Author's response to reviews

Title: A systematic review of attention deficit/hyperactivity disorder and mathematical ability: current findings and future implications.

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

We are pleased that the reviewers found the paper improved after the first round of comments and we have attached a revised version of the manuscript that fully addresses all the new comments raised. We have addressed the reviewer’s comments as detailed below:

Reviewer: Andrea Cipriani

1) I can see that the protocol now is published in PROSPERO. However, only very few details are reported (i.e. it is not specified which is the study design the authors were looking for, there is nothing about the statistical analysis, the actual search terms are not reported so the search strategy is not replicable). By contrast, the manuscript is too detailed in some parts (see pages 6 and 7): all this information should go in the protocol

1A) We are keen to make any improvements that will strengthen our document. In response to the reviewer suggestions we have added information to the protocol as detailed below.

The following information has been added to "Searches"
" An additional manual search of the literature was performed to identify any publications missed by the database search. This was done by hand searching the reference list of all identified articles in the database and filtering these articles through the same inclusion/exclusion criteria (described in the 'eligibility criteria'). A search was conducted on 1 February, 2015 using the following key words:
Keywords = ("attention deficit hyperactivity disorder" OR "ADHD" OR "hyperkinetic disorder") AND ("mathematical ability" OR "math* achievement" OR "acalculia" OR "mathematics").

A new search strategy has been added as supplementary information to the protocol published in PROSPERO. A copy of the search strategy together with a copy of the revised protocol as resubmitted to PROSPERO is attached.

Section 22 "Types of study to be included..." has been amended as follow:

"We will include quantitative, individual cohort/cross-sectional and longitudinal studies. The study design of the papers reviewed will include: cases and control based on presence/absence of ADHD and twin design. Studies will have clear description of samples, statistical methods and results. Studies included will consist of peer-reviewed papers published in English."

We understand that the reviewer suggests moving some of the content on pages 6 and 7 to the PROTOCOL to streamline the paper. However, we believe that not all the content on these pages should feature in the protocol as they will facilitate the understanding of our manuscript without the need to refer to the PROTOCOL. We therefore moved to the protocol only what we believe does not detract from a self-contained description of the searches. However, selected parts have been moved to the protocol such as
Manual search of the literature was performed to identify any publications missed by the database search. This was done by hand searching the reference list of all identified articles in the database and filtering these articles through the same inclusion/exclusion criteria (described in the 'eligibility criteria').

We further followed the reviewer suggestion and added a supplementary document and moved text that may be too detailed to feature in the main document. We have attached a copy of the supplementary materials containing information previously presented as part of the manuscript.

The section of Data Collection Process already features in detail in section 26 of the published protocol. In Section 26 we have also added the Data Items as follow:

- Type of study (cross-sectional or longitudinal)
- Nature of the cases (diagnosis of ADHD in absence of learning disabilities)
- Nature of the control group (healthy controls) and number of healthy controls where a control group was present
- The response rate to the study
- Dropout rates for participants recruited (if longitudinal study)
- Age range and sex by group(s)
- Numbers of cases (ADHD) and if available number for each of the ADHD sub-groups, inattention and hyperactivity- Impulsivity.
- Whether the potential confounding demographic and cognitive factors (IQ, medication - unless temporarily stopped, socio-economic status and gender) were accounted for in the design and/or in their analysis.
- Whether cases were on medication during the test or whether the medication was stopped temporarily prior to testing.
- Name of the mathematics test used to test mathematical performance
- Mean maths score with standard deviation for cases and controls and/or other appropriate means of describing the association between ADHD and maths (e.g. regression, correlation coefficients); if longitudinal study scores at baseline and follow-up
- Whether effects size were included.

We did not include a section on statistical analysis as no statistical analyses were performed as part of this systematic review.

2) I didn't understand why six studies have been excluded from this updated and revised version. It is a significant proportion of the original evidence and I was wondering what would have happened if the studies had not been removed and been included in the published review. Apparently, raising the issue of the protocol helped the selection process. However, to have a freely accessible protocol is now the minimum standard for any systematic review and I encourage the authors to follow this procedure.
2A) We fully agree with the reviewer; publishing the protocol on PROSPERO provides a number of clear advantages although we understand that is not a requirement for publication in BMC Medicine (eg. www.biomedcentral.com/1741-7015/10/130/). The published protocol clearly increases the transparency and structure of any review.

However, to publish the review in PROSPERO, we had to do a major restructuring of the paper and performed an entire new search. This was compulsory in order for the protocol to be accepted and published in PROSPERO as they would not accept a protocol if the review was beyond the stage of data extraction. The overall results and conclusions emerging from this new search matched what was presented previously. However we have taken the opportunity to revisit how we applied our inclusion/exclusion criteria, in part due to the suggestions of the reviewers. For example, the paper by Polderman et al., (one of the papers excluded) used the Pupil Monitoring System in a Dutch sample to assess mathematical abilities. The Dutch pupil monitoring system allows teachers to use the test they best deem appropriate to assess mathematical abilities for their pupils. The paper does not fully describe whether this was a summative test of achievement or a formative assessment. In our criteria we did not include mathematics assessed by standardised school achievement exams (eg. SAT, GCSE). We know that tests and school achievements correlate highly but since we were unsure of the exact nature of these assessment criteria, the paper was removed. Further papers were removed where the sample description was inadequate to fully assess whether children had a borderline mathematical disability rather than low ability. However, there is considerable heterogeneity in the definitions of mathematical abilities.

We preferred to apply our inclusion criteria more strictly when the paper did not allow for a clear judgement. However, even with the exclusion of these papers, the results did not change. The underlying message of our review remains clear: children with poor mathematical ability, but not diagnosed as being maths disabled, show an association with ADHD symptoms. When the studies provided the two subtypes of ADHD, the association was stronger with the inattention component rather than inactivity. This is the first review that looks at this association which is clearly present irrespectively of the 6 studies excluded.

As this paper has been under review since August 2014, two more studies have been published in the meantime and the new search included these.

3) I still have significant doubts about the assessment of the risk of bias. The authors stated that they used the revised CASP, but it is not clear why they used a revised version and who did this revision (and whether it has been validated and replicated).

3A) This review does not appraises clinical trials and therefore instruments for assessing risk of bias in randomised trials are not applicable. We decided to use the CASP instrument, as it was the best match to appraise the quality of the mixed design studies included in this review. The CASP instrument was not used to exclude papers as these had already met the inclusion criteria. The questions from the CASP instrument were preserved and used for the purposes of appraisal rather than inclusion and as such are already validated as part of the
CASP instrument. The same questions from the CASP instrument were arranged as described in section 8. We understand that referring to the CASP instrument as “adapted” suggests we have changed it in some way, which is not the case. We therefore rephrased the description of the CASP instrument.

It is important to note that we did not use the classification of the studies as outcome variable in a statistical analysis and the use of the CASP instrument has no impact on the overall conclusions of the study. The convergent evidence from all studies is clear and independent of any rating we awarded using CASP.

Various published studies have used other instruments in a similar way (eg http://bmjopen.bmj.com/content/suppl/2014/12/22/bmjopen-2014-006414.DC1/bmjopen-2014-006414supp7.pdf).

4) The quality of the reporting should be improved (for instance, PRISMA should not be mentioned in the objectives of the review or Figure 1 should clearly report both the results from the original search and the two additional studies retrieved by the updated search on Feb 1st 2015). Some sections could be condensed or reported as web appendices.

4A) In response to the reviewer’s comment, we have made several changes to the reporting structure which are highlighted in the track-changes version of the manuscript. Prisma is no longer mentioned in the objective as highlighted by the reviewer. We have amended Figure 1 one to include the results from the new search. However, it is important to note that in order to publish the review in PROSPERO, we had to perform an entire new search and this is not just limited to an update. The figure correctly reports the results from the search performed on Feb 1st, 2015. We feel that we should publish the results of the last search only without the need to highlight any discrepancy between this version of the manuscript and any other previous versions submitted prior to major change requests. The search performed on Feb 1st 2015 is the one that matches what presented in the paper and what published on PROSPERO and the only search we refer to.

We have shortened several sections and any information we deemed redundant have been deleted. This is visible in the tracked-changes version of the manuscript. We have also followed the reviewer suggestion and moved some of the content to Supplementary Materials. Efforts have been make to make the paper shorter following comments from both reviewers.

Once again, we are grateful to Prof Cipriani for his detailed and constructive feedback. We feel that the suggestions made have greatly enhanced the quality and presentation of this paper.
Reviewer: Jean-Pascal Lemelin

The authors have responded well to my (and other reviewers') previous comments on the first version of the manuscript. I want to congratulate them in submitting a much improved paper. It is now clearer and more coherent, better structured, rendering its contribution to the scientific literature even more convincing. At this stage, I think that the paper is close to a publishable state, and therefore I only have a few more (minor) comments:

1- There are still some typographical errors in the manuscript. The manuscript should be revised thoroughly to delete these.

1a) In response to the reviewer's comment, we have given the manuscript several extra rounds of proof-reading and we fixed any typographic errors we came across. We further made several changes to improve syntax and flow. We trust the reviewer will find the legibility of the paper improved.

2- This sentence should be revised: "...the mathematical achievement scores decreased over time, showing an increase in lifetime mathematical disability is association lower school achievements later in life [26, 40, 41]."

2a) In response to the reviewer's comment, the paragraph containing the above sentence has been modified as follow: "Additionally, in children with ADHD, mathematical achievement scores decreased over time [26, 40, 41]. As children in the studies were not selected based on mathematical disability, this evidence may suggest a causal link between the disorder and poor school performance later in life."

3- Page 12, High Quality Rating studies section: There is some confusion regarding the number of studies. Authors first say that 19 out of 24 studies show a significant relation between ADHD and math. They then identify 3 other studies not included in the previously listed 19 (studies 30, 39 and 55). It seems that study 39 is a medium quality study (see Table 1). After, they say that 4 of the 24 studies did not show a significant relation between ADHD and math, which doesn't add up. In addition, they identify not four but 3 studies (43-45). In short, this section needs to be revised and clarified so that it is coherent with Table 1 and the following section on medium quality studies.

In response to the reviewer's comment, we have carefully checked all references (some which have not converted from the tracked version of the manuscript submitted) and fully addressed all the concerns above. All references in the text now add up and are consistent with what reported in Table 1 and Table 2.

Just to clarify, the two studies added in the second revision are: Efron et al., (2014) and Pappaioannou et al., (2014). Study 39 refers to the paper by Thorell (2007), which is indeed a medium quality study.

A further change to the High Quality section in the Results includes presenting the two genetics studies (which are rated as high-quality) in this section rather than at the end of the
Results after the *Medium Quality* section (we prioritised based on quality rating rather than design type).

4- When discussing genetically informed studies, environmental correlations should also be identified using rc abbreviation, as it is for genetic correlations (ra).

4a) We have updated Table 2, showing the shared and non-shared environmental correlations (please see updated Table 2, reference 49). In other parts of the manuscript, we now refer to the environmental correction as rc, consistently with the genetic annotation (ra). We have further added a Supplementary document where genetic and environmental correlations/covariances are described in more details.

5- I can't find where in the discussion the need for more longitudinal studies is mentioned as a future direction, nor where the lack of longitudinal studies in the review is specified as a limitation in the limitations section (see my comments on version 1 of the paper). These two observations need to be mentioned more clearly.

5a) In response to the reviewer’s comment we have made several changes to the discussion section. The need for longitudinal studies and the few studies of this kind indentified in this review has been discussed and acknowledged as a limitation. The following has been added to the discussion section:

"This review has identified only four longitudinal studies that explored the association between mathematics and ADHD. Considering the possible developmental changes in the disorders, more efforts should be devoted to longitudinal research to gain a better understanding of the aetiology and development of the disorder. Findings from these studies could lead to a better classification of the disorder and help inform prevention and treatment strategies."

We also added the following in the limitations section:

"Using the association of mathematics with ADHD has allowed highlighting the heterogeneity within the disorder. However, studies exploring the association between mathematics and ADHD are fewer compared to other phenotypes. Therefore, the four longitudinal studies identified in this review, did not allow to fully capture the developmental aspect of ADHD."

Again, we would like to thank Dr. Lemelin for this time and constructive feedback. We feel his comments have greatly improved manuscript.