

Author's response to reviews

Title: Screening rules based upon growth to detect celiac disease: a case-control simulation study

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Author's response to reviews: see over

Revision of manuscript 3961940891638993

Dear Dr Damian Marlee,

Hereby we would like to submit the revised version of our revised manuscript (3961940891638993) entitled "Auxological screening rules to detect Celiac disease: a case-control simulation study". The authors gratefully acknowledge the valuable suggestions made by the referees and appreciate the opportunity to revise our manuscript again. We trust that the changes we made to the manuscript are sufficient to warrant publication in BMC Pediatrics. Please find enclosed the appendix for the authors' responses to the comments of the referees.
Sincerely,

Also on behalf of the co-authors Floor Grote, Wilma Oostdijk, Sabine de Muinck Keizer-Schrama, Bart Boersma, Gerard Damen, Cassandra Csizmadia, Paul Verkerk, Jan Maarten Wit and Stef van Buuren,

Paula van Dommelen

Appendix. Authors' responses to the comments of the reviewer.

Referee 3:

The term "AND" in the fourth rule in table 1 is used in a different (and misleading) context than for the other rules. The use of italic print does not discriminate it sufficiently from the other AND's in the table.

Answer: We agree with the referee. We have now removed this term.

Referee 2:

1. Background section, Page 3: In the first sentence of the second paragraph, the authors should emphasize the difference between classical presentation of Coeliac disease and other presentations. Furthermore, the authors may wish to emphasize that the frequency of the classic presentation appears in many countries to be falling in recent years. Making these points clear would assist in better setting the scene for the study.

Answer: We have now addressed these points in the background.

2. Background section, Page 3: Several points in the second paragraph are un-referenced: these should be referenced appropriately.

Answer: We have now extended our literature list.

3. Background, page 4: the final part of the background section should be revised to make the aims of the study more clear. The term auxological should be explained and defined here - this is a term that will not be familiar to all people.

Answer: We have now revised these sentences to make the aim more clear. Furthermore, we changed the word auxology into growth in the complete manuscript.

4. Methods, page 4: The first subheading to the Methods section (Materials) should be revised to more adequately the content of this subsection.

Answer: We have now changed the material subsection into two different subheadings 'Patients' and 'Reference sample'.

5. Methods, page 4: The first part of the Methods describes the three contributing studies. The numbers of children in each of these studies should be outlined. The authors should emphasise that the first study was prospective.

Answer: We have now amended the following sentence at the end of the Patients paragraph 'In total, we obtained 134 children: 21 children from the first study, 74 children from the second study and 28 children from the third study.' Furthermore, we have now emphasized in this paragraph that the first study was prospective.

6. Methods, page 4 and 5: The second and third studies are described as both retrospective in the first paragraph on page 5. However, study 3 was listed as prospective on page 4. This should be clarified and corrected.

Answer: We have now corrected this, as the third study is retrospective.

7. Methods, page 5: The phrase "...by the parents or the general practitioners before..." should be rephrased in appropriate English. Furthermore, there continue to be various English grammar and sentence construction errors throughout the manuscript that need attention.

Answer: We have now improved the style of written English.

8. Power analysis, page 5: The analysis detailed on page 5 is based upon the 134 cases initially included. Only 122 were, however, included after exclusions. Power analysis should be done in reverse to support a certain number of patients to be required for a study. I would recommend that the authors review this aspect with an appropriately experienced statistician.

Answer: The first and last authors of this manuscript are both statisticians. The power analysis is now based on 26 screened CD children and 96 symptomatic CD children (in total 122 CD children).

9. Page 6: the last paragraph on this page refers to S-Plus version 7.0 - further details of this software are required.

Answer: We changed this into S-Plus version 7.0.3 for Microsoft Windows (2005).

10. Results, page 7: The authors provide some results in the second paragraph and use terms such as "almost similar" and "does not differ much". These are very imprecise and vague terms and do not inspire confidence in the results - this section should be revised and results which are positive provided in firm and clear fashion. Appropriate stats analysis should be given - if p values are <0.05 these should be given: if not then the statements need to reflect the lack of statistical significance.

Answer: We have now revised the second paragraph and we have avoided such words. Furthermore, the power analysis of this study is based on the precision of the sensitivity and specificity. Therefore, we have now given the 95%-confidence intervals for all sensitivities and specificities. Furthermore, the extended McNemar test has now been applied to test the difference in diagnostic performance between the rules. The results of these tests are reported.

11. Results, page 8: Paragraphs 2 and 3 on this page list results with no statistical interpretation at all (there are no P values given). These results need to be presented in a clear fashion, with inclusion of statistical analysis listed clearly. Furthermore, the statistical tests used for these analyses should be provided in a new section entitled Statistical analysis, at the end of the Methods section. Again, further external statistical review would be helpful.

Answer: Paragraph 2 presents the results of the screened CD patients. The growth pattern of the screened CD patients did not differ from the reference population. Therefore, we did not test for statistical differences. The results of paragraph 3 are now given with 95%-confidence intervals. The results from the extended McNemar test for the four best screening rules at 98% specificity are also presented. There is a section entitled 'statistical analysis' at the end of the methods section.

12. Page 8: The last sentence of the results section is also imprecise and vague. This should be remedied.

Answer: We have now given a summary of the values for sensitivity at a 98% specificity. This makes the last sentence more clear.

13. Page 8: The first section of the Discussion includes a repetition of the results (sentence 2). Furthermore, the last section of this paragraph would be best moved to the results (as it appears to introduce a new result that has not been listed in the results section itself.)

Answer: We have now removed this repetition as it was already given in the results (it is not a new result).

14. Discussion: The Discussion should be shortened further and modified to improve readability and clarity.

Answer: We have now shortened the discussion. We now have a short paragraph that presents the main results, two paragraphs about the methodology, two paragraphs about the symptoms of CD, one short paragraph about the sex difference and we have given a final conclusion.

15. Abstract: the abstract provides a gloomy sentence ("discriminate poorly") and then summarises positive results. Initial emphasis of the positive results arising from this study would assist readability and interpretation of the abstract. Similarly, other aspects of the abstract (e.g. the conclusions) should be revised to improve clarity along with correction of English grammar and construction errors.

Answer: We have now avoided such words. Furthermore, we have changed the order of the results and we start with the positive results. The conclusion has also been revised.

16. Table 1 and related text:: Table 1 needs an appropriate title and legend to provide a context to the details provided in the Table. The details of the rules listed are very complicated and hard to follow initially - the authors should provide a clear context in the Methods to describe these rules and the justification of their design.

Answer: The title of table 1 was already given in the manuscript (at another page). We have now added the title directly to the tables. Furthermore, we have now added a summary and an example below table 1. We have also improved the readability of the paragraph 'screening rules' by giving examples and giving a short introduction that explains the use of the table.

17. Table 2 and 3: These tables also need Titles and legends to display the information adequately. Table 3 especially is difficult to understand initially.

Answer: The titles of table 1 and 2 were already given in the manuscript (see previous answer). Furthermore, we have added a footnote below table 3 that refers to table 1 for the interpretations of the simulation values.

18. Figure 1 also needs a legend. One assumed that "starting diet" refers to commencement of GFD rather than to the introduction of solids in mid infancy.

Answer: This legend was already given in the manuscript (at another page). We have now changed 'starting diet' into 'starting gluten-free diet'.

19. Other: The children included in the study that had been investigated with

symptoms (n=96) should be defined further. Did all of these children present with a full range of classical symptoms, or did they have just partial symptoms?? As per comment above, the numbers of children with classic presentation appears to be falling in many areas of the world: this would influence interpretations. In addition, the age of presentation may be changing due to differences in infant feeding practices, length of breastfeeding and improved recognition of potential CD by general practitioners (hence the length of symptoms may be decreasing, meaning less time for nutritional impairment).

Answer: We have now amended in the text that all of these children present with a full range of classical symptoms. We have also amended the referee's comments about the age of presentation in the discussion.

20. the data provided by the authors in this Manuscript is relevant and important in our overall understanding of CD in early childhood. I fear that the presentation of this data in this MS impairs the interpretation and readability of the data. Further improvements in the details and the presentation should enhance the manuscript.

Answer: We have now tried to improve the readability of the manuscript.

Additional points from the editor:

We recommend that you copyedit the paper, as Referee 2 suggests, to improve the style of written English.

Answer: We have now improved the style of written English.

Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (<http://www.wma.net/e/policy/b3.htm>), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Answer: We have now amended this approval in the Methods section.

Informed consent must also be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Answer: We have now amended this informed consent in the Methods section.

Furthermore, we have made two other changes in the manuscript. We changed the time interval between ages for the slowed growth rule (from one month to three months). This has an effect on the diagnostic performance of this rule. Furthermore, we added another rule, the so called 'extended delta rule'.