Author's response to reviews

Title: Lower estimated glomerular filtration rates in patients on long term lithium: a comparative study and a meta-analysis of literature

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

Thank you for your comments and corrections. We have addressed all the issues raised in this revised manuscript. A detailed description of the corrections is given below and relevant revised parts are highlighted in the text;

Editor’s comments

The manuscript was well received. Both reviewers essentially recommend acceptance, although in one case major revisions were advised

Request for copy-editing

The manuscript was corrected and proofread by a native English speaking professional. The track changes were accepted to improve clarity.

Please place your tables in the main manuscript file after the figure legends and references. You should remove the copy from the additional files / figure files.

Done. Other formatting requests regarding tables were also adhered to.

Reviewer 1

Suggested compulsory revisions:

I couldn’t see the matching for gender, perhaps I missed that, but it should be done and should be made clear, as gender has a huge effect on eGFR.

The matching was done for age, gender and comorbidities (diabetes and hypertension). This fact is mentioned in methods. We have used the word ‘sex’ instead of gender. We have changed it to gender.

The Discussion is a bit long and repetitive, it can do with re-writing and concentrating on the main question: lithium’s effect on eGFR.

Done

Table 1 should be simplified, we don’t need to know that some patients were Muslim and we don’t need uninformative rows (where everybody scored 0).

We have removed the unnecessary information from the tables. Now it is much shorter

The paper lacks a figure summarizing the distributions of eGFRe in the populations, according to age, gender. There was no attempt to do a multivariate analysis on eGFR while correcting for age, gender, diabetes/hypertension and duration of lithium treatment.

This study had a prospective design to match for these confounding factors (except for duration of lithium treatment) thus eliminating bias by these confounding factors. The whole aim was to control for
these factors prospectively so there was no need make statistical adjustments such as regression (which is more artificial) on the results.

We did a regression analysis to see the effect of duration of lithium therapy on eGFR values as suggested by the reviewer as we did not match for that in the methodology. Interestingly, as in the paper by tredget et al. we did not find a significant correlation between the two entities (only a non significant negative trend). This fact is now included in the paper (please see under statistical analysis in methods, 3rd paragraph under “results of the study” and the last paragraph under discussion).

Regarding a figure of variation of eGFR with age and gender, we doubt whether it will yield any additional information to interpret the data already explained in the text.

**A relevant study from 2010 escaped their meta-analysis: Tredget J et al. in the J Affective Disorders.**

Thank you for suggesting this study. We have now included the data from this study in our meta-analysis and appropriately adjusted the statistics, table and forest plot (please see table 3, discussion and methods).

**Reviewer 2**

**Meta-analysis results were presented as a forest plot. Publication bias as a potential source of bias was not addressed and should be considered in the revision.**

Agreed. The funnel plot for the meta-analysis is shown below and there is no significant skewing of the plot. The I² statistic for the meta-analysis is <70%. The outlier is the study by Turan et al. which is discussed in the text.
The matching procedure including tightness of fit is not well described. How many patients were potential control patients?

The matching process is now discussed in better detail and the methodology section was restructured (Please see “matching” under methods)

**Estimated GFR is one indicator of CKD. Unfortunately microalbuminuria as an early sign of renal dysfunction was not measured. The authors critically addressed simple classification of patients based on eGFR values.**

The newly published classification on defining at risk groups for CKD now includes albuminuria in addition to GFR/eGFR values. However, these guidelines were not defined when many of these studies were carried out and outcomes were only compared on eGFR values. We also did not measure the albuminuria and that is mentioned as a limitation. However, our intention was to not to classify patients in to CKD stages (as there is ongoing debate about the validity of this classification) and that is mentioned in the discussion (Please see 2\textsuperscript{nd} paragraph of discussion and limitations)

**Presentation of mean eGFR with SD may be somewhat misleading. Median values with interquartile range or with a 95% CI would reveal a more realistic clinical picture of patient conditions.**

Many previous studies have given only the mean GFR and eGFR values with SD. We have done the same for purposes of comparison. However in agreement with the reviewer we have now included a comparison of median values with interquartile range for the lithium group and control group in our study (3\textsuperscript{rd} paragraph of results of the study).

Thank you

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