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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1. Details on data from the four registers

The Medicinal Product Statistics contains data on all prescribed medication purchased at pharmacies from January 1, 1995 and onwards. Information on indication for the drug is not available.

The Danish Medical Register on Vital Statistics contains dates of death.

The Danish National Hospital Register contains data on all patients treated at all somatic hospitals as in- or outpatients in Denmark from January 1, 1977 and onwards as a part of the official Danish health survey. Likewise, all psychiatric admissions have been registered in a nationwide register, The Danish Psychiatric Central Register from 1 April 1970 and onwards. Since 1 January 1994 the ICD-10 has been in use in both registers.

The Danish National Register on Regular Dialysis and Transplantation includes information on start of dialysis and date of renal transplantation from 1994 to 2013. This registry holds information on all patients actively treated for end-stage CKD with either dialysis or transplantation. Only patients with a need of at least 3 months of renal replacement therapy are included in the registry, thereby excluding acute reversible renal failure. The completeness and validity of the registry has recently been confirmed to be highly acceptable.

eAppendix 2. Outcome measures

Definite CKD includes the following ICD-10 diagnoses:

Possible CKD in addition includes the following ICD-10 diagnoses:
N00: glomerulonephritis acuta, N01: glomerulonephritis acuta progressive, N03: glomerulonephritis chronica, N04: Nephrosis, N05: glomerulonephritis non specificata, N06: Proteinuria monosymptomatica cum laesione morphologica specificata, N9.8: glomerulonephropathia in morbis alibi classificatis (in relation to other medical illness), N17: Nephropathia tubulointerstitialisacuta.

eAppendix 3. Sensitivity analyses and calculations of cumulative incidences of definite CKD

Sensitivity analyses were performed in cohort 1 excluding employment status, excluding all other kinds of medication, and excluding anticonvulsants, antipsychotics and antidepressants.
Modifications of linear trends of cumulative lithium exposure were analyzed using likelihood ratio tests in relation to a diagnosis of bipolar disorder, sex, age above 50, employment status and ever previous treatment with anticonvulsants.

Additional post hoc analyses were made on selected anticonvulsants. In these analyses, prescription history was categorized into four groups (0, 1-2, 3-19, >20).

For cohort 2, cumulative incidences of definite chronic kidney disease (narrow definition) were computed stratified to ever versus never exposed to lithium treatment at selected ages using the Aalen-Johansen method and accounting for the competing risk of death without chronic kidney disease. Similar figures were presented stratified for ever versus never exposure to anticonvulsants at selected ages.

eAppendix 4. Characteristics of cohort 1

Cohort 1 comprised data from 1,800,591 persons (877,273 men and 923,318 women) aged between 0 years and 110 years (median 40 years, IQR 23-58 years). Within the limitations of the study period (start: January 1st, 1995, end: kidney disease, death or December 31, 2012) 26,731 patients started treatment with lithium (age at first prescription: median=48 years, IQR=23-58) and 420,959 patients started treatment with anticonvulsants (age at first prescription: median=48 years, IQR=23-58). The main analysis included in total 23,376,108 person years at risk of which 1% were exposed to lithium and 11.4% were exposed to anticonvulsants.

eAppendix 5. Characteristics of cohort 2

Cohort 2 included 10,591 patients with a main diagnosis of a single manic episode/bipolar disorder at first psychiatric contact (as inpatients or outpatients) as recorded in the Danish Psychiatric Central Register (4,392 men and 6,199 women) aged between 8 years and 100 years (median 53 years, IQR 39-65 years). Within the limitations of the study period (start: January 1st, 1995, end: kidney disease, death or December 31, 2012) 6,060 patients started treatment with lithium (age at first prescription: median=53 years, IQR=39-65) and 6,173 patients started treatment with anticonvulsants (age at first prescription: median=51 years, IQR=39-65). The main analysis included in total 81,135 patient years at risk of which 60.9% were exposed to lithium and 49.5% were exposed to anticonvulsants. The number of patients not receiving “other kinds of psychotropic as well as somatic medication” was too small for including this variable.

eAppendix 6. Potential pathogenetic mechanisms involved in the association between bipolar disorder and CKD

The association between bipolar disorder and CKD may, at least in part, involve life style factors, such as smoking, increased alcohol consumption and decreased physical activity, as well as increased somatic comorbidity. Metabolic syndrome, diabetes,
hypertension and cardiovascular disease are associated with both bipolar disorder\textsuperscript{11-17} as well as with CKD.\textsuperscript{18,19} Further, theoretically, genes common for bipolar disorder and kidney disease could explain the increased comorbidity. In accordance with our finding, schizophrenia has been associated with increased risk of CKD after adjustment for somatic comorbidity and use of antipsychotics.\textsuperscript{20} From a biological viewpoint, endothelial dysfunction may be involved in the pathogenesis of diabetes, hypertension and hyperlipidaemia\textsuperscript{21} and in the underlying pathophysiological mechanisms of CKD.\textsuperscript{22} Alteration of the endothelial function may also play a role in schizophrenia\textsuperscript{23} and bipolar disorder.\textsuperscript{24}

eAppendix 7. Potential pathogenetic mechanisms involved in the association between anticonvulsants and CKD

The effects of treatment with anticonvulsants may interact biologically with the effects of unhealthy life factors and somatic comorbidity and in this way increase the risk of developing kidney disease.\textsuperscript{18} It is likely that a variety of synergistic mechanisms contribute to chronic kidney disease in patients continuing use of lithium or anticonvulsants, including aging, cardiovascular factors, oxidative stress, inflammation, nephrogenic diabetes insipidus, acute kidney injury, and medication interactions.\textsuperscript{25} It is also possible that drugs may interact on genes common for bipolar disorder and kidney disease although this hypothesis has never been investigated.

eAppendix 8. Limitations in prior larger controlled studies

Results from previous studies are limited by (1) unsure start and duration of lithium treatment,\textsuperscript{26-28} (2) recall bias, as data on lithium have been partly based on recall from patients,\textsuperscript{26} (3) selected samples of patients (e.g., the first UK study included data from general practitioners but not from secondary care such as psychiatric and nephrology clinics,\textsuperscript{27} (4) no data on psychiatric diagnosis,\textsuperscript{26,28} limited data on somatic illnesses and medication,\textsuperscript{26,28} and no information on the use of other psychotropics,\textsuperscript{26,28} and (5) overestimation of risks of chronic kidney disease, especially among older individuals, as the competing risk of death without chronic kidney disease has not been considered.\textsuperscript{26-28}

A meta-analysis of lithium and the risk of renal failure is presented by McKnight et al.\textsuperscript{29}

eReferences


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