Author's response to reviews

Title: Auxological screening rules to detect Celiac disease: a case-control simulation study

Authors:

Paula P van Dommelen (paula.vandommelen@tno.nl)
Floor FK Grote (F.K.Grote@lumc.nl)
Wilma W Oostdijk (W.Oostdijk@lumc.nl)
Sabine SMPF de Muinck Keizer-Schrama (s.demuinckkeizer-schrama@erasmusmc.nl)
Bart B Boersma (b.boersma@mca.nl)
Godelieve G Damen (g.damen@cukz.umcn.nl)
Cassandra CG Csizmadia (bremauda@wanadoo.fr)
Paul P Verkerk (paul.verkerk@tno.nl)
Jan Maarten JM Wit (J.M.Wit@lumc.nl)
Stef S van Buuren (stef.vanbuuren@tno.nl)

Version: 2 Date: 17 December 2007

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

Hereby we would like to submit the revised version of our 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 reviewers and appreciate the opportunity to revise our manuscript. We trust that the changes we made to the manuscript are sufficient to warrant publication in BMC Pediatrics. Please see appendix for the authors’ responses to the comments of the reviewer.

Sincerely,

Also on behalf of the co-authors Floor Grote, Wilma Oostdijk, Sabine de Muinck Keizer-Schrama, Bart Boersma, Godelieve 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:

Discretionary Revisions

1. The setup leads to clear conclusions and discriminates between asymptomatic (screened) and symptomatic (clinical) forms of CD. For clarity it would be good to name the three groups in a consistent and unambiguous way. The terms screened and unscreened are confusing. I would for example prefer “screened and clinical patients/CD”, or “asymptomatic and symptomatic CD” (although the latter is not necessarily true). It is also not necessary to refer explicitly to group 2 and 3 in the results since these are treated as a single group in the analysis. In the methods is clearly described how the sample was composed and that should be sufficient.

Answer: We agree with the reviewer. We changed the name of the unscreened CD group into ’symptomatic group’. We removed the words ‘group 2 and 3’ in the results. These changes were made in the entire manuscript. We also amended the following sentence in the methods: “asymptomatic (or with symptoms that were not signaled by the parents or the general practitioners before)” for the description of the screened CD group.

2. The PPV or prior probability is calculated by making an assumption about the incidence of CD. I assume that the incidence figure used (0.54/1000) is also prone to some variation. What would be the effect of (small) variations in the incidence? This
should be discussed. Sensitivity analysis could provide a solution for the input of uncertain parameters in the future.

Answer: We agree that it would be interesting to be informed about the effect of small variations in the incidence of CD on PPV. Furthermore, we think that it would also be interesting to know that PPV might change if we keep in mind that children with diseases or genetic disorders other than CD might be detected by some of our rules.

We amended the text in the methods, results and discussion as follows.

Methods: “PPV was calculated, assuming that the average incidence of CD is 0.54 per 1000 live births in the Caucasian population.[4] Sensitivity analyses were performed to calculate the effect of small variations (0.1-1.0/1000) in the incidence of CD on PPV.”

Results: “In children with such slowed growth for BMI SDS the prior-probability of CD (PPV) is 0.86%. PPV varied between 0.16% and 1.59% when changing the incidence of CD from 0.1/1000 to 1.0 per 1000 live births.”

Discussion: “PPV was calculated using the incidence of CD. However, if we keep in mind that children with genetic disorders or diseases other than CD might be detected by some of our rules for failure to thrive, PPV might be higher. For example, if we assume that sensitivity and specificity for the most optimal rule for CD (drop in BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year) is similar to patients with Cystic Fibrosis (CF), then PPV will be 0.53 percent points higher if this is based on the incidence of both CD and CF.[ Bobadilla JL, Macek M, Jr., Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat 2002;19:575-606.]“

3. Finally, a minor flaw in this setup is the reference population. There will – by definition – be at least some cases of (asymptomatic) CD. This is a trivial comment as it will have little impact on the results.

Answer: We amended the text in the discussion as follows.

“If we assume that the incidence of CD is 0.54 per 1000 life births, then there will be one case of CD in our reference group. Therefore, specificity as well as PPV will be very slightly underestimated.”

4. The first and last sentence of the first paragraph in the background section should be revised.

Answer: We agree that the first sentence should be revised as there is already evidence to support growth assessment. We changed the first sentence into “Growth assessment is accepted worldwide and in many countries regularly integrated in child health care systems.”. We prefer to remain the last sentence (“Growth retardation, however, does also imply failure to thrive in terms of slowed growth for weight and BMI.”) as failure to
thrive may also be an important symptom to detect children with genetic disorders or diseases.

Referee 2:

Major Compulsory Revisions

1. The last paragraph of the Introduction suggests that it is “common knowledge” that height is disturbed in children diagnosed with CD. This statement is not referenced, and may no longer be valid.

Answer: We agree that it is now becoming clear that some cases with CD do not show growth retardation. However, we wished to emphasize that in the classic description of CD poor growth is a prominent feature. We changed the sentence “It is already “common knowledge” that a CD patient has a length (or height) deficit and slowed growth for weight, but this is not based on good evidence.” into “So far, it is generally assumed that most CD patients have a diminished growth in terms of length (or height) and weight [Damen GM, Boersma B, Wit JM, Heymans HS. Catch-up growth in 60 children with celiac disease. J Pediatr Gastroenterol Nutr 1994;19:394-400.]”

2. The Methods section provides details of the screening rules. It also refers to some rules that were not helpful, but does not provide details here (only in the Discussion). The details of these rules, whether subsequently helpful or not, should be provided in the Methods section. The utility of these rules can then be presented in the Results, and any relevant interpretation given in the Discussion.

Answer: We have added the explanation of these rules in the methods and amended the rules in table 1.

We added the following paragraph in the methods:

“Screening rules

For this study we formulated several auxological rules for screening that could serve as criteria for referral to a specialist care (see table 1). The first rule signals whether an abnormal slowed growth for length/height, weight or BMI occurs in terms of change in standard deviation scores (SDS) per year in combination with a current SDS below some simulation value (slowed growth rule). We prefer the term slowed growth over the term velocity to indicate the difference in growth in difference in SDS per year as the term velocity commonly refers to cm or kg/year. The second rule refers a child based on an absolute change in length/height SDS, weight SDS or BMI SDS occurs (delta rule). The third rule is the conditional weight gain rule that signals whether a child’s conditional weight gain SDS is below some value [13,14] with the restriction of having a low weight SDS (conditional weight gain rule). The fourth rule leads to referral of a child if height SDS, weight SDS or BMI SDS is low (absolute SDS rule). We also considered rules that take genetic height potential into account. The fifth rule compares the height SDS of the
child to its target height SDS in combination with a height SDS below some simulation value (parental height corrected rule). The sixth rule signals whether a slowed growth for HSDS of the child moves away from the child’s target height (parental height deflection rule). This was added because on the assumption that in the first years of life a correction might be needed for parental height: e.g. a baby that is born with a length of -1 SDS and has a target height of +2 SDS, would be expected to cross the SD lines in upward direction in the first 2-3 years. An acquired growth disorder could disturb this, and theoretically a stable length of this child at -1 SDS over the first 2 years could indicate growth pathology such as CD. Similarly, we included a seventh rule that combined weight and length, in which a slowed growth for length occurs after a slowed growth for weight (combined weight and length deflection rule)."
We amended these rules in Table 1:

<table>
<thead>
<tr>
<th>Screening rule</th>
<th>Definition</th>
<th>Parameter</th>
<th>Interpretation</th>
<th>Simulation values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowed growth *</td>
<td>For ages $e_1$ to 2.5 years, AND $X_2 - X_1 \geq 1/12$ refer if</td>
<td>$e_1$</td>
<td>Age (in years) after which the rule is effective</td>
<td>0, 0.5, 1</td>
</tr>
<tr>
<td></td>
<td>$SDS_2 &lt; f_1$, AND $(SDS_2 - SDS_1)/(X_2 - X_1) &lt; g_1$</td>
<td>$f_1$, $g_1$</td>
<td>SDS cut off level below which $SDS_2$ must lie</td>
<td>-1, -1.3, -1.5, -2, -2.5</td>
</tr>
<tr>
<td>Delta-rule*</td>
<td>For ages $e_2$ to 2.5 years, AND $X_2 &gt; X_1$ refer if</td>
<td>$e_2$</td>
<td>Age (in years) after which the rule is effective</td>
<td>0, 0.5, 1</td>
</tr>
<tr>
<td></td>
<td>$(SDS_2 - SDS_1) &lt; w_1$</td>
<td>$w_1$</td>
<td>Change in SDS</td>
<td>-0.5, -1, -1.5, -2, -2.5</td>
</tr>
<tr>
<td>Condition weight gain rule</td>
<td>For ages $e_3$ to 2.5 years, AND $X_2 &gt; X_1$ refer if</td>
<td>$e_3$</td>
<td>Age (in years) after which the rule is effective</td>
<td>0, 0.5, 1</td>
</tr>
<tr>
<td></td>
<td>Weight SDS $&lt; f_2$ AND $Weight , SDS_{gain} = (weight , SDS_2 - r , weight SDS_1)/(\sqrt{1-r^2}) &lt; w_2$</td>
<td>$f_2$, $w_2$</td>
<td>SDS cut off level below which $SDS_2$ must lie</td>
<td>-1, -1.3, -1.5, -2, -2.5</td>
</tr>
<tr>
<td>Absolute SDS rule*</td>
<td>For ages 0 to $e_4$ years, refer if $SDS &lt; f_3$, AND $SDS &lt; f_4$</td>
<td>$f_3$, $f_4$</td>
<td>SDS cut off level before age $e_4$</td>
<td>-1, -1.3, -1.5, -2, -2.5</td>
</tr>
<tr>
<td></td>
<td>For ages $e_4$ to 2.5 years, refer if $SDS &lt; f_4$</td>
<td>$e_4$</td>
<td>Age (in years) at which the referral level changes</td>
<td>0, 0.5, 1</td>
</tr>
<tr>
<td>Parental height corrected rule</td>
<td>For ages $e_5$ to 2.5 years, refer if $Length , SDS &lt; f_5$, AND</td>
<td>$e_5$, $f_5$</td>
<td>Length SDS cut off level before age $e_5$</td>
<td>-1, -1.3, -1.5, -2, -2.5</td>
</tr>
<tr>
<td></td>
<td>$Length , SDS - TH , SDS &lt; g_1$</td>
<td>$g_1$</td>
<td>Difference between length SDS and target height SDS</td>
<td>-1, -1.3, -1.5, -2, -2.5</td>
</tr>
<tr>
<td>Parental height deflection</td>
<td>For ages $e_6$ to 2.5 years, AND $X_2 &gt; X_1$ refer if</td>
<td>$e_6$</td>
<td>Age (in years) after which the rule is effective</td>
<td>0, 0.5, 1</td>
</tr>
<tr>
<td></td>
<td>$Parental , height , deflection$</td>
<td></td>
<td>Age $X_2$ after $X_1$</td>
<td></td>
</tr>
</tbody>
</table>
We also added the following sentences in the results:

“The low absolute height rule, rules that take genetic height potential into account (parental height corrected rule and parental height deflection rule) and the combined weight and length deflection rule proved less effective.”

We removed the following paragraph in the discussion: “In addition to the slowed growth, delta and conditional weight gain rules we also applied other rules. As these rules proved less effective, we have not included the findings in the discussion. Examples of these include using a low absolute height SDS as cut-off; rules that take genetic height potential into account, by investigating the distance to target height or whether a slowed growth for HSDS of the child moves away from the child’s target height. This was added because on the assumption that in the first years of life, a correction might be needed for parental height: e.g. a baby that is born with a length of -1 SDS and has a target height of +2 SDS, would be expected to cross the SD lines in upward direction in the first 2-3 years. An acquired growth disorder could disturb this, and theoretically a stable length of this child at -1 SDS over the first 2 years could indicate growth pathology such as CD. Similarly, we included a rule that combined weight and length, in which a slowed growth for length occurs after a slowed growth for weight.”

3. The prior-probability of CD is given as 0.86% on page 7. Is this value correct?

Answer: Yes, as PPV in % is 100*sens/(sens+(1-spec)*(1/prev))=
100%*0.339/(0.339+0.021*(1/(0.54/1000)))=0.86
4. The conclusions of the study echo other recent reports.

Answer: As far as we know, no other studies provided evidence that the most sensitive auxological parameter to detect CD children is slowed growth for standardized body mass index. The referee probably means that we recently published two other reports about evidence-based referral criteria in growth monitoring [Buuren van S, Dommelen van P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004;89:336-41. Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama SM, Verkerk PH, Wit JM, van Buuren S. Developing an evidence-based guideline for the referral of short stature. Arch Dis Child. 2007 Oct 1; [Epub ahead of print]]. These reports were mainly focused on short stature and slowed growth for length or height. Our study also assessed other parameters of growth.

5. The study included several small cohorts of children, totaling 122 (after exclusions). This appears to be a relatively small number: can this number be justified?

Answer: The reviewer is right in that it would have been preferable if the number of CD patients had been larger. However, this was the study sample that was available, and we had estimated in the beginning that it would be sufficient to reach valid conclusions. This estimation was based on 134 CD cases (before exclusion). We amended the following text in the method section:

“Power analysis
With 134 CD cases we obtain a 95%-C.I. of +/- 8% for an estimated sensitivity of 50% and with the 2,151 reference children a 95%-C.I. of +/-0.6% for an estimated specificity of 98%.”

Based on 122 cases, the 95% C.I. will be +/-9%.

6. Furthermore, data from these patient cohorts were collected over a long period of time (dating from 1994). The presentation patterns of CD over this time period will likely have changed in the Netherlands (as in other countries), making the conclusions less relevant for the current day situation.

Answer: From the literature it is known that there is an increase of non-classical symptoms involving older children. One may assume that for the age-group included in the present study (0-2.5 years) the performance of the auxological criteria is similar for the present CD-population, since it is the delayed onset of the disease (the non-classical form) that has increased during the recent years, suggesting that the growth impairment becomes apparent much later (see discussion). Furthermore, one might assume that improvements in the availability and quality of food, health and hygiene can lead to an increase in statural growth in the normal population. Various studies have been conducted to identify the secular change [ Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth. Horm Res 1996;45(Suppl 2):8-17]. However, this secular
trend only becomes evident later in life. With regard to BMI, in the age group from birth to 2.5 years of age, no more than 13% of the population examined in 1997 surpassed the P90 for 1980, 54% the P50 and 90% the P10. Since 1965, the height of individuals up to three years of age has remained virtually unchanged [Fredriks AM, Buuren S van, Burgmeier RJF, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in the Netherlands 1955-1997. Pediatric Res 2000;47:316-23]. Therefore we feel that our conclusions are relevant for the current day situation.

7. The Legend for Table 1 needs to be more comprehensive: there are very difficult and confusing concepts to interpret in this Table.

Answer: We changed the legend of Table 1 into “Auxological screening rules with their definitions, interpretation of the used parameters and cut off (simulation) values”.

Referee 1:

Major Compulsory Revisions

I spent some time trying to understand how data were compared. Beside the studies cited it seems that some longitudinal growth data were gathered from school doctors in the Regional health centres. I believe that even in this case there were no fixed schedule of measurements but the measurements were collected in a medical setting. How did these new data implement the old ones? The old ones were gathered only by self-administered questionnaires? Do the new longitudinal data relate to patients on GFD? The mixture of retrospective/prospective old data and new longitudinal data is hard to understand. If the population is the same and the doctors in regional health centres have the auxology of all children in Nederland why do not use the non-celiac ones as controls?

Answer:
The methods of data collection are described in more detail in the original publications. We are sorry that the texts apparently leave room for confusion. We shall respond to each question separately:

Beside the studies cited it seems that some longitudinal growth data were gathered from school doctors in the Regional health centres.

No, it was in the studies cited, not beside, that the data were gathered from the school doctors in the health centers, after the child had been diagnosed as CD. Indeed we were dependent of these retrospective data that were generally collected in a more or less regular scheme (in the Netherlands all children are going for check-up at fixed ages).

As our text appears insufficiently clear on this issue, we changed the following sentence in the discussion “We tried to minimize the problem by gathering extra information about growth from school doctors in the Regional health centres” into “We tried to minimize the problem by gathering extra information in the studies cited about growth from school doctors in the Regional health centres”.


I believe that even in this case there were no fixed schedule of measurements but the measurements were collected in a medical setting.

As stated earlier, health centers use a fixed scheme, but obviously small transgressions may occur.

How did these new data implement the old ones?

There is no question of “new data implementing old ones” we just used the data that we had collected for the three studies performed earlier.

The old ones were gathered only by self-administered questionnaires?

In the first study we obtained the growth data through self-administered questionnaires, in which the parents were asked to collect the growth data from the health centers in their community.

Do the new longitudinal data relate to patients on GFD?

No, as stated in the text, we only used growth data at diagnosis and before that time.

The mixture of retrospective/prospective old data and new longitudinal data is hard to understand.

In essence we used the same method to collect growth data from the three CD groups: after diagnosis, all available growth data were gathered retrospectively.

If the population is the same and the doctors in regional health centres have the auxology of all children in Nederland why do not use the non-celiac ones as controls?

For the control population we needed a well-controlled longitudinally followed sample. Theoretically this could be obtained from a set of health centers, but that would be an enormous additional work load. For efficiency reasons we chose for using available data sets.

The Authors state that it is “common knowledge” that a CD patient has a length (or height) deficit and slowed growth for weight, but this is not based on good evidence. I really appreciate their effort to clarify this issue but I believe that the study will not give a definite information about the usefulness of auxology in CD diagnosis. Moreover, general practitioners and paediatricians with average knowledge of statistical analysis and average patience will have hard time to read the paper as it is.

Answer: We changed the sentence “It is already “common knowledge” that a CD patient has a length (or height) deficit and slowed growth for weight, but this is not based on good evidence.” into “So far, it is generally assumed that most CD patients have a diminished growth in terms of length (or height) and weight, but this is not based on good evidence.” For further discussion on this point, see earlier response to referee 2.

This study provides evidence that asymptomatic toddlers with CD detected by screening grow normally between birth and 2.5 years of age, and that BMI is more important than weight, and much more than length or height, to detect CD children with clinical manifestations. We also give a referral rule that is able to detect one third of the symptomatic CD patients within 2.5 years at the account of 2% of the healthy children. Those insights are new and will help general practitioners and paediatricians to detect CD children by growth monitoring. We think that these conclusions are clear from the abstract. However, we agree that the reader with an average knowledge of statistical analyses will have some difficulties with some of the paragraphs of this manuscript, but
these paragraphs cannot be removed or simplified as the referral rules has to be clarified in detail. Also, Table 1 might be difficult to understand, but this table has to be included in the manuscript as one may use this to implement our rules in a computer system that can be used in child health care. However, to clarify Table 1 we amended two examples in the method section. The first example is given after the explanation of the slowed growth rule: “For example, if \( e_1 = 0.5 \) years, \( f_1 = -1.5 \) length SDS and \( g_1 = -1 \) change in SDS per year. Then a child is referred according to this rule if his/her length was measured after or at 0.5 years of age, again his/her length was measured at least 1 month after the first measurement and this length was below -1.5 SDS, and the difference between the second and first length measurement in years was below -1.” The second example is given after the explanation of the delta rule. “For example, if \( e_2 = 1 \) year and \( w_1 = -2 \) weight SDS, than a child is referred if the second weight measurement is -2 SDS below the first weight measurement and both weights were measured after 1 year of age (or at 1 year of age for the first measurement).”