

17<sup>th</sup> January, 2017

To: Editor-in-chief

The BMJ,  
BMA House,  
Tavistock Square,  
London WC1H 9JP,  
UK

Dear Editor,

Appeal of manuscript: "*Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder: A population based cohort study and meta-analysis*" (manuscript number: BMJ.2016.036742)

We are writing with respect to the above manuscript which was considered for publication in the BMJ and recently rejected after peer-review. We are taking the very unusual step of appealing against the decision to reject and hope that you will accept this appeal and reconsider the journal's decision.

We believe that there are grounds for reconsidering the journal's decision. These are: some oversights in relation to the content of the manuscript by reviewers; incomplete and inaccurate comments by one reviewer (Reviewer 3); and, finally, the importance that BMJ publishes research with potential impact that may provide a different approach to and interpretation of results previously published.

With respect to the review process followed by the journal, feedback from the manuscript review was given to the authors on 6<sup>th</sup> January 2017, which included detailed reviewers' comments.

The comments made by Reviewer 1 (Henrik Larsson) were as follows:

- 1) "...antidepressant exposure status risk periods on page 7 were quite confusing because they are overlapping."
- 2) We would like to highlight that we provided the detailed prescription pattern of antidepressants in our cohort in tables 1 and 2, which were aimed to prevent confusion regarding exposure status. We understand that medication use in real life is somewhat complicated. We therefore believe that it is very important to understand the utilisation of medication in every drug safety study which is why we included this detailed information in tables 1 and 2 in our manuscript. We agree that the data are complex but this is also the reason that it needs to be laid out so that the reader can take time to fully digest the information.
- 3) "...maternal psychiatric illnesses could include indications for disorders not treated with antidepressants. Could the authors also specifically look at associations with maternal diagnoses of indications for antidepressant use (i.e., depression and anxiety)? Lumping all psychiatric disorders into one category creates a lot of confusion, instead of providing additional information." We understand that this may introduce noise, however, diagnoses are not independent of each other. The increase in risk is most likely to be due to increased rates of (probably undiagnosed) ADHD in the mother, which itself is associated with increased rates of depression and anxiety and therefore increased rates of

antidepressant use. Lumping all disorders in this analysis could give us enough statistical power to address this important issue.

- 4) "...it is unclear what information is obtained by comparing risk of ADHD among offspring exposed to different types of medications." We would like to clarify that using an active treatment as a control clearly has an advantage in dealing with confounding by indication. Given our situation where confounding by indication is a serious problem, we believe this analysis is valuable and is a strength in that it overcomes the weakness of previously published literature i.e. confounded by indication.
- 5) Reviewer 1 is also concerned about the issue of exposure misclassification. We agree that this may affect our results which we had already addressed this issue explicitly in our sensitivity analysis and also in the limitation section. More importantly, exposure misclassification will bias the results towards null. However, most of our results were significantly different from null so this is unlikely to affect our conclusion. On the other hand, our analysis with maternal psychiatric illness will not be affected by this issue which supports the validity of our results.

The erroneous comments made by Reviewer 3 (Chris Blagden) were as follows:

- 1) "The numbers are low to consider this a definitive study: for example, only 129 women took antidepressants during pregnancy, and only 9 of these developed ADHD, according to tables 1 and 2. These numbers are too low to permit an effective study demonstrating the authors intent." We would like to clarify that the above comment is not correct. The total number of women who were exposed to antidepressants during pregnancy, as we noted in our manuscript, was 1,252.
- 2) Another comment made by the same reviewer stated that "The authors state that an ADHD diagnosis was defined as ICD-9-CM diagnosis code 314, or a prescription of ADHD medication, namely methylphenidate or atomoxetine. Since methylphenidate and atomoxetine are widely used for purposes other than ADHD, a validating criterion must be introduced for those patients who did not have a correct ICD-9 code." However, in our sensitivity analysis, we had conducted the same alternative analysis by using ADHD diagnosis as case definition. Further, the Reviewer may not be correct as both methylphenidate and atomoxetine are not widely used for other disorders in this age range (6 to 16 years).

We are concerned that such erroneous comments may have misled the editors in coming to a decision.

We are very grateful to have our work reviewed where most of the comments are very constructive and which, given the opportunity to address and respond to such comments would allow us to further improve the manuscript. Importantly all reviewers agree this is an important topic and suitable for BMJ readers. Certain issues and concerns raised by the reviewers have either been addressed in our paper already or need clarification but are not a major flaw in the analysis. As Reviewer 2 pointed out, "The current study adds to the published literature a design that addresses confounding by indication" which we believe is an important issue but to date not one which has been comprehensively addressed. Finally, the paper contains not only primary research but also a meta-analysis of all available data on the topic and it will be make a significant contribution to this important clinical topic in the long run.

While we have worked hard on the study and have aimed to provide a succinct but scientifically robust manuscript, if the Editors require further changes for publication, we would be happy to undertake a revision.

Thank you for considering this appeal.

Yours sincerely,

Ian CK Wong, Kenneth KC Man, Esther W Chan, David Coghill, Patrick Ip, Emily Simonoff, Phyllis KL Chan, Wallis CY Lau, Martijn J Schuemie, and Miriam CJM Sturkenboom.

Correspondence address:  
Research Department of Practice and Policy,  
UCL School of Pharmacy,  
29-39 Brunswick Square,  
London WC1N 1AX.  
Email: [i.wong@ucl.ac.uk](mailto:i.wong@ucl.ac.uk).  
Tel.: +44 (0)2077535800