likely that it simply lacks power for IBS-C because of very few study subjects with that subtype.

-It is stated that: “ The reduction of symptoms were more evident at the end of the study (week 6)”. It is not clear from the results reported. You do not report the development in symptoms. This should be done or removed from the discussion. Not so relevant with the reference (17) when it is written as it is the present study suggesting a treatment period of 6 weeks.

-It is stated: “Furthermore, disease-specific quality of life in our study is also improved significantly in LFD and LGG groups”. This is in complete contrast to what is reported in the result section!!!! In the result section it is stated that “At week 6 no statistically significant improvement in IBS-QoL was observed in the LFD group and LGG group compared to ND group”.

- It is stated that: “Our study revealed that patients treated with LGG improved their IBS-SSSsignificantly at the end of the study”. But this was not significantly different from a no-intervention control group- So does it have any clinical relevance??

-In the LGG section there is extremely long sentences. Not very reader friendly. (One is 7 lines!)

-It is concluded that : “ Our study supports the literature findings that LGG is effective in the treatment of IBS-D and IBS-A. This is major over interpretation of results!

-It is discussed that in effect on symptoms in the ND group could be due to the web-application. There is a complete lack of discussing regression towards the mean in the discussion. This could just be the case. Also because results show that it those being the most “sick”; taking medications, having the lowest IBS-QoL and the highest IBS-SSS at baseline, predicted having a larger effect on IBS-SSS. Meaning those who were most sick at the beginning of the study had a larger effect on their symptoms. This is a well-known phenomenon also in IBS patients that symptoms are recurrent. Patients have periods with severe symptoms and periods with less severe symptoms. So if you start a treatment when they are the most sick you need to consider that they are entering a period with less severe symptoms just because of the natural history of the disorder.

- When stating: That the size of the sample population is large, encouraging confidence in results it should be included that the sample size of IBS-C patients is small.

-it should be discussed if LFD is a relevant treatment when the effect on symptoms and QoL is not much bigger than in the LGG group, but the treatment is so much more demanding. Also in light of more patients dropping out of the LFD group.

## Conclusion

As commented in the previous sections the authors should be careful not to over interpret the data.

## Figures:

On figure 2 it is not possible to differ the groups from each other as the symbols are too dark. How was the p-value obtained? Intuitively it does not seem like there is a significant difference between week 0 and 6 as the confidence intervals overlap?

On figure 4, 5 and 6 it is not possible to see which line represents which group. The stated P-value what does it



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cover? The overall difference, or difference between groups?

There are too many figures in this manuscript. Figure 3a, 3b and 3c could be left out.