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

Mikkel Højlund1,2 | Jane Sterndorff Winkel3 | Mads Nybo4,5 | Jesper Hallas1,3 | Daniel Pilsgaard Henriksen1,3 | Per Damkier1,3,5

1Clinical Pharmacology, Pharmacy, and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark
2Department of Psychiatry Aabenraa, Mental Health Services in the Region of Southern Denmark, Aabenraa, Denmark
3Department of Clinical Pharmacology, Odense University Hospital, Odense, Denmark
4Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark
5Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Correspondence
Mr. Mikkel Højlund, Department of Public Health, Clinical Pharmacology, Pharmacy, and Environmental Medicine, University of Southern Denmark, J.B. Winsløws Vej 19, 2nd floor, DK-5000 Odense, Denmark.
Email: mhoejlund@health.sdu.dk

Funding information
The Beckett foundation, Grant/Award Number: 42282; The Hede-Nielsen Family Foundation

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/1.73m²; 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
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. A number of drugs are considered nephrotoxic, potentially increasing the risk of especially acute kidney injury. 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, while other studies have shown no effect of stable lithium levels over time. 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.

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. 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.

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. 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, the Danish National Prescription Registry, the Danish Civil Registration System and Information on highest educational level from Statistics Denmark. 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. 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. 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. We calculated the eGFR calculated according to the CKD-epi formula and defined the index date as the first recording of an eGFR below 60 ml/min/1.73 m². The first eGFR measured 3 months after the index date also had to be below 60 ml/min/1.73 m², as well as all the measurements in the interval 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. 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 m² 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 m². 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. 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. 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 (<65–65 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 mg/day, Table 3).

#### Table 1 Characteristics of cases and controls

| Patient characteristics | Cases (n = 21 423) | Controls (n = 85 532)* |
|-------------------------|--------------------|------------------------|
| **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.

*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.
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: aORLithium 2.56, 95%CI: 1.71–3.83 vs. aORanticonvulsants 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 2** Association between exposure to lithium and chronic kidney disease by different levels of exposure

| Exposure                                  | Cases (n = 21 423) | Controls (n = 85 532a) | 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)  |
| ≥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)  |

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

aThe 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.
bAdjusted for age, sex, and calendar time by matching.
cAdditionally 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.
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 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).

Our findings align reasonably well with findings from a previous study of a Danish population using CKD hospital diagnoses as outcome. 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 m², 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 m² 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 m² 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. Contrarily, no effect on eGFR was seen in a cohort study of 312 lithium users (mean duration 55 months) when compared with

| Subgroup                          | Cases exposed/unexposed (n = 21,423) | Controlsexposed/unexposed (n = 85,532) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------|-------------------------------------|----------------------------------------|-------------------|----------------------|
| Recent use of NSAID               |                                     |                                        |                   |                      |
| No                                | 169/15645                           | 408/64938                              | 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.

*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.

*Adjusted for age, sex, and calendar time by matching.

*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.
815 controls exposed to other mood-stabilizing drugs when adjusting for sex, age and baseline eGFR. 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. At the same time, evidence emerges that lithium might inhibit glycogen synthase kinase-3β, thus preventing age-related loss of glomerular function.

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, and educational achievement as a proxy for socioeconomic status, which also has been associated with increased risk of CKD. Estimated GFR levels just below 60 ml/min/1.73 m² are unlikely to be symptomatic and are only discovered if the patients have their creatinine measured. 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.

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. 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), as these are predominantly used in-hospital or supplied from outpatient clinics and thus not recorded in the Danish Prescription

| Cumulative duration | Cases | Controls | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---------------------|-------|----------|-------------------|---------------------|
| 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) |

^aThe 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.

^bAdjusted for age, sex, and calendar time by matching.

^cAdditionally adjusted for prior use of second-generation antipsychotics, current use of NSAID, history of hypertension, history of diabetes, and educational achievement.

^dAnticonvulsants 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.
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.

ACKNOWLEDGEMENTS
The authors want to thank Mr. Lars Christian Lund, MD (University of Southern Denmark) for valuable help with data management. This study was partially funded by two grants: one from the Beckett Foundation (no. 42282) and one from the Hede-Nielsen Family Foundation (no ref. number).

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.

ORCID
Mikkel Højlund https://orcid.org/0000-0002-5786-5203
Jane Sterndorff Winkel https://orcid.org/0000-0001-9406-5590
Mads Nybo https://orcid.org/0000-0002-3029-2855
Jesper Hallas https://orcid.org/0000-0002-8097-8708
Daniel Pilsgaard Henriksen https://orcid.org/0000-0003-1303-6195
Per Damkier https://orcid.org/0000-0003-0591-7187

REFERENCES
1. Shorter E. The history of lithium therapy. *Bipolar Disord.* 2009;11(Suppl 2):4-9. doi:10.1111/j.1399-5618.2009.00706.x
2. Belmaker RH. Bipolar disorder. *N Engl J Med.* 2004;351(5):476-486. doi:10.1056/NEJMra035534
3. Goodwin GM, Malhi GS. What is a mood stabilizer? *Psychol Med.* 2007;37(05):609. doi:10.1017/S0033291706009305
4. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry.* 2013;14(3):154-219. doi:10.3109/15622975.2013.770551
5. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: A systematic review and meta-analysis. *Lancet.* 2012;379(9817):721-728. doi:10.1016/S0140-6736(11)61516-X
6. Vestergaard SV, Christiansen CF, Thomsen RW, Birm H, Heide-Jørgensen U. Identification of patients with CKD in medical databases: A comparison of different algorithms. *Clin J Am Soc Nephrol.* 2021;16(4):543-551. doi:10.2215/CJN.15691020
7. Perazella MA. Pharmacology behind Common Drug Nephrotoxicities. *CJASN.* 2018;13(12):1897-1908. doi:10.2215/CJN.00150118
8. Minay J, Paul R, McGarvey D, et al. Lithium usage and renal function testing in a large UK community population: a case-control study. *Gen Hosp Psychiatry.* 2013;35(6):631-635. doi:10.1016/j.genhosppsych.2012.10.016
9. Van Alphen AM, Boschild TM, Kupka RW, Hoekstra R. Chronic kidney disease in lithium-treated patients, incidence and rate of decline. *Int J Bipolar Disord.* 2021;9(1):1. doi:10.1186/s40345-020-00204-2
10. Close H, Reilly J, Mason JM, et al. Renal failure in lithium-treated bipolar disorder: A retrospective cohort study. *PLoS One.* 2014;9(3):e90169. doi:10.1371/journal.pone.0090169
11. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: A retrospective analysis of laboratory data. *Lancet.* 2015;386(9992):461-468. doi:10.1016/S0140-6736(14)61842-0
12. Clos S, Rauchhaus P, Seyern A, Cochrane L, Donnan PT. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: A population-based cohort study. *Lancet Psychiatry.* 2015;2(12):1075-1083. doi:10.1016/S2215-0366(15)00316-8
13. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: A nationwide population-based study. *JAMA Psychiat.* 2015;72(12):1182-1191. doi:10.1001/jamapsychiatry.2015.1834
14. Schoretsanitis G, Filippis R, Brady BM, Homan P, Suppes T, Kane JM. Prevalence of impaired kidney function in patients with long-term lithium treatment: A systematic review and meta-analysis. *Bipolar Disord.* Published online November 23, 2021. bdi.13154. doi:10.1111/bdi.13154
15. Henriksen DP, Damkier P, Hallas J, Nybo M. Sixteen years of creatinine measurements among 460 000 individuals-The Funen Laboratory Cohort (FLaC), a population-based pharmacoepidemiological resource to study drug-induced kidney disease. *Basic Clin Pharmacol Toxicol.* 2019;124(5):582-590. doi:10.1111/bcpt.13167
16. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish national patient registry: A review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

17. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish national prescription registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213

18. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22-25. doi:10.1177/1403494810387965

19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

20. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;39(7_suppl):91-94. doi:10.1177/1403494810394715

21. Henriksen DP, Rasmussen L, Hansen MR, Hallas J, Pottegård A. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. *PLoS ONE*. 2015;10(10):e0140197. doi:10.1371/journal.pone.0140197

22. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1-150. doi:10.1038/kisup.2012.77

23. Stevens LA, Schmid CH, Greene T, et al. Comparative Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study Equations for Estimating GFR Levels Above 60 mL/min/1.73 m2. *Am J Kidney Dis*. 2010;56(3):486-495. doi:10.1053/j.ajkd.2010.03.026

24. Labrecque JA, Hunink MMG, Ikram MA, Ikram MK. Do Case-Control Studies Always Estimate Odds Ratios? *Am J Epidemiol*. 2021;190(2):318-321. doi:10.1093/aje/kwa1167

25. WHOCC. ATC/DDD Index. Accessed November 15, 2021. https://www.whocc.no/atic_ddi_index/

26. de Groot T, Doty R, Damen L, et al. Genetic background determines renal response to chronic lithium treatment in female mice. *Physiol Genomics*. 2021;53(9):406-415. doi:10.1152/physiolgenomics.00149.2020

27. Fang Y, Chen B, Liu Z, et al. Age-related GSK3β overexpression drives podocyte senescence and glomerular aging. *J Clin Invest*. 2022;132(4):e141848. doi:10.1172/JCI141848

28. Højlund M, Lund LC, Herping JLE, Haastrup MB, Damkier P, Henriksen DP. Second-generation antipsychotics and the risk of chronic kidney disease: A population-based case-control study. *BMJ Open*. 2020;10(8):e038247. doi:10.1136/bmjopen-2020-038247

29. Vart P, Gansevoort RT, Joosten MM, Bültmann U, Reijnveld SA. Socioeconomic disparities in chronic kidney disease: A systematic review and meta-analysis. *Am J Prev Med*. 2015;48(5):580-592. doi:10.1016/j.amepre.2014.11.004

30. Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. *Nat Rev DisPrimers*. 2017;3(1). doi:10.1038/nrdp.2017.88

31. Nielsen RE, Kessing LV, Nolen WA, Licht RW. Lithium and renal impairment: A review on a still hot topic. *Pharmacopsychiatry*. 2018;51(05):200-205. doi:10.1055/s-0043-125393

32. Nolen WA, Licht RW, Young AH, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. *Bipolar Disord*. 2019;21(5):394-409. doi:10.1111/bdi.12805

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.