Author's response to reviews

Title: Delay to celiac disease diagnosis and its implications for health-related quality of life

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Author's response to reviews: see over
Dear Dr Kaser,

Thanks for your positive response to our paper! We also thank the reviewers for their valuable comments that have helped us to improve our manuscript.

In the attached letter we have listed the reviewers responses (bold print) followed by our responses (normal print) and examples from the revised manuscript (italics).

Yours sincerely,

Fredrik Norström

_on behalf of all co-authors_
Reviewer #1:

1. Major: it should be tested if the delays are normally distributed or not. I think not, because there is such a big gap between mean and median. Then median should be mainly used in the abstract.
2. Minor: the celiac questionnaire would be interesting and an English translation of the Swedish text preferred.

REPLY:

1. Thanks for your comment. The Cox proportional hazards model is a semi-parametric model commonly used for survival data. It is appropriate to analyze the delay to celiac disease diagnosis from first symptoms with this model. The Cox proportional hazards model is not based on an assumption about normal distribution and a normality test is therefore not applicable.

2. The questionnaire has been translated to English. We have uploaded it and replaced the original version in Swedish. We consider this a valuable addition to the paper.
Reviewer #2:
This is a large study that identified a significant delay in time from the onset of symptoms in coeliac disease to the diagnosis of the condition. By demonstrating an improvement in health-related quality of life after diagnosis and institution of treatment, a preventable burden of ill health has been identified. The study is well designed and executed with the authors aware of the major limitations of the work.

REPLY:
Thank you for the nice summary and judgment of our paper.

Potential sources of bias include the difficulty in recall of symptoms prior to diagnosis - in some cases very many years prior to the study questionnaire being sent. Whilst the authors suggest that recall bias is likely to underestimate the symptoms, the opposite may in fact be the case given the likelihood of positive reinforcement by health professionals encouraging dietary compliance, and membership of a patient group.

REPLY:
Important thoughts about the difficulties in recalling when first symptoms possibly related to celiac disease appeared. We have extended our text to also include this issue.

A recall bias might appear as some responders had their CD diagnosis long ago. This might cause both a low estimate of HRQoL pre-treatment, as well as an overestimate of the delay from first symptoms indicative of CD to CD diagnosis. However, the usual recall pattern is to report fewer episodes of ill health, and therefore previous health problems might instead be underestimated.

Discussion, page 10, paragraph 1

There is an unfortunate but unavoidable response bias as well that probably explains the high rate of dietary compliance (96%) of the 66% that did respond.

REPLY:
We have a high compliance rate among responders which might give a somewhat non-representative sample of the Swedish adult CD population. We mentioned that our results might only be valid for members in the Swedish Society for Coeliacs. We extend our text to also mention that non-responders to the questionnaire might differ from responders. Both of
these groups are likely to have a lower compliance rate, but still we believe it to be high. Nevertheless, we believe that the burden of CD is non-negligible for these groups as well.

We cannot be sure that our results are representative for the whole Swedish CD population. However, even if the results are only valid for responders (66% of invited) to the questionnaire within our study population (members of the Swedish Society for Coeliacs which correspond to about 60% of Swedish adults with CD), they nevertheless show an experienced burden for a sample representing about 40% of Swedish adults with CD, irrespective of age.

Discussion, page 9, paragraph 3

This data does not support the idea of mass screening for coeliac disease, but is further support for a low threshold in testing for the condition in the presence of symptoms.

REPLY:
Case-finding should be intensified as the reviewer suggests. This is also highlighted in our discussion. However, such efforts have been made for a long time in Sweden without the big improvement one would desire. Our data does not deal with the effect of screening directly. However, the results raise the question of what could be done to find cases with diffuse symptoms.

In this regard a potential opportunity has been missed by the investigators in determining which types of symptoms were predominantly experienced by patients and whether this had any impact on the delay in diagnosis.

REPLY:
Gray et al. presented delay from each symptom to diagnosis among members of Coeliac UK in their paper. We agree that including their questions would have added a value. However, we believe it was wise to limit our questionnaire in size and exclude these questions. Our current questions are not suitable for analyzing delay from a specific symptom to diagnosis.

I would find figure 1 easier to understand with the addition of the words 'prior to diagnosis' after 'duration of symptoms' on the abscissa label.

REPLY:
We fully agree with reviewer. We have improved Figure 1 according to suggestion.