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Andres M. Trevino-Alvarez

Mayo Clinic Arizona

Ahmed Elmorshedy

Mayo Clinic Arizona

Vanessa M Pazdernik

Mayo Clinic

Jennifer R. Geske

Mayo Clinic

Marwa Elashry

Mayo Clinic

Ahmed Belasy

Mayo Clinic Arizona

Asmaa Yehia

Mayo Clinic College of Medicine

Sondra Schultz

Mayo Clinic Arizona

Balwinder Singh

Mayo Clinic

Mark A Frye

Mayo Clinic

Osama A. Abulseoud

Abulseoud.osama@Mayo.edu

Mayo Clinic Arizona

Research Article

Keywords:

Posted Date: October 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11285086/v1>

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Additional Declarations: No competing interests reported.

Sex Differences in the Association Between Lithium Treatment and Kidney Function in Patients with and without Bipolar Disorder

Andres M. Trevino-Alvarez^{1,2}, Ahmed Elmorshedy¹, Vanessa M Pazdernik³, Jennifer R. Geske³, Marwa Elashry⁴, Ahmed Belasy⁵, Asmaa Yehia^{6,7}, Sondra Schultz¹, Balwinder Singh⁸, Mark A Frye⁸ and Osama A. Abulseoud^{1,6}

1. Department of Psychiatry and Psychology, Mayo Clinic Arizona, Phoenix, Arizona, United States
2. Department of Neurology, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico
3. Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, United States
4. Department of Internal Medicine, Division of Hospital Internal Medicine, Mayo Clinic, Arizona, United States
5. Department of Nephrology, Mayo Clinic Arizona, Phoenix, Arizona, United States
6. Department of Neuroscience, Graduate School of Biomedical Sciences, Mayo Clinic College of Medicine, Arizona, United States
7. Department of Medical Physiology, Faculty of Medicine, Mansoura University, Mansoura, Egypt
8. Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, United States

*Corresponding author

Osama A Abulseoud, M.D.

Department of Psychiatry and Psychology,
Mayo Clinic

5777 E Mayo Blvd, Phoenix, AZ 85054

Phone: (480) 342-2000

Abulseoud.osama@Mayo.edu

KEY POINTS

Question: Does the effect of lithium treatment on eGFR depend on sex or bipolar disorder diagnosis?

Findings: In this retrospective study, we compared eGFR levels at the beginning and end of the study (average 2 years of lithium use) and found lithium use was associated to greater eGFR decline, particularly in women with a history of lithium toxicity. A longer time between eGFR measurements was also associated with greater eGFR decline.

Meaning: Lithium usage, the gold-standard treatment for bipolar disorder, requires careful eGFR monitoring, particularly in women.

Abstract

Background

Lithium remains one of the most effective long-term treatments for bipolar disorder (BD). However, concerns about kidney function can make decisions about long-term treatment more difficult. The extent to which lithium exposure, BD, and sex contribute to changes in kidney function remains uncertain.

Methods

We conducted a retrospective longitudinal cohort study of 3,458 adults aged ≥ 18 years at their first lithium measurement and with a baseline estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m², including 2,383 with BD and 1,075 without BD. Longitudinal eGFR trajectories were examined using mixed-effects models accounting for age, sex, BD status, cumulative lithium exposure, current and past lithium use, a history of serum lithium concentrations ≥ 1.2 mmol/L, and comorbidity burden. A secondary analysis examined change in eGFR between the first and last measurements in relation to changes in cumulative lithium exposure.

Results

Greater cumulative lithium exposure was consistently associated with lower eGFR across sex and BD groups. Overall, each additional year of lithium exposure was associated with a 1.14 mL/min/1.73 m² lower eGFR (95% CI, -1.29 to -1.00; $p < .001$). Current and past lithium use were also associated with lower eGFR compared with non-use. A history of lithium toxicity, defined as at least one serum lithium concentration ≥ 1.2 mmol/L, was associated with lower eGFR overall (-1.58; 95% CI, -2.19 to -0.97; $p < .001$), with a significant association among females but not males. In the secondary analysis, an increase in cumulative lithium exposure of >2 years was associated with greater eGFR decline across all sex and BD groups. However, interactions between lithium exposure change, sex, and BD status were not significant, providing no clear evidence that this association differed by sex or BD status.

Conclusions

Long-term kidney-function changes were more consistently associated with lithium exposure than with BD itself. Greater cumulative exposure and a history of lithium toxicity were associated with lower eGFR. These findings support continued monitoring of kidney function and lithium levels during long-term treatment while maintaining lithium's important role in the management of BD.

Introduction

Few drugs in psychiatry have remained as clinically valuable as lithium despite ongoing concerns about long-term safety. More than seven decades after its introduction into modern psychiatric practice, lithium still holds a unique place in the treatment of bipolar disorder: its clinical benefits have persisted, while concerns about toxicity, particularly its effects on the kidneys, have followed it throughout its clinical use. Following Cade's 1949 report of its antimanic effects and the subsequent clinical investigations of Schou and colleagues, lithium became an established treatment for bipolar disorder and continues to be an important part of its management [1], [2], [3]. Despite the development of many newer mood-stabilizing therapies, lithium remains the gold-standard maintenance treatment, with strong evidence for relapse prevention, particularly for manic episodes [4], [5]. Its clinical importance extends beyond mood stabilization, with evidence also supporting a reduction in suicide risk - one of the most serious outcomes of bipolar disorder [6], [7]. However, these benefits come with an important clinical challenge. Lithium has a narrow therapeutic index and is primarily cleared by the kidneys, therefore, regular serum monitoring and assessment of kidney function are essential for its long-term safety [8], [9]. Concerns about long-term renal toxicity have therefore contributed to hesitation to initiate or continue lithium despite its well-established efficacy [7] [10]. Although long-term lithium treatment has been associated with declining kidney function, a critical question remains unresolved: how much of this decline is actually due to lithium itself? Aging, baseline kidney function, comorbidities, concomitant medications, treatment duration, and previous episodes of toxicity may all affect renal function in patients taking lithium [11], [12].

This question is especially difficult in bipolar disorder (BD), because lithium exposure may not be the only factor affecting the kidney. Emerging evidence suggests that BD itself may be associated with additional renal risk, independent of lithium exposure. In a population-based cohort of patients with mood disorders receiving long-term lithium, a diagnosis of bipolar disorder, along with older age and hypertension, was associated with a higher risk of chronic kidney disease (CKD) [13]. Several clinical factors may contribute to this risk, as patients with BD commonly have conditions associated with impaired renal function, including hypertension, diabetes, and cardiovascular disease, and are often exposed to several medications over the course of their illness [13], [14]. However, studies that have tried to separate the effects of bipolar disorder from those of lithium have not reached a consistent conclusion. In a large Swedish cohort, patients with bipolar or schizoaffective disorder did not show a faster age-related decline in eGFR than the general population after lithium exposure duration was considered, while longer lithium exposure (>10 years) was associated with an additional decline in kidney function [15]. Comparisons with other mood-stabilizing treatments add to this uncertainty. Lithium was not associated with a higher risk of CKD or acute kidney injury than valproate in one large Swedish cohort [16], while more recent data from patients with bipolar disorder found a higher risk of stage 3 or greater CKD with lithium than with non-lithium medication [17]. Together, these findings show how closely the effects of lithium, BD, medical comorbidities, and other treatments can overlap. Therefore, examining patients with and without bipolar disorder while accounting for their lithium exposure may help differentiate the effects associated with lithium from those related to the underlying disorder and provide a clearer picture of their relationship with kidney function.

Beyond diagnosis and medical comorbidities, sex may also be important when considering changes in kidney function during lithium treatment. Even without lithium exposure, kidney function differs between women and men. Women generally have lower baseline GFR, while men often show a faster decline with age and a greater risk of kidney disease progression [18], [19], [20]. However, studies of patients receiving lithium have shown a less consistent pattern. Some long-term lithium cohorts reported greater eGFR decline or a higher burden of CKD in women [21], [22], [23], while another study reported lower eGFR more

frequently in men [24], leaving the role of sex in lithium-associated kidney changes uncertain. Another factor that may influence renal outcomes is exposure to elevated lithium concentrations. Periods of elevated serum lithium have been associated with a higher subsequent risk of acute kidney injury and CKD, although the thresholds used across studies have varied [16], [25], [26]. Together, these findings suggest that both sex and periods of elevated lithium exposure may be relevant to changes in kidney function during long-term treatment, although their relationship with eGFR remains unclear.

These uncertainties highlight the need to consider lithium exposure, bipolar disorder, and sex together when evaluating long-term changes in kidney function. Previous studies have examined these factors separately, making it difficult to understand their relative contribution to changes in eGFR [15]. This is relevant in BD, where lithium may be used for many years and decisions about continuing treatment depend on balancing its clinical benefits with long-term renal safety. In the present study, we examined longitudinal eGFR trajectories in adult women and men with and without BD while accounting for cumulative lithium exposure, current and previous lithium use, age, and comorbidity burden. We also examined whether a history of lithium toxicity, defined as a serum lithium concentration ≥ 1.2 mmol/L before an eGFR measurement, was associated with kidney-function trajectories. By evaluating these factors, we look forward to better understanding the relationship between lithium treatment and kidney function and to clarifying the role of sex and BD in this association.

Methods

a. Study population and data extraction

The study was approved by the Institutional Review Board of Mayo Clinic (protocol #23-010281). We used electronic health record (EHR) data to identify male and female patients who were older than 18 years at their first lithium measurement, had available lithium and creatinine data, and had authorized the use of their records for research. Patients were included if they had at least two serum lithium and creatinine measurements between January 1, 2013, and December 31, 2023. Data were obtained from Mayo Clinic sites in Rochester, Florida, and Arizona, as well as the Mayo Clinic Health System.

b. Sex, BD diagnosis, and clinical characteristics

Data on sex, psychiatric diagnoses, and medical conditions were collected from the EHR. BD diagnosis and other clinical conditions were identified from the problem list and clinical records documented within 1 year of the first serum creatinine measurement.

c. Lithium exposure and duration

Lithium exposure was identified using serum lithium measurements and prescription records. For each serum lithium measurement, the collection and result dates and the measured lithium concentration were extracted. Lithium values reported below the limit of detection (e.g., “<0.1” mmol/L) were converted to zero and subsequently excluded. When multiple lithium measurements were available on the same day, the median value was used to represent the daily lithium concentration.

Lithium exposure periods were defined primarily by laboratory dates, with prescription records used to confirm continued treatment when lithium measurements were unavailable. A lithium level within 365 days of the previous lithium-related date was considered part of the same exposure period. When no lithium level was available, an active prescription was used to support continued treatment. If neither a lithium level nor a prescription was available, the previous exposure period was considered ended, and any later evidence of lithium use was marked as the start of a new exposure interval. As a secondary approach, laboratory and prescription dates were considered together, with exposure treated as continuous, provided no gap exceeded 365 days.

For both approaches, cumulative lithium exposure was calculated as the sum of the identified exposure intervals. Prescription dates before 2013 were used only to establish treatment history and were excluded from the main analyses.

d. Classification of lithium exposure status

Lithium exposure status was determined in relation to each creatinine/eGFR measurement. When there was no evidence of active lithium use at the time of the kidney-function measurement, participants were classified according to their total lithium exposure during the study period. Those with <6 months of total lithium exposure were classified as non-users. Among participants with >6 months of total exposure, measurements obtained during an active lithium period, supported by a lithium level or prescription, were classified as current users. However, those with measurements obtained after a previous treatment period, without a current lithium level or prescription, were classified as past users.

Lithium-related variables used in the analyses included exposure status (non-user, current, or past), cumulative exposure duration, and a history of lithium toxicity, defined as at least one serum lithium concentration ≥ 1.2 mmol/L before the corresponding eGFR measurement.

e. Kidney function measures

Serum creatinine measurements were extracted from laboratory test results or panels that identified serum or plasma specimens, with results reported in mg/dL. Records reported in units other than mg/dL or related to urine measurements, historical values, ratios, fractionated sodium, or microalbumin were excluded. Creatinine values reported below the limit of detection as “<0.1”, “<0.2”, or “<0.4” mg/dL were excluded, while values reported as “<0.5” mg/dL were converted to zero. Estimated glomerular filtration rate (eGFR) was calculated using the race-free 2021 CKD-EPI creatinine equation, implemented with the *CKDEpi2021.creat* function from the *nephro R package* [27], [28]. When multiple creatinine or eGFR values were available on the same day, the median was used to represent the daily measurement. Patients whose first observed eGFR during the study period was <60 mL/min/1.73 m² were excluded so that the analysis focused only on individuals with a baseline eGFR ≥ 60 mL/min/1.73 m². The final analytic sample included 3,458 participants. Kidney function outcomes included longitudinal changes in eGFR and individual eGFR trajectories.

f. Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were summarized as mean $\pm$ standard deviation (SD), while non-normally distributed variables were reported as median (interquartile range [IQR]). Categorical variables were summarized as counts and percentages. Categorical variables were compared using Pearson’s chi-square test, while continuous variables were compared using the Kruskal-Wallis rank-sum test. Differences by sex and BD status, including their interaction, were examined using linear models for continuous variables, generalized linear models for binary variables, and multinomial models for variables with more than two categories. (Tables 1 and 2)

Longitudinal changes in eGFR were analyzed using linear mixed-effects models (Table 3). Fixed effects included BD diagnosis, sex, age at first eGFR measurement, cumulative lithium exposure (years), lithium exposure status (non-user, past, or current), history of lithium toxicity, and comorbidity burden. Lithium exposure variables were determined in relation to the corresponding eGFR measurement. Comorbidity burden was quantified using a modified Charlson Comorbidity Index (CCI), calculated as the sum of 16 disease categories, excluding renal disease, with comorbidities assessed during the year before the index (first observed) eGFR measurement [29]. Renal disease was excluded from the CCI to avoid overadjustment and because kidney function was the outcome of interest.

Because the relationship between age and eGFR may not be linear, age was modeled using a restricted cubic spline with three knots [30]. Interactions between sex and both the linear and nonlinear age were included in the overall model, and additional models were examined by sex and BD status. Random intercepts and slopes for age were included for each participant to account for repeated measurements and differences in individual eGFR trajectories over time. Model performance was evaluated using the intraclass correlation coefficient (ICC) and marginal and conditional R² values, which reflected the variance explained by the fixed effects alone and by the full model, respectively. Predicted eGFR trajectories were also generated under scenarios of no lithium exposure and lithium treatment from age 40 to 45 years (Figure 1).

Linear regression was used to examine the change in eGFR between the first and last measurements among participants with at least two eGFR measurements (Table 4). Based on an exploratory assessment of the relationship between lithium exposure and eGFR change (Supplementary Figure 1), change in cumulative lithium exposure was categorized as ≤ 2 years or > 2 years. The secondary model included age at the index measurement, the time between the first and last eGFR measurements, change in lithium exposure, sex, and BD status. Two-way and three-way interactions among lithium exposure change, sex, and BD status were also included. Predicted marginal effects were used to explain changes in eGFR across sex and BD groups (Figure 2). Model fit was summarized using R^2 and adjusted R^2 . All analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

a. Demographics by BD status and sex

A total of 3,458 participants were analyzed, including 2,383 with BD (68.9%) and 1,075 without BD (31.1%). In two-way models, sex was associated with age at the index date ($p = 0.045$) and marital status ($p < 0.001$). Females were slightly younger and more frequently classified as divorced/separated/widowed or married/life partnership across both diagnostic groups. No main effects of BD status or sex-by-BD interaction were observed for the remaining demographic variables. The cohort was predominantly White (>90%) and non-Hispanic (>92%), with no significant differences by sex or BD status and no sex-by-BD interactions. (Table 1)

b. Baseline and follow-up eGFR by BD status and sex

At baseline, eGFR did not differ significantly by sex ($p = 0.93$) or BD status ($p = 0.17$). During follow-up, females had a longer follow-up duration and a greater number of eGFR measurements than males across both BD and non-BD groups ($p < 0.001$ and $p = 0.012$, respectively). Participants with BD also had longer follow-up ($p < 0.001$) and more eGFR measurements than those without BD ($p = 0.007$). At the last eGFR measurement, eGFR was lower in females than in males ($p = 0.027$), while no significant difference was observed between those with and without BD ($p = 0.46$). (Table 2)

Lithium exposure status at the last eGFR measurement also differed by sex ($p < 0.001$) and BD status ($p = 0.029$), with no significant sex-by-BD interaction ($p = 0.71$). Overall, 31.0% ($n = 1,071$) of participants were current lithium users, 52.6% ($n = 1,820$) were past users, and 16.4% ($n = 567$) had never used lithium. When participants with and without BD were combined within each sex, 33.0% of males (503 of 1,523) were current users compared with 29.4% of females (568 of 1,935). Participants with BD were more classified as past or current users than those without BD. The distribution of lithium exposure duration at the last eGFR measurement differed by sex ($p = 0.006$) and BD status ($p < 0.001$), with no significant sex-by-BD interaction ($p = 0.99$). Exposure of ≥ 30 days was more common among participants with BD than among those without BD in both females (70% vs. 61%) and males (67% vs. 57%). (Table 2)

A history of lithium toxicity (≥ 1.2 mmol/L) was observed in 18.5% of the cohort and was more common among participants with BD across both sexes. Among females, 21.7% (296 of 1,365) of those with BD had a history of elevated lithium concentration compared with 14.9% (85 of 570) of those without BD. A similar pattern was observed among males, with corresponding proportions of 18.6% (189 of 1,018) and 13.7% (69 of 505), respectively. In the two-way analysis, BD status was significantly associated with a history of lithium toxicity ($p = 0.015$), while the main effect of sex ($p = 0.061$) and the sex-by-BD interaction ($p = 0.65$) were not significant. (Table 2)

c. Longitudinal associations with eGFR

In the longitudinal mixed-effects model, BD was associated with a higher eGFR overall (1.25; 95% CI, 0.06 to 2.43; $p = 0.039$). In sex-stratified analyses, this association remained significant among females (1.56; 95% CI, 0.02 to 3.11; $p = 0.048$) but not among males (0.91; 95% CI, -0.91 to 2.73; $p = 0.33$). Increasing age was consistently associated with lower eGFR across all models (all $p < 0.001$). In the overall model, the interactions between male sex and both the linear and nonlinear age were significant ($p < 0.001$ and $p = 0.005$, respectively), indicating that the association between

age and eGFR differed by sex. The nonlinear age was also significant among males overall and among males with BD (both $p < 0.001$), but not among males without BD ($p = 0.48$). (Table 3)

Greater cumulative lithium exposure was consistently associated with lower eGFR across all models (all $p \leq 0.002$). In the overall model, each additional year of cumulative lithium exposure was associated with a 1.14 mL/min/1.73 m² decrease in eGFR (-1.14; 95% CI, -1.29 to -1.00; $p < 0.001$). Compared with participants who had never used lithium, past use was associated with lower eGFR (-1.85; 95% CI, -2.31 to -1.38; $p < 0.001$), with a greater reduction observed with current use (-3.80; 95% CI, -4.21 to -3.39; $p < 0.001$). (Table 3)

A history of lithium toxicity (≥ 1.2 mmol/L) was also associated with lower eGFR overall (-1.58; 95% CI, -2.19 to -0.97; $p < 0.001$). In sex-stratified models, the association was significant among females (-2.68; 95% CI, -3.44 to -1.92; $p < 0.001$) but not among males (0.39; 95% CI, -0.63 to 1.40; $p = 0.45$). The overall model had a conditional R² of 0.914, while the intraclass correlation coefficient was 0.90, indicating substantial clustering of repeated eGFR measurements within participants. (Table 3)

Predicted eGFR declined with increasing age across all sexes and BD groups in the absence of lithium exposure. When lithium exposure was modeled between ages 40 and 45 years, predicted eGFR decreased following the transition from never to current use at age 40, with a further change in the trajectory after the transition to past use at age 45. After age 45, eGFR continued to decline across all groups, with the lowest predicted values by age 80 observed among males with BD. (Figure 1)

d. Change in eGFR by lithium exposure duration

As a secondary analysis, the change in eGFR from the first to the last measurement was examined among 3,127 participants with at least two eGFR measurements. Exploratory analyses showed that greater increases in cumulative lithium exposure were associated with greater declines in eGFR in females (rho = -0.1844; Pearson $r = -0.2037$; both $p < .001$) and males (rho = -0.1877; $r = -0.2041$; both $p < .001$) (Supplementary Figure 1).

A longer interval between the first and last measurements was associated with greater eGFR decline (-1.16; 95% CI, -1.34 to -0.97; $p < 0.001$). The model included interactions between changes in lithium exposure, sex, and BD status, with females without BD and ≤ 2 years of lithium exposure serving as the reference group. An increase in cumulative lithium exposure of > 2 years was associated with a greater decline in eGFR compared with an increase of ≤ 2 years (-5.78; 95% CI, -9.77 to -1.79; $p = 0.005$). Baseline age, sex, and BD status were not significant (all $p \geq 0.067$). None of the two-way or three-way interactions between lithium exposure change, sex, and BD status were statistically significant (all $p \geq 0.20$), indicating that the association between long-term lithium exposure and eGFR decline did not differ significantly by sex or BD status. (Table 4)

Predicted marginal effects showed a consistent pattern across all sex and BD groups, with greater declines in eGFR among participants with lithium exposure increased by > 2 years compared with those with exposure increased by ≤ 2 years. Significant differences between the two exposure groups were observed among females without BD ($p = 0.005$), females with BD ($p = 0.009$), males without BD ($p = 0.03$), and males with BD ($p = 0.001$) (Figure 2).

Discussion

In this retrospective longitudinal cohort, changes in kidney function were more consistently associated with lithium exposure than with BD itself. Greater cumulative lithium exposure was associated with lower eGFR, and an increase in lithium exposure of more than 2 years was linked to greater eGFR decline across sex and BD groups. However, none of the interaction analyses showed that this association differed significantly by sex or BD status. A history of lithium toxicity (≥ 1.2 mmol/L) was also associated with lower eGFR overall. In sex-stratified analyses, this association was significant among females but not among males, suggesting a possible sex-related pattern that requires further study. BD itself was not associated with greater eGFR decline. Taken together, these findings indicate the importance of cumulative lithium exposure and elevated lithium concentrations when considering long-term kidney function, while the roles of BD and sex appear less clear.

These findings are clinically important because lithium remains one of the most effective long-term treatments for BD, with established benefits for relapse prevention and potential protection against suicide [31], [32], [33], [34], [35]. At the same time, concerns about adverse effects, particularly declining kidney function and elevated lithium concentration, can influence decisions about starting or continuing treatment. In this context, our findings support a balanced approach that maintains lithium's clinical benefits while recognizing its long-term renal risks [11] and the need for continued monitoring of kidney function.

Sex may also play a role in kidney-function changes during lithium treatment. In our model, the relationship between age and eGFR differed by sex, consistent with evidence that renal aging and kidney disease progression differ between females and males [20], [36]. A history of lithium toxicity was associated with lower eGFR among females but not among males. This may be particularly relevant given evidence that females with BD, especially those with manic or mixed features, can reach higher serum lithium concentrations than males despite similar doses [37]. This highlights the importance of carefully monitoring lithium levels alongside mood symptoms in women during treatment. More broadly, these findings add to the mixed evidence on sex differences in lithium-associated kidney changes without fully resolving this question [21], [22], [23], [24]. Differences in renal physiology and hormonal influences may contribute to these patterns [38], [39]. However, the interaction between sex and lithium exposure duration was not significant in our secondary analysis. Therefore, our findings suggest a possible sex-related pattern but do not establish a clear difference in susceptibility to lithium-associated kidney-function decline between sexes.

The renal handling of lithium provides a potential explanation for the relationship between greater exposure and declining kidney function. Lithium is freely filtered at the glomerulus and subsequently reabsorbed along the nephron, particularly in the proximal tubule, while entry into collecting-duct principal cells occurs mainly through the epithelial sodium channel (ENaC) [40], [41]. Prolonged intracellular lithium exposure can disrupt several pathways involved in tubular function, including glycogen synthase kinase 3 beta (GSK3 β) signaling and aquaporin-2 (AQP2) regulation, while also activating extracellular signal-regulated kinase (ERK1/2) and p38 mitogen-activated protein kinase, nuclear factor kappa B (NF- κ B) associated inflammatory signaling, G2 cell-cycle arrest, and finally tubulointerstitial fibrosis [40], [42], [43], [44]. These mechanisms are consistent with pathological studies showing predominantly tubulointerstitial injury, often accompanied by microcyst formation, although glomerular lesions may also occur [43], [45]. Together, these renal effects may help explain why greater cumulative exposure was associated with lower eGFR and greater decline in kidney function (Figure 3).

Our findings also fit with previous clinical studies linking longer lithium exposure and elevated lithium concentrations with poorer kidney outcomes, although the strength of these associations has varied across studies [46], [47], [48], [49]. The relationship may also be bidirectional, as declining kidney function can reduce lithium clearance and increase serum lithium concentrations, while repeated periods of elevated lithium exposure may contribute to further renal injury [17], [50], [51]. Patients receiving lithium may be particularly vulnerable to toxicity during intentional or accidental overdose, dehydration or febrile illness, or when taking medications that reduce lithium excretion (e.g., NSAIDs, ACE inhibitors) [8], [52], [53]. This close relationship between lithium exposure and kidney function supports individualized long-term follow-up that considers cumulative exposure, serum concentrations, kidney function, and other renal risk factors, particularly during prolonged treatment or after elevated lithium levels.

Our study has several strengths. These include a large longitudinal sample, repeated eGFR measurements, inclusion of participants with and without BD, and detailed assessment of lithium exposure across both females and males. The analysis also considered cumulative exposure, current and past lithium use, elevated lithium concentrations, age, and comorbidity burden. However, several limitations should be considered. The retrospective EHR design is subject to incomplete documentation, differences in follow-up, and unmeasured confounding. Concomitant medications, including antipsychotics and other drugs that may affect kidney function or lithium concentrations, were not included in the models. Information on daily lithium dose and dosing frequency was also unavailable. Kidney function could not be directly compared between periods on and off lithium because some lithium exposure intervals did not have corresponding creatinine/eGFR measurements. In addition, lithium exposure before the study period or outside the Mayo Clinic system may not have been fully available in the EHR. Because participants with a baseline eGFR <60 mL/min/1.73 m² were excluded, the findings may not be generalized to individuals with reduced baseline kidney function. Finally, the ≥ 1.2 mmol/L threshold was based on laboratory measurements and may not represent clinically documented lithium toxicity in every case.

In conclusion, greater lithium exposure was consistently associated with lower eGFR and greater kidney-function decline. BD did not significantly alter this relationship, supporting a stronger relationship between the observed renal changes and lithium exposure than with the underlying diagnosis. A history of lithium toxicity was also associated with lower eGFR, although our findings do not establish a clear sex-specific effect. Overall, these findings support continued long-term renal monitoring, particularly with prolonged lithium exposure or a history of elevated levels, while maintaining the important clinical role of lithium in the treatment of BD.

Ethics approval and consent to participate: The study protocol was approved by the Mayo Clinic Institutional Review Board (protocol #23-010281). All subjects authorized the use of their data for research purposes. Obtaining a signed informed consent from each subject was waived by the IRB due to the retrospective nature of the study

Consent for publication: All authors consent to publication.

Availability of data and materials: Access to clinical data files is restricted due to patient confidentiality. Requests for deidentified clinical data can be made to the corresponding author

Competing interests: The authors have nothing to declare

Funding: This research work is funded by the Department of Psychiatry and Psychology at the Mayo Clinic, Arizona and by the Edli Foundation (OAA).

AI Declaration: During the preparation of this work, the authors used AI to improve grammar and structure, with no use in the methodology or results. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

Author contribution:

Author initials	Conceptualization and design	Clinical Data Extraction	Data validation	Data analysis	Data interpretation	Manuscript writing	Manuscript critical review
AMT					√	√	√
AE					√	√	√
VMP		√	√	√	√	√	√
JRG		√	√	√	√	√	√
ME					√	√	√
AB					√	√	√
AY					√	√	√
SS					√	√	√
BS					√	√	√
MAF					√	√	√
OAA	√				√	√	√

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Tables and Figures

Table 1. Participant demographic characteristics stratified by bipolar (Bipolar vs. Non-Bipolar) and sex. Associations between demographic variables (age, race, ethnicity, and marital status) and group factors (sex, bipolar, and their interaction) were assessed using two-way models (linear for continuous variables and multinomial for categorical variables).

Characteristic	Bipolar (N=2383)		Non-Bipolar (N=1075)		p-value		
	Males (N=1018)	Females (N=1365)	Males (N=505)	Females (N=570)	Sex	Bipolar	Interaction
Age at index date (years)	39.7 (14.9)	38.4 (15.1)	40.1 (15.5)	39.6 (16.2)	0.045	0.55	0.51 ¹
Race					0.78	0.053	0.66 ²
White	928 (91.2%)	1248 (91.4%)	459 (90.9%)	519 (91.1%)			
Black	38 (3.7%)	44 (3.2%)	10 (2.0%)	14 (2.5%)			
Others/Unknown	52 (5.1%)	73 (5.3%)	36 (7.1%)	37 (6.5%)			
Ethnicity					0.33	0.077	0.88 ²
Hispanic	31 (3.0%)	57 (4.2%)	17 (3.4%)	22 (3.9%)			
Non-Hispanic	967 (95.0%)	1284 (94.1%)	468 (92.7%)	529 (92.8%)			
Other/Unknown	20 (2.0%)	24 (1.8%)	20 (4.0%)	19 (3.3%)			
Marital status					<0.001	0.11	0.85 ²
Divorced/Separated/Widowed	149 (14.6%)	305 (22.3%)	61 (12.1%)	100 (17.5%)			
Married/Life Partnership	314 (30.8%)	473 (34.7%)	141 (27.9%)	194 (34.0%)			
Other/Unknown	555 (54.5%)	587 (43.0%)	303 (60.0%)	276 (48.4%)			
¹ Linear model							
² Multinomial model							

Table 2. Participant demographics and study characteristics, including baseline and follow-up eGFR and lithium use, stratified by bipolar disorder and sex.

Characteristic	Non-Bipolar (N=1075)		Bipolar (N=2383)		p-value		
	Females (N=570)	Males (N=505)	Females (N=1365)	Males (N=1018)	Sex	Bipolar	Interaction
Start of study							
Modified CCI	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 4)	0.75	0.12	0.14 ¹
eGFR (first)	100.0 (18.3)	101.1 (19.6)	102.6 (18.2)	102.5 (19.5)	0.93	0.17	0.38 ¹
Age	39.6 (16.2)	40.1 (15.5)	38.4 (15.1)	39.7 (14.9)	0.045	0.55	0.51 ¹
Days on lithium at first eGFR					<0.001	0.004	0.029 ²
0	426 (75%)	349 (69%)	983 (72%)	704 (69%)			
<30	101 (18%)	108 (21%)	272 (20%)	168 (17%)			
≥30	43 (8%)	48 (10%)	110 (8%)	146 (14%)			
Duration of study							
Number of eGFR measurements per person	8 (3, 16)	5 (2, 12)	9 (4, 18)	7 (4, 15)	0.012	0.007	0.25 ¹
Study length per person, years	4.8 (3.8)	3.9 (3.5)	5.6 (3.7)	4.9 (3.5)	<0.001	<0.001	0.50 ¹
End of study							
eGFR (last)	92.3 (21.5)	96.5 (21.8)	93.7 (20.8)	95.7 (22.1)	0.027	0.46	0.15 ¹
Lithium status at last eGFR					<0.001	0.029	0.71 ²
Non-User	97 (17%)	116 (23%)	176 (13%)	178 (17%)			
Past	314 (55%)	223 (44%)	780 (57%)	503 (49%)			
Current	159 (28%)	166 (33%)	409 (30%)	337 (33%)			
Days on lithium at last eGFR					0.006	<0.001	0.99 ²
0	97 (17%)	116 (23%)	176 (13%)	178 (17%)			

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<30	127 (22%)	100 (20%)	231 (17%)	153 (15%)			
≥30	346 (61%)	289 (57%)	958 (70%)	687 (67%)			
Among those ≥30, N=2280	605.1 (726.2)	637.3 (770.2)	836.4 (896.8)	834.6 (872.7)	0.97	<0.001	0.67 ¹
Any lithium toxicity	85 (15%)	69 (14%)	296 (22%)	189 (19%)	0.061	0.015	0.65 ³
¹ lm							
² multinom; nnet							
³ glm; lm							

Table 3. Fixed and random effects estimate for longitudinal eGFR models. Estimates and 95% confidence intervals (CI) are derived from linear mixed-effects models. The Overall model includes sex-by-age interactions, while subsequent columns present stratified analyses for females and males, further subdivided by bipolar disorder (BD) status. Random effects account for inter-individual variation in baseline eGFR and rate of decline over time. Marginal R² represents variance explained by fixed effects; conditional R² represents total variance explained by the full model.

	Overall		Females						Males					
			All Females		BD Females		Non-BD Females		All Males		BD Males		Non-BD Males	
Predictors	Estimates (95% CI)	p	Estimates (95% CI)	p	Estimates (95% CI)	p	Estimates (95% CI)	p	Estimates (95% CI)	p	Estimates (95% CI)	p	Estimates (95% CI)	p
Bipolar														
No (reference)	0		0						0					
Yes	1.25 (0.06, 2.43)	0.039	1.56 (0.02, 3.11)	0.048					0.91 (-0.91, 2.73)	0.33				
Age	-0.90 (-0.99, -0.81)	<0.001	-0.89 (-0.98, -0.80)	<0.001	-0.87 (-0.98, -0.76)	<0.001	-0.94 (-1.10, -0.78)	<0.001	-0.62 (-0.73, -0.52)	<0.001	-0.55 (-0.69, -0.40)	<0.001	-0.80 (-0.95, -0.65)	<0.001
Age'	0.03 (-0.10, 0.15)	0.69	0.06 (-0.06, 0.19)	0.34	0.05 (-0.10, 0.20)	0.48	0.07 (-0.16, 0.31)	0.53	-0.39 (-0.54, -0.24)	<0.001	-0.54 (-0.74, -0.34)	<0.001	-0.08 (-0.28, 0.13)	0.48
Sex														
Female (reference)	0													
Male	0.29 (0.15, 0.43)	<0.001												
Male × Age	-0.36 (-0.55, -0.17)	<0.001												
Male × Age'	-7.45 (-12.60, -2.30)	0.005												
Cumulative lithium exposure, years	-1.14 (-1.29, -1.00)	<0.001	-1.14 (-1.33, -0.95)	<0.001	-1.11 (-1.32, -0.90)	<0.001	-1.42 (-1.83, -1.00)	<0.001	-1.19 (-1.42, -0.95)	<0.001	-1.31 (-1.58, -1.04)	<0.001	-0.78 (-1.27, -0.29)	0.002
Lithium exposure status														
Non-User (reference)	0		0		0		0		0		0		0	
Past	-1.85 (-2.31, -1.38)	<0.001	-2.36 (-2.94, -1.78)	<0.001	-2.54 (-3.23, -1.85)	<0.001	-1.97 (-3.03, -0.91)	<0.001	-0.85 (-1.62, -0.08)	0.03	-1.26 (-2.17, -0.35)	0.007	0.23 (-1.24, 1.69)	0.76
Current	-3.80 (-4.21, -3.39)	<0.001	-3.83 (-4.34, -3.31)	<0.001	-4.76 (-5.37, -4.14)	<0.001	-1.16 (-2.13, -0.19)	0.019	-3.69 (-4.36, -3.02)	<0.001	-3.78 (-4.57, -2.99)	<0.001	-3.65 (-4.91, -2.39)	<0.001
Lithium toxicity														

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No (reference)	0		0		0		0		0		0		0	
Yes	-1.58 (- 2.19, - 0.97)	<0.001	-2.68 (- 3.44, - 1.92)	<0.001	-1.44 (- 2.29, - 0.59)	<0.001	-7.75 (- 9.43, - 6.06)	<0.001	0.39 (- 0.63, - 1.40)	0.45	0.85 (- 0.30, - 2.01)	0.15	-0.19 (- 2.26, - 1.89)	0.86
Modified CCI	0.78 (- 0.73, - 2.29)	0.31	0.94 (- 0.92, - 2.81)	0.32	1.43 (- 0.77, - 3.63)	0.20	0.19 (- 3.31, - 3.69)	0.92	0.40 (- 2.12, - 2.92)	0.76	0.71 (- 2.43, - 3.85)	0.66	0.67 (- 3.98, - 5.31)	0.78
Random Effects														
σ^2	147.43		144.57		141.14		152.01		151.7		142.61		171.6	
τ_{00}	1332.45		1338.13		1371.23		1217.55		1284.92		1879.5		371.06	
τ_{11}	0.71		0.71		0.73		0.64		0.69		0.98		0.2	
ρ_{01}	-0.94		-0.95		-0.95		-0.94		-0.94		-0.95		-0.8	
ICC	0.9		0.9		0.91		0.89		0.89		0.93		0.68	
N _{subjects}	3458		1935		1365		570		1523		1018		505	
Observations	45758		27723		20019		7704		18035		12970		5065	
Marginal R2 / Conditional R2	0.132 / 0.914		0.129 / 0.915		0.121 / 0.918		0.154 / 0.906		0.140 / 0.909		0.110 / 0.937		0.265 / 0.768	

Table 4. Change in eGFR between first and last measurement (excluding all who have only 1 measurement) (N=3127).

Predictors	Estimates (95% CI)	p
Age at index date	-0.01 (-0.05, 0.03)	0.62
Time between first and last eGFR	-1.16 (-1.34, -0.97)	<0.001
Δ Lithium		
≤2 years		
>2 years	-5.78 (-9.77, -1.79)	0.005
Bipolar		
No (reference)		
Yes	-0.38 (-2.35, 1.58)	0.70
Sex		
Female (reference)		
Male	2.25 (-0.16, 4.66)	0.067
Δ Lithium [>2 years] × Bipolar [Yes]	2.94 (-1.52, 7.39)	0.20
Δ Lithium [>2 years] × Male	0.90 (-4.89, 6.70)	0.76
Bipolar [Yes] × Male	-0.65 (-3.58, 2.28)	0.66
Δ Lithium [>2 years] × Male × Bipolar [Yes]	-2.17 (-8.80, 4.45)	0.52
Observations	3127	
R2 / R2 adjusted	0.083 / 0.080	

Figure 1. Predicted eGFR across age for females (left) and males (right) with and without bipolar disorder (BD), estimated from sex- and BD-specific models. Models included restricted cubic splines for age, cumulative lithium exposure, lithium exposure status, any lithium toxicity, and modified CCI, with random intercepts and age slopes per patient. **(A)** Predicted trajectories assuming no lithium exposure throughout life. **(B)** Predicted trajectories assuming lithium use from age 40–45. Visible discontinuity reflects changes in modeled exposure status. Shaded areas represent 95% confidence intervals.

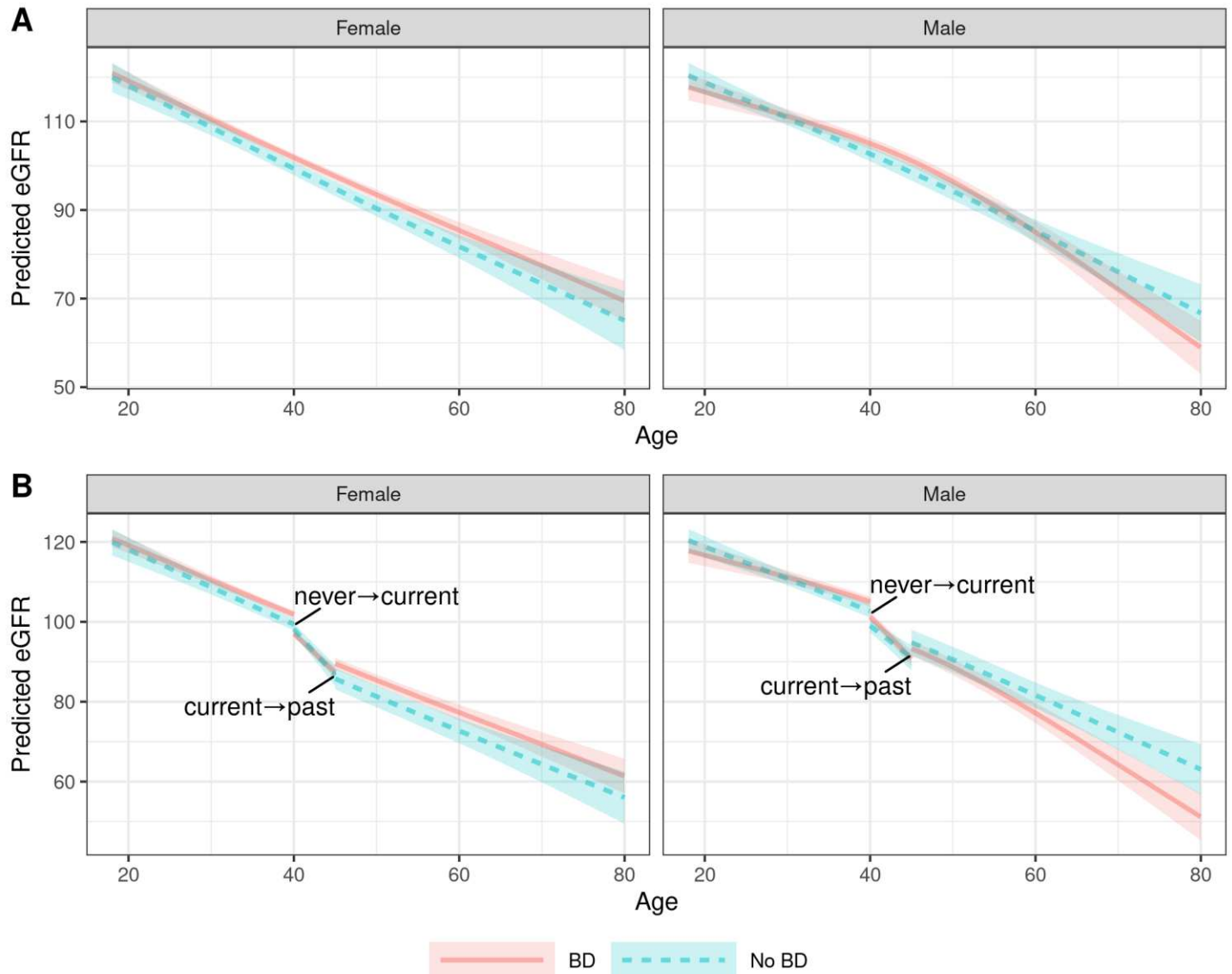


Figure 2. Predicted change from first to last eGFR for females (left) and males (right) with and without bipolar disorder (BD) by corresponding change in lithium exposure categorized by greater than 2 years (N=3127).

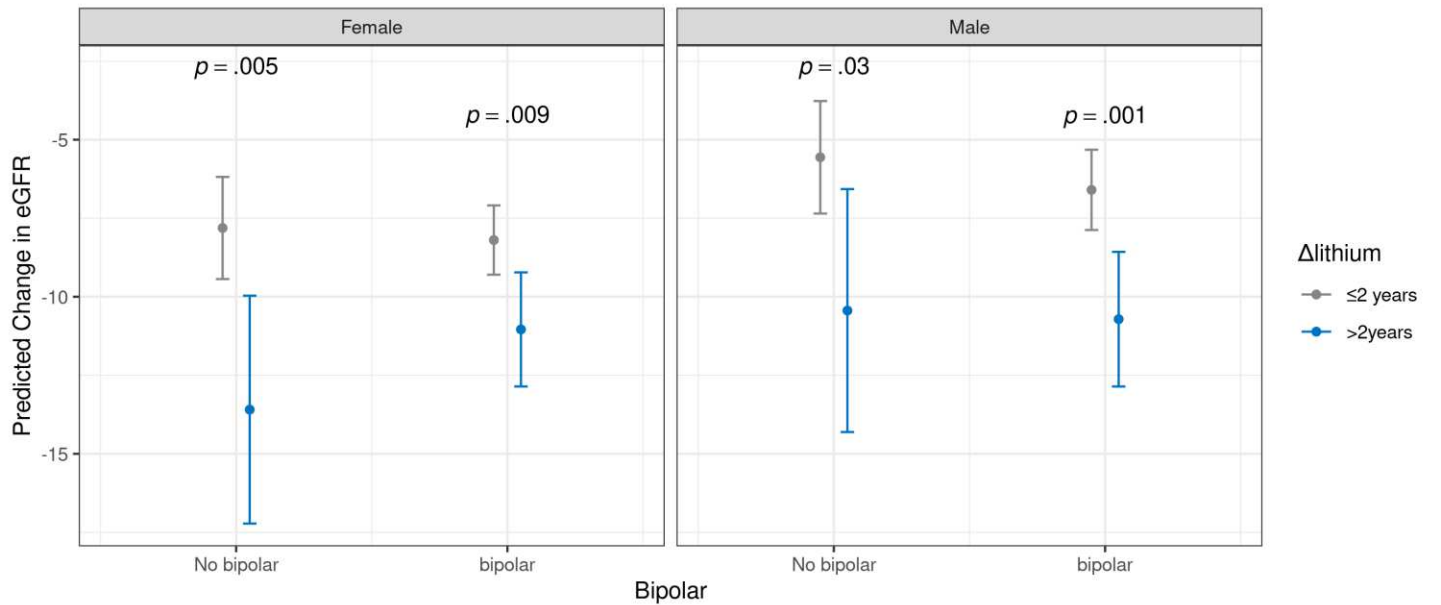
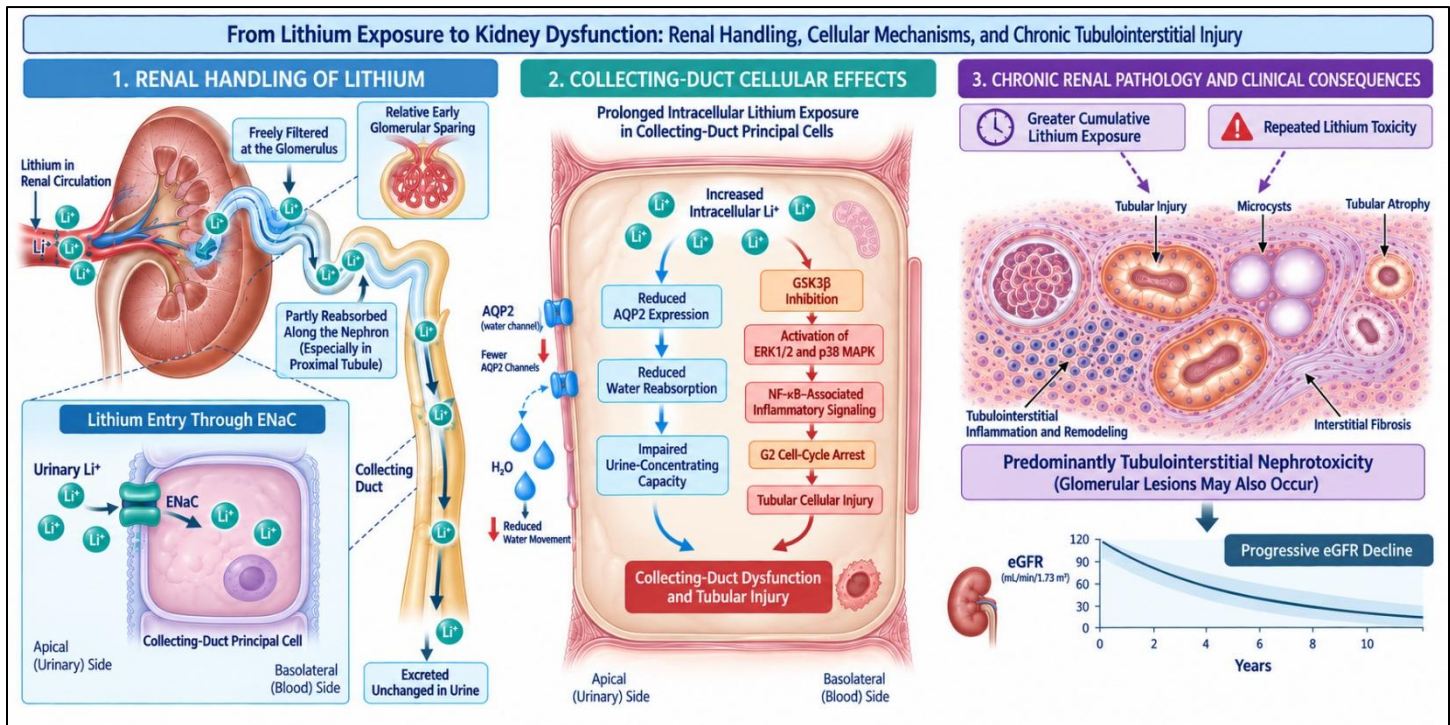


Figure 3: Proposed pathway linking chronic lithium exposure and collecting-duct lithium accumulation to impaired water handling, tubulointerstitial fibrosis, microcyst formation, and progressive eGFR decline. Abbreviations: AQP2, aquaporin 2; eGFR, estimated glomerular filtration rate; ENaC, epithelial sodium channel; ERK, extracellular signal-regulated kinase; GSK3 β , glycogen synthase kinase 3 beta; NF- κ B, nuclear factor kappa B; p38 MAPK, p38 mitogen-activated protein kinase.



Supplementary Figure 1. Exploratory scatterplots of change in eGFR (Δ eGFR) as a function of change in cumulative lithium exposure duration, stratified by sex (Left: females; Right: males). Across both panels, larger declines in eGFR were observed with greater increases in lithium exposure duration. The dashed vertical line denotes the 2-year threshold used to dichotomize exposure change in subsequent analyses.

