Author's response to reviews

Title: Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample

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

Again, many thanks for your attention to our proposed manuscript, resubmitted as a possible contribution to BMC Psychiatry. We would once more like to express our gratitude for the time and effort to improve the text. We agree with the comments made by Referee 2, and have done our best to address them accordingly. The reviewer’s critique and suggestions in normal (upright) typeface is followed by the authors’ responses in *italics* throughout this cover letter. Please note that the references to pages and lines in the reviews are according to this submission, and may possibly not coincide with the pages and lines of the earlier submission. So, hereby attached is the revised version of the manuscript, which we hope will meet the high standards set by the journal.

Yours truly,

Tomas Larson

1. I think it should highlight that the excellent psychometric properties regard ASD above all in the abstract also in the discussion section.

*The psychometric properties of ASD have now been highlighted in the Abstract and on page 14 in Discussion, and finally it is also mentioned as a conclusion on page 19.*

2. The text is still sometimes unnecessary cumbersome, therefore I would also recommend a final read-through and language correction, preferably by a native English person.

*The manuscript has now been proofread by a native English person.*

3. I think the Assessment of NPD section in the introduction can be removed altogether. I furthermore still find the assessment instrument part in the introduction very confusing, as it doesn’t fill any function. It does not provide a review of existing, competing instruments to the A-TAC at all, nor does it relate anything about the pros and cons of these mentioned competing instruments. If it is to remain there, it should have a function and be more specified
as to the non-existence of other instruments similar to the A-TAC (I am unsure of whether other exists).

We concur; the Assessment of NDP section and the rundown of other instruments have been removed.

4. The following part may be deleted (page 11): “Most screening inventories in psychiatry have more than one possible score; deciding where to place the threshold or the cut-off that divides subjects into “disorder present” or “disorder absent” is not arbitrary. The scores that are chosen as cut-off values are determined by maximizing sensitivities (identifying all true cases), while not compromising specificities (excluding all true non-cases).”

The indicated section has now been deleted.

5. And I would still like to have a reference to the determination of the AUC values

The reference to the AUC values has been included: Reference number 18. Tape TG: Interpreting Diagnostic Tests [http://darwin.unmc.edu/dxtests/]

6. Finally, I don’t understand why it is not possible to calculate sensitivity and specificity for a 2x2 table of all disorders (NDP) vs any screen positivity?

We may have misunderstood the Referee before, and have now added a description of the suggested 2x2-table, sensitivity, specificity and DOR for any NDP, as suggested. The text in Results now reads: “Of the 198 children who screened positive for any NDP at baseline, 108 (55%) received at least one clinical DSM diagnosis of an NDP at follow-up. Of the 252 children who were screen-negative for NDPs at baseline (the majority of whom were screen-negative co-twins to screen-positive siblings, and therefore constituted a high-risk group), 51 (20%) received at least one clinical diagnosis of an NDP, while 201 (80%) received no clinical NDP diagnosis at follow-up. A 2 × 2 contingency table of true and false positives and negatives for all NDPs yielded a sensitivity of 0.68, a specificity of 0.69, and a DOR of 4.7 for the A-TAC’s ability to capture any NDP (Table 1).”
7. Some of the reason for this is undoubtedly due to using screen negative twins as controls, which is not a randomly selected sample. Had the group of screen negative children from normal controls been higher, the figures would have looked better. A section on this should be added in the discussion, I see that it is mentioned in the limitations but rather saying that it is representative of the population, which I find a bit hard to accept given that the NPD are highly heritable. The rate of NPDs in this group is also quite high (20%), contradicting the assumption of representatively of the general population.

Please, see the section added to Limitations under point number 9.

8. There is a long section on PPV in the limitations, which I think can be removed altogether as we decided to report DOR.

We agree; this section has now been removed.

9. The authors would be better advised to say something about the low DOR/AUC for other disorders than ASD (especially ADHD), and here I would believe that the twin sample bias may have a bearing, and the time lag between screening and the clinical assessment.

This has now been addressed in the Limitation section on page 18: “Moreover, the A-TAC showed comparatively low DOR/AUC for disorders other than ASDs (especially AD/HD). This may be attributed principally to the time lag between the screening and the clinical assessment and perhaps also to a “twin sample bias” suggested to be inherent in using a screen-negative group that largely consists of genetically at-risk siblings. Given that NDPs are under complex and multivariate genetic influences and tend to follow a waxing and waning course, a longitudinal twin sample may compromise probabilistic measures, including NPVs and PPVs, since discordant co-twins will be more likely than other pairs to oscillate above or under a cut-off. Despite this reasoning, however, the notion of a twin sample bias is dubious since numerous studies have reported that twins differ only marginally from singletons [31, 32, 33]; even if same-sex twins may not be representative of the general
population, is it unlikely that this circumstance would have had any substantial effects on the results presented here.”