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# One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database

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## ABSTRACT

**Objectives:** Lithium is a mainstay of bipolar disorder treatment, however, there are still differences in opinion on the effects of lithium use on renal function. The aim of this analysis was to determine if there is an association between short-term exposure to various elevated lithium levels and estimated-glomerular filtration rate (eGFR) at ≤3 months, 6 months (±3 months) and 1 year (±3 months) follow-up.

**Setting:** Norfolk-wide (UK) lithium register and database.

**Participants:** 699 patients from the Norfolk database.

**Primary outcome measures:** eGFR change from baseline at ≤3 months, 6 months (±3 months) and 1 year (±3 months) after exposure to a lithium level within these ranges: 0.81–1.0 mmol/L (group 2), 1.01–1.2 mmol/L (group 3) and 1.21–2.0 mmol/L (group 4). The reference group was patients whose lithium levels never exceeded 0.8 mmol/L.

**Results:** Compared to the reference group, groups 3 and 4 showed a significant decrease in eGFR in the first 3 months after exposure ( $p=0.047$ and $p=0.040$ ). At 6 months (±3 months) postexposure group 4 still showed a decline in eGFR, however, this result was not significant ( $p=0.298$ ).

**Conclusions:** These results show for the first time that a single incident of a lithium level >1.0 mmol/L is associated with a significant decrease in eGFR in the following 3 months when compared to patients whose lithium levels never exceeded 0.8 mmol/L. It is still not known whether the kidneys can recover this lost function and the impact that more than a single exposure to a level within these ranges can have on renal function. These results suggest that lithium level monitoring should be undertaken at least every 3 months, in line with current UK guidelines and not be reduced further until the impact of more than one exposure to these lithium levels has been fully established.

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## Strengths and limitations of this study

- A large cohort of real-world patients was analysed, which is representative of other lithium-taking populations studied.
- The lithium level ranges studied represent current practice and consensus agreement within the UK.
- Diabetes mellitus, hypertension and cardiac disease are prominent risk factors for renal glomerular function in the general as well as lithium-treated populations. However, this data was not reliably available from the database and could therefore not be included in the analysis.
- The duration of lithium treatment before the analysis is not known; it was only known that the patients had been on lithium for at least 1 year prior to the analysis.

despite its effectiveness there are some disadvantages to its use including its narrow therapeutic range and adverse effects on the endocrine system. Several of these adverse effects are related to the plasma levels of lithium and as such it requires monitoring. Lithium is primarily renally excreted, and a declining glomerular filtration rate will increase the risk of lithium toxicity due to systemic accumulation. This is of particular concern in an ageing population where there is postulated age-related decline in renal function.[3] The range of levels suggested for a safe and effective therapeutic target for lithium within the UK has changed since the initial discovery of its narrow therapeutic range and now lies between 0.4 and 1.0 mmol/L.[1] Levels above 0.8 mmol/L have not only been associated with a limited increase in efficacy, but have also been linked to higher risks of renal toxicity, unwanted side effects and fluctuations of lithium level.[4]

From a recent systematic review and meta-analysis, there is a small amount of evidence that supports the theory that lithium is associated with an increased risk of

## INTRODUCTION

Lithium is a mainstay of bipolar disorder treatment showing effectiveness in manic and depressed phases of the illness.[1] [2] However,

progressive tubular damage. However, good quality evidence on the long-term effects of lithium use on glomerular renal function is lacking.[5–7] A meta-analysis of case–control studies, conducted by McKnight *et al*, demonstrated a reduction in urinary concentrating ability of 15% in lithium-treated patients compared to controls, with a mean observation time of 1 year. A small decline in glomerular filtration rate was also observed (0–5 mL/min). The quality and quantity of the primary evidence available was the main limitation of this study with high-quality data from long-term randomised or controlled cohort studies scarce, and all included observational studies had relatively small sample sizes from 10 to 346 patients.[5]

Owing to the narrow therapeutic range of lithium and its effects on the endocrine system, UK national guidance recommends that lithium levels are monitored at least every 3 months and renal and thyroid function is monitored every 6 months.[1] A county-wide lithium database and register (System TDM) was implemented in Norfolk, UK in May 2002. Following the introduction of the database the rates of lithium testing and monitoring have improved, helping the county to achieve national standards for the past 10 years with no known cases of toxicity due to inadequate monitoring.[8] Owing to the size of the cohort of patients on the database it is hoped that this analysis, as part of ongoing research, will establish the quantitative effect of different lithium levels on glomerular renal function expanding on work carried out by Rej *et al*,[9] Aiff *et al*[10] and Bendz *et al.*[11]

### Aim and objective

The aim and objective of this analysis was to establish the effects on eGFR at ≤3 months, 6 months (±3 months) and 1 year (±3 months) follow-up post exposure to a single lithium level within specified ranges, when patients are monitored in line with current UK recommendations for three monthly lithium level tests.

### METHODS

The Norfolk county wide database (System TDM) has over 10 years' worth of data collected during routine clinical practice allowing a retrospective cohort study to be performed with a relatively large sample size.

### Data extraction

Local research governance approval was received in order to use the database, and for this specific project. Data was then extracted from the database and analysed to determine the effect of short-term exposures to different lithium level ranges on eGFR at ≤3 months, 6 months (±3 months) and 1 year (±3 months). All patients registered on the database had data collected in routine clinical care, which was then retrospectively accessed for analysis. The following anonymised data were passed onto the research team: database ID, date of registration, date of test results and results for: lithium and creatinine, patient's year of birth and gender.

### The sample

Patients were included for analysis if they were registered on the database between its inception in 2002 to the end of January 2013 and had at least one lithium and creatinine reading recorded. The lithium level ranges chosen to be analysed were: all levels ≤0.8 mmol/L (reference group) and one exposure to 0.81–1.0, 1.01–1.2 or 1.21–2.0 mmol/L, as these ranges reflect current UK practice and consensus agreement.[1 12] The reference group was made up of patients whose lithium levels never exceeded 0.8 mmol/L in the time they were registered on the database. Lithium levels that remained in the same range for the 3 months after the initial test were classed as the same exposure, as this is the routine monitoring frequency within the UK. The first instance of a level within the highest group recorded was classed as the point of exposure and started the follow-up period. After all exposure events, patients remained on lithium for the duration of the follow-up period they were included in, be this ≤3 months, 6 months (±3 months) or 1 year (±3 months). If lithium levels recorded during this follow-up period again exceeded 0.8 mmol/L, eGFR levels up to the last known lithium reading ≤0.8 mmol/L were used and after that the patient was not included in the analysis. Levels above 5.0 mmol/L were not included for analysis as these were likely to have been erroneous levels.[13] Patients who had creatinine levels outside of the range 30–1500 µmol/L were also excluded, as the simplified modification of diet in renal disease (MDRD) equation used was not validated for levels outside of this range.[14] To determine the start point for follow-up for patients in the reference group, the median time patients in the exposure groups were registered on the database before their exposure event was added to the date of joining the database for patients in the reference group to create a pseudo exposure date. The follow-up periods of ≤3 and 6 months (±3 months) are in line with the current UK guidance for three monthly monitoring, allowing for leeway in the test frequency due to using real-life data. The final time point for follow-up was taken as 1 year (±3 months) and this was used as the time period reference group.

### Statistical analysis

STATA SE V.12.1 was used for the analysis (StataCorp, 2011, *Stata Statistical Software: Release 12*. College Station, Texas, USA: StataCorp LP). Lithium patients from the database were classified according to exposure group, and their gender and age at the time of the exposure event was recorded and used to calculate eGFR. A random effects repeated measures mixed model with an interaction with time was run to establish if there was a relationship between follow-up eGFR and the lithium level exposure group, adjusting for baseline eGFR.

## RESULTS

In total, data for 2712 patients were extracted for the research team. Following exclusions of patients who did not have the required data recorded there were 699 patients left for inclusion in the analysis, with ages ranging from 18 to 96 at the time of exposure. Figure 1 describes the process of sample selection.

Table 1 shows the basic demographics of the patients who were included for analysis and demonstrates that the balance of males and females and different ages at exposure was maintained. There were only 16 patient records with levels recorded 2.01–5.0 mmol/L, so no further analysis was performed on this group as the small sample size is associated with a lack of statistical reliability.

The percentage change in mean eGFR from baseline to ≤3 months, 6 months (±3 months) and 1 year (±3 months) of follow-up is presented in table 2. The major change in eGFR was in the first 3 months following the exposure. Table 3 shows the results from a random effects repeated measures mixed model with an interaction with time. The ≤0.8 mmol/L exposure group and the 1 year (±3 months) time period were used in this model as the reference groups. Using the simplified MDRD equation, gender and age are taken into consideration when calculating eGFR so no further adjustments were required.

Being in exposure groups 3 or 4 leads to a significant decrease in eGFR at ≤3 months follow-up (interaction $p=0.047$ and $p=0.040$, respectively) as detailed in table 3. No other main effects or interactions were significant, suggesting that eGFR levels seem to recover over time.

## DISCUSSION

The results from this analysis show for the first time that a single exposure to a lithium level >1.0 mmol/L is associated with an increased risk of renal impairment in the first 3 months after exposure with a percentage change of −3 and −5, respectively. However, by 6 months
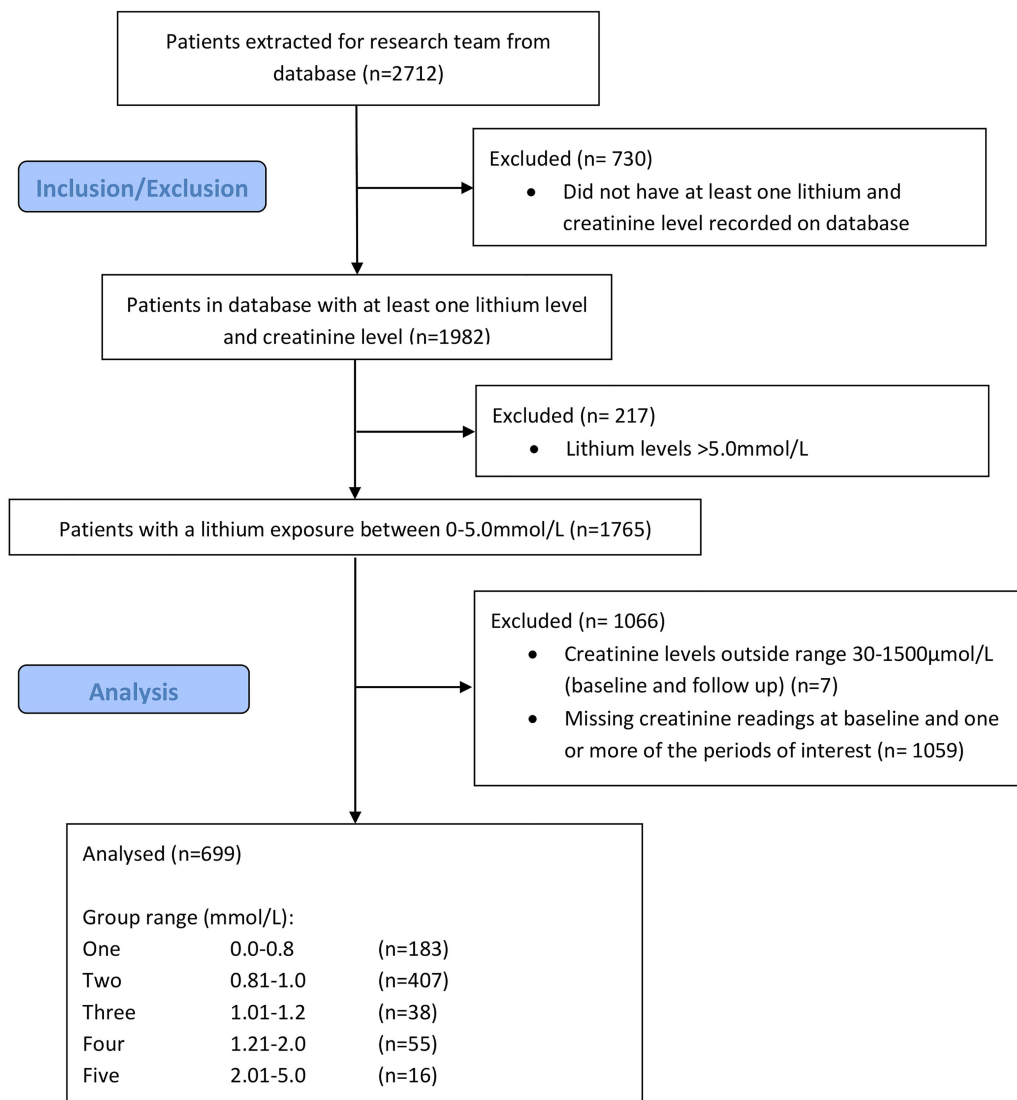


**Figure 1** Process of sample selection.

| Table 1 Baseline demographics (all figures are number, (%)) | | Gender | Age | | | | | |
|---|---|---|---|---|---|---|---|---|
| Exposure group | n | Female | <20 | 20–29 | 30–39 | 40–49 | 50–59 | >60 |
| <0.8 mmol/L (group 1) | 183 | 101 (55.2) | 0 (0) | 9 (4.9) | 26 (14.2) | 41 (22.4) | 36 (19.7) | 71 (38.8) |
| 0.81–1.0 mmol/L (group 2) | 407 | 251 (61.7) | 0 (0) | 16 (3.9) | 34 (8.4) | 62 (15.2) | 79 (19.4) | 216 (53.1) |
| 1.01–1.2 mmol/L (group 3) | 38 | 24 (63.2) | 0 (0) | 1 (2.6) | 4 (10.5) | 3 (7.9) | 9 (23.7) | 21 (55.3) |
| 1.21–2.0 mmol/L (group 4) | 55 | 31 (56.4) | 1 (1.8) | 2 (3.6) | 3 (5.5) | 9 (16.4) | 12 (21.8) | 28 (50.9) |

(±3 months) there is no detectable difference from the mean baseline eGFR. Further work is ongoing to fully establish the extent of recovery of the kidneys from multiple exposures of these lithium levels. It has been shown from a previous national audit in 2009 that only 30% of patients had lithium levels taken at a frequency meeting current National Institute for Health and Care Excellence guidelines for three monthly lithium levels.[15] Even assuming that patients are monitored in line with this guidance, patients could remain at these levels for up to 4 months and it is not yet clear if the detrimental effects on eGFR of each single exposure are additive. These findings not only suggest that a single exposure to a lithium level >1.01 has a significant effect on eGFR in the 3 months after exposure, but the higher the level the greater the effect.

The population studied is relatively comparable to other lithium taking populations in terms of age and gender of patients. The mean age of our sample at the time of exposure was 59, which is slightly higher than the means seen in a national audit from 2009 and a recent cohort study using data from 1990 to 2007 of 55 and 48.8, respectively.[15 16] This is to be expected for our sample as compared to the rest of the UK, as Norfolk has a higher percentage of population over the age of 65.[17] Given the worldwide aging population and their associated increased sensitivity to adverse effects with relatively low serum levels for multiple medicines including lithium, the Norfolk data set presents an opportunity to further examine lithium levels and their effect on older adults (age >60).[9 10]

A recent retrospective cohort study confirmed that any exposure to lithium is associated with an increased risk of renal failure. However, the role of duration of lithium exposure and the variation of risk at different lithium levels used in practice could not be confirmed.[16] By comparing different ranges of lithium level exposures to a reference group of lithium-treated patients whose levels never exceeded 0.8 mmol/L, the variation of risk from single exposures of the different lithium levels used in practice could be determined.

There are several limitations to this analysis. First, there is no untreated group studied, due to the retrospective nature of the study design, to compare the decline in renal function seen over the follow-up periods to those patients who were not exposed to lithium at all. The eGFR was calculated for all patients using the simplified MDRD equation. However, as race

was not recorded the calculated eGFR results could not be corrected for any African-American patients. Owing to the predominantly Caucasian population studied this is not likely to have been a significant factor.[18] As eGFR is affected by age, fractional age was used in the analysis to minimise this impact. The results of the analysis are not changed by analysing plasma creatinine instead of eGFR. Diabetes mellitus, hypertension and cardiac disease are prominent risk factors for renal glomerular function in the general as well as lithium-treated populations, however, these data were not reliably available from the database and could therefore not be included in the analysis. Duration of lithium treatment has been linked with a decline in renal function, however, the full duration of lithium treatment before the analysis is not known; it was only known that patients had been on lithium for 1 year prior to analysis.[9 19]

This analysis focused on single exposures to various lithium levels and the association with eGFR in ≤3 and 6 months (±3 months) post exposure. If the decline in renal function is reflected in a longer follow-up period with multiple exposure events it could have significant consequences for the routine monitoring of lithium and the follow-up monitoring of patients who have ever had lithium levels >1.0 mmol/L, whether or not they continue with lithium treatment. Determining if the number of exposures the kidney has from different lithium levels and the duration of these exposures or if it is the degree of the lithium level that determines the impact on renal function is clinically relevant for continued monitoring. Currently this analysis suggests that even short-term exposure to elevated lithium levels has a significant impact on glomerular renal function in the first 3 months following exposure, and regular monitoring of lithium levels and timely responses to these levels is critical.[19] It is still not known whether the kidneys can fully recover this lost function or if the effects of multiple exposures are additive; as such we suggest that lithium level monitoring should be undertaken at least every 3 months, in line with current UK guidelines, and not be reduced further until the impact of more than one exposure to these lithium levels has been fully established. 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. The results of this analysis and the on-going further work

**Table 2** Change in eGFR by exposure group and time period

| Exposure group | Baseline Mean eGFR (95% CI) n | ≤3 months Mean eGFR (95% CI) n | Percentage change from baseline | 6 months (±3 months) Mean eGFR (95% CI) n | Percentage change from baseline | 12 months (±3 months) Mean eGFR (95% CI) n | Percentage change from baseline |
|---|---|---|---|---|---|---|---|
| ≤0.8 mmol/L (group 1) | 70.7 (68.4 to 73.0) 183 | 69.8 (66.3 to 73.3) 111 | −0.26 | 71.1 (68.5 to 73.8) 145 | 1.02 | 68.8 (65.5 to 72.1) 138 | −0.20 |
| 0.81–1.0 mmol/L (group 2) | 70.6 (68.8 to 72.3) 407 | 69.6 (67.6 to 71.6) 368 | −1.77 | 71.8 (69.4 to 74.2) 277 | 0.63 | 71.3 (68.2 to 74.3) 174 | 0.61 |
| 1.01–1.2 mmol/L (group 3) | 73.5 (67.9 to 79.1) 38 | 70.1 (64.1 to 76.1) 35 | −3.88 | 78.4 (71.1 to 85.6) 22 | 3.88 | 71.4 (63.4 to 79.3) 13 | 8.24 |
| 1.21–2.0 mmol/L (group 4) | 72.1 (67.1 to 77.1) 55 | 66.7 (60.7 to 72.6) 51 | −5.40 | 69.8 (61.8 to 77.8) 29 | 0.81 | 73.6 (64.2 to 83.1) 21 | 3.35 |

eGFR, estimated-glomerular filtration rate.

**Table 3** Random effects repeated measures mixed model to predict eGFR, adjusting for baseline eGFR

| Independent variable | Coefficient (95% CI) | p Value | | Coefficient (95% CI) | p Value |
|---|---|---|---|---|---|
| Exposure | | | Exposure×time interactions | | |
| 0.81–1.0 mmol/L (group 2) | 0.23 (−1.75 to 2.24) | 0.814 | Group 2×time 1 | −1.16 (−3.42 to 1.10) | 0.314 |
| 1.01–1.2 mmol/L (group 3) | 2.78 (−2.11 to 7.68) | 0.266 | Group 2×time 2 | −0.57 (−2.72 to 1.58) | 0.603 |
| 1.21–2.0 mmol/L (group 4) | 0.43 (−3.48 to 4.44) | 0.834 | Group 3×time 1 | −5.18 (−10.3 to −0.08) | 0.047 |
| Time | | | Group 3×time 2 | −1.91 (−7.13 to 3.31) | 0.473 |
| ≤3 months (time 1) | −0.35 (−2.17 to 1.47) | 0.705 | Group 4×time 1 | −4.45 (−8.70 to −0.19) | 0.040 |
| 6 months (±3 months)(time 2) | 0.83 (−0.82 to 2.50) | 0.322 | Group 4×time 2 | −2.29 (−6.61 to 2.02) | 0.298 |

eGFR, estimated-glomerular filtration rate.

could impact on monitoring guidance for patients on lithium, and even those who have ceased treatment, if they have ever been exposed to a level that is shown to have a negative impact on renal function.

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