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Lithium and the risk of chronic kidney disease: A population-based case–control study

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Abstract

The association between lithium use and chronic kidney disease (CKD) needs further evaluation. We aimed to investigate this association using Danish nationwide healthcare registers and routinely collected plasma creatinine measurements from the Funen Laboratory Cohort. We conducted a case–control study nested within the population of Funen, 2001–2015. Incident cases of CKD (estimated glomerular filtration rate <60 ml/min/1.73m^2; $n = 21\,432$) were matched with four CKD-free controls on age, sex and calendar time ($n = 85\,532$). We estimated odds ratios (OR) for the association between lithium exposure and CKD using conditional logistic regression models, adjusted for known risk factors for CKD. Ever-use of lithium was associated with an increased risk of CKD (adjusted OR [aOR]: 1.57; 95% confidence interval [CI]: 1.33–1.85). A stronger association was seen with current use of lithium (aOR: 1.92; 95%CI: 1.58–2.33) and long-term use of lithium (>10 years: aOR: 3.02; 95%CI: 2.00–4.56). Furthermore, we found evidence of a dose–response relationship between cumulative dose of lithium and the risk of CKD. In conclusion, the use of lithium, especially long-term, is associated with an increased risk of CKD, although the extent to which detection bias and confounding by indication contribute to the association is unclear. Monitoring of kidney function in lithium users remains mandatory to identify individuals in which switching to alternative medications should be considered.

KEYWORDS
case–control study, chronic kidney disease, lithium, pharmacoepidemiology, psychopharmacology

1 | BACKGROUND

Lithium has been used to treat bipolar disease since the 1950s and is considered an almost gold standard mood stabilizer with substantial evidence of efficacy as antimanic and relapse preventive treatment and some evidence of efficacy in the treatment of depressive episodes associated with bipolar disorder.[1–4] Despite documented effectiveness, the clinical use of lithium requires skilful and careful monitoring and management due to

its narrow therapeutic range and concerns of intoxication and potential organ toxicities.[5]

Chronic kidney disease (CKD) is a common disease; based on laboratory-based criteria, the estimated life-time prevalence in Denmark is between four and eight cases per 100 inhabitants.[6] A number of drugs are considered nephrotoxic, potentially increasing the risk of especially acute kidney injury.[7] However, not all patients exposed to the various potential nephrotoxins develop kidney disease.

The association between use of lithium and CKD has long been debated. Some population-based studies have found a clinically significant decline in estimated glomerular filtration rate (eGFR) among lithium users,[8–11] while other studies have shown no effect of stable lithium levels in the therapeutic range on the rate of eGFR decline over time.[12] A nationwide Danish study using hospital diagnoses to identify CKD found that maintenance treatment with lithium was associated with an increased rate of CKD but that the use of lithium was not associated with an increased rate of end-stage CKD.[13]

A recent meta-analysis of observational studies has suggested that one fourth of the patients treated with lithium may develop moderate or advanced CKD after long-term treatment, with a two-fold increased risk compared with patients receiving treatments other than lithium.[14] Interestingly, lithium might also have an impact on thyroid and parathyroid function as well, potentially increasing the risk of hypothyroidism and raising total plasma calcium concentration.[11]

Using the comprehensive high-quality Danish registers, combining prescription information with laboratory data, we aimed to assess the association between use of lithium and the subsequent risk of CKD.

2 | MATERIALS AND METHODS

We performed a population-based case–control study of incident CKD cases among inhabitants residing on the island of Funen, Denmark, who had at least two measurements of plasma creatinine between 2001 and 2015. We compared the use of lithium among individuals with incident CKD with a disease-free control population.

2.1 | Data sources

We used information from the Funen Laboratory Cohort (FLaC), which contains information regarding all laboratory results of all inhabitants of Funen who, within the study period, had at least one measurement of plasma creatinine.[15] A total of 460 365 patients out of 693 843 inhabitants on Funen had their creatinine measured between 2001 and 2015. We linked creatinine measurements to several nationwide Danish administrative registers: The Danish National Patient Registry,[16] the Danish National Prescription Registry,[17] the Danish Civil Registration System[18,19] and Information on highest educational level from Statistics Denmark.[20] It is possible to conduct true population-based register-linkage studies covering the entire population due to the Danish National Health Service, which provides universal tax-supported healthcare for the entire Danish population, and because all Danish inhabitants are assigned a unique personal 10-digit identifier (Central Personal Register [CPR] number) at birth.[18] The CPR number allows unambiguous linkage between all health-related registers.

2.2 | Source population

All adults with more than one creatinine measurement, living on Funen and the surrounding islands in the period of January 2001 to December 2015, were eligible for inclusion in the study as either cases or controls. Funen is a part of the Region of Southern Denmark, which is considered a representative geographical area for the entire Danish population for a range of health-related, educational and demographic parameters.[21] We defined an observation period for each individual, starting at the first creatinine measurement during the study period and ending at the last recorded creatinine measurement within the study period. We only included individuals with normal kidney function at the start of the observation period. In case of emigration from the island of Funen, the observation period ended on the date of last creatinine measurement before emigration.

2.3 | Cases

We defined cases as individuals who developed CKD during the observation period, and CKD was defined according to the Kidney Disease-Improving Global Outcomes (KDIGO) guidelines.[22] We calculated the eGFR calculated according to the CKD-epi formula[23] and defined the index date as the first recording of an eGFR below 60 ml/min/1.73 m^2. The first eGFR measured 3 months after the index date also had to be below 60 ml/min/1.73 m^2, as well as all the measurements in the in-between period (from the index date to 3 months after), to ensure that cases had CKD. We excluded individuals with a discharge diagnosis of renal disease according to the definition of definite or possible CKD, as proposed by Kessing et al.[13] before the date of biochemically assessed

CKD (WHO International Classification of Diseases, 10th revision [ICD-10]: N00-01, N03-06, N08.8, N14.1, N14.2, N16.8, N17-19, N25.1 and N26-27). We also excluded individuals with any eGFR measurement below 60 ml/min/1.73 m^2 before the study start in 2001.

2.4 | Controls

Each case was matched to four population controls on age, sex and calendar time and assigned an index date corresponding to the date of the corresponding case's date of incident CKD. We then used risk-set sampling and excluded controls who fulfilled the same exclusion criteria as described for cases. All controls were required to have at least one creatinine recorded in the year after the index date, to ensure that controls had not developed CKD since their last creatinine measurement, and this measurement had to be above or equal to 60 ml/min/1.73 m^2. Thereby, both cases and controls were required to have confirmatory measurements of their status. Cases could be selected as controls before they became cases, and we allowed that individuals could be selected as controls more than once. By these criteria, the generated odds ratio (OR) is an unbiased estimate of the incidence ratio that would have emerged from a cohort study embedded in the source population.[24] Details on the study design are depicted in Figure S1 and details on the cohort attrition in Figure 1.

2.5 | Exposure

We obtained information on prescription fills for lithium from the Danish National Prescription Register (Anatomical Therapeutic Chemical Classification [ATC]: N05AN01). Cumulative exposure to lithium was assessed as the total number of defined daily doses (DDD) filled during the observation period. According to the WHO Collaborating Centre for Drug Statistics methodology, 24 mmol of lithium corresponds to 1 DDD.[25] Total duration of treatment with lithium (within the observation period) was assessed based on prescription fills for lithium. We constructed treatment episodes by assigning a duration to each prescription corresponding to 90 days. If a new prescription was filled before the end of the subsequent, the date of the new prescription was used as start for the subsequent episode. The total duration of treatment episodes for each individual was then summarized. The 90-day duration for each prescription was based on the waiting time distribution in prevalent users of lithium (the distribution of days between prescription fills).

2.6 | Covariates

We included the following potential confounders in our analysis: (i) sex, age and calendar time (accounted for by the sampling procedure); (ii) recent use of nonsteroidal anti-inflammatory drugs (NSAIDs); (iii) history of hypertension and diabetes; and (iv) highest achieved level of education as a proxy for socioeconomic status. Recent use of NSAIDs was defined as filling of prescriptions within 1 year before the index date. Relevant ICD-10 diagnoses and ATC codes for covariate assessment are listed in Appendix S1.

2.7 | Statistical analysis

Demographic characteristics were presented as absolute numbers and proportions or medians and interquartile ranges (IQR) as appropriate. Our primary analysis was

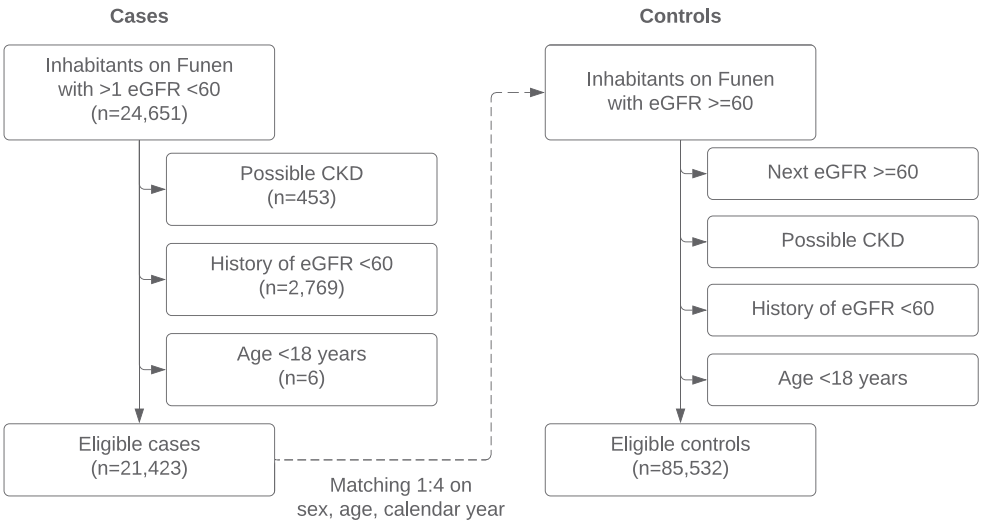

FIGURE 1 Selection of cases and controls

the risk of CKD in relation to ever-use of lithium. As aid to the interpretation of the main result, we also analysed the risk of CKD in relation to current use, cumulative dose of lithium and cumulative duration of treatment with lithium. We used conditional logistic regression to estimate OR with 95% confidence intervals (CI) for the association between exposure and incident CKD. Using conditional logistic regression, we computed crude and adjusted ORs (aOR). The adjusted model included the following predefined clinically relevant potential confounders: recent use of NSAIDs, use of second-generation antipsychotics, history of diabetes or hypertension and highest achieved level of education.

We conducted subgroup analyses by stratifying on history of risk factors for CKD (diabetes, hypertension and prior acute kidney injury [AKI]) and age group (</≥65 years). We also performed two supplementary analyses: firstly, by exploring a potential dose–response relation, using logistic regression among all lithium users and restricted cubic splines with knots at the value for the 10th, 50th and 90th percentile for cumulative doses among cases. Secondly, we compared the risk of incident CKD from total treatment duration among lithium users with that of anticonvulsant users (ATC code: N03). In this analysis, total treatment duration was assessed similarly to that of lithium users as described above. A sensitivity analysis was computed, where controls were not required to have normal eGFR measurement(s) in the year following the index date to investigate if this criterion would introduce selection bias from otherwise eligible controls being excluded. Furthermore, we conducted control analyses to assess the association between CKD and known risk factors (history of diabetes or hypertension and use of NSAIDs) and with a negative control exposure (topical ocular antibiotics, ATC code: S01AA), which is not considered to be associated with CKD. R v.3.5.1 (R Core Team, Vienna, Austria) was used for all analyses.

2.8 | Other

This study was approved by the Danish Data Protection Agency (2008-58-0034) and the Danish Patient Safety Authority (3-3013-809/1). According to Danish legislation, studies based solely on register data do not require approval from an ethics review board.

3 | RESULTS

We identified 21 423 cases of incident CKD in the source population between 2001 and 2015 (Figure 1). Hereof, 48% were males and the median age was 71 years (IQR: 64–78 years). Additionally, the study population included 85 532 CKD-free population controls. History of diabetes, hypertension and acute kidney injury was more prevalent among cases than controls (14 vs. 10%, $p < 0.001$; 65 vs. 55%, $p < 0.001$; and 11 vs. 3%, $p < 0.001$, respectively). Further characteristics of cases and controls are described in Table 1.

3.1 | Main analysis

In total, 210 (1.0%) cases had filled prescriptions for lithium compared with 528 (0.6%) of controls, yielding an aOR for CKD with ever-use of lithium of 1.57 (95%CI: 1.33–1.85; Table 2). Among cases, 158 were current users of lithium, compared with 335 individuals in the control population, yielding an aOR with current use of lithium of 1.92 (95%CI: 1.58–2.33). We found an increasing risk of CKD with increasing cumulative dose of lithium (≤180

TABLE 1 Characteristics of cases and controls

Patient characteristics	Cases ($n = 21\,423$)	Controls ($n = 85\,532$)[a]
Demographics		
Male sex, *n* (%)	10 271 (48)	40 986 (48)
Age, median (IQR)	71 (64–78)	71 (64–78)
Exposure to lithium, *n* (%)	210 (1)	528 (0.6)
History of mental disorders, *n* (%)		
Any psychiatric diagnosis	1548 (7)	4826 (6)
Bipolar disease	120 (1)	353 (<1)
Major depression	549 (3)	1726 (2)
Schizophrenia	74 (<1)	217 (<1)
No psychiatric diagnosis	19 875 (93)	80 706 (94)
Other comorbidities, *n* (%)		
Diabetes	3054 (14)	8521 (10)
Hypertension	13 954 (65)	47 184 (55)
Acute kidney injury	2432 (11)	2494 (3)
Exposure to other medications, *n* (%)		
Second-generation antipsychotics	560 (3)	1826 (2)
Recent use of NSAIDs	5609 (26)	20 166 (24)
Highest achieved level of education, *n* (%)		
Short (7–10 years)	10 248 (48)	38 201 (45)
Medium (11–12 years)	6780 (32)	27 795 (32)
Long (13 + years)	2684 (13)	12 743 (15)
Unknown	1711 (8)	6793 (8)

Abbreviations: IQR, interquartile range; *n*, number; NSAID, nonsteroidal anti-inflammatory drugs.

[a]The number of controls were not exactly four times the number of cases as controls were required to satisfy the same criteria as cases, including having another creatinine measurement within 3 months of the first.

TABLE 2 Association between exposure to lithium and chronic kidney disease by different levels of exposure

Exposure	Cases ($n = 21\,423$)	Controls ($n = 85\,532$)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Never-use	21,213	85,004	1 (reference)	1 (reference)
Ever-use	210	528	1.59 (1.36 to 1.87)	1.57 (1.33 to 1.85)
Current use	158	335	1.89 (1.56 to 2.29)	1.92 (1.58 to 2.33)
Cumulative dose of lithium				
≤180 DDD	127	368	1.38 (1.13 to 1.69)	1.34 (1.09 to 1.65)
181–365 DDD	51	111	1.86 (1.33 to 2.59)	1.90 (1.35 to 2.66)
366–730 DDD	28	44	2.52 (1.57 to 4.06)	2.54 (1.57 to 4.10)
>730 DDD	(n < 5)	5	3.20 (0.86 to 11.9)	2.81 (0.73 to 10.7)
Cumulative duration of treatment				
<1 year	64	137	1.67 (1.22 to 2.29)	1.58 (1.15 to 2.18)
1–2 years	73	81	2.27 (1.51 to 3.43)	2.16 (1.42 to 3.28)
3–4 years	47	143	1.19 (0.82 to 1.73)	1.08 (0.74 to 1.58)
v5–10 years	68	175	1.53 (1.14 to 2.04)	1.50 (1.12 to 2.02)
>10 years	45	73	2.59 (1.75 to 3.85)	2.56 (1.71 to 3.83)

Abbreviations: CI, confidence interval; DDD, WHO defined daily dose; *n*, number; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio.
[a]The number of controls were not exactly four times the number of cases as controls were required to satisfy the same criteria as cases, including having another creatinine measurement within 3 months of the first.
[b]Adjusted for age, sex, and calendar time by matching.
[c]Additionally adjusted for prior use of second-generation antipsychotics, current use of NSAID, history of hypertension, history of diabetes, and educational achievement.

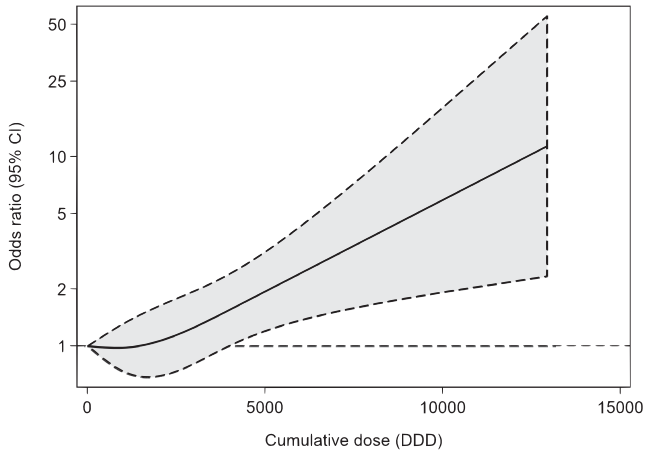

FIGURE 2 Supplementary analysis of the association between chronic kidney disease and cumulative dose of lithium

DDD aOR: 1.34, 181–365 DDD aOR: 1.90, 366–730 DDD aOR: 2.54, >730 DDD aOR: 2.81; Table 2). However, there were too few individuals with cumulative use of lithium >730 DDD to allow for a meaningful inferential analysis. In a supplementary analysis using restricted cubic splines, the OR for CKD continued to increase with increasing cumulative dose (Figure 2). Long-term use of lithium was strongly associated with increased risk of CKD > 10 years (aOR: 2.56; 95%CI: 1.71–3.83; Table 2) compared with shorter duration of treatment.

3.2 | Subgroup analyses

Lithium users with diabetes had a stronger association with CKD than those without diabetes, but due to the low number of exposed diabetics, the CI for this group was wider than for nondiabetics (diabetes: aOR: 1.79 95%CI: 1.13–2.81 vs. no diabetes: aOR: 1.56 95%CI: 1.30–1.86). Other risk factors for CKD (use of NSAIDs, hypertension, prior AKI and age ≥65 years) were not clearly associated with stronger association between lithium use and CKD (Table 3). The absolute risk of CKD in the study population was 3.4% for individuals <65 years and 16% for individuals ≥65 years. For individuals with or without prior AKI, the absolute risk was 41% and 4.6%, respectively.

3.3 | Supplementary and sensitivity analyses

The risk of CKD was not increased in long-term treatment with anticonvulsants as it was seen in long-term treatment with lithium (>10 years of treatment: $aOR_{Lithium}$ 2.56, 95%CI: 1.71–3.83 vs. $aOR_{anticonvulsants}$ 0.86, 95%CI: 0.69–1.07; Table 4). The risk of CKD in relation to lithium exposure increased, when including controls who did not require normal eGFR measurements in

TABLE 3 Subgroup analysis of the association between exposure to lithium and chronic kidney disease

Subgroup	Casesexposed/ unexposed ($n = 21\,423$)	Controlsexposed/ unexposed ($n = 85\,532$)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Recent use of NSAID				
No	169/15645	408/64958	1.72 (1.43 to 2.06)	1.73 (1.44 to 2.09)
Yes	41/5568	120/20046	1.23 (0.85 to 1.74)	1.17 (0.80 to 1.68)
Diabetes				
No	175/18194	477/76534	1.54 (1.29 to 1.83)	1.56 (1.30 to 1.86)
Yes	35/3019	51/8470	1.93 (1.24 to 2.95)	1.79 (1.13 to 2.81)
Hypertension				
No	104/7365	317/38031	1.69 (1.35 to 2.11)	1.57 (1.24 to 1.97)
Yes	106/13848	211/46973	1.70 (1.34 to 2.15)	1.60 (1.26 to 2.03)
Prior AKI				
No	187/18804	513/82625	1.60 (1.35 to 1.89)	1.62 (1.36 to 1.93)
Yes	23/2409	15/2379	1.51 (0.80 to 2.97)	1.81 (0.93 to 3.63)
Age group				
<65 years	89/5750	211/23160	1.70 (1.32 to 2.17)	1.56 (1.20 to 2.03)
≥65 years	121/15463	317/61844	1.53 (1.23 to 1.88)	1.56 (1.25 to 1.93)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; DDD, WHO defined daily dose; *n*, number; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

[a]The number of controls were not exactly four times the number of cases as controls were required to satisfy the same criteria as cases, including having another creatinine measurement within 3 months of the first.

[b]Adjusted for age, sex, and calendar time by matching.

[c]Additionally adjusted for prior use of second-generation antipsychotics, current use of NSAID, history of hypertension (not in analyses of association with hypertension), history of diabetes (not in analyses of association with diabetes), and highest educational achievement.

the year following their assigned index date (aOR: 1.83, 95%CI: 1.53–2.19 vs. 1.57, 95%CI: 1.33–1.85; Table S1). Analyses confirmed that each of the assumed risk factors included in the model was positively associated with increased risk of CKD in the population (Table S2) and that a negative control exposure (use of antibiotic eye-drops) was not associated with increased risk of CKD (aOR: 0.94; 95%CI: 0.89–0.99; Table S2).

4 | DISCUSSION

In this population-based case–control study, using creatinine measurements to estimate GFR and identify incident CKD, we found ever-use and current use of lithium to be associated with an increased risk of incident CKD (57% and 92%, respectively). The risk of CKD increased with increasing cumulative dose of lithium and duration of treatment from an aOR of 0.99 (95%CI: 0.66–1.50) for 3–4 years of cumulative duration to an aOR of 2.56 (95%CI: 1.71–3.83) for more than 10 years of cumulative duration.

Our findings align reasonably well with findings from a previous study of a Danish population using CKD hospital diagnoses as outcome.[13] In this study, a hazard ratio of 3.65 (95%CI: 2.64–5.05) was identified for patients receiving at least 60 prescriptions for lithium, but no signal emerged for fewer than 60 prescriptions. As increase in creatinine and subsequent reduction in eGFR do not ensure that a diagnosis of CKD is identified, much less coded, our analysis based on creatinine measurements adds substantial details. Our finding suggests that even less than 6 months of lithium treatment may be associated with an increased risk of CKD defined as eGFR below 60 ml/min/1.73 m^2, even though this finding might be related to an increased risk of CKD with the conditions for which lithium is used. In a recent descriptive study,[9] where 12% of 1012 patients were treated with lithium for an average of 9 years, eGFR fell below 60 ml/min/1.73 m^2 from normal values at initiation of therapy/study start. A case–control study similarly reported higher percentage of eGFR values below 60 ml/min/1.73 m^2 compared with matched controls (17 versus 13%, respectively). In this study, outcomes were less valid as eGFR could have been based on a single creatinine measurement.[8] Contrarily, no effect on eGFR was seen in a cohort study of 312 lithium users (mean duration 55 months) when compared with

TABLE 4 Association between exposure to lithium or anticonvulsants and chronic kidney disease by different levels of exposure

Cumulative duration	Cases ($n = 21\,423$)	Controls ($n = 85\,532$)[a]	Crude OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Lithium				
<1 year	64	137	1.67 (1.22 to 2.29)	1.58 (1.15 to 2.18)
1–2 years	73	81	2.27 (1.51 to 3.43)	2.16 (1.42 to 3.28)
3–4 years	47	143	1.19 (0.82 to 1.73)	1.08 (0.74 to 1.58)
5–10 years	68	175	1.53 (1.14 to 2.04)	1.50 (1.12 to 2.02)
>10 years	45	73	2.59 (1.75 to 3.85)	2.56 (1.71 to 3.83)
Anticonvulsants[d]				
<1 year	1617	5381	1.15 (1.08 to 1.23)	1.09 (1.02 to 1.17)
1–2 years	331	854	1.44 (1.25 to 1.65)	1.32 (1.14 to 1.52)
3–4 years	365	1192	1.15 (1.01 to 1.31)	1.10 (0.96 to 1.25)
5–10 years	268	1239	0.81 (0.70 to 0.93)	0.79 (0.68 to 0.91)
>10 years	139	558	0.87 (0.70 to 1.08)	0.86 (0.69 to 1.07)

[a]The number of controls were not exactly four times the number of cases as controls were required to satisfy the same criteria as cases, including having another creatinine measurement within 3 months of the first.
[b]Adjusted for age, sex, and calendar time by matching.
[c]Additionally adjusted for prior use of second-generation antipsychotics, current use of NSAID, history of hypertension, history of diabetes, and educational achievement.
[d]Anticonvulsants defined as all drugs within ATC group N03.
Abbreviations: CI, confidence interval; DDD, WHO defined daily dose; *n*, number; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

815 controls exposed to other mood-stabilizing drugs when adjusting for sex, age and baseline eGFR.[12] While the underlying pathophysiological mechanism through which lithium potentially could reduce renal function remains unclear, it has been suggested that genetic susceptibility may confer an increased risk of lithium-induced decline in eGFR.[26] At the same time, evidence emerges that lithium might inhibit glycogen synthase kinase-3β, thus preventing age-related loss of glomerular function.[27]

There are several strengths with the present analysis: Firstly, we improved the outcome definition by using creatinine measurements to assess cases of incident CKD, rather than relying on hospital diagnoses, as most cases of uncomplicated early-stage CKD in Denmark are handled in primary care. To verify that individuals were in fact cases of incident CKD or eligible as controls, we required at least two measurements for each individual to confirm this status. This means that relying on discharge diagnoses to identify CKD would have underestimated the true incidence of CKD in the population. Secondly, we were able to adjust for several confounders in relation to the risk of CKD, including use of second-generation antipsychotics which we previously have identified as associated with CKD,[28] and educational achievement as a proxy for socioeconomic status, which also has been associated with increased risk of CKD.[29] Estimated GFR levels just below 60 ml/min/1.73 m^2 are unlikely to be symptomatic and are only discovered if the patients have their creatinine measured.[30] It is conceivable that patients taking lithium would have more creatinine measurements than others as a direct consequence of lithium use or because of frequent physician contact, or both. Thereby, they would occasionally have a CKD diagnosed that would go undetected in others. This potential upward bias in our study (or in other studies) is to a large extent mitigated by nesting our study in a population defined by having multiple creatinine measurements. However, we cannot rule out some residual bias by this mechanism. Finally, we were able to include all eligible cases and controls from a population considered representative for Denmark.[21]

However, a number of limitations with the present analysis must be acknowledged: Firstly, treatment with lithium is likely to result in frequent measurements of creatinine, which could result in more lithium users incidentally crossing the threshold defining CKD. Particularly asymptomatic low-grade CKD would be vulnerable to such ascertainment bias. Secondly, the indications for treatment with lithium (e.g. bipolar disorder) might itself be associated with an increased risk of developing renal impairment.[31] Thirdly, we were not able to adjust for exposure to a range of other potentially nephrotoxic agents (e.g., aminoglycosides, intravenous X-ray contrast and platin-based chemotherapy),[7] as these are predominantly used in-hospital or supplied from outpatient clinics and thus not recorded in the Danish Prescription

Register. Fourthly, the total number of cases and controls exposed to lithium was relatively low. Fifthly, information on general risk factors as body weight, smoking and lifestyle were not included in our data sources. Lastly, we were not able to assess the overall decline in renal function during treatment with lithium with the present study design and thus not provide data to support if such decline is of clinically relevant magnitude.

Regular monitoring of kidney function in patients receiving lithium is mandatory given the increased risk of CKD. Additionally, the plasma concentration of lithium should be measured regularly and kept at a proper level to reduce this risk.[32]

Use of lithium is associated with increased risk of CKD. The risk increases with cumulative dose and duration of use, although the extent to which detection bias contributes to the association is unclear. Therefore, when treatment-emergent decline in renal function is identified, it should carefully be evaluated whether treatment with lithium should continue or needs to be discontinued and replaced by alternative medications, such as anticonvulsants or antipsychotics. The decision to stop treatment with lithium should consider the prior psychiatric history, as lithium might be the only efficacious treatment for a given patient. Ideally, this decision should be taken in close collaboration between patient, psychiatrists, nephrologists, and a clinical pharmacologist.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used for this study are not publicly available due to confidentiality issues. Data can be obtained through application to Statistics Denmark.

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