Author's response to reviews

Title: Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study

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Author's response to reviews: see over
Dear Editor,
Thank you for the possibility to revise our manuscript titled: Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. We are grateful for the valuable comments of the editor and reviewers and have now made changes to the manuscript accordingly. Revised sentences are highlighted in red and responses to comments are showed item by item below. We hope that the revised manuscript will be acceptable for publication in the BMC Gastroenterology.

Sincerely yours,
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Editorial Requirements:
After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.
Response: The manuscript has now been revised by a native English speaking linguistic experienced on scientific writing.

Reviewer #1
Method section:
1. The selection of controls must be better described. Now it is unclear how, and where, they were chosen so that they could be comparable with the coeliac disease subjects. The reader needs to be informed about the criteria for being selected as a control. If the only criterion was the currently mentioned (about no first-degree relatives with coeliac disease), it needs to be specified that no actions were taken regarding similarities between the populations in terms of e.g. home district, age and sex. Depending on what is added to the method section it is also likely that the limitations of the comparability between the coeliac disease and the control population need to be mentioned in the discussion section.
Response: We used healthy controls to define the level of increased symptoms and reduced quality of life. Although the controls were not specifically matched with the study group, it seems that the proportion of subjects with increased gastrointestinal symptoms was quite similar than previously seen in general population (see for example Eur J Gastroenterol Hepatol 2010;22:354–360, Am J Gastroenterol 2001;96:3130-7, Am J Gastroenterol 2010;105:822-32, World J Gastroenterol 2006;12:2661-6). This issue is now further clarified as suggested (see Methods, page 5, paragraph 1, lines 1-3 and Discussion, page 11, paragraph 1, lines 13-14).

2. The criterion # 1 SD is used to define both increased gastrointestinal symptoms and a reduced health-related quality of life. It is not well motivated why this criterion is used. You refer to studies by Häuser, Zeltzer and Wilt. The papers by Häuser and Zeltzer (no knowledge about Wilt as it was not easily accessible on internet) have not explicitly stated why they chose this criterion. Even if it was well motivated by them, there is still a lack of information as why this criterion is feasible for GSRS and PGWB, as they have used different measurements in their studies (also the case for Wilt). I have not used GSRS or PGWB myself. For that reason I have no recommendation on methods for analyses of these measurements. Your analysis method might be a good alternative. Thus, I do not dismiss the criterion used in the paper, but it needs to be better formulated why it has been used. If you lack good references you should try to motivate, and defend, the choice of criterion in the discussion section.
Response: The aim was to identify subjects with persistent symptoms clearly disturbing their daily life. Hence, we decided to use this fairly objective cut-off value used also in previous studies. It is true that evidence supporting the method is somewhat limited but, as shown in previous response, it turned out to be quite accurate. This issue has now been further discussed as suggested (see page 11, paragraph 1, lines 9-13) and two new references have been provided (references 43 and 44).

3. The factors that are tested for a relation with both increased gastrointestinal symptoms and a reduced health-related quality of life are not defined in the methods section. Some of the factors included in Table 2 and Table 3 might be easily understood, but some of them are harder to judge on. The reader should be informed about definitions in methods section, and at least the less obvious ones should be clarified also in Table 2 and Table 3. For instance, I am unsure about how duration of symptoms is measured from the article. It seems obvious that it was collected from the interview, and I also think that it is measured from first experienced symptoms to diagnosis. It is also unclear if you have asked about any symptom or if you have listed a few symptoms. There is as well as a lack of definition to what group those with exactly 10 years duration of symptom belong (it is possible with exactly 10 years of symptom, isn’t it?). The definition of this factor might be the most unclear, but there are also other variables where the definition is not clear.

Response: We agree and have now clarified these issues as suggested (see page 4, paragraph 2, lines 6-9 and page 4, paragraph 3). Also, the definition for the symptoms duration has been specified (see Tables 2 and 3).

Result section
4. The mean totals and ranges are specified for cases and controls, but not the SD. Add the value of SD so that the threshold values for high GSRS and low PGWB are available in the paper. Currently it is not even possible to guess the thresholds. I also want it to be specified in the methods section if SD is derived based on cases and/or controls. Currently it is only said that it is 1 SD higher than the control mean. My interpretation is that SD is derived based on controls.

Response: The requested threshold values have now been provided (see Methods, page 5, paragraph 3, lines 9-11 and page 5, paragraph 4, line 6 to page 6, paragraph 1, lines 1-2).

Discussion:
5. Page 9, paragraph 2. You mention that coeliac patients showed reduced health-related quality of life while on a gluten-free diet. There is no such evidence in the paper. You only present mean PGWB total score for study group and controls. I suggest that you add such comparison for both GSRS and PGWS in the result section and also specify the test for such comparison in method section. I assume that such a test will give you evidence for your statement.

Response: This comparison has now been carried out as requested (see Methods, page 6, paragraph 4, lines 4-5 and Results page 7, paragraph 3, lines 12-13 and page 8, paragraph 1, lines 9-10).

6. No information about case criterion, i.e. # 1 SD higher or lower, in Table 2 and Table 3. These tables are based on comparing cases and non-cases and this information is too important to not include.

Response: This information has now been provided (see Tables 2 and 3, footnotes).

Minor Essential Revisions
Abstract:
1. “Patients with extraintestinal presentation at diagnosis had fewer current symptoms”.
   Specify who you are comparing to.
   Response: The comparison has now been specified as requested (see page 2, paragraph 3, line 4).

Background:
2. You have written “even well-treated coeliac patients have often failed to attain well-being similar to that of the population in general”. Besides Hallert [1998] and Usai [2007], that you refer to, I can only identify Häuser [2006] that have shown this for quality of life, while Casellas [2008], Gray [2010], Kolsteren [2001], Nachman [2009], Norström [2011], Tontini [2011], van Koppen [2010], and Zarkadas [2006], have all shown similar quality of life between coeliac disease patients and the general population. For other issues related to well-being have comparisons rarely been done with persons without coeliac disease diagnosis. My interpretation is therefore that this sentence needs to be rewritten.
   Response: We agree and the sentence has now been revised (see page 3, paragraph 1, lines 8-10). Further, two new references have been provided (references 9 and 10).

3. The main aim of the paper is to find predictors for poorer health-related quality of life in those with coeliac disease. You have referred to Kurppa [2011]. It would add value to the paper if you mentioned the most notable of these factors already in the background section, and then with most focus on the ones you chose to look at yourself.
   Response: The aims of our study have been further clarified as suggested (see page 3, paragraph 2, lines 3-4).

Method section:
4. On first occasion that you use SD write the word in full form. I am unsure if the standard deviation at individual level or the standard deviation for the mean (commonly called standard error of the mean) is used for comparisons. If the standard error of the mean is used is SD not a proper short form as it is generally referred to the standard deviation at individual level. Could be worth giving both the standard deviation and the threshold value in result section to avoid any doubts on the definition of it.
   Response: This issue is now clarified and the abbreviation written in full form (see page 5, paragraph 3, lines 9-10).

Result section:
5. Second row at page 7, “food intolerance and gastrointestinal or any” should be “food intolerance, other gastrointestinal disease, and any”, or a similar phrasing.
   Response: This sentence is now corrected as suggested (see page 7, paragraph 3, line 10).

6. Row 8-9 at page 7. You show that both the group <10 years and >10 years with symptoms have worse health-related quality of life than those without symptoms. You have written “long duration of symptoms”, which needs to be corrected as both short and long duration give evidence of a worse health-related quality of life according to Table 3.
   Response: This issue has now been clarified (see Results page 8, paragraph 1, lines 3-5).

Discussion:
7. At top of page 10 you write “well-defined study cohort”. As also mentioned later in same paragraph you admit a limitation in your selection, which potentially could cause a selection bias. This contradicts the phrasing “well-defined”. Are you referring to members of your
cohort having a well-defined coeliac disease diagnosis? If that is the case you should rewrite the sentence or else you reasonably should remove the word “well-defined”.
Response: The sentence has now been modified (see Discussion page 11, paragraph 1, lines 1-2).

Tables:
8. Specify in table 2 and table 3 that you have used bivariate logistic regression.
Response: Statistical method has now been provided (see Tables 2 and 3, footnotes).

References:
9. Add dots to surnames also for other authors than Mäki, e.g. Ström and Grännö.
Response: Dots have now been added.

Discretionary Revisions
1. Some of the references in the background section are a bit out of date. I think that the authors should consider updating with more recent and relevant references.
Response: The outdated references have been replaced by more recent ones as suggested (see references 6, 10 and 11)

2. You replace missing with mean value of the item for PGWB and GSRS. How do you motivate this? Maybe it might be an alternative to replace with median values instead?
Response: Both values have been used in the literature, but it is true that in this case use of median would be more logical. However, in our study only a few answers were missing, and this change had no impact on the results whatsoever.

3. At start of the discussion section you refer to more symptoms being shown by Cranney et al. They have not defined symptoms in a similar way as your paper as far as I can interpret it. Is your statement valid? It is also hard to compare with Midhagen et al as they seem to lack a definition on how they define symptoms in their paper. They do report a higher proportion though with same measurement as yours.
Response: This problem has now been further discussed as suggested (see Discussion, page 8, paragraph 2, lines 2-5).

Reviewer #2
1) Background, page 3, line 6: The Authors define “poor growth in children and osteoporosis as complications of coeliac disease”. This is not correct since the scientific community agrees that only intestinal malignancies (lymphoma, small bowel carcinoma), refractory celiac disease, ulcerative jejunoileitis, collagenous sprue are true complications of coeliac disease, whereas poor growth and osteoporosis as well as many other signs and symptoms are part of the clinical presentation of coeliac disease. So, poor growth and osteoporosis should be defined as “clinical manifestations of coeliac disease” and not “complications”.
Response: This issue has now been further clarified as suggested (see page 3, paragraph 1, line 5).
In addition, two previous references have been removed and one new added (reference 2).

2) Result section (page 7, line 2): It has been reported that “non-coeliac food intolerance also increased the risk of persistent symptoms.” I agree with this statement, but I think that this concept should be expanded since it is mandatory to define which food intolerances are involved in the persistence of functional gastrointestinal symptoms in treated coeliac disease. In the literature it has been reported that both lactose and fructose intolerance can have a role in maintaining symptoms after GFD, so for the reader it could be interesting to have
some information on the prevalence of these 2 food intolerances (and others, if detected) in the large series of coeliac patients studied.
Response: The lacking information has now been provided as requested (see Results, page 7, paragraph 2, lines 5-6).

3) Result section (page 7, line 9): It would be useful for the reader to define the nature of gastrointestinal co-morbidities responsible for persisting symptoms in treated coeliac disease. As stated in the discussion, irritable bowel syndrome is probably a frequent cause, but what about gastro-esophageal reflux disease, which, based on literature data, has been found in 66% of coeliac patients (Barratt SM, Eur J Gastroenterol Hepatol 2011)? The Authors should specify the nature of gastrointestinal co-morbidities and their relative occurrence in determining the persistence of symptoms in treated coeliac disease.
Response: More detailed information for the gastrointestinal disorders has now been provided (see Results, page 7, paragraph 2, lines 6-8).

4) In the discussion the Authors should take into consideration the possible role of a high intake of commercial gluten free-products, rich in additives and preservatives in inducing functional gastrointestinal symptoms in treated coeliac disease, as reported by previous paper (Hopman E et al, Scand J Gastroenterol 2008).
Response: We agree and have now further discussed this issue as suggested (see Discussion, page 11, paragraph 2, lines 5-8 and reference 47).

5) Discussion section (page 9, line 14): It has been rightly underlined the role of psychiatric disturbances in the persistence of symptoms in treated coeliac disease, but the Authors do not indicate the kind of psychiatric disorders and this information should be provided to the reader.
Response: This important issue has now been further discussed (see Discussion, page 10, paragraph 3, lines 5-7).