Author's response to reviews

Title: Patient characteristics associated with treatment initiation among paediatric patients with Attention-Deficit/Hyperactivity Disorder symptoms in a naturalistic setting in Central Europe and East Asia

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

Re “Patient characteristics associated with treatment initiation among paediatric patients with Attention-Deficit/Hyperactivity Disorder symptoms in a naturalistic setting in Central Europe and East Asia” by Jihyung Hong et al

We thank the journal for the opportunity to improve our paper and hereby resubmit a revised version incorporating suggestions made by reviewers. Our responses to reviewers are followed in a next section.

Many thanks for your time and consideration.

Yours sincerely,

Jihyung Hong
Response to Reviewer 1’s comments

Reviewer’s report:
Thank you for the opportunity to review this important and interesting and well written manuscript. My review particularly focuses on the conduct and presentation of the statistical analyses. I have detailed some comments below that may help in amending and clarifying areas of concern.
With thanks and best regards
Fiona Mensah
We thank you a lot for your time and comments.

• Major Compulsory Revisions
1. Study Design and Patient Sample: Please clarify the proximity of the baseline assessment to the diagnosis and prescription of initial treatment, I wasn’t able to be sure whether there was any gap between these. This has important implications, for example not being involved in bullying and being asked to take part in social activities (over the last 4 weeks) could be a consequence of effective treatment being put into place immediately before the baseline assessment was made.

   Diagnosis was made at study entry (i.e. baseline). Given that our study included patients “who had not been previously diagnosed with or treated for ADHD” (page 7), the prescription of initial treatments was made at study entry (i.e. baseline) or during follow-up. “Baseline data were collected from the routine outpatient visit in which patients were enrolled” (i.e. study entry=baseline) (page 8). At the baseline assessment, patients/parents were asked to indicate whether patients had been involved in bullying in the past 4 weeks or had been invited to a social activity in the past 4 weeks etc. Therefore, these outcomes cannot be consequences of treatments.

   To make this clearer, we have changed the wording from “in the past 4 weeks” to “in the 4 weeks before baseline” in the text and in Table 2.

   This was because we compared patient age and clinical severity of more than two groups (i.e. no treatment, other treatment, psychotherapy only, pharmacotherapy only, and combination) in Table 1 (as explained in the second paragraph in page 9). We have re-listed all five treatment groups in the stat section (the third paragraph in page 9). Although this non-parametric Kruskal-Wallis Tests are valid for this purpose, the p-values we actually presented earlier were those from one-way ANOVA (parametric) because we used t-tests (parametric) for Table 2 and the same size deemed sufficient for parametric tests, as you pointed out. This has been corrected as follows (page 9).

   “Mean patient age and clinical severity by different types of treatments or no treatments prescribed at baseline (i.e., no treatments/interventions, other treatments, psychotherapy only, pharmacotherapy only, and the combination of psychotherapy and pharmacotherapy) were first examined and compared using one-way analysis of variance.”

2. Statistical Analysis: The mean patient age and clinical severity by type of treatment or no treatment were initially examined and then the authors quote that these were compared using the Kruskal-Wallis test. This seemed inconsistent as this test would be applicable for a non-parametric comparison rather than comparison of means, please clarify this decision and if necessary present medians and inter-quartile range in accord with the Kruskal-Wallis test. It is likely that the t-test would be robust for a sample of this size even if the data have some skewness so could be used as an alternative. Please see for further guidance: Lumley T, Diehr P, Emerson S, Chen L. The Importance Of The Normality Assumption In Large Public Health Data Sets. Annual Review of Public Health. 2002/05/01 2002;23(1):151-169. It should also be indicated on Table 1 how the p value is derived.

   This was because we compared patient age and clinical severity of more than two groups (i.e. no treatment, other treatment, psychotherapy only, pharmacotherapy only, and combination) in Table 1 (as explained in the second paragraph in page 9). We have re-listed all five treatment groups in the stat section (the third paragraph in page 9). Although this non-parametric Kruskal-Wallis Tests are valid for this purpose, the p-values we actually presented earlier were those from one-way ANOVA (parametric) because we used t-tests (parametric) for Table 2 and the same size deemed sufficient for parametric tests, as you pointed out. This has been corrected as follows (page 9).

   “Mean patient age and clinical severity by different types of treatments or no treatments prescribed at baseline (i.e., no treatments/interventions, other treatments, psychotherapy only, pharmacotherapy only, and the combination of psychotherapy and pharmacotherapy) were first examined and compared using one-way analysis of variance.”

3. The analyses were repeated for each of the regions without a formal test of whether there were differential effects according to region (i.e. a test of interaction between region and the explanatory variable of interest). This can lead to differences being asserted between regions that are chance variability rather than really being differential effects. Please address this and comment on the capacity of the sample to reliably identify whether the effects of the explanatory variables differ according to region.

   Table 1 demonstrates clear differences in mean patient age and clinical severity (CGI-ADHD-S and CSI-4) of five treatment groups between Central Europe and East Asia.
Given that we focused on the association between treatment initiation and “a set of patient characteristics” and also regions exhibit clear differences in age and clinical severity by treatment groups, it would be very relevant to conduct (exploratory) subgroup analyses by region, as already conducted and presented in our study. No further analyses have thus been carried out.

4. Patient characteristics: Figure 1 presents the types of treatments prescribed at baseline using a series of pie charts. It is difficult to compare the fractions of the charts by eye using this format and would be recommendable to consider using a bar chart as an alternative.

We have replaced the pie charts with a stacked bar chart.

5. In Table 3 it is important to present all of the effects rather than presenting only the significant effects. Please see for further guidance: Sterne JA, Smith GD, Cox D. Sifting the evidence—what's wrong with significance tests? Another comment on the role of statistical methods. Bmj. 2001;322(7280):226-231.

We have presented three sets of the results (for all; for East Asia; and for Central Europe) in Table 3. Given a number of baseline variables included in each model, we feel that it is more efficient and clearer to present the odds ratios of those variables significantly associated with treatment initiation. Instead, we have listed the baseline variables included in the models as a footnote to Table 3.

6. Discussion: page 14, paragraph 2. Please also give 95% confidence intervals for results that don't meet statistical significance. (Colegrave N, Ruxton GD. Confidence intervals are a more useful complement to nonsignificant tests than are power calculations. Behavioral Ecology. 2003;14(3):446-447.)

We have provided additional 95% CIs on top of p-values in the discussion section.

7. Page 15, paragraph 2. In this discussion please consider the timing of the baseline assessment relative to the diagnosis as in point 1.

As explained for the point 1, the baseline assessment such as participating in social activities is not the consequences of effective treatment being put in place. As we have mentioned that the initiation of treatment was made at baseline or later, and also we have emphasized in Table 2 that the baseline assessment such as social activities refers to “during 4 weeks before study entry”, we believe that the confusion over the timing of the baseline assessment relative to the diagnosis and treatment would be minimal. No changes have thus been made.

• Minor Essential Revisions

8. Page 15, paragraph 1. I would recommend strengthening the final sentence so this reads ‘Further research, necessarily culturally sensitive, is required …’

We have removed the wording “preferably” in the original sentence (“Further research, preferably culturally sensitive, is required…”).

9. Please amend Table 2 so that % is in the row headings rather than in the body of the table.

~%’s have been removed and instead put into each row heading in Table 2.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Response to Reviewer 2’s comments

Reviewer’s report:

General comment:
This is a very informative study, addressing a topic so far poorly investigated. The main limitation of the study is clearly identified and acknowledged (“the patients included in our study were diagnosed with the symptoms of ADHD, not necessarily with ADHD itself”) and does not impact on the overall quality of the study.
The paper is very well written.

We thank you a lot for your time and kind comments.

I only have some suggestions to improve the quality of the paper (MINOR ESSENTIAL REVIEWS):

Introduction, l 2: please change to “characterised by the core symptoms of inattention and/or hyperactivity/impulsivity”


We have amended the text and updated the reference 2 as suggested (page 4).

In the introduction, I think it would be worthy to mention that a possible factor influencing decision regarding pharmacological treatment is the concern regarding possible adverse effects of medication, although usually adverse evenst can be safely managed. A paper that may be mentioned is here is the recent one published by the Europea ADHD guidelines group (Cortese et al., J Child Psychol Psychiatry, 2013)

We have added the following wordings in the introduction (page 4):

“Although European guidelines are, in general, more conservative about the use of pharmacotherapy as a first-line therapy for ADHD due to concerns over potential adverse events during treatment with ADHD medications (albeit rare and mostly manageable [12]),...”. (12: Cortese et al., 2013).

Discussion

“There is now high-quality evidence supporting the efficacy and effectiveness of a range of pharmacological treatments and behavioural therapies in the treatment of children and adolescents with ADHD”: the efficacy of behavioral interventions for ADHD core symptoms has been challenged by a recent meta-analysis (Sonuga Barke et al., Am J Psychiatry, 2013); this should be mentioned

We have amended the sentence as follows (page 12):

“There is now high-quality evidence supporting the efficacy and effectiveness of a range of pharmacological treatments and behavioural therapies in the management of children and adolescents with ADHD [8, 10]. In addition, a number of psychological interventions are also available as treatment options for ADHD, although their effects have been challenged by a recent meta-analysis limited to trials with “probably blind” assessment [26: Sonuga-Barke et a., 2010]”.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.