Author’s response to reviews

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

Authors:

Maria Grazia Tosto (maria.tosto@kcl.ac.uk)
Sukhleen Momi (sukhleen.momi@kcl.ac.uk)
Philip Asherson (philip.asherson@kcl.ac.uk)
Karim Malki (karim.malki@kcl.ac.uk)

Version: 2 Date: 6 March 2015

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

We would like to thank the reviewer’s for their time and expert opinion on our paper. We feel that their comments and suggestions have greatly improved the manuscript. We are submitting a revised version of the manuscript that addresses all the reviewers concerns. Changes to manuscript are detailed below.

**Reviewer one: Prof Ruth Shalev**

1. The message of the review can well be transmitted in a significantly shortened format.

1a) We are pleased that Prof Shalev has found the review timely and of interest and agrees with the importance of the findings. Were possible, we have shortened several sections to make the paper more concise and direct without changing the meaning. This is particularly relevant for the results section, which has been considerably shortened. Details of the changes can be found in the track-changes version of the manuscript.

We would like to thank Prof Shalev for her time and expert opinion of the paper.

**Reviewer two: Prof Andrea Cipriani**

1) It is necessary to have the protocol of the review in order to be able to check the consistency between the two documents and adequately comment on the review itself (a lot of information is missing in the manuscript, for instance re. the search strategy). If so, this review does not meet the minimum standard for publication in a scientific journal (please, visit PROPERO at http://www.crd.york.ac.uk/PROSPERO/).

1a) At the time of first submission and during the pre-submission enquiry we did not discuss publishing the protocol on PROSPERO. Indeed there are other systematic reviews that have been published in BMC Medicine in the absence of a published protocol.


On page 2 of the above published review, the following statement appears:
"Methods-- Protocol and registration-- We did not register the protocol for this review."

On the other hand we have to agree with the reviewer and cannot find a compelling reason not to publish the protocol on PROSPERO. In order to publish the review with PROSPERO we had to start a new search, revising the criteria following several suggestions that the reviewer made. This caused some delays in the resubmission of this paper for which we apologise but it was necessary in order to comply with PROSPERO guidelines. The protocol is now published on PROSPERO [registration number: CRD42015016186]. Additional information on the search protocol has been added to the manuscript.
2) Overall, the reporting of the manuscript is not properly organised and structured as it should be (the authors mentioned the PRISMA statement (http://www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1000097&representation=PDF) but they do not seem to follow the instructions carefully.

2A) We thank the reviewer for the thorough assessment. In response to the reviewer’s comment, we have revised the organisation and structure of the manuscript strictly adhering to PRISMA guidelines. This involved several changes and the addition of several subheadings that can be seen in the track-changes version of the manuscript. All the PRISMA items now appear in the manuscript in the order suggested by the PRISMA checklist.

2i) In the submitted manuscript some of the results are reported in the method section (for instance, the number of studies retrieved by the search)

2ii) a lot of information is missing from the search strategy (for instance, the full list of the search terms and key words),

2iii) the paragraph of the search strategy is written before the inclusion/exclusion criteria, no information about the statistical analysis in the method section, etc.

2i-iiiA) The points above have all been addressed in the revised version. Additional changes have been made beyond the ones suggested by the reviewer in order to adhere strictly to PRISMA checklist and are visible in the "track-changes" version of the manuscript. The number of studies retrieved at each stage of the search has now been added to figure 1. A new "search strategy" section clearly states the keywords used. Several sections have been re-arranged or added to be consistent with the items and items order in the PRISMA checklist. The Eligibility Criteria section now appears before the search strategy.

3) Quality of the studies: I couldn’t find a clear consistency between references 17 and 18 (as quoted by the authors) and what the authors did in their paper. As far as I can see, the authors changed the items of ref. 17 (see http://media.wix.com/ugd/dded87_19dd1d558a9977c0e0b30cedf86a9da7.pdf) and added the answers to the questions as a final score, which is not the intent of the CASP appraisal tool.

3a) We have changed the references accordingly. We further added a detail explanation of the how the adapted version of the CASP appraisal instrument was used in our review to assess the quality of the papers included.

4) The authors seem to divert once more from the correct interpretation of the CASP guidelines. For instance, in the reported link a few lines above it is written that "...the first two questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions".

4a) Quality assessment for each of the papers used in the review was conducted following CASP guidelines. We have evaluated each of the 10 questions from the CASP instrument as detailed in the section "Risk of bias in individual studies". The CASP questions were adapted to be a good match to the topic and design of the studies included in this review and all questions fall under one of the 10 questions in the CASP appraisal tool. The questions reported in the paper were formulated based on
the "hints" for each of the questions in the CASP guidelines. For example, question 5 of CASP states: "Was the data collected in a way that addressed the question? " The hint provided by CASP suggests to consider whether the setting was justified, if the researcher has made the method explicit, if the form of the data is clear etc. These are covered by our questions 8 and 10 as detailed in the manuscript. Some of the hints suggested by CASP were not applicable to the quantitative studies we reviewed. The order of the questions we have used address the 10 CASP point has been arranged differently to fall under the following subheadings: Objectives, Participant Selection and Methodology and Outcome Measurements. Although the order of our questions differs from the one proposed by CASP, this does not have an impact on the overall assessment of the papers.

5) Looking at Table 1 of the submitted manuscript, ref 55 (Barkley et al., 1991) does not meet the first criterion or ref 41 (Hannula et al) does not meet the second criterion. Why did the authors include these studies?

5A) As part of the revision of this manuscript we have repeated the entire search and went through the selection process again. As a result the following six papers have excluded, as they did not fully met the criteria.

Barkley et al.,
Hannula et al.,
Mahone et al.,
Mayes et al.,
Polederman et al.,
Solanto et al.,

Two additional references have been added: Ref 36 & 66. These are references that have been published while the paper was under first review.

6) the classification into High, medium and low quality seems to me absolutely arbitrary and without any backing reference. Am I correct? I think that a clear explanation of how the authors addressed the quality issue and why we can find these (at least apparent) inconsistencies is needed.

6a) In response to the reviewer’s comment, we have added an explanation of how we classified studies into high, medium and low quality. We used an adapted version of the CASP instrument that enabled us to evaluate each paper based on the major items listed by CASP. Two of the authors evaluated each paper using the CASP-adapted checklist and disagreements were resolved by discussion, with involvement of a third review author.

7) Please, add the number of pages to the manuscript!

7a) Done!

8) Can you add the date of the search?

8a) The date of the search now appears under the new subheading "Search".

9) Why did you include people with a diagnosis of ADHD or without a diagnosis and only with symptoms according to a (standardised????) rating scale (quote: "...participants of any age who had a diagnosis of ADHD (DSM-defined ADHD or ICD-defined hyperkinetic disorder) or were assessed for
symptoms of the disorder on ADHD validated scales,...")? I think this can generate some important heterogeneity in the sample and reduce the validity of the results. Can you explain your choice?

9A) In response to the reviewer's comment we have clarified the above in the section "Eligibility Criteria". We have revised the terminology used and added an explanation of "ADHD-validated scales". In the cognitive literature, children are often assessed using DSM-derived instruments such as the Conners scale which is a popular research and clinical tool for obtaining parental reports of childhood behavior problems. For example, several papers on ADHD from the TEDS (Twin Early Development Study) use this scale.


The following reference has been added to the manuscript:


10) Can you clarify which are the "appropriate tests used to determine mathematical ability"? This is something that it is usually specified in the review protocol.

10a) We have clarified what we mean by appropriate test and listed all the tests used to assess mathematical ability in the 'Eligibility criteria' point d). In the cognitive literature there are several standardised tests that are widely used and these have now been listed in the published protocol. However, mathematics is a wide domain and there are many less known tests that have been equally validated and those researchers in the field use according to their particular research question. For example, Kaufmann & Nuerk used a battery of tests that assessed a very specific aspect of mathematical abilities.

11) There are some white empty boxes near the beta coefficient on page 9 and Table 2. I'm sorry, but I don't understand the meaning. Can you explain?

11a) The table has been revised and updated.

12) All the results section in the manuscript basically duplicates results reported in Table 2. I think that the table is much clearer and I would reduce the result section to the very minimum (cross referencing Table 2)

12a) We agree with the reviewer; this was also noted by reviewer one. We have removed redundant information from the results section and referred to the table where appropriate.

13) Why DSM is one of the keywords of the manuscript?

13a) We have removed DSM from the keywords.

14) Please, clarify Figure 1 (or the text) should report the broad categories/reasons for exclusion of
the more than 2000 references originally retrieved (otherwise, the criticism could be that the search was not appropriately done, too broad or too imprecise)

14a) Figure 1 has been revised following the reviewer's suggestion.

15) Add a proper legend for Figure 1. Why is the figure so small if compared with the rest of the manuscript? A better resolution would be of help.

15a) We have re-written the legend for figure 1. We are not sure why the figure appears small as the uploaded file was a full A4 size image. This may have something to do with how the PDF is compiled by the manuscript submission system. We will make sure to upload a larger image and ask the copy-editor to feature it prominently in the paper. We agree the figure is important.

16) The discussion should be based on the results of the review and be more balanced, taking into full consideration all the limitations of the studies and the heterogeneity of the population. I don't think the quality of the evidence retrieved by this manuscript is robust enough and I frankly doubt that this evidence can be used to back any clear statement of causal association between ADHD and mathematical ability. I would be more cautious, but this is matter of interpretation and I leave it to the authors.

16a) We appreciate the comment. We feel the review is important and timely as suggested by Reviewer one and Reviewer three. The evidence points to an association between ADHD and mathematics but it is not our intent to suggest causality. The differential relationship between the two components of ADHD and mathematics, which emerges from this review, may point at heterogeneity within the disorder. The statement in the discussion on causality is in reference to the low genetic overlap between the two ADHD domains rather than with mathematics.

17) I’m sorry, but I don’t think the very last statement of the conclusion section is Pertinent to the previous discussion. Can you clarify?

17a) We wanted to highlight that future studies will likely recruit cases and define subtypes using slightly different diagnostic algorithms since changes to the DSM rubric have been introduced as part of DSM-V. However, we have moved this statement elsewhere in the discussion.

We are grateful to Prof Cipriani for his time and thorough review of our paper. We feel the comments and detailed suggestions have improved the review substantially.

* * * * *

Reviewer 3

This paper is an interesting systematic review of the studies investigating the relationship between ADHD and math ability, with a specific emphasis on the studies examining the associations between math and the two main components of ADHD separately, i.e. attention and hyperactivity-impulsivity.
Results on the whole suggest a substantial negative link between ADHD and math ability. This relationship appears to be stronger between math and the inattention component of ADHD. Behavioral genetic studies suggest a strong genetic correlation between math and ADHD, again, greater for the inattention component of ADHD. This review is timely within the fields of developmental psychology, genetics, medicine and education. The paper is in general well-written, and has the potential to contribute in a significant way to the scientific literature. My comments and concerns are organized around sections.

1-
Authors have used the PRISMA guidance to conduct their review of the literature, which is strength of the study. Authors should however indicate the whole name (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) when they first use this acronym in the manuscript. They should also either describe a little bit more what exactly PRISMA is or give a few chosen references to which readers can refer in order to obtain more information about these protocols/guidelines.

1a) In response to the reviewer’s suggestion, we have reported the entire name and added a relevant reference. The following has been added.

Section: Objectives

"Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [1] was used to report published data with focus on the following:

• The co-occurrence of mathematical problems and ADHD in all age groups
• Explore whether mathematics has a differential relationship with each of the two components of ADHD; inattentiveness and hyperactivity."

The following reference has also been added:

doi:10.1371/journal.pmed.1000100

2- With regard to the selection criteria, the authors chose to retain all studies assessing math performance using tests to avoid bias in the assessment of mathematical ability introduced by discrepancy in curricula and school programmes, except for one study. What was the justification to include this particular study, added to the fact that the quality of this study was rated as medium?

2a) We fully agree with the reviewer. Following the suggestions made by reviewer two, 6 papers have been excluded from the review and two new papers have been included. One of the papers excluded was by Polderman et al., which we believe is the paper referred to by the reviewer. The paper used PMS (Pupil Monitoring System) test as outcome measure. The Dutch pupil monitoring system allows teachers to use the test they best deem appropriate to assess mathematical abilities for their pupils. As a full description of the test is not available, we interpreted the test assessing performance rather than achievement based on curricula. One of the current debates is that the term ‘standards’ can be used both in conjunction with the content and the skills candidates are viewed as needing to attain the scores. We did give the paper a low score on the relevant criteria (point 8 of CASP quality assessment) but following the new search we decided to remove it from the review as the outcome measure was incompletely described. Indeed one of the challenges of this
review was to make sense of the heterogeneity among different tests used to assess mathematical abilities. While diagnosis of ADHD is confined to few established diagnostic algorithms, the assessment of mathematical performance relies on a wide range of tests.

3) The small number of available longitudinal studies for the review?

3a) We fully agree with the reviewer. Unfortunately several of the longitudinal studies did not meet the inclusion criteria. We do hope that the message of our paper may lead to more longitudinal studies on the topic.

4) As for the medication question, authors chose to include studies that did not take medication into account (i.e., studies for which there was no control of medication) and also studies that adjusted the data analysis for usage of medication or asked the participants to stop medication a few hours before the math assessment (i.e., studies for which the medication was controlled in one way or the other). Authors reveal that the majority of studies (74%), especially the ones with high quality ratings, demonstrated a significant association between ADHD and math ability even after controlling for IQ, age, socioeconomic status and other potential attenuating factors such as psychostimulant medication. Is it possible, using the available results, to investigate the impact of this latter potential moderator further? 23 studies out of 38 did not control this specific variable. This should also be noted more specifically as a limitation.

4a) We would have liked to have uncovered more studies where children were not medicated but pharmacotherapy is often used as first line treatment for the disorder. Due to varying symptomatology found among ADHD diagnosed children, it is important to determine which children are more likely to be affected in a subject that is crucial for academic success of a child in the long run. Indeed, at the reviewer suggested, these findings are advantageous to our understanding of this complex disorder and they could also help develop non-pharmacological, psychosocial interventions that go beyond simply the reduction of ADHD symptoms. In response to the reviewer's comment, the following has been added the Results section:

"Out of the 22 studies that used medicated cases or did not report medication status, 86% (19 studies) reported an association between mathematics and ADHD. Only 58% (7) that did not include medicated cases reported a significant association."

The following has also been added as a limitation:

"Finally, the effect of medications cannot be fully accounted for."

5) With regard to quality assessment: If the response rate to the study was sufficiently high (>40%), this would be regarded as an indicator of quality. The 40% seems low to me. Can the authors better justify the choice of this %?

5a) The response rate to all the studies reviewed far exceeded the 40% threshold. The choice to use this threshold was made prior to conducting the search and it was literature informed. Several reviews used a minimum response rate of 40% or above.

6) For cross-sectional studies, studies with a score of 7 or above were rated as 'high' quality studies, those with 4 to 6 points were rated as 'medium' quality. 19 out of 34 cross-sectional studies had a score of either 6 or 7 (56%). It is therefore possible that measurement error played a role here in the comparison of medium and high quality studies' results. Authors discuss the limitations associated
with the choice of using the set scale provided in the CASP checklist tool. However, this specific limitation within their own sample of studies needs to be mentioned.

6a) This is a valid point. We believe that what plays an important role is the bias within each study because the robustness of evidence is based on each study. In this review we do not compare across studies but just summarised converging/diverging evidence through narrative. The review shows compelling evidence for the association between mathematical abilities and ADHD and if a study misses the classification by very little; this may have minor impact on the overall outcome. However this limitation has been addressed in the discussion. It is worth noting that using the CASP adapted checklist tool, no study was found to be of low quality.

7) The small number of longitudinal studies in the review is a limitation of the review, and should be acknowledged, but it also should be identified as a focus for future studies.

7a) We fully agree with the reviewer and we hope that this review may be used to promote future studies that explore the differential relationship between ADHD and mathematics. This has now been mentioned in the discussion as a future direction.

8) In the results section, when authors report on some specific studies’ results, it is in some cases difficult to infer which analyses were used to generate the reported results, and this leads to difficulties in interpreting the reported statistics. For example, for the Massetti et al. study (30), authors report some beta coefficients that draw attention. A beta statistic of -6.49 is reported, along with a z statistic. A beta is usually within the -1 to 1 range. Can the authors indicate which analyses generated such results so readers are better able to understand the reported statistics and their precise meaning?

8a) We agree with the review. Some of the values reported in the table were confusing. In response to the reviewer’s comment we have revised the table adding additional information and improving the legibility and presentation.

9) Regarding the Massetti et al. study (30), the authors report that Massetti et al. were unable to demonstrate a significant correlation between ADHD-C subtype (n = 85) and mathematical ability (β = −2.55, z = −1.92, p = 0.06). Since p = .06 and n=85, I would nuance this statement.

9a) We do appreciate that the table was somewhat confusing, particularly for the above reference. We have added additional information and made it clearer. As the reviewer mentioned, the study by Massetti reports no significance for the combined (c) type when the assessment of the subtype is carried out on less strict criteria and no significance for the hyperactive subtype only. However there is a significant association for the inattentive subtype only, which may point at the differential relationship between ADHD and mathematics. However we agree with the reviewer and indeed the statistically non-significant association between the combined ADHD type and mathematical abilities may mask the effect of the inattentive domain of the disorder. It could be argued if the statistical threshold for the combined type was reached, for example with increased sample size, this could be driven by the inattentive domain of the disorder given the strong association with mathematics by the subtype alone. The following has been added to the Results section of the paper: "Massetti et al. [41] did not find significant correlation between ADHD-C subtype (n = 85) and mathematical ability (β = −2.55, z = −1.92, p = 0.06) during 8 years-period of assessments. However,
using a restricted sample of 73 children who exhibited both hyperactive and inattentive symptoms from the first assessment, the association between ADHD-C subtype and mathematics was significant for the same period of time (β = - 7.27, z=-3.61, p<0.0005)."

10) These three sentences should be revised and clarified: 1- Barry et al. [35] and Biederman et al. [53] reported negative correlation coefficient values between ADHD symptoms and mathematical ability in comparison to controls (β = -0.32, -10.8 and p = < 0.05, < 0.001, respectively); 2- In another study, Biederman et al. [54] reported a negative association between mathematical ability and adults with diagnosed childhood-onset ADHD (p < 0.001); 3- Polderman et al. [12] reported a significantly negative phenotypic correlation between attentional problems and mathematical ability at age 5 and 7 with test measures in grade 2, grade 4 and grade 6.

10a) The results and discussion section has been amended and shorted following the suggestions from reviewer one and two. As mentioned in response to comment 2, the paper by Polderman et al., has been removed.

We would like the thank Dr. Lemelin for his time and detail review of the paper.