Author's response to reviews

Title: Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study

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Author's response to reviews: see over
Dear Editor,

We thank you and the reviewers for your review of our manuscript “Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study” MS: 1492041410118616

The constructive critique has helped us improve our manuscript. Below you find the point by point response to the questions raised and revisions indicated.

Reviewer 1

The manuscript by Myléus et al. is an important and very well-written study about the health-related quality of life in children with celiac disease. I have just a few, mostly minor and technical, comments for the manuscript.

1. Background, ps 4-5. The introduction section is rather long and could be more concise. For example, it is not necessary to explain celiac disease with details since most of the readers are well-familiar with the condition.

Response: We agree with the reviewer that the introduction could be more concise. We have revised the introduction by removing some of the details (p 4, lines 2-3, 7 p 5, line 3 and 7-8). However, we think that since the current journal targets a general audience a bit more information regarding celiac disease is needed, compared to journals aiming towards pediatricians or gastroenterologist.

2. Methods, p 6. The authors state that “subjects with Marsh I-II, right genetics and positive response to GFD suffer from CD”. I mostly agree with this, but wonder whether references 32-33 in fact investigated this issue? Were endomysial antibodies measured? Maybe some other references supporting these criteria should be provided.

Response: The diagnostic criteria used in this study are the same as used in the ETICS-study at large (reference 32-33), and we do not think it is within the scope of this manuscript to go into detail regarding this aspect. Additional information about serological markers used (including EMA) has been included (p 6, lines 10-14). The reviewer is correct that the reference 32-33 does not investigate the issue and to avoid confusion they have been removed from this section.

3. Also, later patients with “potential celiac disease” are mentioned, but it remains somewhat unclear how they are defined. The authors rightly say that many “asymptomatic” subjects in fact experience improved symptoms while on a GFD; are these potential those with positive TG2-ab, right genetics but no response to GFD? Or were they not willing to start a GFD?

Response: We thank the reviewer for pointing out this unclarity. Potential celiac disease was defined as children with elevated serological markers but normal small intestinal biopsy or lack of confirmatory biopsy. These children were excluded from further analyses since they did not have a certain celiac disease diagnosis. This has been clarified in the Methods section (p 7, lines 3-6) and first section Results (p 9, line 20).

4. Measures, p 7 + Discussion. Is the “Kidscreen” validated questionnaire and have it been used before in CD? I think one reason for negative results might be that it is a generic instrument which might not be sensitive enough to detected minor differences between CD patients and controls. This issue should be discussed.

Response: The point by the reviewer is well taken. Kidscreen has demonstrated acceptable validity and reliability when used among children and adolescents, including such populations from Sweden but has, to our knowledge, not been tested among children with celiac disease. To
assess the HRQoL among the children with undetected celiac disease we had to use a generic questionnaire (as they did not know they had celiac disease at the time of the measurement). To be able to compare, the same instrument was used also for those with diagnosed disease. However, we agree that the generic instrument might not capture all aspects of living with celiac disease. Additional information is added in the Methods section (p 7, line 29 and p 8, lines 1-3) and the issue has been included in the discussion (p 13, lines 20-24).

5. Page 8, compliance. Adherence to GFD was measured by TG2 and those with positive antibodies were defined as non-compliant. I think it is OK but it is important to remember that in some children (in particular 2009 group) with high baseline levels it may take a few years before the antibodies normalize despite a strict diet.
Response: We agree that in some children high anti-body levels might not normalize within a year, despite a strict gluten-free diet. However, in this case the tTG antibodies for estimating adherence were only used for those with diagnosed disease (the others did not yet know that they had celiac disease) and they were in diagnosed (in mean) about 7 years prior to the study.

6. Discussion, p 13. It is stated that the compliance was high (92%) compared with other studies. For example in #41 adherences indeed was slightly lower (88%), but in those number also occasional dietary failures were counted. TG2abs are not very sensitive to detected occasional gluten intake: thus I suspect that 92% is an overestimation of a very strict GFD, serological markers should be combined with dietary analysis in order to get accurate estimation of the compliance.
Response: The issue of measuring adherence with the gluten-free diet is complex and we agree that a full dietary analysis is needed to get a complete estimation. In this case, it was not within the scope of the paper, but adding the tTG analyses gave an indication of the proportion adhering to the gluten-free diet. Since we agree that the tTG estimation could be overestimating the adherence, and the proportion was so high albeit without clear correlation between tTG and HRQoL, we did not investigate this potential influence further. This has been included in more detail in the discussion (p 14, lines 5-8).

7. Tables & Figures: Table 1. A few technical notes: maybe celiac disease abbreviation (also in Table 2) can be denoted already in the title of the table and thus one line form the footnote could be removed. Also, the (%) can be denoted after “Characteristics” and subsequently removed from the four other lines of the table. Table 2, footnote: there is small misspelling in line 2 (, and…?) Figures 2-3. The mean score is from 65 to 100? I assume that it is from 0 to 100, then may you should start from 0 but then “cut” the y axis.
Response: We thank the reviewer for the comments. They have been revised accordingly.

Reviewer 2
This study is well-designed, performed and presented. The research group is one of the world leaders in the area of the epidemiology of celiac disease. The results are relevant to the debate on how to investigate the celiac iceberg, i.e. by case-finding or mass screening.

1. P 2 line 11 (abstract) rephrase as follows: when anti-TTG antibodies were elevated...
Response: Thank you for the comment, the sentence has been rephrased.

2. Page 6, lines 12-13 and 21: the authors should specify the anti-transglutaminase antibody level used for deciding further investigation (small intestinal biopsy).
Response: We agree that the reader can benefit from more information regarding the screening procedure including antibody levels. This has been added into the manuscript (p 6, lines 10-14)

Yours sincerely,
Anna Myléus
on behalf of all the co-authors