PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	One lithium level >1.0mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database
AUTHORS	Kirkham, Emma; Skinner, Jane; Anderson, Timothy; Bazire, Stephen; Twigg, Michael; Desborough, James

VERSION 1 - REVIEW

REVIEWER	Soham Rej McGill University and University of Toronto, Canada
REVIEW RETURNED	08-Jul-2014

GENERAL COMMENTS	This is a well-written paper whose results attempt to systematically quantify the effects of elevated lithium levels on renal function in older adults. Given the relative paucity of data in this area and richness of the Norfolk dataset, this paper is definitely of interest. However even though many of the limitations were well described, there are a number of modifications that will be required to enhance the reliability of the reported findings Methods: The MDRD formula (which laboratories often use) can allow easy calculation of eGFR from creatinine, age, and sex. The literature is conflicted with regards to the association between lithium duration and decreased renal function, with more studies using creatinine finding a correlation, compared to eGFR studies - likely because creatinine and muscle mass lowers with aging. I would strongly recommend using eGFR as the outcome measure for this study. Acute moderate-severe lithium toxicity (even at 1.21-2mmol/L) is well known to potentially cause acute renal failure which can greatly affect creatinine/eGFR. The more controversial and interesting research question that you are asking is whether lithium intoxication can lead to sustained decreases in renal function. Was there a one year follow-up after the recorded level of 1.21-2mmol/L? What was the time between lithium toxic events and the end of follow-up - this will greatly affect the change of eGFR (renal function) from baseline Given that levels up to 2mmol/L could be due to ingestion and levels above 2mmol/L could be due to accidental toxicity (e.g. if a new diuretic medication is added), and both could be potentially treated with renal replacement therapy, it is not clear why levels above 2.0 were excluded Diabetes Mellitus, Hypertension, and Cardiac Disease are prominent risk factors for renal glomerular function (OR>2), both in general (Coresh et al. 2007, JAMA) and lithium populations (Rej et al. 2014,

	Am J Geri Psych) - ideally these factors should be entered into the multivariate models, or otherwise mentioned as a very important limitation. One should also control for baseline eGFR, as this can greatly impact change in eGFR (pts with low eGFR are less likely to have drastic declines). Results: It is strange that only 613 patients' data were analyzed, when 1700patients data were available - although possible given your definition for group#3. How patients were excluded could be explained (maybe with a flow diagram) The baseline eGFR should be reported, as should the change in eGFR in each group over one year follow-up (perhaps with a univariate ANOVA to compare whether groups differed before multivariate analysis) The mean lithium level (and standard deviation), as well as the frequency with which patients in each group were monitored for lithium levels should be reported. Unobserved toxicity events may potentially confound the results Was lithium duration prior to the follow-up period known? During the follow-up period, do we know whether patients continuously used lithium (or what duration of 1 year follow-up included lithium use)? If duration is known, it should be included in the multivariate model, if not, it should be mentioned as a limitation. Given the worldwide aging population and their increased sensitivity adverse effects with relatively low serum levels (Sproule et al. 2000, Forester et al. Am J Geri Psych), the Norfolk dataset presents an opportunity to examine lithium levels and their effect on older adults (age>65). I highly recommend repeating the main analyses of this study in patients aged>65 and reporting this. My hunch is that even levels of 0.8-1.2 will be detrimental in that sub-population, although the data will reveal the truth. Additional comments: Although some prominent papers have been cited (McKnight et al in Lancet 2012 and the work of Bendz and Schou from the 80s), please consider citing more recent work in the Introduction and Discussion, also relevant to this paper, including Rej et al 2013 - Drugs and Aging, van Melick 2013 Drugs and Aging, as well as a number of studies that have investigates >300 (and often thousands of patients) - Aiff et al 2014 European Neuropsychopharmacology, Bendz et al 2010 Kidney International, Rej et al 2014 Am J Geri Psych, another recent study in General Hospital Psychiatry

REVIEWER	Blair Grace University of Adelaide, Australia
REVIEW RETURNED	09-Jul-2014

GENERAL COMMENTS	Nice writing style, but could be much shorter. The analysis needs to be redone, and results presented graphically. Suggestions include: - This is a repeated measures analysis, so individual patients should

	be random effects. - eGFR (which is essentially 1/creatinine with an age adjustment) should also be presented and discussed for as many patients as you can. This deals with age, and allows for more indepth discussion. eGFR is also well understood by nephrologists. I suggest CKDepi - As you are discussing changes over time, please present some data on initial readings. Abstract Present mean final or change in creatinine and/or eGFR throughout. This is much more meaningful than coefficients of an inverse. (do the tests on the inverse or eGFR however) We do not usually report the stats package in Abstract. Intro Most of Page 4 can be trimmed. Also clarify that you are talking about UK guidelines. Aims and Objectives should be combined and made really clear. Methods Bit long, and will have to be redone after the stats are tidied up Please redo analysis, with a statistician. Please include eGFR for those patients where this can be calculated Results Please present data on initial levels. Graphs are much clearer. Options include: box plot of initial and final creatinine / eGFR by the 3 groups. Please transpose tables, and include p-values for Table 1. Table 2 is just default Stata output, please tidy up - I normally remove SE and T, and put the CI in brackets next to the coef. Coefficients of inverse measures are pretty meaningless. Fine to use these for generating P-values, but present something more useful for clinicians. Discussion - too long First sentence needs to be really tidy. Do not mention 'not just exposure' because you did not look at Limitations paragraph: - please discuss how regression to the mean may affect your results and conclusions - Discuss duration of Li treatment (which is associated with kidney function). E.g. this may affect kidney function and therefore serum Li. Other comments: Please be careful talking about 'effects' - probably better to talk about 'associations' for a paper like this. There have been some recent discussions about monitoring in the Medical Journal of Australia (Roxanas I think). This may be relevant to your discussion, and may make it more international.

REVIEWER	Adam, William Rural Health Academic Centre, Melbourne Medical School, University of Melbourne, Australia
REVIEW RETURNED	09-Jul-2014

GENERAL COMMENTS	Presentation of the results should be enhanced to enable readers to draw own conclusions and clarify clinical significance. Base plasma creatinines for the groups should be included, and if they differ, which i doubt, this could affect statistical analysis of the results (ie should you use % change or actual change). details of degree of change in plasma creatinine would help define the clinical significance of the differences. By my calculation, in the absence of hard data, the greater annual change in plasma creatinine in group 3 compared to group 2 was circa 5%, which is clinically significant in patients on long term treatment (ie possible loss of 50% of renal function over 10 years). the Authors should also briefly discuss the possibility that the changes in plasma creatinine are due to changes in tubular secretion and not GFR, as these are less likely to have a long term impact on GFR. English/typo . 3rd last line methods 'was looked extrapolating'. first line aim and objective- perhaps 'renal glomerular function' Table 2 first column should be not be titled 'inverse creatinine' but rather 'Independant variables'. this table could include base line inverse creatinines, and units (eg l/umol)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Soham Rej
Institution and Country McGill University and University of Toronto, Canada
Please state any competing interests or state ‘None declared’: None Declared

Methods:

2. I would strongly recommend using eGFR as the outcome measure for this study.

We have changed our analysis from using creatinine to using eGFR; eGFR was manually calculated for all patients using the MDRD formula. The MDRD Study equation is the most thoroughly validated equation and is currently considered superior to other methods of approximating GFR. As race was not recorded on the database no corrections could be applied for African-American patients, which is why it was not initially calculated and used for this analysis. However taking into consideration the reviewers’ suggestions eGFR has now been calculated and the fact that we are unable to correct for race is noted in the limitations, however this is likely to affect very few patients in the database.

3. Acute moderate-severe lithium toxicity (even at 1.21-2mmol/L) is well known to potentially cause acute renal failure which can greatly affect creatinine/eGFR. The more controversial and interesting research question that you are asking is whether lithium intoxication can lead to sustained decreases in renal function. Was there a one year follow-up after the recorded level of 1.21-2mmol/L?

The potential for renal failure after acute moderate-severe lithium toxicity is well known. With the break down in the analysis of follow up at ≤3 months, 6 months (±3 months) and one year (±3

months) as the reference group the differences in association with lithium toxicity and eGFR over the one year (±3 months) following exposure can be determined. After all exposure events patients remained on lithium for the duration of the follow-up group they were included in. If lithium levels recorded during this follow-up period again exceeded 0.8mmol/L, eGFR levels up to the last known lithium reading ≤0.8mmol/L were used and after that the patient was not included in the analysis.

4. What was the time between lithium toxic events and the end of follow-up - this will greatly affect the change of eGFR (renal function) from baseline

The follow up period was split to further analyse the difference in effect at ≤3, 6 months (±3 months) and one year (±3 months) after a single exposure to a lithium level within one of the ranges.

5. Given that levels up to 2mmol/L could be due to ingestion and levels above 2mmol/L could be due to accidental toxicity (e.g. if a new diuretic medication is added), and both could be potentially treated with renal replacement therapy, it is not clear why levels above 2.0 were excluded

Levels above this have been studied prior to this research so were not originally presented. There were only a total of 16 patients who had levels recorded between 2.01 and 5.0mmol/L within the sample and only six of these had readings at one year (±3 months). It is not possible to draw conclusions from such small numbers in categories so they were not included in the presented results. Levels above 5.0mmol/L were excluded as these are likely to have been erroneous levels.

6. Diabetes Mellitus, Hypertension, and Cardiac Disease are prominent risk factors for renal glomerular function (OR>2), both in general (Coresh et al. 2007, JAMA) and lithium populations (Rej et al. 2014, Am J Geri Psych) - ideally these factors should be entered into the multivariate models, or otherwise mentioned as a very important limitation.

The data to include these well known risk factors was not reliably available from the database and as such could not be included in the model. This has been added as a limitation of the paper.

7. One should also control for baseline eGFR, as this can greatly impact change in eGFR (pts with low eGFR are less likely to have drastic declines).

Baseline eGFR for the one year (average of all measurements from the closest measurements to 365 days to one day before exposure) prior to the exposure event was calculated and added as a predictor variable in the model.

Results:
8. It is strange that only 613 patients' data were analyzed, when 1700patients data were available - although possible given your definition for group#3. How patients were excluded could be explained (maybe with a flow diagram)

A diagram showing the process of sample selection has been added, now 699 patients were analysed. This should aid to see why there was such a decrease in patients from the initial sample. Most patients were lost as they were missing creatinine levels at either baseline or in the periods of interest for follow-up.

9. The baseline eGFR should be reported, as should the change in eGFR in each group over one year follow-up (perhaps with a univariate ANOVA to compare whether groups differed before multivariate analysis)

Please see above for description of baseline eGFR reporting. Analysis was re-run a random effects

repeated measures model with an interaction with time, with baseline eGFR as a covariate.
10. The mean lithium level (and standard deviation), as well as the frequency with which patients in each group were monitored for lithium levels should be reported. Unobserved toxicity events may potentially confound the results

Due to the change in the way the data has been analysed there are now repeated measure per patient, for different values of the follow-up time periods. The first instance of a level within the highest group recorded was classed as the point of exposure for the purpose of the follow-up.

Patients included in the analysis were on the database for an average of 2244 days (SD 1168) and the mean number of measurements was 28.2 (SD 15.5). The average interval between lithium readings was 82.4 (SD 65.6).

11. Was lithium duration prior to the follow-up period known?

Only the duration of time the patient had been registered on the data base was known, not the full duration of lithium treatment. This is mentioned as a limitation.

12. During the follow-up period, do we know whether patients continuously used lithium (or what duration of 1 year follow-up included lithium use)? If duration is known, it should be included in the multivariate model, if not; it should be mentioned as a limitation.

Patients were on lithium for the whole of the follow-up group they were included in, be that ≤3, 6 months (±3 months) or one year (±3 months), otherwise they would not have been in the database. If lithium levels recorded during this follow-up period again exceeded 0.8mmol/L, eGFR levels up to the last known lithium reading ≤0.8mmol/L were used and after that the patient was not included in the analysis. Patients were included in the analysis if they had a creatinine level at baseline and for at least one of the follow up periods before the next lithium level ≥0.81mmol/L.

13. Given the worldwide aging population and their increased sensitivity adverse effects with relatively low serum levels (Sproule et al. 2000, Forester et al. Am J Geri Psych), the Norfolk dataset presents an opportunity to examine lithium levels and their effect on older adults (age>65). I highly recommend repeating the main analyses of this study in patients aged>65 and reporting this. My hunch is that even levels of 0.8-1.2 will be detrimental in that sub-population, although the data will reveal the truth.

Further analysis on this age group and single and multiple exposures to various lithium levels is being done as part of further analysis and is not reported in this paper.

Additional comments:

14. Although some prominent papers have been cited (McKnight et al in Lancet 2012 and the work of Bendz and Schou from the 80s), please consider citing more recent work in the Introduction and Discussion, also relevant to this paper, including Rej et al 2013 - Drugs and Aging, van Melick 2013 Drugs and Aging, as well as a number of studies that have investigates >300 (and often thousands of patients) - Aiff et al 2014 European Neuropsychopharmacology, Bendz et al 2010 Kidney International, Rej et al 2014 Am J Geri Psych, another recent study in General Hospital Psychiatry

Relevant references from work done by Rej et al, Aiff et al, and Bendz et al included as this paper expands on their work looking at different lithium levels and their effects on eGFR.

Reviewer: 2
Reviewer Name Blair Grace

Institution and Country University of Adelaide,
Australia
Please state any competing interests or state 'None declared': None declared

15. Nice writing style, but could be much shorter.

We have made efforts to reduce the work count by reducing the content of the introduction and streamlining the article in general.

16. The analysis needs to be redone, and results presented graphically.

The analysis has been redone; please see responses to previous reviewer comments which detail how the analysis has been redone. We do not feel that graphs add to the interpretation of results with the new data presented.

17. This is a repeated measures analysis, so individual patients should be random effects.

The analysis has now been redone as a random effects repeated measures model, with effects for exposure group and time period with an interaction of exposure group and time period, with baseline eGFR adjusted for as a covariate.

18. eGFR (which is essentially 1/creatinine with an age adjustment) should also be presented and discussed for as many patients as you can. This deals with age, and allows for more in-depth discussion. eGFR is also well understood by nephrologists. I suggest CKDepi

Please see the response to point one for detail on our use of eGFR in the redone analysis.

19. As you are discussing changes over time, please present some data on initial readings.

In table 2 baseline and final eGFR results (mean and 95% CI) are now included.

Abstract:
20. Present mean final or change in creatinine and/or eGFR throughout. This is much more meaningful than coefficients of an inverse. (do the tests on the inverse or eGFR however)

The analysis has been redone using calculated eGFR and in addition to the mean baseline and final eGFR results in table 2 the percentage change in mean eGFR from baseline for each group is now also calculated.

21. We do not usually report the stats package in Abstract.

The detail of the stats package has been removed from the abstract.

Intro

22. Most of Page 4 can be trimmed.

As detailed in our response to point 15 the introduction has been streamlined and much of what was detailed on page four has been removed as on reflection it was not directly relevant to the aims and objectives of this paper.

23. Also clarify that you are talking about UK guidelines.

Where guidelines are referred to in the text they are now clearly referred to as UK guidelines or UK practice.

24. Aims and Objectives should be combined and made really clear.

Aims and Objectives have been combined and now read: The aim and objective of this analysis was to establish the effects on eGFR after 0-3 and 3-9 months follow-up after a single exposure to set lithium level ranges when patients are monitored in line with current UK recommendations for three monthly lithium level tests.

Methods:
25. Bit long, and will have to be redone after the stats are tidied up

The analysis has been redone as detailed above in responses to the first reviewer and the method amended and streamlined in-line with this.

26. Please redo analysis, with a statistician.

A statistician has been involved from the outset and agrees with reviewers suggestions to improve the quality of the analysis.

27. Please include eGFR for those patients where this can be calculated

Please see response to point one for further details.

Results:
28. Please present data on initial levels.

In table 2 baseline and final eGFR results (mean and 95% CI) are now included.

29. Graphs are much clearer. Options include: box plot of initial and final creatinine / eGFR by the 3 groups.

Graphs did not aid the interpretation of results in this case; they were considered but rejected by authors.

30. Please transpose tables, and include p-values for Table 1.

Table 1 kept the same as clearly detailed the baseline demographics; we did not feel that adding p-values was appropriate for this descriptive table. Age and sex are taken into account in the calculation of eGFR.

31. Table 2 is just default Stata output, please tidy up - I normally remove SE and T, and put the CI in brackets next to the coef. Coefficients of inverse measures are pretty meaningless. Fine to use these for generating P-values, but present something more useful for clinicians.

This is now table 3 and has been tidied up. We have now included baseline and final eGFR means and percentage change as detailed in our response to point 20 in table 2.

Discussion:

32. - too long

The discussion has been reduced to the recommended maximum of five paragraphs following the BMJ Open guidelines.

33. First sentence needs to be really tidy. Do not mention 'not just exposure' because you did not look at

The first sentence now reads: The results from this analysis show that the lithium level to which the patient is exposed is associated with an increased risk of renal impairment in the first three months after exposure.

Limitations paragraph:
34. - please discuss how regression to the mean may affect your results and conclusions.

We do not feel that regression to the mean is a likely explanation of the results here.

35. - Discuss duration of Li treatment (which is associated with kidney function). E.g. this may affect kidney function and therefore serum Li.

Please see full response to this from point 11.

36. Other comments:
Please be careful talking about 'effects' - probably better to talk about 'associations' for a paper like this.

There have been some recent discussions about monitoring in the Medical Journal of Australia (Roxanas I think). This may be relevant to your discussion, and may make it more international.

We have tried to use associations rather than effects in the article text. The impact of duration of lithium treatment (Roxanas et al) has been referenced in the in discussion as adds to the conclusion where both articles discuss the need for frequent lithium monitoring and timely responses to lithium levels.

Reviewer: 3
Reviewer Name W.R.Adam
Institution and Country Rural Health Academic Centre, Melbourne Medical School, University of Melbourne, Australia
Please state any competing interests or state ‘None declared’: none declared

37. Presentation of the results should be enhanced to enable readers to draw own conclusions and clarify clinical significance. Base plasma creatinines for the groups should be included, and if they differ, which I doubt, this could affect statistical analysis of the results (i.e. should you use % change or actual change). Details of degree of change in plasma creatinine would help define the clinical significance of the differences. By my calculation, in the absence of hard data, the greater annual change in plasma creatinine in group 3 compared to group 2 was circa 5%, which is clinically significant in patients on long term treatment (i.e. possible loss of 50% of renal function over 10 years). The Authors should also briefly discuss the possibility that the changes in plasma creatinine are due to changes in tubular secretion and not GFR, as these are less likely to have a long term impact on GFR.

Data is now presented as initial and final mean eGFR and the analysis has been re-done using eGFR not creatinine. Baseline eGFR is included as a covariate in the model, so differences in this have been adjusted for. (NB: because not all follow up measurements were available for all patients, the % change calculated on an individual basis is different from that obtained from the differences in group means)

38. English/typo . 3rd last line methods 'was looked extrapolating'.

Due to streamlining the article as suggested in point 15 this text has been removed.

39. First line aim and objective- perhaps 'renal glomerular function'

Once again due to suggestions to streamline the article and reduce the word count, in particular combining the aim and objective this has been amended as detailed above in response to point 24.

40. Table 2 first column should be not be titled 'inverse creatinine' but rather 'Independant variables'. this table could include base line inverse creatinines, and units (eg l/umol)

Table 2 first column now titled Exposure group and includes baseline (mean) and follow-up (mean) eGFR results with 95% CI.

VERSION 2 – REVIEW

REVIEWER	Soham Rej University of Toronto, Canada
REVIEW RETURNED	10-Sep-2014

GENERAL COMMENTS	Dr. Kirkham and colleagues have nicely integrated our comments, which appears to have fine-tuned their results and their implications. It is quite interesting that lithium toxicity >1 (as opposed to >0.8) leads to eGFR decreases in 3 months post-toxicity, but that this resolves within 6-month follow-up. An excellent contribution to the literature!

REVIEWER	Adam, William University of melbourne, australia
REVIEW RETURNED	11-Sep-2014

GENERAL COMMENTS	I disagree with the us of 'renal impairment' in the title and discussion to describe 'a small acute fall in eGFR'. And also with the use of the expression ' risk of renal impairment' for these short term small reversible changes in renal function. I would suggest adding 'over time' to the last sentence of the results section. More importantly I note the use of eGFR instead of plasma creatinine, which i did not suggest, but other referees did. Use of eGFR has its own issues. First, about 25 % of the subjects will have a fall in eGFR because they had a birthday during the 3 month period and age is one of the determinants of eGFR. Given the age profile of the study this measn the eGFR will fall by 1 ml/min in about 75% of that 25%. While this effect is unlikley to impact on the results because (inverse) plasma creatinine was used for analysis in the first draft. This issue needs to be addressed, perhaps by a comment that the reults were not

	changed by analysing plasma creatinine instead of GFR. I also think a comment to the effect that 'A small change in GFR of 5 ml/min in an individual patient may well be due to variability in measurement of plasma creatinine, and is unlikley to lead to any action, unless it was sustained or there was further deterioration. Another reason for regular monitoring'. If these concerns were addessed I think the paper would be suitable for publication

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Soham Rej
Institution and Country McGill University and University of Toronto, Canada
Please state any competing interests or state ‘None declared’: None Declared

1. [Miss] Kirkham and colleagues have nicely integrated our comments, which appears to have fine-tuned their results and their implications. It is quite interesting that lithium toxicity >1 (as opposed to >0.8) leads to eGFR decreases in 3 months post-toxicity, but that this resolves within 6-month follow-up.

An excellent contribution to the literature!

We would like to extend our thanks to Soham Rej for their positive comment on our contribution to the literature on this subject.

Reviewer: 3
Reviewer Name W.R.Adam
Institution and Country Rural Health Academic Centre, Melbourne Medical School, University of Melbourne, Australia
Please state any competing interests or state ‘None declared’: none declared

2. I disagree with the use of 'renal impairment' in the title and discussion to describe 'a small acute fall in eGFR'. And also with the use of the expression ' risk of renal impairment' for these short term small reversible changes in renal function. I would suggest adding 'over time' to the last sentence of the results section.

The title does not use the term renal impairment but acute decline in eGFR as follows: One lithium level >1.0mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database.

We feel that the use of the term risk of renal impairment is justified in the discussion as this is clarified by explaining this is in the first three months after exposure. We cannot confirm from these results that this is indeed reversible hence this has not been stated.

Over time has been added in to the last sentence of the results section as suggested.

3. More importantly I note the use of eGFR instead of plasma creatinine, which I did not suggest, but other referees did. Use of eGFR has its own issues. First, about 25 % of the subjects will have a fall in eGFR because they had a birthday during the 3 month period and age is one of the determinants of eGFR. Given the age profile of the study this means the eGFR will fall by 1 ml/min in about 75% of that 25%. While this effect is unlikely to impact on the results because (inverse) plasma creatinine was used for analysis in the first draft. This issue needs to be addressed, perhaps by a comment that the results were not changed by analysing plasma creatinine instead of GFR.

We used eGFR as suggested by the other reviewers in this revision as we felt this made the results clearer in a clinical sense. Fractional age was used in the analysis so having a birthday would only mean going from, for example, 40.99 to 41.00 so would not have the dramatic impact on eGFR as suggested above, though eGFR would decline gradually with age.

4. I also think a comment to the effect that 'A small change in GFR of 5 ml/min in an individual patient may well be due to variability in measurement of plasma creatinine, and is unlikely to lead to any action, unless it was sustained or there was further deterioration. Another reason for regular monitoring'. If these concerns were addressed I think the paper would be suitable for publication

The following sentence has been added in to the final paragraph: A small change in GFR of 5 ml/min in an individual patient may well be due to variability in measurement of plasma creatinine, and is unlikely to lead to any action, unless it was sustained or there was further deterioration which is another reason for regular monitoring.