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Lithium toxicity following co-prescription of lithium and ACEI/ARBs: A population-based cohort study

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

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Abstract

Guidelines caution against co-prescribing angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) together with lithium, as this may increase lithium levels leading to toxicity. We conducted a population-based retrospective cohort study using administrative health data in Ontario, Canada, to evaluate the 90-day risk of any hospital encounter with lithium toxicity, all-cause mortality, and all-cause hospitalization in chronic lithium users newly prescribed an ACEI or ARB between 2002 and 2021. Modified Poisson regression was used to estimate risk ratios (RR). ACEI/ARB use versus non-use was not associated with a higher 90-day risk of lithium toxicity (2.20% vs. 1.75%, risk ratio [RR] 1.25, 95% confidence interval [CI] 0.86-1.84), and was associated with a lower risk of 90-day all-cause mortality (0.75% vs. 2.05%, RR 0.36, 95% CI 0.22-0.61). While there are potential concerns about confounding in this analysis, these findings suggest that warnings in guidelines and drug monographs against using ACEIs and ARBs with lithium may be unwarranted.

Keywords: angiotensin converting enzyme inhibitor, angiotensin receptor blocker, lithium toxicity, administrative data, cohort study

Summary for Lay Audience

Lithium is a medication commonly used for the treatment of various psychiatric disorders, such as bipolar disorder. Lithium users are at risk of lithium toxicity if they use other drugs that impair lithium's elimination from the body. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are two classes of drugs used to treat high blood pressure and some types of heart and kidney diseases. ACEIs and ARBs are among medications that are suspected to cause lithium toxicity in chronic lithium users, based on case reports and case series. We used health administrative databases to examine adult chronic lithium users who were prescribed an ACEI/ARB and we assessed lithium toxicity. We found that in the first 90 days after being prescribed an ACEI/ARB, patients did not have a higher risk of lithium toxicity compared to a similar group of people not taking ACEI/ARBs. We suggest that the safety warnings and concerns about co-prescription of lithium and ACEI/ARBs and the risk of lithium toxicity might be revisited.

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Contents

List of Figures

List of Tables

List of Appendices

List of Abbreviations

- **ACEI** Angiotensin Converting Enzyme Inhibitor
- **ARB** Angiotensin Receptor Blocker
- **ADR** Adverse Drug Reaction
- **NSAIDs** Non-steroidal Anti-inflammatory Drugs
- **GFR** Glomerular Filtration Rate
- **eGFR** estimated Glomerular Filtration Rate
- **ICES** Institute for Clinical Evaluative Sciences
- **ODB** Ontario Drug Benefits Database
- **OLIS** Ontario Laboratories Information System
- **ICD** International Classification of Disease
- **CKD-EPI** Chronic Kidney Disease Epidemiology Collaboration
- **CI** Confidence Interval
- **RR** Risk Ratio

Introduction

Lithium is a mood-stabilizing medication used to treat various psychiatric disorders especially bipolar disorder. Canadian practice guidelines recommend lithium as a first-line medication to treat bipolar disorder. Bipolar disorder is a psychiatric condition primarily characterized by episodes of mania and depression. (1).

Lithium is linked with a high probability of adverse drug reactions (ADR) since it has a narrow therapeutic index. Therefore, conditions that increase serum lithium levels may increase the risk of lithium toxicity. This particularly applies to concurrent use of other medications (2, 3). ACEIs (Angiotensin-Converting Enzyme Inhibitors) and ARBs (Angiotensin Receptor Blockers) are two drug classes that may cause elevations in serum lithium levels.

The interaction between lithium and ACEI/ARBs on the risk of lithium toxicity is described in at least 15 case reports (4–19). There are several mechanisms by which concurrent use of these medications can lead to decreased lithium clearance and a higher risk of lithium intoxication (described in section 1.5.1).

We conducted a population-based, retrospective, cohort study in patients taking lithium chronically to determine whether new ACEI/ARB use associates with a higher 90-day risk of lithium toxicity compared with non-use.

1.1 Bipolar disorder

Bipolar disorder is a chronic mood disorder characterized by alternating episodes of mania and depression (20). The disease starts with a presentation of an acute episode of mania or depression (21, 22). In the manic phase, patients present with an elevated and irritable mood, increased energy and activity, and decreased sleep (21, 22). Mania has a sudden onset and often lasts several weeks to months (23). A depressive phase is characterized by a significant change in mood, energy, and sleep. Patients slow in their mental and physical activities and have less energy. (22). Depression may have a sudden or slow onset that lasts for several months (23).

Patients with bipolar disorder frequently experience disruptions in mood (21). Therefore, if the disease is left untreated, patients will struggle to maintain employment and interpersonal relationships (24–26). Furthermore, one-third to one-half of bipolar patients attempt suicide (27), and the risk of death by suicide in this population is estimated to be 20 times higher than the general population (27).

The prevalence of the bipolar disorder is estimated to be between one and two percent in Canada (28), which aligns with the disorder's worldwide prevalence. According to a worldwide survey study published in 2011, bipolar disorder has a lifetime prevalence of one percent, and 2.4 percent if subthreshold types are also considered (29). Bipolar disorder is a lifelong disease (20) that primarily manifests at an average age of 25 years (1). When the first acute episode occurs at an age of 50 years or older, it is referred to as older-age bipolar disorder (OABD) (30)

1.2 Treatment of bipolar disorder

Pharmacological treatment is fundamental for successfully managing patients with bipolar disorder (31). Pharmacotherapy plus psychosocial interventions in euthymia (i.e. when patients enter a remission phase after presenting with an acute phase of mania or depression) can

decrease the risk of relapse and reduce the number and duration of hospital admissions (20). Pharmacotherapy, which is the mainstay for the treatment of bipolar disorder (32) consists of a mood stabilizer alone or in combination with an antipsychotic or antidepressant (20). In addition to lithium, three anticonvulsant medications, valproate, carbamazepine, and lamotrigine, are mood-stabilizing medications (31).

1.2.1 Acute phase management

The primary goal of treating acute episodes of a bipolar disorder is to control the symptoms to ensure the safety of the patient and the people around them, and to return patients back to their normal level of psychosocial function (20, 21). Mood stabilizers and antipsychotics are the mainstays of managing acute bipolar mania and depression (20). According to the latest Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines for the management of patients with bipolar disorder, lithium and valproate should be the first choices for the acute management of mania (1). The guidelines also recommend lithium (preferably) or lamotrigine for the treatment of acute bipolar depression (1, 21). These recommendations for first-line medications were developed based on the strength level of the evidence for efficacy, as well as safety and tolerability issues (1).

1.2.2 Long-term management (maintenance treatment)

Considering the chronic nature of bipolar disorder, almost all patients need maintenance treatment to prevent subsequent episodes, reduce residual symptoms, reduce the risk of suicide, and restore functioning and quality of life (1, 21). This preventive strategy combines pharmacological, psychological, and lifestyle approaches starting from the first episode (20). Lithium and valproate have the best empirical evidence for use as maintenance treatment (1, 21).

1.3 Lithium

Although lithium is effective in treating acute episodes, its primary value is in the long-term management of bipolar disorder (33). Based on the available clinical practice guidelines, lithium remains the "gold standard" treatment for preventing recurrences in bipolar disorder (33, 34). Evidence also supports lithium's considerable effectiveness in preventing suicidal behaviour in this population (33).

1.3.1 Lithium dosing and serum levels

Since lithium has a narrow therapeutic index (i.e. a small difference between the minimum effective concentrations and minimum toxic concentrations in blood), it is crucial to maintain serum lithium levels within a specific range. By keeping lithium levels in this range, a balance between effectiveness and adverse effects can be achieved (35).

Lithium is usually started at low doses, such as 300 mg three times daily, with the dose titrated up to achieve serum lithium levels between 0.5 and 1.2 mmol/L based on the clinical response and adverse effects. Steady-state levels are reached about five days after lithium administration (21). Therefore, it is recommended to check serum lithium levels within five days of initiation, dose change, or concomitant medication change until two consecutive levels are within the therapeutic range. Serum lithium levels should be checked every three to six months thereafter (34). Most clinical practice guidelines for treating bipolar disorder recommend serum lithium levels between 0.6 to 0.8 (or 1.0) mmol/L during maintenance treatment (34). Elderly patients might need lower lithium levels (and consequently lower doses of lithium) to achieve therapeutic effects (36).

1.3.2 Monitoring lithium treatment

In addition to monitoring serum lithium levels during maintenance treatment, the general medical history of patients should be reviewed before starting lithium. Special attention should be given to organs that may affect or be affected by lithium, including renal, thyroid, and cardiac function. Pregnancy and dermatologic disorders should also be considered before starting lithium (21). During the first six months of lithium treatment, renal function should be tested every 2–3 months, and thyroid function should be evaluated once or twice. Renal and thyroid function may be checked every six months to one year thereafter in stable patients (21).

1.4 Angiotensin Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

Renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood pressure by managing blood volume, and arterial tone (37). The cascade in this system starts with the secretion of renin from the kidneys in response to various stimuli, such as hypotension. Renin catalyzes the conversion of angiotensinogen to angiotensin I in the circulating blood. In the next step, the angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II induces the secretion of aldosterone from the adrenal gland. Excessive levels of angiotensin II and aldosterone can lead to arterial hypertension, heart remodelling, and kidney damage (38). On the basis of these physiologic considerations, inhibition of RAAS is a target in the treatment of hypertension, heart failure, and chronic kidney disease (37). Angiotensin-converting enzyme inhibitors inhibit the synthesis of angiotensin II, while angiotensin receptor blockers block the function of angiotensin II by blocking its action on corresponding receptors.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly indicated for the treatment of heart failure (39, 40), hypertension (41, 42), and

kidney diseases (43). Several studies demonstrated ACEIs' and ARBs' effect in decreasing mortality and morbidity in these patient populations (44–46).

1.5 Lithium toxicity

Lithium toxicity usually occurs when the concentration of serum lithium rises above the therapeutic range. In most patients, symptoms of toxicity appear when serum lithium levels exceed 1.5 mmol/L (33, 47). Neurological symptoms such as confusion, drowsiness, slurred speech, psychomotor slowing, ataxia, hyperreflexia, and coarse tremors are predominant symptoms of lithium toxicity. In severe cases of toxicity, seizures, coma and death may occur (48, 49).

Annual reports of the American Association of Poison Control Centers' National Poison Data System (NPDS) reveal almost 7000 cases of lithium toxicity per year (50, 51). A study in Ontario also estimated that nearly four percent of chronic lithium users had at least one hospital encounter with lithium toxicity within nine years of study duration (2). Lithium toxicity occurs in acute and chronic settings. Acute toxicities occur when a large amount of lithium is ingested at once. Chronic lithium toxicity occurs in chronic lithium users when the elimination of lithium from the body decreases leading to drug accumulation (52, 53). While the number of acute lithium toxicities registered in poison centres is much larger than chronic toxicity cases, chronic intoxications are more severe and more complicated (48, 52).

Lithium is not metabolized in the human body and is excreted almost completely by the kidneys (35). Several conditions have been shown to be probable risk factors for lithium toxicity. Main risk factors include: older age, female sex, decreased kidney function (referred to as chronic kidney disease), hypovolemia and concurrent use of diuretics, NSAIDs and possibly ACEI/ARB (the focus of this study). (2, 3, 53–55)

1.5.1 ACEI/ARB-induced lithium toxicity

There are several mechanisms to explain the higher risk of lithium toxicity with ACEI/ARB use. One mechanism is the inhibition of angiotensin II by preventing its synthesis (by ACEIs) or function (by ARBs). Angiotensin II is a substance that helps increase intraglomerular pressure by causing vasoconstriction in efferent arterioles in the kidneys. This pressure is needed to maintain a proper glomerular filtration rate (GFR). When ACEI/ARBs inhibit angiotensin II, intraglomerular pressure and the subsequent GFR will decrease. Since lithium is almost exclusively eliminated from the human body by filtration through the kidneys, a lower GFR will decrease lithium clearance and lead to drug accumulation in the body (2, 4, 56, 57). The change in GFR caused by ACEI/ARBs might not have consequences in a normal kidney, but a kidney with reduced function is more dependent on angiotensin II for producing an acceptable GFR (4). Patients on chronic lithium therapy are at risk for developing lithium-induced nephropathies (58), making them more susceptible to a lack of angiotensin II. (19).

Another suggested mechanism is the inhibition of aldosterone synthesis by ACEIs and ARBs. Aldosterone is a hormone responsible for sodium reabsorption in human kidney tubules. A lack of aldosterone caused by ACEIs and ARBs will result in sodium depletion. Since the transporters accountable for exchanging sodium in the proximal and distal tubules and collection duct also transport lithium through cell membranes, sodium depletion can cause compensatory reabsorption of lithium, and less lithium clearance. (2, 56, 57).

Angiotensin II also has dypsogenic effects. While lithium users mostly suffer from polyuria, a lack of angiotensin II can impair thirst response, contributing to dehydration and lithium toxicity (56, 57).

1.6 Other mood stabilizers' toxicity

The other medications used to treat bipolar disorder are also associated with side effects.

Hepatotoxicity is the most serious adverse event associated with valproate. Monitoring is required for hematologic abnormalities, including low platelet count, low white blood count, and, in some cases, bone marrow suppression during valproate therapy (31). Lamotrigine, which is overall the best-tolerated medication in this class, can cause a rash like the Stevens-Johnson rash, which is a life-threatening situation (31).

Carbamazepine is associated with reduced tolerability during rapid dose titration, and its potential for interaction (as a strong cytochrome enzyme inducer) with other psychiatric and nonpsychiatric medications. Carbamazepine also has an FDA boxed warning for agranulocytosis, and aplastic anemia (31). When all efficacy, safety, and tolerability parameters are considered, lithium remains the preferred choice among mood stabilizers (1).

Literature Review

2.1 Search strategy and quality assessment of prior studies

We reviewed Medline (1946 to June 2022) and Embase (1947 to June 2022) databases to find the studies investigating the risk of lithium toxicity after initiating ACEI/ARBs. For both databases, the search strategy consisted of keywords such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and lithium. The complete search strategy is included in Appendix B.

We looked for clinical trials and population-based studies. The studies were included if they had investigated an association between the addition of an ACE/ARB to lithium and the risk of toxicity or adverse effects as a primary or secondary outcome. We also captured studies investigating the association of the co-prescription on lithium clearance and serum lithium levels. For quality assessment of the included studies, the Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies (59) was used (see Appendix A)

2.2 Summary of previous literature

Five studies met our criteria for inclusion. These studies include one pharmacokinetic study in healthy subjects, one cross-sectional study, and three case-control studies of chronic lithium users. Outcomes assessed were serum lithium levels, lithium clearance, and hospital admissions due to lithium toxicity. Study descriptions and limitations are summarized in Table 2.1. Quality assessment of the studies showed good quality scores (21 and 20) for two studies (2, 56), and fair quality scores (15, 18, and 19) for the other three studies (60–62).

2.3 Co-prescription of ACEI/ARB and lithium, and the risk of lithium toxicity

The first study assessing the probable effect of ACEI/ARBs on serum lithium levels was conducted in 1992. Dasgupta et al. (60) conducted a pharmacokinetic study on healthy human subjects after some case reports were published claiming the occurrence of lithium toxicity due to initiation of ACEI/ARBs (6, 17, 18). The study concluded that there was no statistically significant difference between the lithium levels of the subjects before and after initiation of enalapril (an ACEI). Later in 1996, a case-control study on 20 chronic lithium users showed an almost 25% decrease in estimated lithium clearance after initiating an ACEI, which was both clinically and statistically significant (56).

One case-control and one cross-sectional study assessed the association between co-prescription of potentially interacting medications with lithium and serum lithium levels. Wilting et al. and Scherf-Clavel et al. could not find a statistically significant association between lithium levels and co-prescription of ACEI/ARBs (61, 62). However, another case-control study investigating the clinical relevance of the possibly interacting medications with lithium found that among elderly lithium users who experience a hospital admission with lithium toxicity, the risk of

toxicity is most significant after the start of treatment with ACEIs or loop diuretics (2). The risk of hospitalization with lithium toxicity was estimated to be 7.6 times higher in those who started an ACEI within 28 days before the admission date (2).

There are also many case series and case reports in the literature describing the impact of ACEIs or ARBs on lithium toxicity (4–10, 19). However, Hommers et al. reported a case series of successful ACEI treatments without toxicity in chronic lithium users (63).

The conflicting findings from prior studies highlight the need for better evidence on this topic. Better information would inform better prescribing, with the goal of avoiding unnecessary patient harm.

Table 2.1. Literature summary of five published studies assessing the risk of lithium toxicity, increase in serum lithium levels or decrease in lithium clearance in patients receiving lithium and ACEIs or ARBs together

Author (year)	Study description	Results		Limitations	Quality score[a]
Dasgupta et al. (1992) (40)	A pharmacokinetic study on healthy human subjects. In a 26-day outpatient study, **nine healthy** men took lithium for 10 days, lithium and enalapril for 10 days, and lithium alone again for 6 days. Serum lithium levels were measured as outcomes.	There were **no statistically significant** differences between mean serum lithium levels during treatment with lithium alone and during treatment with the lithium/enalapril combination. However, one subject showed a 31% increase in serum lithium level after enalapril was added.		Recruiting **healthy** subjects. Used a low dose of both lithium and enalapril for a short period.	15
Finley et al. (1996) (36)	A case-control study. **20 Patients** clinically stabilized on lithium before ACE inhibitor exposure (captopril, enalapril, or lisinopril), had at least one inpatient steady-state *lithium concentration* (or two outpatient concentrations)during the year before ACE inhibitor therapy; and (3) had at least one inpatient (or two outpatient) steady-state lithium concentration between14 and 365 days after initiation of ACE inhibitor therapy. Concurrent users of the medications known to affect lithium's pharmacokinetic	The mean steady-state lithium concentration was 0.64 mEq/liter before ACE inhibitor therapy and 0.86 mEq/liter after initiation. The estimated lithium clearance was **decreased** by 25.6% overall, a trend that was **both clinically and statistically significant (p < 0.0001)**. Four of the 20 patients displayed symptoms consistent with lithium toxicity after receiving an ACE inhibitor (e.g., increased tremor, ataxia, confusion).		Small sample size	21

	disposition (e.g., thiazide diuretics, theophylline, nonsteroidal anti-inflammatory agents) were excluded. 1) lithium serum concentrations; 2) estimated lithium clearance values; and (3) signs and symptoms of lithium toxicity before and after initiation of ACE inhibitor(s) were the outcomes. Paired Student's t-test and Wilcoxon's signed rank test to compare to assess differences before and after ACEI. Regression analysis for assessing the effect of confounders on the lithium clearance.	The time course of the interaction appears to be delayed in nature. In three study subjects, lithium concentrations were determined frequently during the first month of combination therapy. These concentrations remained stable for the first few weeks and rose dramatically thereafter.			
Juurlink et al. (2004) (2)	Population-based nested case-control study of multiple linked healthcare databases over 10 years (January 1, 1992, to December 31, 2001) in Ontario. Among elderly chronic lithium users. Exposure**:** Prescriptions for any diuretic (alone or in combination with another agent), an ACE inhibitor, or any prescription NSAID (including selective cyclooxygenase-2 inhibitors) before the date of toxicity.	During the 10-year study period, 413 patients were admitted to the hospital with lithium toxicity (out of 10615 lithium users). **RR (95%CI) of lithium toxicity** and new use of ACEI was **7.6 (2.6–22.0) if ACEI** was dispensed 28 days before and **6.1 (1.7–21.7)** if ACEI was dispensed 14 days before the index date (adjusted for confounders including adjusting for use of other interacting meds).		Cases were only patients admitted to a hospital (not ED and outpatient visits). Misdiagnose during hospitalization, and miscoding tends to attenuate these observations. The sample size was small, and estimates were imprecise. Administrative data were used, and	20

	Cases: Patients hospitalized with lithium toxicity Four controls were matched to the cases in age, sex, and continuous use of lithium on the index date (date of toxicity). Outcome: the odds ratio obtained from conditional logistic regression was used to estimate the relative risk and 95% confidence interval hospital admission for lithium toxicity.	The risk of toxicity appeared to be greatest after the start of treatment with ACE inhibitors or loop diuretics.		therefore there was no direct measure of compliance, lithium levels, or nonprescription drugs (possibly including some NSAIDs). The data include no direct measure of renal function. Only patients aged 66 and older were studied, and the findings may not be generalizable to younger patients.	
Wilting et al. (2005) (42)	Multicentre retrospective case–control study was conducted among patients receiving long-term treatment with lithium for whom lithium serum concentrations were under hospital laboratory control, during the time period of January 1997 until January 2003 (51 cases and 51 control). patients were at least **1**8 years of age and on lithium treatment for at least 3 months. To be eligible for participation all participants (cases and controls) had to have at least two subsequent lithium serum concentrations within the therapeutic range (0.6–1.2 mmol/L). From this study base	5.9% of controls vs. 7.8% of cases were RAS inhibitor users (which was **not a significant difference)**. The only important exposure resulting lithium elevated levels was exposure to antobiotics: Probably not because of the antibiotic itself, but as a result of infection (fever and dehydration).		Data was gathered on elevated lithium serum levels only and no data on the actual appearance of (toxic) side-effects of lithium. No access to information on possible concomitant use of over-the-counter medication. The withdrawal of the potentially interacting agents could also influence lithium serum levels which was not assessed in the study.	19

	Cases: were defined as all patients with a lithium serum level of ‡1.3 mmol/L, in combination with an increase in lithium serum level of at least 50% compared with the previous lithium serum level. **Controls** had to have a lithium serum level on the case index date (±1 week) within the therapeutic range (0.6– 1.2 mmol/L). In addition, the difference between the lithium serum level on the index date and the previous lithium serum level had to be <50%. **Exposure:** NSAIDs, diuretics, RAS inhibitors and antibiotics) and theophylline. at least one year prior to the index date. Logistic regression was used for elevated lithium serum levels.			Missing data on comorbidity associated with fever and poor fluid intake could be of great importance. Stringent criteria may have resulted in the lack of enough laboratory parameters. As lithium clearance is largely influenced by disturbances in electrolyte and fluid homeostasis and renal function, missing data on laboratory parameters could be of considerable importance. Small sample size	
Scherf-Clavel et al. (2020) (41)	A retrospective study among inpatients who had serum lithium concentrations available between January 2008 and December 2015 during routine therapeutic drug monitoring (TDM). The information on co-medications was qualitatively gathered.	ACEIs and ARBs were not associated with increased lithium levelsUsing ACEIs showed 0.004 mmol/L decrease (p=0.834) in lithium levels, and using ARBs showed 0.049 mmol/L increase in lithium levels (p=0.108). **None of them were statistically significant**.		Unable to determine the time interval since when patients were receiving the drug combination.Did not consider the dose of the interacting meds and each medication separately because of the small sample size.Adherence was not	18

	The association between lithium levels and the use of interacting medications was assessed with linear regression.			assessedSome risk factors of lithium toxicity such as dehydration status was not assessed although information on sodium status was available and taken into account.	

Abbreviations: ACEI=Angiotensin-converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker, RR=risk ratio, CI=confidence interval, NSAIDs= Non-steroidal Anti-inflammatory Drugs, RAS=renin angiotensin system, TDM=therapeutic drug monitoring, ED=emergency department

[a] Modified Downs and Black checklist was used for the assessment of qualities (Appendix A). The tool was modified for question 27 in our review. It was simplified to a choice of giving either 1 or 0 points depending on whether there was sufficient power to detect a clinically important effect. We gave all included studies a score from 0 to 28, grouped into the following four quality levels: excellent (26 to 28), good (20 to 25), fair (15 to 19) and poor (14 or less).

Rationale and Research Questions

3.1 The need for research

Several guidelines, including Canadian and US guidelines (1, 64) caution on prescribing ACEI/ARBs to lithium users, and recommend close monitoring of serum lithium levels when these medications are added to patients' drug regimen. Although there is a considerable number of case reports in the literature that report lithium toxicity after ACEI/ARB co-prescriptions, the evidence from research studies is inconsistent.

As described earlier, on the one hand, lithium is one of the best choices available for the treatment of bipolar disorder that should be used lifelong. On the other hand, ACEI/ARBs are commonly used medications for various cardiovascular diseases. Some of these diseases, such as hypertension, have a very high prevalence (23% in Canada) (65), which will result in co-prescribing lithium and ACEI/ARBs in a large population. To better understand the safety of co-administration of lithium and ACEI/ARBs, we conducted a population-based study in older adults to investigate the 90-day risk of a hospital encounter with lithium toxicity, all-cause hospitalization, and all-cause mortality in chronic lithium users who recently started ACEIs or ARBs, compared to non-ACEI/ARB users.

3.2 Research questions and hypothesis

3.2.1 Primary research question

1) Do older adults who are chronic lithium users and who are newly dispensed ACEI/ARBs, compared to patients with similar baseline characteristics who are not dispensed ACEI/ARBs, have an altered 90-day risk of a hospital encounter (hospitalization or emergency department visit) with lithium toxicity?

3.2.2 Secondary research questions

1) Do older adults who are chronic lithium users and are newly dispensed ACEI/ARBs, compared to patients with similar baseline characteristics who are not dispensed ACEI/ARBs, have an altered 90-day risk of all-cause mortality?

2) Do older adults who are chronic lithium users and are newly dispensed ACEI/ARBs, compared to patients with similar baseline characteristics who are not dispensed ACEI/ARBs, have an altered 90-day risk of all-cause hospitalization?

Methods

4.1 Study design and setting

Using Ontario's linked administrative health databases, we conducted a population-based retrospective cohort study of adults aged 50 years or older from April 1, 2002, to October 31, 2021. Ontario has over 13.4 million residents, 38.2% of whom are 50 years or older (66). The Ontario Health Insurance Plan (OHIP) is the single-payer for all Ontario residents and provides universal access to physician and hospital services. Those aged 65 years and older (16.7% of the Ontario population) are also covered by Ontario Drug Benefit (ODB) program. In addition to adults 65 years and older, the ODB program covers prescription drugs for people on social assistance (Ontario Disability Support Program or Ontario Works), people residing in homes for special care and long-term care homes, people receiving professional home care services, and registrants in the Trillium Drug Program.

Ontario administrative health databases provide a rich source of information. Using these databases can in some cases better address selection and information bias associated with prospective studies. They also allow for large sample sizes, and potentially long follow-up periods. Currently, these databases are being used extensively in population-based health outcomes research (67–70)

We conducted this study at the Institute for Clinical Evaluative Sciences (ICES), where Ontario

administrative health databases are housed. Based on section 45 of Ontario's Personal Health Information Protection Act, using the data of these databases does not need a review or approval by a Research Ethics Board. To report our results, we used the RECORD-PE guideline. This guideline is used to report observational pharmacoepidemiological studies that use collected data from electronic health records (including primary care databases, registries, and administrative healthcare claims) (71).

4.2 Data sources

We used the following eight administrative health databases housed at ICES to obtain data on patient characteristics, drug exposure, outcomes, and covariates. These databases are linked using unique encoded identifiers. All the databases used in this study had been used in previous pharmacoepidemiologic and drug safety studies (72–83).

Ontario Drug Benefits (ODB) Database: This database contains prescription dispensing information for a wide range of outpatient medications included in the ODB formulary. Prescription information in the ODB database is available for patients 65 years and older and those requiring social assistance or long-term care with a high level of accuracy (an error rate of 0.7%) (84). We used this database to define the cohort of lithium users and to identify exposure to ACEIs or ARBs. Evidence of other prescription drugs that can contribute to lithium toxicity, including diuretics, calcium channel blockers, NSAIDs and renin inhibitors, was also obtained from this database.

Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), and Same Day Surgery (SDS): The CIHI-DAD and CIHI-SDS collect patients' demographic, diagnostic and procedural information during hospitalizations and same-day surgeries. The coding of diagnoses and procedures is based on the Ninth Revision of the International Classification of Disease system (ICD-9) before 2002 and the Tenth Revision (ICD-10) after 2002. We

determined baseline comorbidities as covariates and hospital admissions with lithium toxicity as a primary outcome from CIHI databases.

National Ambulatory Care Reporting System (NACRS) database: NACRS contains data for all hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics, and emergency departments. We used this database to assess emergency department visits with lithium toxicity as a primary outcome and baseline comorbidities as covariates.

Ontario Health Insurance Plan (OHIP) database: Most physicians in Ontario submit billing claims using codes outlined in the OHIP Schedule of Benefits. These codes capture information on inpatient, outpatient, and laboratory services rendered to a patient. In addition, OHIP includes information on the physicians' specialty, the nature of the service, and diagnostic information. We used this database to obtain each patient's baseline characteristics and comorbid conditions.

Ontario Mental Health Reporting System (OMHRS) Database: OMHRS collects data on patients in adult designated inpatient mental health beds. The diagnosis codes in OMHRS are based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) definitions. We used the DSM-IV codes provided in Appendix D. In addition to data from CIHI and OHIP databases, we obtained baseline psychiatric conditions from OMHRS.

Registered Persons Database of Ontario (RPDB): The RPDB captures vital statistics, including sex, date of birth, postal code and date of death. We obtained patient demographics (age and sex), income quintiles (based on average neighbourhood incomes), and residence location (urban or rural) from RPDB. Using RPDB, we also ascertained all-cause mortality as a secondary outcome.

Canadian Organ Replacement Register (CORR): This database records the activity level and outcome of organ transplantation and renal dialysis. We used CORR to exclude kidney transplant

recipients and patients on dialysis.

Ontario Laboratories Information System (OLIS): This database includes hospital-lab and community-lab information since 2007. This information consists of both order-level information (patients' demographics and provider information) and test result information (values and units). We used OLIS to obtain serum creatinine measurements and assess kidney function. Evidence of at least one lithium level measurement in follow-up (surveillance) was also obtained from OLIS as an additional outcome. OLIS includes comprehensive records of both community-based and hospital-based laboratories.

4.3 Patients

We established a cohort of patients 50 years and older with evidence of at least one lithium prescription from April 1, 2002, to October 31, 2021. We restricted the age to 50 years and older since being 50 years and older has been shown to be a risk factor for lithium toxicity (55).

Within the defined cohort, exposed patients were those who had at least one prescription for ACEIs or ARBs. The prescription date was determined as the index date (referred to as the cohort entry date). The day supply of the closest lithium prescription prior to the index date needed to cover the index date. Moreover, to ensure that the selected patients were chronic lithium users, evidence of at least two lithium prescriptions was needed during a 210-day look-back window from the index date. Excluding the exposed patients from the first defined cohort of lithium users, we obtained the unexposed (control) group.

Patients were excluded from both groups if any of the following existed: (1) evidence of any ACEI/ARB prescription in the 180 days prior to the index date (as we wanted to only capture new users), (2) evidence of a prescription for another medication on the index date that could contribute to lithium toxicity including diuretics (thiazides, loop diuretics, and potassium-sparing diuretics), calcium channel blockers, NSAIDs and renin inhibitors, (3) evidence of a

prescription of another ACEI or ARB on the index date, (4) Evidence of end-stage renal disease (chronic dialysis or kidney transplant) prior to the index date, and (5) evidence of hospitalization or emergency department visit in 2 days prior to or on the index date to ensure that we were only capturing new outpatient prescriptions. Among exposed patients, we picked the first eligible ACEI/ARB prescription in cases of multiple eligible prescriptions since study patients could only enter the cohort once. Among unexposed patients, we picked a random lithium prescription.

4.4 Baseline characteristics

We assessed baseline comorbidities and baseline medications in the five years and 120 days prior to the cohort entry, respectively. Health care utilization was assessed with physician visits and diagnostic and screening tests in the one year prior to the index date. For patients whose serum creatinine measurements were available, we calculated baseline kidney function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that does not consider race (85). Codes for demographics and baseline characteristics are provided in Appendix D.

4.5 Matching

We used propensity score matching to eliminate systematic differences in the measured baseline characteristics of the comparison groups. Matching allowed us to form a matched set of exposed and unexposed patients with a similar probability of receiving ACEI/ARBs given a set of measured baseline covariates (86). We estimated propensity scores using a logistic regression model with 66 baseline characteristics because of their potential influence on the outcomes or segregation of patients between the comparison groups (Appendix E). After that, we matched

each ACEI/ARB user to one non-ACEI/ARB user on the logit of the propensity score (within calipers of width ± 0.2 x the standard deviation). There are several types of matching techniques including individual matching and frequency matching (87). In greedy matching, an ACEI/ARB user is first selected at random and then matched to the nearest non-ACEI/ARB user, even if that non-user would have been a better match for a subsequent ACEI/ARB user. This process is then repeated until non-ACEI/ARB users have been matched to all ACEI/ARB users or until the list of ACEI/ARB users for whom a matched non-ACEI/ARB user can be found has been exhausted (86). An alternative to greedy matching is optimal matching, in which matches are formed to minimize the total within-pair difference of the propensity score. In this study, we used greedy matching technique. We used a greedy matching over optimal matching since the evidence shows in studies using large administrative health databases this method is faster, simpler to implement, and not inferior to optimal matching regarding developing balanced groups for comparison (88). We used matching without replacement. Those without successful matches were excluded from the analyses.

We anticipated the 66 variables used for matching to be complete. We expected prescriber information would be missing in up to 25% of patients based on the results of prior studies (77, 79). For income quintile, we expected up to 0.5% of patients would have a missing value based on the results of prior studies (77, 79). The missing values were re-classified into the "income quintile 3". For location of residence, we expected up to 0.2% of patients would have a missing value based on the results of prior studies (80, 81). The missing values for the variable "rural residence" were re-classified into the "No" category.

4.6 Outcomes

Our primary outcome was a hospital encounter (hospitalization or emergency department visit) with lithium toxicity in any diagnosis field. We defined lithium toxicity with an algorithm of ICD-10 codes. Based on this algorithm, patients were considered lithium toxic if they had one

of the codes T568, T435, Y495, X41, and X49, while not having T432 during their hospital encounter (see Appendix F). Our research team validated this algorithm using lithium lab values as a reference in another study. In that study, lithium toxicity was defined as a value $\geqslant$ 1.5 mmol/L. The validation showed this algorithm has a sensitivity and specificity of 75% and 88% for lithium toxicity. Positive and negative predictive values were also estimated to be 66% and 92%, respectively.

We restricted our analysis to 90 days after the index date since the nature of the interaction between lithium and ACEI/ARBs might be delayed. In a case-control study assessing the interaction between ACEI/ARBs and lithium, based on lithium clearance values, the investigators realized that lithium levels start to increase after a few weeks following a prescription for ACEI/ARBs, while remaining constant for the first few weeks (56). Moreover, most of the case reports indicate that the symptoms of lithium toxicity present at least three weeks after the initiation of ACEI/ARBs (5, 7, 11, 14, 89). Although cases of either rapid intoxication (9, 12) and very delayed (almost six months) intoxication (16) are reported in the literature, most toxicity presents between three to five weeks following ACEI/ARB administration. (4).

As secondary outcomes, we looked at all-cause mortality and all-cause hospitalization within 90 days following the index date. We also assessed surveillance as an additional outcome, which was defined as having at least one record of a lithium level measurement within the 90 days following the index date.

4.7 Statistical analyses

We compared baseline characteristics between exposed and unexposed groups using the standardized difference. This metric describes differences between group means relative to the pooled standard deviation and is considered a meaningful difference if greater than 10% (90). The use of standardized differences is preferred over statistical hypothesis testing (using P

values) for assessing balance in baseline characteristics between propensity score matched groups (91–93). The standardized difference is not influenced by sample size (92, 93).

We estimated risk ratios (RR) and 95% confidence intervals (CI) for the primary and secondary outcomes using modified Poisson regression.

We also evaluated the association between the exposure and the outcomes in three subgroups, (1) ACEI-only users, (2) ARB-only users, and (3) patients 66 years and older. To assess the association in the first two groups, we identified ACEI-only and ARB-only users from the unmatched cohort. Then, we did the propensity score matching (as described in section 4.5) to match ACEI-only users (and ARB-only users) to non-ACEI/ARB users (unexposed cohort). Due to the small sample size for ARB-only users, we were unable to find a suitable match of unexposed users, which precluded this group from further analysis. To assess the association in the third group,we restricted our cohort to patients 66 years and older first. Then, we did the propensity score matching (as described in section 4.5) to match ACEI/ARB users to non-ACEI/ARB users (unexposed cohort).

We conducted all analyses with SAS enterprise guide version 7.1. In all outcome analyses, we interpreted two-tailed P values less than 0.05 as statistically significant.

Results

5.1 Cohort characteristics

5.1.1 Unmatched cohort

Cohort selection is presented in Figure 5.1. We identified 2,698 chronic lithium users who were newly dispensed an ACEI or ARB (exposed group) and 18,693 chronic lithium users who were not newly dispensed ACEIs or ARBs (unexposed group). Baseline characteristics before and after matching are provided in Table 5.2 and Appendix G.

The mean age of the unmatched cohort was 66 years for the exposed group and 64 years for the unexposed group. Fifty-four percent of the the exposed group and 57% of the unexposed group were women. Among the exposed group, 1,984 (73.5%) patients were ACEI users, and 714 (26.5%) patients were ARB users. The most frequent ACEI and ARB prescribed were ramipril and candesartan, dispensed to 1,152 (58% of the ACEI users) and 199 (28% of the ARB users) patients, respectively. ACEI/ARBs prescription information is provided in Table 5.1.

Prior to matching, the patients in the exposed group compared to the unexposed group had more diagnoses of chronic kidney disease (8.5% vs. 5.7%), were more likely to take thiazide diuretics (6.6% vs. 2.3%), loop diuretics (4.7% vs. 2.6%), prescription NSAIDs (6.9% vs. 5.1%), and calcium channel blockers (11.9% vs. 5.9%). Among the exposed group, ACEI or ARB was

mostly prescribed by general practitioners (71%). Prescriber information was not available for 13% of the exposed group. The information on socioeconomic status was not available for 14 (0.5%) patients of the exposed group and 94 (0.5%) patients of the unexposed group. Location of residence could not be ascertained for six (0.2%) exposed and 48 (0.3%) unexposed patients.

5.1.2 Matched cohort

A total of 2,680 exposed patients were successfully matched to 2,680 unexposed patients. The two groups were well-balanced and showed no meaningful differences in over 130 measured baseline characteristics: demographics, comorbid conditions, medications, and health care utilization (Appendix G). The mean age of the matched cohort was 66 years for the exposed and unexposed groups, and 54% of the matched cohort were women for both groups. Of 2,680 exposed patients, 1,971 (73.5%) were ACEI users, and 709 (26.5%) were ARB users. Prescriber information for the prescription of ACEI/ARBs was not available for 350 (13%) of exposed patients. General practitioners were the most frequent prescribers of ACEIs or ARBs (71%).

5.2 Main analysis

The outcomes are shown in Table 5.3. Across the entire cohort, in the 90 day follow-up period, 106 (2.0%) patients had a record of hospital encounter with lithium toxicity, 75 (1.4%) patients died, 707 (13.2%) patients were hospitalized for any reason, and 1244 (23.2%) had evidence of surveillance (at least one record of lithium level measurement).

The 90-day risk of lithium toxicity in the exposed group compared to the unexposed group was not significantly different (2.20% vs. 1.75%, RR 1.25, 95% CI 0.86-1.84, P value 0.24).

ACEI/ARB use compared to non-use was associated with a lower 90-day risk of all-cause mortality (0.75% vs. 2.05%, RR 0.36, 95% CI 0.22-0.61, P value 0.0001). The 90-day risk

of all-cause hospitalization in the exposed group compared to the unexposed group was not significantly different (12.61% vs. 13.77%, RR 0.92, 95% CI 0.8-1.05, P value 0.20).

The 90-day risk of surveillance in the exposed group compared to the unexposed group was not significantly different (23.96% vs. 22.46%, RR 1.07, 95% CI 0.97-1.18, P value 0.20).

5.3 Additional analysis

Baseline characteristics of ACEI-only users before and after matching are provided in Appendix H. The outcomes are shown in Table 5.4. The 90-day risk of lithium toxicity in ACEI-only users compared to non-ACEI/ARB users was not significantly different (2.19% vs. 1.42%, RR 1.54, 95% CI 0.96-2.54, P value 0.07).

ACEI-only use compared to non-ACEI/ARB use was associated with a lower 90-day risk of all-cause mortality (RR 0.29, 95% CI 0.16-0.52, P value <0.0001). The 90-day risk of all-cause hospitalization in ACEI-only users compared to non-ACEI/ARB users was not significantly different (13.01% vs. 13.83%, RR 0.94, 95% 0.8-1.10, P value 0.45).

The 90-day risk of surveillance in ACEI-only users compared to non-ACEI/ARB users was not significantly different (22.78% vs. 21.50%, RR 1.06, 95% CI 0.94-1.19, P value 0.33).

Baseline characteristics of patients $\geqslant$ 66 years before and after matching are provided in Appendix I. The outcomes are shown in Table 5.5. Among this population, the 90-day risk of lithium toxicity in ACEI/ARB users compared to non-ACEI/ARB users was not significantly different (2.38% vs. 1.87%, RR 1.27, 95% CI 0.77-2.08, P value 0.35).

Among patients $\geqslant$ 66 years, ACEI/ARB use compared to non-ACEI/ARB use was associated with a lower 90-day risk of all-cause mortality (RR 0.40, 95% CI 0.22-0.73, P value <0.01). The 90-day risk of all-cause hospitalization in ACEI/ARB users compared to non-ACEI/ARB users was not significantly different (14.76% vs. 14.90%, RR 0.99, 95% 0.83-1.18, P value

0.91). The 90-day risk of surveillance in ACEI/ARB users compared to non-ACEI/ARB users was significantly different (24.62% vs. 21.31%, RR 1.15, 95% CI 1.01-1.32, P value 0.04).

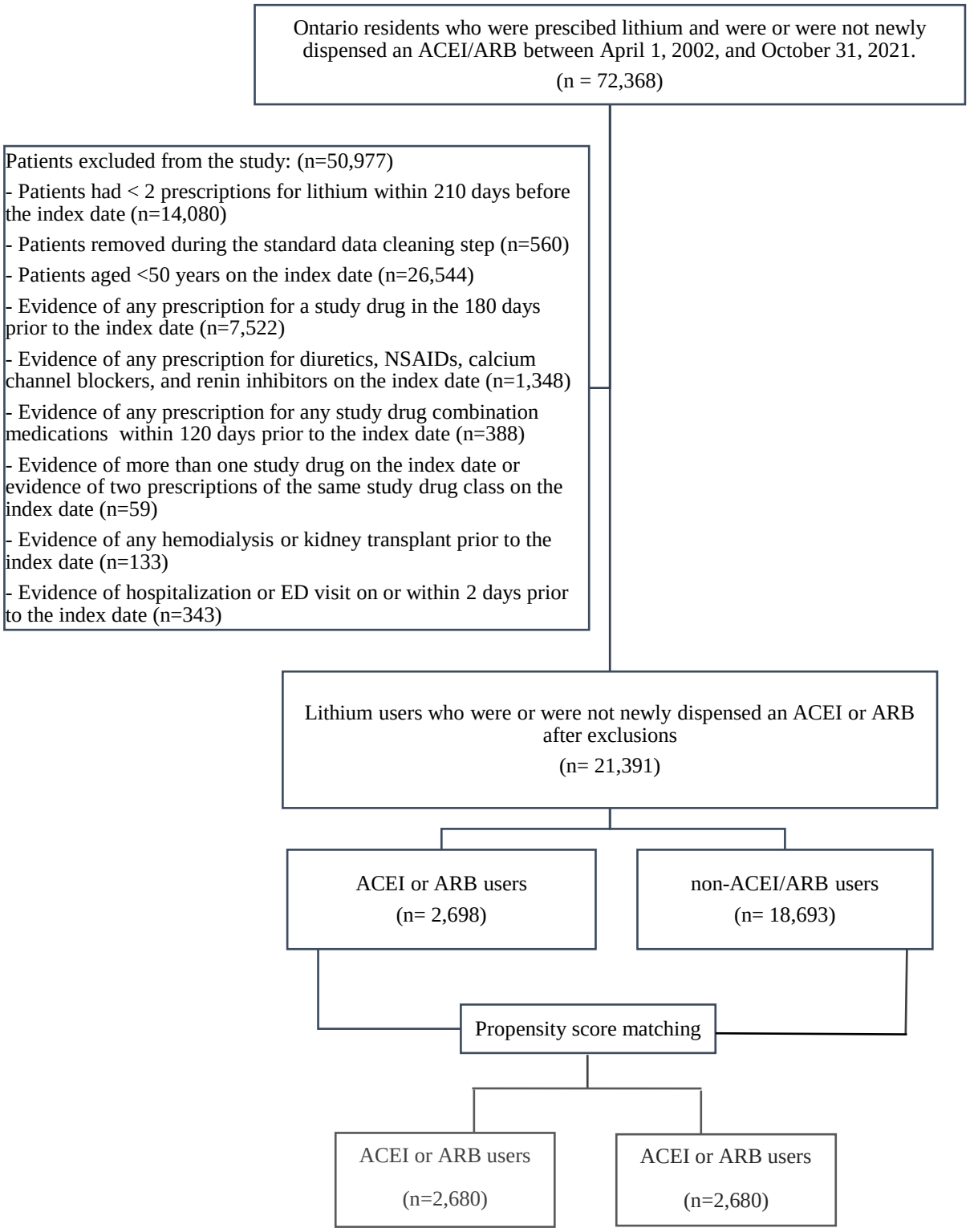

Figure 5.1. Flow diagram of the cohort build

Table 5.1. Prescription information for the exposed group[a]

ACEIs (n = 1984)	Benazepril	<6, combined with cilazapril
	Captopril	<6, combined with cilazapril
	Cilazapril	22 (1.1)[b]
	Enalapril	98 (4.9)
	Fosinopril	30 (1.5)
	Lisinopril	97 (4.9)
	Perindopril	451 (22.7)
	Quinapril	52 (2.6)
	Ramipril	1152 (58.1)
	Trandolapril	82 (4.1)
ARBs (n = 714)	Candesartan	199 (27.9)
	Eprosartan	<6, combined with irbesartan
	Irbesartan	130 (18.2)
	Losartan	73 (10.2)
	Olmesartan	42 (5.9)
	Telmisartan	159 (22.3)
	Valsartan	111 (15.5)
ACEI/ARBs prescriber information[c]	GP/FP	1908 (70.7)
	Cardiologist	137 (5.1)
	Internist	79 (2.9)
	Other	220 (8.1)

Abbreviations: GP/FP = general practitioner/family physician

[a]Data are reported as numbers (percentage)

[b]Percentages reported for each medication are the percentage in the associated drug class.

[c]Prescriber information was not available for 354 (13.1%) exposed patients

Table 5.2. Baseline characteristics of chronic lithium users who were or were not newly dispensed an ACEI/ARB before and after matching[a]

Variables	Unmatched			Matched		
	non-ACEI/ARB users (n = 18,693)	ACEI/ARB users (n = 2,698)	Standardized difference[b]	non-ACEI/ARB users (n = 2,680)	ACEI/ARB users (n = 2,680)	Standardized difference[b]
Demographics						
Age, mean (SD), years	64.2 (10.6)	66.0 (9.5)	18%	66.2 (10.4)	66.0 (9.5)	2%
Women	10671 (57.1)	1461 (54.2)	6%	1462 (54.6)	1452 (54.2)	1%
Rural residence[c]	2346 (12.6)	363 (13.5)	3%	381 (14.2)	361 (13.5)	2%
Long-term care	1792 (9.6)	120 (4.4)	20%	123 (4.6)	119 (4.4)	1%
Income quintile[d]						
1	5580 (29.9)	755 (28)	4%	755 (28.2)	752 (28.1)	0%
2	4040 (21.6)	559 (20.7)	2%	520 (19.4)	554 (20.7)	3%
3	3453 (18.5)	501 (18.6)	0%	497 (18.5)	496 (18.5)	0%
4	2820 (15.1)	460 (17)	5%	465 (17.4)	456 (17)	1%
5	2800 (15)	423 (15.7)	2%	443 (16.5)	422 (15.7)	2%
Comorbidities[e]						
Acute kidney injury	577 (3.1)	88 (3.3)	1%	92 (3.4)	88 (3.3)	1%
Alcoholism	1480 (7.9)	137 (5.1)	11%	122 (4.6)	136 (5.1)	2%
Bipolar disorder	13395 (71.7)	1931 (71.6)	0%	1912 (71.3)	1917 (71.5)	0%
Chronic kidney disease	1068 (5.7)	229 (8.5)	11%	244 (9.1)	227 (8.5)	2%
Chronic liver disease	1152 (6.2)	133 (4.9)	6%	148 (5.5)	132 (4.9)	3%
Cirrhosis	651 (3.5)	76 (2.8)	4%	75 (2.8)	75 (2.8)	0%
Diabetes insipidus	46 (0.2)	7 (0.3)	2%	13 (0.5)	7 (0.3)	3%

Diabetes Mellitus	1065 (5.7)	391 (14.5)	30%	390 (14.6)	380 (14.2)	1%
Major hemorrhage	824 (4.4)	120 (4.4)	0%	125 (4.7)	120 (4.5)	1%
Congestive heart failure	942 (5)	194 (7.2)	9%	205 (7.6)	188 (7)	2%
Hyperparathyroidism	53 (0.3)	8 (0.3)	0%	12 (0.4)	8 (0.3)	2%
Hypertension	2561 (13.7)	654 (24.2)	27%	656 (24.5)	640 (23.9)	1%
Hyponatremia	5646 (30.2)	896 (33.2)	6%	874 (32.6)	885 (33)	1%
Hypothyroidism	3038 (16.3)	472 (17.5)	3%	471 (17.6)	470 (17.5)	0%
Hypercalcemia	139 (0.7	23 (0.9)	2%	26 (1)	22 (0.8)	2%
Lithium toxicity at baseline[f]	1443 (7.7)	233 (8.6)	3%	214 (8)	231 (8.6)	2%
Rhabdomyolysis	214 (1.1)	26 (1)	1%	30 (1.1)	26 (1)	1%
Sepsis	265 (1.4)	39 (1.4)	0%	35 (1.3)	39 (1.5)	2%
Charlson comorbidity index[g]						
0	15999 (85.6)	2154 (79.8)	15%	2230 (83.2)	2143 (80)	8%
1	1309 (7)	273 (10.1)	11%	194 (7.2)	271 (10.1)	10%
2	766 (4.1)	147 (5.4)	6%	135 (5)	146 (5.4)	2%
3+	619 (3.3)	124 (4.6)	7%	121 (4.5)	120 (4.5)	0%
Medication use[h]						
Antibiotics	2099 (11.2)	379 (14)	8%	352 (13.1)	375 (14)	3%
Anticonvulsants	700 (3.7)	93 (3.4)	2%	72 (2.7)	93 (3.5)	5%
Calcium channel blockers	1111 (5.9)	321 (11.9)	21%	342 (12.8)	314 (11.7)	3%
Loop diuretics	487 (2.6)	127 (4.7)	11%	129 (4.8)	122 (4.6)	1%
Thiazide diuretics	429 (2.3)	178 (6.6)	21%	172 (6.4)	171 (6.4)	0%
Potassium-sparing diuretics	94 (0.5)	26 (1)	6%	29 (1.1)	25 (0.9)	2%
NSAIDs	957 (5.1)	185 (6.9)	8%	204 (7.6)	181 (6.8)	3%
Laboratory measurement[i]						

Baseline eGFR[j]						
Not reported[k]	8653 (46.3)	1430 (53)	13%	1406 (52.5)	1419 (52.9)	1%
< 30 mL/min/1.73 m^2	107 (0.6)	21 (0.8)	2%	25 (0.9)	21 (0.8)	1%
30 ≤ 45 mL/min/1.73 m^2	424 (2.3)	80 (3)	4%	68 (2.5)	80 (3)	3%
45 ≤ 60 mL/min/1.73 m^2	1279 (6.8)	189 (7)	1%	179 (6.7)	186 (6.9)	1%
60 ≤ 90 mL/min/1.73 m^2	4988 (26.7)	631 (23.4)	8%	633 (23.6)	628 (23.4)	0%
90+ mL/min/1.73 m^2	3242 (17.3)	347 (12.9)	12%	369 (13.8)	346 (12.9)	3%
Baseline serum lithium level[l]						
Not reported	10616 (56.8)	1619 (60)	6%	1571 (58.6)	1606 (59.9)	3%
0 ≤ 0.6 mmol/L	3418 (18.3)	441 (16.3)	5%	465 (17.4)	439 (16.4)	3%
0.6 ≤ 1 mmol/L	3796 (20.3)	498 (18.5)	5%	513 (19.1)	496 (18.5)	2%
1 ≤ 1.5 mmol/L	803 (4.3)	130 (4.8)	2%	123 (4.6)	129 (4.8)	1%
1.5 ≤ 2 mmol/L	54 (0.3)	9 (0.3)	0%	7 (0.3)	9 (0.3)	0%

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation

[a]A complete table of baseline characteristics including all measured covariates are provided in Appendix G. Data are presented as the number (percentage) of patients unless otherwise reported.

[b] A value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

[c] Rural residence was defined as a population of < 10,000 people. Residential information was not available for 6 (0.2%) ACEI/ARB users and 48 (0.3%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into the "No" category during matching.

[d] Income was categorized into fifths of average neighbourhood income on the index date. Income was not available for 14 (0.5%) ACEI/ARB users and 94 (0.5%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into income quintile 3 during matching.

[e] Comorbid conditions in the five years preceding the index date were considered.

[f]This indicates a history of previous lithium toxicity within one year prior to the index date. Since There is inter-individual variability in patients' sensitivity, and tolerance to lithium (94) and patients could experience lithium toxicity while having therapeutic lithium levels (95, 96), a previous lithium toxicity may be an indicator of being more sensitive or intolerable to lithium. Therefore, we tried to match this variable that could impact

the outcome in the comparison groups.

[g]Charlson comorbidity index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.

[h] Baseline medication use in the 120 days preceding the index date was considered. Renin-inhibitors are not included in the table since they were used by less than six patients in each group.

[i] Most recent laboratory test values in a 365–day period before the cohort entry date.

[j] eGFR was calculated for patients with available SCr using the CKD-EPI equation that does not consider race.

[k]These patients either not checked SCr within one year prior to the index date, or the lab that checked their SCr was not linked with OLIS.

[l] For levels higher than 2 mmol/L, there were less than 6 patients in each cell.

Table 5.3. The 90-day risk of primary and secondary outcomes in ACEI/ARB users compared to non-ACEI/ARB users

Outcome	Events, n (%)		Risk Ratio (95% CI)	P value
	ACEI/ARB users (n=2680)	non-ACEI/ARB users (n=2680)		
Primary outcome				
Hospital encounter with lithium toxicity[a]	59 (2.20)	47 (1.75)	1.25 (0.86 - 1.84)	0.24
Secondary outcomes				
All-cause mortality	20 (0.75)	55 (2.05)	0.36 (0.22 - 0.61)	0.0001
All-cause hospitalization	338 (12.61)	369 (13.77)	0.92 (0.80 - 1.05)	0.20
Additional outcome				
Surveillance[b]	642 (23.96)	602 (22.46)	1.07 (0.97 – 1.18)	0.20

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval

[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. The algorithm of ICD-10 codes used to identify lithium toxicity is provided in Appendix F.

[b]This variable was evaluated by having at least one record of lithium level measurement.

Table 5.4. The 90-day risk of primary and secondary outcomes in ACEI-only users compared to non-ACEI/ARB users

Outcome	Events, n (%)		Risk Ratio (95% CI)	P value
	ACEI-only users (n=1967)	non-ACEI/ARB users (n=1967)		
Primary outcome				
Hospital encounter with lithium toxicity[a]	43 (2.19)	28 (1.42)	1.54 (0.96 – 2.45)	0.07
Secondary Outcomes				
All-cause mortality	*	*	0.29 (0.16 - 0.52)	<0.0001
All-cause hospitalization	256 (13.01)	272 (13.83)	0.94 (0.80 - 1.10)	0.45
Additional outcome				
Surveillance[b]	448 (22.78)	423 (21.50)	1.06 (0.94 – 1.19)	0.33

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval

[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. The algorithm of ICD-10 codes used to identify lithium toxicity is provided in Appendix F.

[b]This variable was evaluated by having at least one record of lithium level measurement.

* ICES policy prohibits disclosure of exact numbers when there is a small-cell (n < 6).

Table 5.5. The 90-day risk of primary and secondary outcomes in patients ≥ 66 years old

Outcome	Events, n (%)		Risk Ratio (95% CI)	P value
	ACEI/ARB users (n=1389)	non-ACEI/ARB users (n=1389)		
Primary outcome				
Hospital encounter with lithium toxicity[a]	33 (2.38)	26 (1.87)	1.27 (0.77 – 2.08)	0.35
Secondary Outcomes				
All-cause mortality	*	*	0.40 (0.22 - 0.73)	<0.01
All-cause hospitalization	205 (14.76)	207 (14.90)	0.99 (0.83 - 1.18)	0.91
Additional outcome				
Surveillance[b]	342 (24.62)	296 (21.31)	1.15 (1.01 – 1.32)	0.04

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval

[a]Based on hospital presentation (emergency room or hospitalization) assessed by hospital diagnosis codes. The algorithm of ICD-10 codes used to identify lithium toxicity is provided in Appendix F.

[b]This variable was evaluated by having at least one record of lithium level measurement.

* ICES policy prohibits disclosure of exact numbers when there is a small-cell (n < 6).

Discussion

6.1 Summary and interpretation of study results

In this retrospective cohort study, we did not find a significant increase in the 90-day risk of lithium toxicity in older adults dispensed ACEIs or ARBs compared to non-users. We also found that the 90-day risk of all-cause mortality was significantly lower in chronic lithium users who were dispensed ACEIs or ARBs compared to non-users.

This study is one of the few studies investigating the potential interaction between ACEI/ARBs and lithium. The previous studies evaluated this interaction using surrogate outcomes, such as the change in lithium clearance or serum lithium levels. However, serum lithium levels are not necessarily related to the occurrence of lithium intoxication. There is inter-individual variability in patients' sensitivity and tolerance to lithium (94) and patients could experience lithium toxicity while having therapeutic lithium levels (95, 96).

To our knowledge, there is one study investigating hospital admission with lithium toxicity in chronic lithium users newly dispensed ACEIs. This study by Juurlink et al. (2), is a case-control study assessing the use of interacting medications with lithium during a look-back window from the hospital admission date with lithium toxicity. The authors concluded that the risk of hospital admission with lithium toxicity in chronic lithium users who were newly dispensed ACEIs was six to seven times higher than non-ACEI users. Our results, however, contradict these results.

There are some reasons that may explain the discrepancy between our results and the study by Juurlink et al. First, they included patients 65 years and older, that are more susceptible to lithium toxicity, compared to the population included in our study (who were 50 years and older). However, our additional analysis among patients over 66 did not show a signal of harm in ACEI/ARB users compared to non-users. One of the limitations of Juurlink et al.'s study, which the authors also mentioned, was a small sample size. The study was conducted among 413 patients admitted to the hospital with lithium toxicity and their matched controls. Although they found a significant increase in toxicity in ACEI users, the estimates were imprecise, and confidence intervals were wide (e.g. RR 7.6, 95% CI 2.6-22). Moreover, although cases and controls were matched on age, sex and duration of lithium use, and the estimates were adjusted for some confounders such as other medications interacting with lithium and diagnosis of kidney diseases and hemodialysis, they were not matched on other baseline characteristics that could impact the outcome or decision to prescribe an ACEI or ARB. In our study, we matched the comparison groups in many baseline characteristics to make them more comparable regarding the treatment assignment, and health care access. Finally, no baseline eGFR or lithium levels were available in the study by Juurlink et al. In our study, we matched the exposed and unexposed groups on baseline eGFR and lithium levels. Additionally, patients on hemodialysis and kidney transplant recipients could be more susceptible to lithium toxicity, and we excluded such patients from our study.

In chronic lithium users, co-prescription with an ACEI/ARB was associated with a lower 90 day risk of all-cause mortality compared to non-ACEI/ARB use. ACEIs and ARBs have been shown earlier to reduce mortality in various populations, including people with diabetes, hypertension and chronic kidney disease (44–46). ACEIs and ARBs inhibit the synthesis or function of angiotensin II. Since Angiotensin II is a crucial mediator to several target-organ damages, blocking it could result in decreasing mortality. Inhibition of Angiotensin II decreases different markers that cause atherogenesis, endothelial dysfunction, fibrosis, and thrombosis (97). Our study suggests that despite a biologically plausible interaction between ACEI/ARBs and lithium leading to lithium toxicity, there may be a decrease in mortality that might outweigh the possible

intoxication by these medications. However, since the duration of follow-up was small in this study, the benefits of ACEI/ARBs in reducing mortality in chronic lithium users should be evaluated in longer follow-up duration. Also, the magnitude of the observed benefit is likely implausible, suggesting the finding should be confirmed in additional studies.

6.2 Study strengths and limitations

To our knowledge, this study is the first cohort study assessing the risk of lithium toxicity in lithium users newly prescribed with ACEI/ARBs. Using administrative data provided us with a large population of interest. We assessed hospital encounters with lithium toxicity as an outcome rather than surrogate outcomes such as serum lithium levels.

However, using administrative data for health research purposes has limitations. Outcomes were ascertained using diagnostic codes. Trained coders translate the diagnostic and procedural information written on the medical records into codes. The codes might not be entirely valid, which could result in misclassification of the outcomes. For this study, we used an algorithm of the codes for lithium toxicity that was 75% sensitive and had a positive predictive value of 66%. Although we wanted codes with better validity, we do not expect the misclassification was differential between the exposed and unexposed groups.

Another limitation of observational studies using administrative data is the possibility of residual confounding. Information on some variables, such as hydration status, which is a key factor in lithium toxicity, is not included in the administrative data. We tried to minimize the effect of residual confoundings by creating comparison groups that were matched in over 130 baseline characteristics, including some variables such as using diuretics, hemorrhage or sepsis that could affect the volume status. However, given the observed finding on the outcome of mortality with a magnitude that is not clinically plausible, we expect there is some confounding in these analyses.

Due to the extensive availability of guidelines cautioning on the use of ACEI/ARBs in lithium users, physicians might not prescribe these drug classes to those more susceptible to becoming lithium toxic. Another possibility is that when physicians prescribe ACEI/ARBs to lithium users, they monitor lithium levels more closely and stop ACEI/ARBs if the lithium levels start to rise. This could prevent these patients from experiencing the outcome and result in underestimating the risk of toxicity in those using lithium and ACEI/ARBs. However, we could not find any significant difference in serum lithium level measurements between ACEI/ARB users and non-users in this study.

We only checked hospital encounters with lithium toxicity in this study. Therefore, if the toxicities were mild enough to be managed outside hospitals, they were not captured. Information on prescription drug adherence also could not be obtained from administrative databases, only that prescribed drugs were dispensed from an outpatient pharmacy.

We acknowledge we used a non ACEI/ARB group as our referent as we lacked a suitable active comparator. We tried to overcome this limitation by matching the exposed cohort to the unexposed cohort using the baseline characteristics affecting treatment assignment.

Another limitation of our study is limited statistical power, particularly for the ACEI-only analysis. The 95% CIs were wide and quite imprecise.

6.3 Study implications

Although there were not enough controlled studies on the risk of lithium toxicity in ACEI/ARB users, guidelines always caution against using this combination (1, 64), primarily based on the case reports. The results of this study suggest that the risk described in some previous studies may be overstated. However, study limitations prevent us from making this assertion with substantial certainty. It remains prudent for physicians to still prescribe ACEI/ARBs to lithium uses with caution. Future studies are needed to further characterize this potential adverse

drug-drug interaction.

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Appendices

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Appendix A. Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies

Item	Criteria	Possible Answers
Reporting		
1	*Is the hypothesis/aim/objective of the study clearly described?*	Yes = 1 No = 0
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	*Are the characteristics of the patients included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.	Yes = 2 Partially = 1 No = 0
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	*Have the characteristics of patients lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	Yes = 1 No = 0
External validity		
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0

12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to determine = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - bias		
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Yes = 1 No = 0 Unable to determine = 0
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - confounding (selection bias)		
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information	Yes = 1 No = 0 Unable to determine = 0

	concerning the source of patients included in the study.	
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
23	*Were study subjects randomized to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.	Yes = 1 No = 0 Unable to determine = 0
24	*Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 Unable to determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 Unable to determine = 0
26	*Were losses of patients to follow-up taken into account?* If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
Power		
27*	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y%.	Yes = 1 No = 0 Unable to determine = 0

Appendix B. Search strategies for literature review

Database		Search Terms	
Ovid Medline	1	exp Lithium Compounds/ or exp Lithium/ or exp Lithium Carbonate/	30,170
	2	((lithium adj2 carbonate) or lithium).mp. /freq=2	48,139
	3	exp Angiotensin-Converting Enzyme Inhibitors/	46,383
	4	(((Angiotensin-converting or angiotensin converting) adj2 enzyme adj3 inhibitor?) or acei?).mp.	48,229
	5	(benazepril or captopril or cilazapril or perindopril or ramipril or enalapril or fosinopril or lisinopril or quinapril or trandolapril).mp. /freq=2	25,789
	6	exp Angiotensin Receptor Antagonists/	26,751
	7	((angiotensin adj2 receptor adj3 (blocker? or antagonist?)) or arb?).mp.	24,095
	8	(candesartan or eprosartan or irbesartan or losartan or olmesartan or valsartan or telmisartan).mp. /freq=2	18,870
	9	1 or 2	48,197
	10	3 or 4 or 5 or 6 or 7 or 8	81,590
	11	9 and 10	**140**
Ovid MEDLINE(R) ALL <1946 to June 10, 2022>			
Ovid Embase	1	exp lithium/ or exp lithium carbonate/ or exp lithium derivative/ or exp lithium salt/	73,458
	2	((lithium adj2 carbonate) or lithium).mp. /freq=2	54,902
	3	exp dipeptidyl carboxypeptidase inhibitor/	191,250
	4	(((Angiotensin-converting or angiotensin converting) adj2 enzyme adj3 inhibitor?) or acei?).mp.	40,600
	5	(benazepril or captopril or cilazapril or perindopril or ramipril or enalapril or fosinopril or lisinopril or quinapril or trandolapril).mp. /freq=2	49,658
	6	exp angiotensin receptor antagonist/	107,564
	7	((angiotensin adj2 receptor adj3 (blocker? or antagonist?)) or arb?).mp.	76,623
	8	(candesartan or eprosartan or irbesartan or losartan or olmesartan or valsartan or telmisartan).mp. /freq=2	38,500
	9	1 or 2	87,627
	10	3 or 4 or 5 or 6 or 7 or 8	247,669
	11	9 and 10	1,697
	12	limit 11 to english language	**1,460**

Appendix C. The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	Abstract
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	Chapter 1, 2 &3
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	Chapter 3
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	Chapter 4
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	Chapter 4
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See	Chapter 4

	Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	explanatory document for guidance related to matched designs.	
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	Chapter 4, Appendices D, E & F
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	—	8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	Chapter 4 & Appendix D
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	Chapters 4 & 6
Study size				
10	Explain how the study size was arrived at.	—	—	Chapter 5: Figure 1
Quantitative variables				

11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	Chapter 4
		Statistical methods		
12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	Chapter 4
		Data access and cleaning methods		
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.	—	N/A
		Linkage		
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	Chapter 4
		Results		
		Participants		
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	Chapter 5: Figure 1
		Descriptive data		
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information	—	—	Chapter 5: Table 2

	on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).			
		Outcome data		
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	Chapter 5: Table 3
		Main results		
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	Chapter 5: Table 3
		Other analyses		
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Chapter 5: Table 4
		Discussion		
		Key results		
18	Summarise key results with reference to study objectives.	—	—	Chapter 6
		Limitations		
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	Chapter 6
		Interpretation		
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when	Chapter 6

			relevant. **[A: Original text indicated this item was RECORD (ie, not RECORD-PE)?]**	
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	Chapter 6
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	N/A
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	N/a

Abbreviations: RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology.

Appendix D. Coding definitions for baseline characteristics

Variable	Database	Codes
Demographics		
Age	RPDB	
Sex	RPDB	
Location of residence – Rural status	RPDB	RURAL
Socioeconomic status (neighbourhood income quintiles)	RPDB	INCQUINT
Local Health Integration Network (LHIN)	RPDB	LHIN
Entry year		
Prescribing physician	IPDB	MAINSPECIALTY
Comorbidities		
Acute kidney injury	CIHI-DAD	ICD-9: 584 ICD-10: N17
Alcoholism	CIHI-DAD	ICD-9: 303, 3050 ICD-10: E24, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721
	OHIP	OHIP dx: 303
Atrial fibrilation	CIHI-DAD	ICD-9: 4273 ICD-10: I48
Bipolar disorder	CIHI-DAD	ICD-9: 2960, 2961, 2964, 2965, 2966, 2967, 2968 ICD-10: F300, F301, F302, F308, F309, F310, F311, F312, F313, F314, F315, F316, F317, F318, F319
	OHIP	OHIP dx: 296 OHIP fee: Q020
	OMHRS	DSM-IV: 29600, 29601, 29602, 29603, 29604, 29605, 29606, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650, 29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 29670, 29680, 29689
Cancer	CIHI-DAD	ICD9: V10, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 173, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 1950, 1951, 1952, 1953, 1954, 1955, 1958, 196, 197, 198, 1990, 1991, 2000, 2001, 2002, 2008, 2010, 2011, 2012, 2014, 2015, 2016, 2017, 2019, 2020, 2026, 2028, 2029, 203, 204, 205, 206, 207, 208, 230, 231, 232, 233, 234

		ICD-10: 80003, 80006, 80013, 80023, 80033, 80043, 80102, 80103, 80106, 80113, 80123, 80203, 80213, 80223, C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C8800, C8808, C90, C91, C92, C93, C94, C95, C96, C97, D00, D01, D02, D03, D04, D05, D06, D07, D09, Z850, Z851, Z852, Z853, Z854, Z855, Z856, Z857, Z858, Z859, 80303, 80313, 80323, 80333, 80343, 80413, 80423, 80433, 80443, 80453, 80502, 80503, 80513, 80523, 80702, 80703, 80706, 80713, 80723, 80733, 80743, 80753, 80762, 80763, 80772, 80802, 80812, 80823, 80903, 80913, 80923, 80933, 80943, 80953, 81103, 81202, 81203, 81213, 81223, 81233, 81243, 81303, 81402, 81403, 81406, 81413, 81423, 81433, 81443, 81453, 81473, 81503, 81513, 81523, 81533, 81543, 81553, 81603, 81613, 81623, 81703, 81713, 81803, 81903, 82003, 82013, 82102, 82103, 82113, 82203, 82213, 82303, 82313, 82403, 82413, 82433, 82443, 82453, 82463, 82473, 82503, 82513, 82603, 82612, 82613, 82623, 82632, 82633, 82703, 82803, 82813, 82903, 83003, 83103, 83123, 83143, 83153, 83203, 83223, 83233, 83303, 83313, 83323, 83403, 83503, 83703, 83803, 83813, 83903,

		84003, 84013, 84103, 84203, 84303, 84403, 84413, 84423, 84503, 84513, 84603, 84613, 84623, 84703, 84713, 84723, 84733, 84803, 84806, 84813, 84903, 84906, 85002, 85003, 85012, 85013, 85023, 85032, 85033, 85042, 85043, 85103, 85113, 85123, 85202, 85203, 85213, 85222, 85223, 85303, 85403, 85413, 85423, 85433, 85503, 85603, 85623, 85703, 85713, 85723, 85733, 85803, 86003, 86203, 86303, 86403, 86503, 86803, 86933, 87003, 87103, 87202, 87203, 87213, 87223, 87233, 87303, 87403, 87412, 87413, 87422, 87423, 87433, 87443, 87453, 87613, 87703, 87713, 87723, 87733, 87743, 87803, 88003, 88006, 88013, 88023, 88033, 88043, 88103, 88113, 88123, 88133, 88143, 88303, 88323, 88333, 88403, 88503, 88513, 88523, 88533, 88543, 88553, 88583, 88903, 88913, 88943, 88953, 88963, 89003, 89013, 89023, 89103, 89203, 89303, 89333, 89403, 89413, 89503, 89513, 89603, 89633, 89643, 89703, 89713, 89723, 89803, 89813, 89903, 89913, 90003, 90203, 90403, 90413, 90423, 90433, 90443, 90503, 90513, 90523, 90533, 90603, 90613, 90623, 90633, 90643, 90703, 90713, 90723, 90803, 90813, 90823, 90833, 90843, 90853, 90903, 91003, 91013, 91023, 91103, 91203, 91243, 91303, 91333, 91403, 91503, 91703, 91803, 91813, 91823, 91833, 91843, 91853, 91903, 92203, 92213, 92303, 92313, 92403, 92503, 92513, 92603, 92613, 92703, 92903, 93103, 93303, 93623, 93643, 93703, 93803, 93813, 93823, 93903, 93913, 93923, 94003, 94013, 94103, 94113, 94203, 94213, 94223,

		94233, 94243, 94303, 94403, 94413, 94423, 94433, 94503, 94513, 94603, 94703, 94713, 94723, 94733, 94803, 94813, 94903, 95003, 95013, 95023, 95033, 95043, 95103, 95113, 95123, 95203, 95213, 95223, 95233, 95303, 95393, 95403, 95603, 95613, 95803, 95813, 95903, 95913, 95933, 95943, 95953, 96503, 96523, 96533, 96543, 96553, 96573, 96583, 96593, 96603, 96613, 96623, 96633, 96643, 96653, 96663, 96673, 96703, 96713, 96723, 96733, 96743, 96753, 96843, 96853, 96863, 96873, 96763, 96773, 96803, 96813, 96823, 96833, 96903, 96913, 96923, 96933, 96943, 96953, 96963, 96973, 96983, 97003, 97013, 97023, 97053, 97063, 97073, 97093, 97113, 97123, 97133, 97143, 97203, 97223, 97233, 97313, 97323, 97403, 97413, 97603, 97613, 97623, 97633, 97643, 98003, 98013, 98023, 98033, 98043, 98203, 98213, 98223, 98233, 98243, 98253, 98263, 98273, 98303, 98403, 98413, 98423, 98503, 98603, 98613, 98623, 98633, 98643, 98663, 98673, 98683, 98703, 98803, 98903, 98913, 98923, 98933, 98943, 99003, 99103, 99303, 99313, 99323, 99403, 99413
	OHIP	OHIP dx: 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 173, 174, 175, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 230, 231, 232, 233, 234
Chronic kidney disease	CIHI-DAD	ICD-9: 4030, 4031, 4039, 4040, 4041, 4049, 583, 584, 585, 586, 5888, 5889, 592, 5939, 2504 ICD-10: E102, E112, E132, E142, I12, I13, N00, N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, N20, N21, N22, N23
	OHIP	OHIP dx: 403, 585
Chronic liver disease	CIHI-DAD	ICD-9: 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 571, 2750, 2751, 7891, 7895 ICD-10: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
	OHIP	OHIP dx: 571, 573, 70 OHIP fee: Z551, Z554

Chronic lung disease	CIHI-DAD	ICD-9: 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 5069, 5081, 515, 516, 517, 5185, 5188, 5198, 5199, 4168, 4169 ICD-10: I272, I278, I279, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99
	OHIP	OHIP dx: 491, 492, 493, 494, 496, 501, 502, 515, 518, 519 OHIP fee: J889, J689
Cirrhosis	CIHI-DAD	ICD-9: 5712, 5715, 5716 ICD-10: K703, K743, K744, K745, K746
	OHIP	OHIP fee: 571
Coronary disease	CIHI-DAD	ICD-9: 412, 410, 411, 413, 414, 4292, 4296, 4297 ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 CCI: 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483
	OHIP	OHIP dx: 410, 412, 413 OHIP fee: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448
Dementia	CIHI-DAD	ICD-9: 2900, 2901, 2903, 2904, 2908, 2909, 2948, 2949, 3310, 3311, 3312, 2941, 797 ICD-10: F065, F066, F068, F069, F09, F00, F01, F02, F03, F051, G30, G31, R54
	OHIP	OHIP dx: 290, 331, 797
	OMHRS	DSM-IV: 29040, 29041, 29042, 29043, 29120, 29282, 29410, 29411, 29480, 78090
Diabetes melitus	ODB	
Diabetes insipidus	CIHI-DAD	ICD-9: 2535 ICD-10: E232
Heart failure	CIHI-DAD	ICD-9: 425, 5184, 514, 428 ICD-10: I099, I420, I425, I426, I427, I428, I429, I43, I50, I255, J81 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR CCP: 4961, 4962, 4963, 4964
	OHIP	OHIP dx: 428 OHIP fee: R701, R702, Z429
Edema	CIHI-DAD	ICD-9: 7823 ICD-10: R600, R601, R609
Pulmunary edema	CIHI-DAD	ICD-9: 5184 ICD-10: J81
Hyperuricemia	CIHI-DAD	ICD-9: 7906 ICD-10: E790
Hypercalcemia	CIHI-DAD	ICD-9: 2754 ICD-10: E835

Thyroxicosis	CIHI-DAD	ICD-9: 24240, 24241, 24280, 24281, 24290, 24291 ICD-10: E050, E051, E052, E053, E054, E055, E058, E059
Hyperaldosteronism	CIHI-DAD	ICD-9: 2551 ICD-10: E260, E261, E268, E269
Hyperparathyroidism	CIHI-DAD	ICD-9: 2520 ICD-10: E21
Hypokaliema	CIHI-DAD	ICD-9: 2768 ICD-10: E876
Hyponatremia	CIHI-DAD	ICD-9: 2761 ICD-10: E871
Hypothyroidism	CIHI-DAD OHIP	ICD-9: 243, 2440, 2441, 2442, 2443, 2448, 2449 ICD-10: E030, E031, E032, E033, E034, E035, E038, E039, E890 OHIP dx: 243, 244
Hemorrhage	CIHI-DAD	ICD-9: 56881, 5997, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5693, 53501, 53511, 53521, 7847, 7863, 6238, 6262 ICD-10: K661, N020, N021, N022, N023, N024, N025, N026, N027, N028, N029, R310, R311, R318, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, R040, R042, R048, R049, N898, N920, N921 CCI: 1LZ19HMU1, 1LZ19HMU2, 1LZ19HMU9, 1LZ19HHU9A, 1LZ19HHU9J, 1LZ19HHU1A, 1LZ19HHU1J, 1LZ19HHU3J, 1LZ19HHU4J, 1LZ19HHU2A, 1LZ19HHU2J, 1LZ19HHU5J CCP: 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309
HIV	CIHI-DAD OHIP	ICD-9: 042, 043, 044, 176 ICD-10: B24, Z21, C46 OHIP dx: 042, 043, 044
Connective tissue disease	CIHI-DAD	ICD-9: 7108, 7109 ICD-10: L940, L941, L942, L943, L944, L945, L946, L948, L949
Inflammatory bowel disease	CIHI-DAD	ICD-9: 555, 556 ICD-10: K50, K51
Hypotension	CIHI-DAD	ICD-9: 458 ICD-10: I95
Sepsis	CIHI-DAD	ICD-9: 0031,0362,0380,0381,0382,0383,0384,0388,0389 ICD-10: A021,A392,A393,A394,A400,A401,A402,A408,A409,A410,A411,A412,A403,A414,A4159,A413,A4150,A4151,A4152,A4158,A4180,A4188,A427,A419
Essential tremor	CIHI-DAD	ICD-10: G250

Hyperplasia of prostate	CIHI-DAD	ICD-9: 600 ICD-10: N40
	OHIP	OHIP dx: 600
Rhabdomyolysis	CIHI-DAD	ICD-9: 7288, 9586
		ICD-10: M628, T796
Prostatitis	CIHI-DAD	ICD-9: 6010, 6011, 6012 ICD-10: N410, N411, N412
	OHIP	OHIP dx: 601
Multiple sclerosis	CIHI-DAD	ICD-9: 340 ICD-10: G35
	OHIP	OHIP dx: 340
Retention of urine	CIHI-DAD	ICD-9: 7882 ICD-10: R33
Osteoporosis	CIHI-DAD	ICD-9: 7330 ICD-10: M80, M81, M82
	OHIP	OHIP dx: 733
Raynaud's syndrome	CIHI-DAD	ICD-9: 4430 ICD-10: I730
	OHIP	OHIP dx: 443
Gout	CIHI-DAD	ICD-9: 274 ICD-10: M10
	OHIP	OHIP dx: 274
Hospital encounter with lithium toxicity	CIHI-DAD	ICD-9: 9698, 9859 ICD-10: T438, T439, T568, T569, T435, Y495
Migraine	CIHI-DAD	ICD-9: 3460, 3461, 3462, 3468, 3469 ICD-10: G43
	OHIP	OHIP dx: 346
Myocardial infarction	CIHI-DAD	ICD-9: 410 ICD-10: I21, I22
Obesity	CIHI-DAD	ICD-9: 2780 ICD-10: E660, E661, E662, E668, E669
	OHIP	OHIP dx: 278
Parkinson's disease	CIHI-DAD	ICD-9: 332 ICD-10: G20, F023
Peripheral vascular disease	CIHI-DAD	ICD-9: 4402, 4408, 4409, 5571, 4439, 444 ICD-10: I700, I702, I708, I709, I731, I738, I739, K551 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87LA, 1KA87LA, 1KE57 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159
	OHIP	OHIP fee: R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649

Schizophrenia	CIHI-DAD	ICD-9: 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2970, 2971, 2972, 2973, 2978, 2979, 2980, 2981, 2983, 2984, 2988, 2989 ICD-10: F060, F062, F105, F107, F115, F117, F125, F127, F135, F137, F145, F147, F155, F157, F165, F167, F175, F177, F185, F187, F195, F197, F200, F201, F202, F203, F204, F205, F206, F208, F209, F220, F228, F229, F230, F231, F232, F233, F238, F239, F24, F250, F251, F252, F258, F259, F28, F29
	OHIP	OHIP dx: 291, 292, 295, 297, 298 OHIP fee: Q021
	OMHRS	DSM-IV: 29130, 29150, 29211, 29212, 29381, 29382, 29510, 29520, 29530, 29540, 29560, 29570, 29590, 29710, 29730, 29880, 29890
Seizure	CIHI-DAD	ICD-9: 345 ICD-10: G40, G41
Stroke	CIHI-DAD	ICD-9: 430, 431, 432*, 4340, 4341, 4349, 435, 436, 3623 ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340
Depression	CIHI-DAD	ICD-9: 2962, 2963, 3000, 3002, 3003, 3004, 3091, 311 ICD-10: F063, F064, F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F338, F339, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431
	OHIP	OHIP dx: 311
	OMHRS	DSM-IV: 29189, 29284, 29289, 29383, 29384, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 30000, 30001, 30002, 30021, 30022, 30023, 30029, 30030, 30040, 30113
Arrythmia	CIHI-DAD	ICD-9: 4261, 4262, 4263, 4264, 4265, 4266, 4267, 4268, 4269, 427, 7850 ICD-10: I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001
	OHIP	OHIP fee: G178, G179, G249, G261, G259, Z443, Z431, Z437
Healthcare utilisation		
Number of any hospitalizations	CIHI-DAD	
Number of any emergency room visits	NACRS	
GP/FP visits	OHIP IPDB	

Cardiologist visits	OHIP IPDB	
Internist visits vists	OHIP IPDB	
Neurologist vists	OHIP IPDB	
Geriatrician visits	OHIP IPDB	
Psychiatrist visits	OHIP IPDB	
Nephrologist visits	OHIP IPDB	
Calcium test	OHIP	OHIP fee: L045, L046
Lithium lab test	OHIP	OHIP fee: L157
Serum creatinine test	OHIP	OHIP fee: L065, L067, L068
TSH test	OHIP	OHIP fee: G016, L341
Bone mineral density	OHIP	OHIP fee: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888
Cardiac cathetherization	CIHI-DAD OHIP	CCI: 3IJ30GP, 3HZ30GP, 2HZ24GPKJ, 2HZ24GPKL, 2HZ24GPKM, 2HZ24GPXJ, 2HZ28GPPL, 2HZ71GP, 3IP10, 3IS10 CCP: 4995, 4996, 4997, 4892, 4893, 4894, 4895, 4896, 4897, 4898 OHIP fee: G296, G297, G299, G300, G301, G304, G305, G306, G297, G509
Cardiac stress test	CIHI-DAD	ICD-10: G315, G174, G111, G112, G319, G582, G583, G584, J604, J606, J607, J608, J609, J611, J612, J613, J667, J807, J808, J809, J804, J811, J812, J813, J867, J666, J866 CCI: 2HZ08, 3IP70 CCP: 341, 342, 343, 344, 605
Carotid endarterectomy	OHIP	OHIP fee: N220, R792
Carotid ultrasound	CIHI-DAD OHIP	CCI: 3JE30, 3JG30 CCP: 281 OHIP fee: J201, J501, J189, J489, J190, J191, J490, J491, J492
Cataract surgery	OHIP	OHIP fee: E140
Cervical cancer screening	OHIP	OHIP fee: E430, G365, G394, L713, L812
Chest x-ray	OHIP	OHIP fee: X090, X091, X092, X195
Cholesterol test	OHIP	OHIP fee: L117, L055, L056, L156, G001, G013, Q183
Colorectal cancer screening	OHIP	OHIP fee: G004, L179, L181, Q043, Q152, X112, X113, Z535, Z536, Z555, Z580
Heart valve replacement	OHIP	OHIP fee: R728, R735, R738, R772
PTH test	OHIP	OHIP fee: L330
Hyperkaliema	CIHI-DAD	ICD-10: E875
Computed tomography of head	OHIP	OHIP fee: X188, X400, X401, X402, X405, X408

Computed tomography of extremities	OHIP	OHIP fee: X127, X412, X413
Computed tomography of neck	OHIP	OHIP fee: X124, X403, X404
Computed tomography of thorax	OHIP	OHIP fee: X125, X406, X407
Computed tomography of spine	OHIP	OHIP fee: X128, X415, X416
Computed tomography of pelvis	OHIP	OHIP fee: X231, X232, X233
Computed tomography of abdomen	OHIP	OHIP fee: X126, X409, X410
Coronary aniogram	CIHI-DAD OHIP	CCI: 3IP10, 3IS10 CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898 OHIP fee: G297, G509
Echocardiography	CIHI-DAD OHIP	CCI: 3IP30 CCP: 0282 OHIP fee: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581
Electroencephalography	OHIP	OHIP fee: G414, G415, G416, G417, G418, G540, G542, G544, G545, G546, G554, G555
Holter monitoring	OHIP	OHIP fee: G311, G320, G647, G648, G649, G650, G651, G652, G653, G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Coronary revascularization	CIHI-DAD OHIP	CCI: 1IJ50, 1IJ26, IIJ27, 1IJ57, 1IJ76, 1IJ57GQ, 1IJ54GQAZ CCP: 480, 481, 482, 483 OHIP fee: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262
Prostate specific antigen test	OHIP	OHIP fee: Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133
Mammography	OHIP	OHIP fee: X172, X178, X184, X185, X201
Influenzae vaccination	OHIP	OHIP fee: G590, G591
Hearing test	OHIP	OHIP fee: G153, G154, G440, G441, G442, G443, G448, G450, G451, G452, G525, G526, G529, G530, G533, G815, G816
Cystoscopy	OHIP	OHIP fee: Z606, Z607, Z628, Z632, Z633, Z634
Transurethral resection of the pro	CIHI-DAD	CCI: 1QT59BAAD, 1QT59BAAG, 1QT59BAAW, 1QT59BAAZ, 1QT59BACG, 1QT59BAGX, 1QT87BA, 1QT87BAAG, 1QT87BAAK
Pulmonary function test	OHIP	OHIP fee: J301, J303, J304, J305, J306, J307, J308, J309, J310, J311, J313, J315, J316, J317, J318, J319, J320, J322, J323, J324, J327, J328, J330, J331, J332, J333, J334, J335, J340, J341, E450, E451
Laboratory measurements		
Serum creatinine lab value	OLIS	14334-7, 3719-2
Serum lithium lab value	OLIS	14682-9

Abbreviations: CCI = Canadian Classification of Health Interventions (available after 2002), CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (before 2002), CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database, CORR = Canadian Organ Replacement Register, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, GP/FP = general practitioner/family practitioner, ICD-9 = International Classification of Diseases, Ninth Revision, ICD-10 = International Classification of Diseases, Tenth Revision, IPDB = Institute for Clinical Evaluative Sciences (ICES) Physician Database, LHIN = Local Health Integration Network, ODB = Ontario Drug Benefit, OHIP = Ontario Health Insurance Plan, OMHRS = Ontario Mental Health Reporting System, RPDB = Registered Persons Database of Ontario, OLIS = Ontario Labratories Information System, TSH = Thyroid Stimulating Hormone, PTH = Parathyroid Hormone

Appendix E. Variables included in the propensity score

Demographics	Age Sex Cohort entry year Rural residence Neighbourhood income quintile
Comorbidities	Hyperparathyroidism Hypercalcemia Hypothyroidism Thyrotoxicosis Diabetes Hypertension Coronary artery disease Chronic kidney disease Acute kidney injury Diabetes insipidus Edema Pulmonary edema Major hemorrhage Cirrhosis Congestive heart failure Sepsis Alcoholism Bipolar disorder Hospital encounter with lithium toxicity at baseline Charlson comorbidity index Obesity Depression
Baseline medications	NSAIDs Renin inhibitors Acetylsalicylic acid Calcium channel blockers Thiazide diuretics Loop diuretics Potassium-sparing diuretics Vitamin K antagonists Corticosteroids Statins

Health care utilization	Long-term care use Parathyroid test Calcium test Urinalysis Osmolality Lithium test TSH test Serum creatinine test At-home physician visits Number of general practitioner visits Number of internist visits Number of cardiology visits Number of psychiatrist visits Flu shot Carotid endarterectomy Cardiac catheterization Cardiac stress test Cholesterol test Echocardiography
Other	Lithium prescriber's characteristics Number of drug names OlIS eligibility Lithium level availability eGFR availability

Abbreviations: TSH = Thyroid stimulating hormone, OLIS = Ontario Laboratories Information system, eGFR = estimated glomerular filtration rate

Appendix F. Coding definitions for hospital encounter with lithium toxicity

ICD-10 codes	Definitions
T568	Toxic effect of other metals
T435	Poisoning by other and unspecified antipsychotics and neuroleptics
Y495	Other antipsychotics and neuroleptics causing adverse effect in therapeutic use
X41	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X49	Accidental poisoning by and exposure to other and unspecified chemicals and noxious substances
T432*	Poisoning by other and unspecified antidepressants

Abbreviations: ICD-10 = International Classification of Diseases, tenth revision

*Patients were identified as lithium toxic if they had either of the codes T568, T435, Y495, X41, X49, while not having T432

Appendix G. Baseline characteristics of chronic lithium users who were or were not newly dispensed an ACEI/ARB before and after matching[a]

Variables	Unmatched			Matched		
	non-ACEI/ARB users (n = 18,693)	ACEI/ARB users (n = 2,698)	Standardized difference[b]	non-ACEI/ARB users (n = 2,680)	ACEI/ARB users (n = 2,680)	Standardized difference[b]
Demographics						
Age, mean (SD), years	64.2 (10.6)	66.0 (9.5)	18%	66.2 (10.4)	66.0 (9.5)	2%
Women	10671 (57.1)	1461 (54.2)	6%	1462 (54.6)	1452 (54.2)	1%
Year of cohort entry						
2002	980 (5.2)	165 (6.1)	4%	182 (6.8)	162 (6)	3%
2003	960 (5.1)	168 (6.2)	5%	188 (7)	166 (6.2)	3%
2004	819 (4.4)	180 (6.7)	10%	184 (6.9)	180 (6.7)	1%
2005	775 (4.1)	158 (5.9)	8%	160 (6)	158 (5.9)	0%
2006	725 (3.9)	173 (6.4)	11%	148 (5.5)	171 (6.4)	4%
2007	717 (3.8)	173 (6.4)	12%	164 (6.1)	170 (6.3)	1%
2008	759 (4.1)	137 (5.1)	5%	114 (4.3)	136 (5.1)	4%
2009	756 (4)	172 (6.4)	11%	169 (6.3)	168 (6.3)	0%
2010	754 (4)	147 (5.4)	7%	162 (6)	145 (5.4)	3%
2011	785 (4.2)	129 (4.8)	3%	125 (4.7)	129 (4.8)	0%
2012	765 (4.1)	156 (5.8)	8%	137 (5.1)	155 (5.8)	3%
2013	820 (4.4)	131 (4.9)	2%	142 (5.3)	131 (4.9)	2%
2014	822 (4.4)	116 (4.3)	0%	118 (4.4)	116 (4.3)	0%
2015	863 (4.6)	109 (4)	3%	111 (4.1)	109 (4.1)	0%
2016	947 (5.1)	121 (4.5)	3%	139 (5.2)	121 (4.5)	3%

2017	1010 (5.4)	111 (4.1)	6%	101 (3.8)	111 (4.1)	2%
2018	1071 (5.7)	104 (3.9)	8%	94 (3.5)	104 (3.9)	2%
2019	1251 (6.7)	101 (3.7)	14%	109 (4.1)	101 (3.8)	2%
2020	1403 (7.5)	88 (3.3)	19%	72 (2.7)	88 (3.3)	4%
2021	1711 (9.2)	59 (2.2)	31%	61 (2.3)	59 (2.2)	1%
Rural residence[c]	2346 (12.6)	363 (13.5)	3%	381 (14.2)	361 (13.5)	2%
Long-term care	1792 (9.6)	120 (4.4)	20%	123 (4.6)	119 (4.4)	1%
Income quintile[d]						
1	5580 (29.9)	755 (28)	4%	755 (28.2)	752 (28.1)	0%
2	4040 (21.6)	559 (20.7)	2%	520 (19.4)	554 (20.7)	3%
3	3453 (18.5)	501 (18.6)	0%	497 (18.5)	496 (18.5)	0%
4	2820 (15.1)	460 (17)	5%	465 (17.4)	456 (17)	1%
5	2800 (15)	423 (15.7)	2%	443 (16.5)	422 (15.7)	2%
LHIN[e]						
1	991 (5.3)	162 (6)	3%	151 (5.6)	162 (6)	2%
2	1777 (9.5)	252 (9.3)	1%	262 (9.8)	252 (9.4)	1%
3	990 (5.3)	131 (4.9)	2%	128 (4.8)	129 (4.8)	0%
4	2761 (14.8)	393 (14.6)	1%	346 (12.9)	388 (14.5)	5%
5	477 (2.6)	89 (3.3)	4%	82 (3.1)	89 (3.3)	1%
6	776 (4.2)	120 (4.4)	1%	117 (4.4)	118 (4.4)	0%
7	1943 (10.4)	267 (9.9)	2%	266 (9.9)	265 (9.9)	0%
8	1537 (8.2)	253 (9.4)	4%	245 (9.1)	251 (9.4)	1%
9	1616 (8.6)	231 (8.6)	0%	251 (9.4)	230 (8.6)	3%
10	1137 (6.1)	137 (5.1)	4%	180 (6.7)	137 (5.1)	7%
11	2369 (12.7)	321 (11.9)	2%	322 (12)	319 (11.9)	0%

12	852 (4.6)	107 (4)	3%	123 (4.6)	106 (4)	3%
13	1114 (6)	171 (6.3)	1%	151 (5.6)	170 (6.3)	3%
14	353 (1.9)	64 (2.4)	3%	56 (2.1)	64 (2.4)	2%
Lithium prescriber's information						
General practitioner/Family physician	7983 (42.7)	1279 (47.4)	9%	1249 (46.6)	1267 (47.3)	1%
Psychiatrist	6548 (35)	893 (33.1)	4%	907 (33.8)	890 (33.2)	1%
Other	4162 (22.3)	526 (19.5)	7%	524 (19.6)	523 (19.5)	0%
Comorbidities[f]						
Acute kidney injury	577 (3.1)	88 (3.3)	1%	92 (3.4)	88 (3.3)	1%
Alcoholism	1480 (7.9)	137 (5.1)	11%	122 (4.6)	136 (5.1)	2%
Angina	1450 (7.8)	378 (14)	20%	335 (12.5)	367 (13.7)	4%
Atrial fibrillation/flutter	384 (2.1)	58 (2.1)	0%	89 (3.3)	57 (2.1)	7%
Bipolar disorder	13395 (71.7)	1931 (71.6)	0%	1912 (71.3)	1917 (71.5)	0%
Chronic kidney disease	1068 (5.7)	229 (8.5)	11%	244 (9.1)	227 (8.5)	2%
Chronic liver disease	1152 (6.2)	133 (4.9)	6%	148 (5.5)	132 (4.9)	3%
Chronic obstructive pulmonary disease	4963 (26.6)	722 (26.8)	0%	728 (27.2)	714 (26.6)	1%
Cirrhosis	651 (3.5)	76 (2.8)	4%	75 (2.8)	75 (2.8)	0%
Coronary artery disease	2142 (11.5)	561 (20.8)	25%	540 (20.1)	544 (20.3)	0%
Dementia	3913 (20.9)	482 (17.9)	8%	513 (19.1)	475 (17.7)	4%
Diabetes insipidus	46 (0.2)	7 (0.3)	2%	13 (0.5)	7 (0.3)	3%
Diabetes Mellitus	1065 (5.7)	391 (14.5)	30%	390 (14.6)	380 (14.2)	1%
Edema	90 (0.5)	9 (0.3)	3%	10 (0.4)	9 (0.3)	2%
Pulmonary edema	22 (0.1)	7 (0.3)	4%	8 (0.3)	6 (0.2)	2%
Glaucoma	874 (4.7)	118 (4.4)	1%	105 (3.9)	118 (4.4)	3%
Major hemorrhage	824 (4.4)	120 (4.4)	0%	125 (4.7)	120 (4.5)	1%

Congestive heart failure	942 (5)	194 (7.2)	9%	205 (7.6)	188 (7)	2%
Hyperparathyroidism	53 (0.3)	8 (0.3)	0%	12 (0.4)	8 (0.3)	2%
Hypertension	2561 (13.7)	654 (24.2)	27%	656 (24.5)	640 (23.9)	1%
Hypokalemia	359 (1.9)	37 (1.4)	4%	48 (1.8)	36 (1.3)	4%
Hyponatremia	5646 (30.2)	896 (33.2)	6%	874 (32.6)	885 (33)	1%
Hypothyroidism	3038 (16.3)	472 (17.5)	3%	471 (17.6)	470 (17.5)	0%
Hypercalcemia	139 (0.7	23 (0.9)	2%	26 (1)	22 (0.8)	2%
Lithium toxicity at baseline[g]	1443 (7.7)	233 (8.6)	3%	214 (8)	231 (8.6)	2%
Migraine	1256 (6.7)	175 (6.5)	1%	190 (7.1)	174 (6.5)	2%
Myocardial infarction	212 (1.1)	74 (2.7)	12%	64 (2.4)	70 (2.6)	1%
Obesity	1479 (7.9)	323 (12)	14%	312 (11.6)	318 (11.9)	1%
Parkinson's disease	1167 (6.2)	185 (6.9)	3%	197 (7.4)	182 (6.8)	2%
Peripheral vascular disease	101 (0.5)	30 (1.1)	7%	21 (0.8)	30 (1.1)	3%
Schizophrenia	8024 (42.9)	1045 (38.7)	9%	1016 (37.9)	1037 (38.7)	2%
Seizure	344 (1.8)	29 (1.1)	6%	37 (1.4)	28 (1)	4%
Ischemic stroke	197 (1.1)	53 (2)	7%	35 (1.3)	53 (2)	5%
Transient ischemic attack	92 (0.5)	23 (0.9)	5%	22 (0.8)	22 (0.8)	0%
Depression	9477 (50.7)	1204 (44.6)	12%	1209 (45.1)	1197 (44.7)	1%
Ventricular arrhythmia	3875 (20.7)	532 (19.7)	2%	549 (20.5)	526 (19.6)	2%
Inflammatory bowel disease	138 (0.7)	14 (0.5)	3%	19 (0.7)	14 (0.5)	3%
Leukemia	225 (1.2)	35 (1.3)	1%	36 (1.3)	35 (1.3)	0%
Cancer	4611 (24.7)	720 (26.7)	5%	669 (25)	716 (26.7)	4%
Prostatic hyperplasia	1581 (8.5)	286 (10.6)	7%	301 (11.2)	283 (10.6)	2%
Prostatitis	493 (2.6)	78 (2.9)	2%	89 (3.3)	77 (2.9)	2%
Hypotension	313 (1.7)	45 (1.7)	0%	39 (1.5)	45 (1.7)	2%

Rhabdomyolysis	214 (1.1)	26 (1)	1%	30 (1.1)	26 (1)	1%
Multiple sclerosis	173 (0.9)	23 (0.9)	0%	17 (0.6)	23 (0.9)	3%
Urinary retention	358 (1.9)	53 (2)	1%	59 (2.2)	52 (1.9)	2%
Sepsis	265 (1.4)	39 (1.4)	0%	35 (1.3)	39 (1.5)	2%
Tremor	69 (0.4)	11 (0.4)	0%	8 (0.3)	11 (0.4)	2%
Osteoarthritis	1610 (8.6)	196 (7.3)	5%	255 (9.5)	195 (7.3)	8%
Raynaud's syndrome	555 (3)	114 (4.2)	6%	116 (4.3)	114 (4.3)	0%
Gout	530 (2.8)	109 (4)	7%	99 (3.7)	105 (3.9)	1%
Charlson comorbidity index[h]						
0	15999 (85.6)	2154 (79.8)	15%	2230 (83.2)	2143 (80)	8%
1	1309 (7)	273 (10.1)	11%	194 (7.2)	271 (10.1)	10%
2	766 (4.1)	147 (5.4)	6%	135 (5)	146 (5.4)	2%
3+	619 (3.3)	124 (4.6)	7%	121 (4.5)	120 (4.5)	0%
Medication use[i]						
Alpha-adrenergic blocking agents	191 (1)	34 (1.3)	3%	42 (1.6)	34 (1.3)	3%
Platelet reducing agents	239 (1.3)	61 (2.3)	8%	57 (2.1)	58 (2.2)	1%
Antibiotics	2099 (11.2)	379 (14)	8%	352 (13.1)	375 (14)	3%
Anticonvulsants	700 (3.7)	93 (3.4)	2%	72 (2.7)	93 (3.5)	5%
Antipsychotics	4160 (22.3)	512 (19)	8%	573 (21.4)	509 (19)	6%
Antiarrhythmic agents	35 (0.2)	10 (0.4)	4%	13 (0.5)	8 (0.3)	3%
Aspirin	267 (1.4)	79 (2.9)	1%	88 (3.3)	76 (2.8)	3%
Benzodiazepines	3167 (16.9)	486 (18)	3%	482 (18)	481 (17.9)	0%
Calcium channel blockers	1111 (5.9)	321 (11.9)	21%	342 (12.8)	314 (11.7)	3%
Vitamin k antagonists	222 (1.2)	17 (0.6)	6%	17 (0.6)	17 (0.6)	0%
Loop diuretics	487 (2.6)	127 (4.7)	11%	129 (4.8)	122 (4.6)	1%

Thiazide diuretics	429 (2.3)	178 (6.6)	21%	172 (6.4)	171 (6.4)	0%
Potassium-sparing diuretics	94 (0.5)	26 (1)	6%	29 (1.1)	25 (0.9)	2%
Tricyclic antidepressants	3091 (16.5)	430 (15.9)	2%	443 (16.5)	427 (15.9)	2%
Digoxin	112 (0.6)	20 (0.7)	1%	31 (1.2)	19 (0.7)	5%
Iron preparations	491 (2.6)	66 (2.4)	1%	79 (2.9)	65 (2.4)	3%
H2 receptor antagonist	447 (2.4)	86 (3.2)	5%	79 (2.9)	85 (3.2)	2%
Cholinergic blocking agents	569 (3)	70 (2.6)	2%	98 (3.7)	70 (2.6)	6%
Corticosteroids	634 (3.4)	131 (4.9)	8%	129 (4.8)	128 (4.8)	0%
Beta-adrenergic agonists	982 (5.3)	164 (6.1)	3%	159 (5.9)	161 (6)	0%
NSAIDs	957 (5.1)	185 (6.9)	8%	204 (7.6)	181 (6.8)	3%
Alkalinizing agents	101 (0.5)	10 (0.4)	1%	9 (0.3)	10 (0.4)	2%
Selective serotonin reuptake inhibitors	3150 (16.9)	469 (17.4)	1%	477 (17.8)	467 (17.4)	1%
Statins	2511 (13.4)	606 (22.5)	24%	598 (22.3)	593 (22.1)	0%
Typical antipsychotics	660 (3.5)	99 (3.7)	1%	84 (3.1)	98 (3.7)	3%
Vasodilator antihypertensive drugs	274 (1.5)	95 (3.5)	13%	70 (2.6)	87 (3.2)	4%
Warfarin	270 (1.4)	58 (2.1)	5%	77 (2.9)	56 (2.1)	5%
Cholinesterase inhibitors	461 (2.5)	56 (2.1)	35	80 (3)	55 (2.1)	6%
Overactive bladder drugs	384 (2.1)	82 (3)	6%	72 (2.7)	82 (3.1)	2%
Levothyroxine	2715 (14.5)	436 (16.2)	5%	447 (16.7)	431 (16.1)	2%
Number of unique drug names						
0-4	11806 (63.2)	1514 (56.1)	15%	1524 (56.9)	1512 (56.4)	1%
5-9	4421 (23.7)	787 (29.2)	12%	737 (27.5)	779 (29.1)	4%
10-14	1850 (9.9)	310 (11.5)	5%	311 (11.6)	305 (11.4)	1%
15-19	497 (2.7)	72 (2.7)	0%	85 (3.2)	70 (2.6)	4%
20+	119 (0.6)	15 (0.6)	0%	23 (0.9)	14 (0.5)	5%

Healthcare utilization[j]						
GP/FP visits						
0-4	6079 (32.5)	642 (23.8)	19%	724 (27)	642 (24)	7%
5-9	4951 (26.5)	863 (32)	12%	749 (27.9)	858 (32)	9%
10-14	3143 (16.8)	534 (19.8)	8%	491 (18.3)	530 (19.8)	4%
15-19	1607 (8.6)	269 (10)	5%	261 (9.7)	266 (9.9)	1%
20+	2913 (15.6)	390 (14.5)	3%	455 (17)	384 (14.3)	7%
Internist visits						
0	14095 (75.4)	1906 (70.6)	11%	1950 (72.8)	1896 (70.7)	5%
1	2155 (11.5)	370 (13.7)	7%	335 (12.5)	369 (13.8)	4%
2	824 (4.4)	134 (5)	3%	147 (5.5)	134 (5)	2%
3+	1619 (8.7)	288 (10.7)	7%	248 (9.3)	281 (10.5)	4%
Cardiologist visits						
0	12719 (68)	1593 (59)	19%	1642 (61.3)	1592 (59.4)	4%
1	3300 (17.7)	513 (19)	3%	509 (19)	512 (19.1)	0%
2	1186 (6.3)	246 (9.1)	11%	203 (7.6)	242 (9)	5%
3+	1488 (8)	346 (12.8)	16%	326 (12.2)	334 (12.5)	1%
Geriatrician visits						
0	17964 (96.1)	2585 (95.8)	2%	2562 (95.6)	2570 (95.9)	1%
1	329 (1.8)	44 (1.6)	2%	49 (1.8)	43 (1.6)	2%
2	132 (0.7)	28 (1)	3%	19 (0.7)	27 (1)	3%
3+	268 (1.4)	41 (1.5)	1%	50 (1.9)	40 (1.5)	3%
Nephrologist visits						
0	17882 (95.7)	2527 (93.7)	9%	2503 (93.4)	2510 (93.7)	1%
1	457 (2.4)	97 (3.6)	7%	87 (3.2)	97 (3.6)	2%

2	182 (1)	41 (1.5)	5%	42 (1.6)	41 (1.5)	1%
3+	172 (0.9)	33 (1.2)	3%	48 (1.8)	32 (1.2)	5%
Neurologist visits						
0	16768 (89.7)	2383 (88.3)	4%	2396 (89.4)	2368 (88.4)	3%
1	1000 (5.3)	162 (6)	3%	161 (6)	161 (6)	0%
2	445 (2.4)	76 (2.8)	3%	52 (1.9)	75 (2.8)	6%
3+	480 (2.6)	77 (2.9)	2%	71 (2.6)	76 (2.8)	1%
Psychiatrist visits						
0	7836 (41.9)	1238 (45.9)	8%	1214 (45.3)	1232 (46)	1%
1	1185 (6.3)	166 (6.2)	0%	171 (6.4)	161 (6)	2%
2	961 (5.1)	171 (6.3)	5%	130 (4.9)	169 (6.3)	6%
3+	8711 (46.6)	1123 (41.6)	10%	1165 (43.5)	1118 (41.7)	4%
Number of hospitalizations						
0	15603 (83.5)	2206 (81.8)	4%	2192 (81.8)	2197 (82)	1%
1	2098 (11.2)	351 (13)	6%	319 (11.9)	346 (12.9)	3%
2	592 (3.2)	90 (3.3)	1%	96 (3.6)	89 (3.3)	2%
3+	400 (2.1)	51 (1.9)	1%	73 (2.7)	48 (1.8)	6%
Number of emergency departments visits						
0	10543 (56.4)	1524 (56.5)	0%	1563 (58.3)	1518 (56.6)	3%
1	3716 (19.9)	574 (21.3)	3%	520 (19.4)	568 (21.2)	4%
2	1838 (9.8)	246 (9.1)	2%	225 (8.4)	242 (9)	2%
3+	2596 (13.9)	354 (13.1)	2%	372 (13.9)	352 (13.1)	2%
Calcium test	3675 (19.7)	519 (19.2)	1%	520 (19.4)	514 (19.2)	1%
Lithium test	11463 (61.3)	1853 (68.7)	16%	1866 (69.6)	1840 (68.7)	2%
Serum creatinine test	13960 (74.7)	2230 (82.7)	20%	2231 (83.2)	2212 (82.5)	2%

TSH test	12727 (68.1)	1995 (73.9)	13%	1998 (74.6)	1980 (73.9)	2%
At home physician services	923 (4.9)	111 (4.1)	4%	132 (4.9)	111 (4.1)	4%
Bone mineral density test	1147 (6.1)	185 (6.9)	3%	216 (8.1)	183 (6.8)	5%
Cardiac catheterization	75 (0.4)	64 (2.4)	17%	42 (1.6)	57 (2.1)	4%
Cardiac stress test	1171 (6.3)	322 (11.9)	20%	294 (11)	312 (11.6)	2%
Carotid ultrasound	367 (2)	113 (4.2)	13%	95 (3.5)	111 (4.1)	3%
Chest Xray	5652 (30.2)	955 (35.4)	11%	855 (31.9)	942 (35.1)	7%
Cataract	379 (2)	76 (2.8)	5%	63 (2.4)	74 (2.8)	3%
Cervical cancer screening	1322 (7.1)	213 (7.9)	3%	205 (7.6)	211 (7.9)	1%
Colorectal cancer screening	2336 (12.5)	425 (15.8)	9%	434 (16.2)	424 (15.8)	1%
Cholesterol test	8566 (45.8)	1661 (61.6)	32%	1625 (60.6)	1645 (61.4)	2%
CT abdomen	1316 (7)	175 (6.5)	2%	196 (7.3)	173 (6.5)	3%
CT extremities	126 (0.7)	20 (0.7)	0%	17 (0.6)	19 (0.7)	1%
CT head	2648 (14.2)	407 (15.1)	3%	382 (14.3)	404 (15.1)	2%
CT neck	229 (1.2)	26 (1)	2%	27 (1)	26 (1)	0%
CT pelvis	1232 (6.6)	172 (6.4)	1%	174 (6.5)	170 (6.3)	1%
CT spine	324 (1.7)	49 (1.8)	1%	44 (1.6)	49 (1.8)	2%
CT thorax	1055 (5.6)	139 (5.2)	2%	150 (5.6)	138 (5.1)	2%
Echocardiography	1604 (8.6)	479 (17.8)	27%	455 (17)	463 (17.3)	1%
Electroencephalography	288 (1.5)	50 (1.9)	3%	32 (1.2)	49 (1.8)	5%
Flu shot	5433 (29.1)	1129 (41.8)	27%	1143 (42.6)	1116 (41.6)	2%
Cytoscopy	583 (3.1)	98 (3.6)	3%	109 (4.1)	96 (3.6)	3%
Hearing test	557 (3)	115 (4.3)	7%	95 (3.5)	110 (4.1)	3%
Mammography	2109 (11.3)	305 (11.3)	0%	294 (11)	304 (11.3)	1%
Prostate specific antigen (PSA) test	680 (3.6)	121 (4.5)	5%	113 (4.2)	120 (4.5)	1%

Holter monitoring	675 (3.6)	165 (6.1)	12%	150 (5.6)	162 (6)	2%
Parathyroid hormone testing	586 (3.1)	115 (4.3)	6%	123 (4.6)	115 (4.3)	1%
Pulmonary function test	1207 (6.5)	232 (8.6)	8%	208 (7.8)	228 (8.5)	3%
Urinalysis	7870 (42.1)	1341 (49.7)	15%	1369 (51.1)	1332 (49.7)	3%
Osmolality	50 (0.3)	12 (0.4)	2%	9 (0.3)	12 (0.4)	2%
Laboratory measurement[k]						
Baseline eGFR[l]						
Not available[m]	8653 (46.3)	1430 (53)	13%	1406 (52.5)	1419 (52.9)	1%
<30 mL/min/1.73 m^2	107 (0.6)	21 (0.8)	2%	25 (0.9)	21 (0.8)	1%
30 ≤ 45 mL/min/1.73 m^2	424 (2.3)	80 (3)	4%	68 (2.5)	80 (3)	3%
45 ≤ 60 mL/min/1.73 m^2	1279 (6.8)	189 (7)	1%	179 (6.7)	186 (6.9)	1%
60 ≤ 90 mL/min/1.73 m^2	4988 (26.7)	631 (23.4)	8%	633 (23.6)	628 (23.4)	0%
90+ mL/min/1.73 m^2	3242 (17.3)	347 (12.9)	12%	369 (13.8)	346 (12.9)	3%
Serum lithium level[n]						
Not available	10616 (56.8)	1619 (60)	6%	1571 (58.6)	1606 (59.9)	3%
0 ≤ 0.6 mmol/L	3418 (18.3)	441 (16.3)	5%	465 (17.4)	439 (16.4)	3%
0.6 ≤ 1 mmol/L	3796 (20.3)	498 (18.5)	5%	513 (19.1)	496 (18.5)	2%
1 ≤ 1.5 mmol/L	803 (4.3)	130 (4.8)	2%	123 (4.6)	129 (4.8)	1%
1.5 ≤ 2 mmol/L	54 (0.3)	9 (0.3)	0%	7 (0.3)	9 (0.3)	0%

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CT = computed tomography, GP/FP = general practitioner/family physician, TSH = thyroid stimulating hormone, eGFR = estimated glomerular filtration rate, LHIN = Local Health Integration Network, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation

[a] Data are presented as the number (percentage) of patients unless otherwise reported.

[b] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

[c] Rural residence was defined as a population of < 10,000 people. Residential information was not available for 6 (0.2%) ACEI/ARB users and 48 (0.3%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into the "No" category during matching.
[d] Income was categorized into fifths of average neighbourhood income on the index date. Income was not available for 14 (0.5%) ACEI/ARB users and 94 (0.5%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into income quintile 3 during matching.
[e] LHIN refers to health authorities responsible for the regional administration of public healthcare services in Ontario.
[f] Comorbid conditions in the five years preceding the index date were considered.
[g]This indicates a history of previous lithium toxicity within one year prior to the index date. Since There is inter-individual variability in patients' sensitivity, and tolerance to lithium (94) and patients could experience lithium toxicity while having therapeutic lithium levels (95, 96), a previous lithium toxicity may be an indicator of being more sensitive or intolerable to lithium. Therefore, we tried to match this variable that could impact the outcome in the comparison groups.
[h] Charlson comorbidity index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.
[i] Baseline medication use in the 120 days preceding the index date was considered. Renin-inhibitors are not included in the table since they were used by less than six patients in each group.
[j] Health care utilization in the one year preceding the index date was considered.
[k] Most recent laboratory test values in a 365–day period before the cohort entry date.
[l]eGFR was calculated using the CKD-EPI equation that does not consider race, for patients with available SCr.
[m] These patients either not checked SCr within one year prior to the index date, or the lab that checked their SCr was not linked with OLIS.
[n] For levels higher than 2 mmol/L, there were less than 6 patients in each cell.

Appendix H. Baseline characteristics of chronic lithium users who were or were not newly dispensed an ACEI before and after matching[a]

Variables	Unmatched			Matched		
	non-ACEI/ARB users (n = 18,693)	ACEI-only users (n = 1,984)	Standardized difference	non-ACEI/ARB users (n = 1,967)	ACEI-only users (n = 1,967)	Standardized difference[b]
Demographics						
Age, mean (SD), years	64.2 (10.6)	66.1 (9.6)	18%	66.1 (10.3)	66.1 (9.6)	1%
Women	10671 (57.1)	1053 (53.1)	8%	1054 (53.6)	1052 (53.5)	0%
Year of cohort entry						
2002	980 (5.2)	145 (7.3)	9%	155 (7.9)	144 (7.3)	2%
2003	960 (5.1)	151 (7.6)	10%	179 (9.1)	151 (7.7)	5%
2004	819 (4.4)	151 (7.6)	14%	153 (7.8)	150 (7.6)	1%
2005	775 (4.1)	131 (6.6)	11%	127 (6.5)	130 (6.6)	0%
2006	725 (3.9)	141 (7.1)	14%	125 (6.4)	138 (7)	2%
2007	717 (3.8)	134 (6.8)	13%	133 (6.8)	130 (6.6)	1%
2008	759 (4.1)	97 (4.9)	4%	91 (4.6)	97 (4.9)	1%
2009	756 (4)	116 (5.8)	8%	103 (5.2)	114 (5.8)	3%
2010	754 (4)	104 (5.2)	6%	96 (4.9)	102 (5.2)	1%
2011	785 (4.2)	94 (4.7)	2%	108 (5.5)	94 (4.8)	3%
2012	765 (4.1)	113 (5.7)	7%	116 (5.9)	112 (5.7)	1%
2013	820 (4.4)	91 (4.6)	1%	82 (4.2)	91 (4.6)	2%
2014	822 (4.4)	84 (4.2)	1%	73 (3.7)	83 (4.2)	3%
2015	863 (4.6)	84 (4.2)	2%	99 (5)	84 (4.3)	3%
2016	947 (5.1)	86 (4.3)	4%	81 (4.1)	86 (4.4)	1%

2017	1010 (5.4)	83 (4.2)	6%	78 (4)	82 (4.2)	1%
2018	1071 (5.7)	69 (3.5)	11%	68 (3.5)	69 (3.5)	0%
2019	1251 (6.7)	44 (2.2)	22%	36 (1.8)	44 (2.2)	3%
2020	1403 (7.5)	40 (2)	26%	40 (2)	40 (2)	0%
2021	1711 (9.2)	26 (1.3)	36%	24 (1.2)	26 (1.3)	1%
Rural residence[c]	2346 (12.6)	273 (13.8)	4%	278 (14.1)	267 (13.6)	1%
Long-term care	1792 (9.6)	103 (5.2)	17%	92 (4.7)	103 (5.2)	2%
Income quintile[d]						
1	5580 (29.9)	552 (27.8)	5%	549 (27.9)	548 (27.9)	0%
2	4040 (21.6)	416 (21)	1%	413 (21)	412 (20.9)	0%
3	3453 (18.5)	382 (19.3)	2%	384 (19.5)	378 (19.2)	1%
4	2820 (15.1)	335 (16.9)	5%	335 (17)	331 (16.8)	1%
5	2800 (15)	299 (15.1)	0%	286 (14.5)	298 (15.1)	2%
LHIN[e]						
1	991 (5.3)	105 (5.3)	0%	104 (5.3)	104 (5.3)	0%
2	1777 (9.5)	186 (9.4)	0%	177 (9)	185 (9.4)	1%
3	990 (5.3)	102 (5.1)	1%	104 (5.3)	101 (5.1)	1%
4	2761 (14.8)	296 (14.9)	0%	258 (13.1)	293 (14.9)	5%
5	477 (2.6)	64 (3.2)	4%	52 (2.6)	63 (3.2)	4%
6	776 (4.2)	81 (4.1)	1%	89 (4.5)	80 (4.1)	2%
7	1943 (10.4)	201 (10.1)	1%	214 (10.9)	201 (10.2)	2%
8	1537 (8.2)	172 (8.7)	2%	174 (8.8)	171 (8.7)	0%
9	1616 (8.6)	166 (8.4)	1%	177 (9)	164 (8.3)	2%
10	1137 (6.1)	111 (5.6)	2%	130 (6.6)	110 (5.6)	4%
11	2369 (12.7)	240 (12.1)	2%	233 (11.8)	238 (12.1)	1%

12	852 (4.6)	71 (3.6)	5%	98 (5)	69 (3.5)	7%
13	1114 (6)	137 (6.9)	4%	114 (5.8)	136 (6.9)	5%
14	353 (1.9)	52 (2.6)	5%	43 (2.2)	52 (2.6)	3%
Lithium prescriber's information						
General practitioner	7983 (42.7)	930 (46.9)	8%	882 (44.8)	919 (46.7)	4%
Psychiatrist	6548 (35)	638 (32.2)	6%	644 (32.7)	635 (32.3)	1%
Other	4162 (22.3)	416 (21)	3%	441 (22.4)	413 (21)	3%
Comorbidities[f]						
Acute kidney injury	577 (3.1)	65 (3.3)	1%	52 (2.6)	65 (3.3)	4%
Alcoholism	1480 (7.9)	103 (5.2)	11%	95 (4.8)	103 (5.2)	2%
Angina	1450 (7.8)	299 (15.1)	23%	244 (12.4)	290 (14.7)	7%
Atrial fibrillation/flutter	384 (2.1)	47 (2.4)	2%	66 (3.4)	46 (2.3)	7%
Bipolar disorder	13395 (71.7)	1424 (71.8)	0%	1427 (72.5)	1410 (71.7)	2%
Chronic kidney disease	1068 (5.7)	161 (8.1)	9%	166 (8.4)	158 (8)	1%
Chronic liver disease	1152 (6.2)	93 (4.7)	7%	92 (4.7)	93 (4.7)	0%
Chronic obstructive pulmonary disease	4963 (26.6)	532 (26.8)	0%	546 (27.8)	528 (26.8)	2%
Cirrhosis	651 (3.5)	50 (2.5)	6%	40 (2)	50 (2.5)	3%
Coronary artery disease	2142 (11.5)	450 (22.7)	30%	422 (21.5)	435 (22.1)	1%
Dementia	3913 (20.9)	370 (18.6)	6%	402 (20.4)	364 (18.5)	5%
Diabetes insipidus	46 (0.2)	7 (0.4)	4%	6 (0.3)	7 (0.4)	2%
Diabetes Mellitus	1065 (5.7)	301 (15.2)	31%	273 (13.9)	291 (14.8)	3%
Glaucoma	874 (4.7)	77 (3.9)	4%	67 (3.4)	76 (3.9)	3%
Major hemorrhage	824 (4.4)	85 (4.3)	0%	84 (4.3)	84 (4.3)	0%
Congestive heart failure	942 (5)	156 (7.9)	12%	134 (6.8)	153 (7.8)	4%
Hyperparathyroidism	53 (0.3)	8 (0.4)	2%	9 (0.5)	8 (0.4)	1%

Hypertension	2561 (13.7)	477 (24)	27%	457 (23.2)	467 (23.7)	1%
Hypokalemia	359 (1.9)	27 (1.4)	4%	40 (2)	27 (1.4)	5%
Hyponatremia	5646 (30.2)	664 (33.5)	7%	628 (31.9)	652 (33.1)	3%
Hypothyroidism	3038 (16.3)	350 (17.6)	3%	339 (17.2)	348 (17.7)	1%
Hypercalcemia	139 (0.7)	18 (0.9)	2%	14 (0.7)	18 (0.9)	2%
Lithium toxicity at baseline[g]	1443 (7.7)	176 (8.9)	4%	168 (8.5)	173 (8.8)	1%
Migraine	1256 (6.7)	117 (5.9)	3%	145 (7.4)	116 (5.9)	6%
Myocardial infarction	212 (1.1)	59 (3)	13%	38 (1.9)	57 (2.9)	7%
Obesity	1479 (7.9)	223 (11.2)	11%	207 (10.5)	221 (11.2)	2%
Parkinson's disease	1167 (6.2)	147 (7.4)	5%	155 (7.9)	144 (7.3)	2%
Peripheral vascular disease	101 (0.5)	25 (1.3)	8%	11 (0.6)	25 (1.3)	7%
Schizophrenia	8024 (42.9)	787 (39.7)	7%	774 (39.3)	779 (39.6)	1%
Seizure	344 (1.8)	26 (1.3)	4%	20 (1)	26 (1.3)	3%
Ischemic stroke	197 (1.1)	50 (2.5)	11%	21 (1.1)	48 (2.4)	10%
Transient ischemic attack	92 (0.5)	20 (1)	6%	16 (0.8)	20 (1)	2%
Depression	9477 (50.7)	887 (44.7)	12%	873 (44.4)	882 (44.8)	1%
Ventricular arrhythmia	3875 (20.7)	397 (20)	2%	398 (20.2)	390 (19.8)	1%
Inflammatory bowel disease	138 (0.7)	8 (0.4)	4%	19 (1)	8 (0.4)	7%
Leukemia	225 (1.2)	24 (1.2)	0%	19 (1)	24 (1.2)	2%
Cancer	4611 (24.7)	510 (25.7)	2%	513 (26.1)	504 (25.6)	1%
Prostatic hyperplasia	1581 (8.5)	209 (10.5)	7%	220 (11.2)	204 (10.4)	3%
Prostatitis	493 (2.6)	60 (3)	2%	84 (4.3)	58 (2.9)	8%
Hypotension	313 (1.7)	38 (1.9)	2%	25 (1.3)	38 (1.9)	5%
Rhabdomyolysis	214 (1.1)	21 (1.1)	0%	18 (0.9)	20 (1)	1%
Multiple sclerosis	173 (0.9)	15 (0.8)	1%	14 (0.7)	15 (0.8)	1%

Urinary retention	358 (1.9)	39 (2)	1%	31 (1.6)	39 (2)	3%
Sepsis	265 (1.4)	32 (1.6)	2%	29 (1.5)	31 (1.6)	1%
Tremor	69 (0.4)	10 (0.5)	1%	7 (0.4)	10 (0.5)	1%
Osteoarthritis	1610 (8.6)	151 (7.6)	4%	179 (9.1)	151 (7.7)	5%
Raynaud's syndrome	555 (3)	94 (4.7)	9%	88 (4.5)	94 (4.8)	1%
Gout	530 (2.8)	80 (4)	7%	61 (3.1)	77 (3.9)	4%
Charlson comorbidity index[h]						
0	15999 (85.6)	1553 (78.3)	19%	1624 (82.6)	1544 (78.5)	10%
1	1309 (7)	215 (10.8)	13%	154 (7.8)	213 (10.8)	10%
2	766 (4.1)	115 (5.8)	8%	98 (5)	112 (5.7)	3%
3+	619 (3.3)	101 (5.1)	9%	91 (4.6)	98 (5)	2%
Medication use[i]						
Alpha-adrenergic blocking agents	191 (1)	28 (1.4)	4%	39 (2)	28 (1.4)	5%
Platelet reducing agents	239 (1.3)	47 (2.4)	8%	43 (2.2)	45 (2.3)	1%
Antibiotics	2099 (11.2)	279 (14.1)	9%	245 (12.5)	276 (14)	4%
Anticonvulsants	700 (3.7)	60 (3)	4%	60 (3.1)	60 (3.1)	0%
Antipsychotics	4160 (22.3)	377 (19)	8%	447 (22.7)	374 (19)	9%
Antiarrhythmic agents	35 (0.2)	9 (0.5)	5%	6 (0.3)	8 (0.4)	2%
Aspirin	267 (1.4)	69 (3.5)	14%	67 (3.4)	68 (3.5)	1%
Benzodiazepines	3167 (16.9)	368 (18.5)	4%	364 (18.5)	366 (18.6)	0%
Calcium channel blockers	1111 (5.9)	216 (10.9)	18%	212 (10.8)	212 (10.8)	0%
Vitamin k antagonists	222 (1.2)	11 (0.6)	6%	10 (0.5)	11 (0.6)	1%
Loop diuretics	487 (2.6)	97 (4.9)	12%	88 (4.5)	94 (4.8)	1%
Thiazide diuretics	429 (2.3)	132 (6.7)	21%	124 (6.3)	126 (6.4)	0%
Potassium-sparing diuretics	94 (0.5)	17 (0.9)	5%	14 (0.7)	17 (0.9)	2%

Tricyclic antidepressants	3091 (16.5)	322 (16.2)	1%	316 (16.1)	319 (16.2)	0%
Digoxin	112 (0.6)	20 (1)	4%	18 (0.9)	19 (1)	1%
Iron preparations	491 (2.6)	49 (2.5)	1%	60 (3.1)	49 (2.5)	4%
H2 receptor antagonist	447 (2.4)	70 (3.5)	7%	71 (3.6)	70 (3.6)	0%
Cholinergic blocking agents	569 (3)	59 (3)	0%	63 (3.2)	59 (3)	1%
Corticosteroids	634 (3.4)	99 (5)	8%	105 (5.3)	97 (4.9)	2%
Beta-adrenergic agonists	982 (5.3)	127 (6.4)	5%	104 (5.3)	127 (6.5)	5%
NSAIDs	957 (5.1)	145 (7.3)	9%	148 (7.5)	143 (7.3)	1%
Alkalinizing agents	101 (0.5)	8 (0.4)	1%	10 (0.5)	8 (0.4)	1%
Selective serotonin reuptake inhibitors	3150 (16.9)	346 (17.4)	1%	358 (18.2)	344 (17.5)	2%
Statins	2511 (13.4)	449 (22.6)	24%	418 (21.3)	442 (22.5)	3%
Typical antipsychotics	660 (3.5)	74 (3.7)	1%	65 (3.3)	74 (3.8)	3%
Vasodilator antihypertensive drugs	274 (1.5)	82 (4.1)	16%	60 (3.1)	79 (4)	5%
Warfarin	270 (1.4)	50 (2.5)	8%	52 (2.6)	49 (2.5)	1%
Cholinesterase inhibitors	461 (2.5)	47 (2.4)	1%	53 (2.7)	47 (2.4)	2%
Overactive bladder drugs	384 (2.1)	63 (3.2)	7%	47 (2.4)	63 (3.2)	5%
Levothyroxine	2715 (14.5)	307 (15.5)	3%	325 (16.5)	304 (15.5)	3%
Number of unique drug names						
0-4	11806 (63.2)	1095 (55.2)	16%	1119 (56.9)	1090 (55.4)	3%
5-9	4421 (23.7)	608 (30.6)	16%	550 (28)	599 (30.5)	5%
10-14	1850 (9.9)	215 (10.8)	3%	242 (12.3)	213 (10.8)	5%
15-19	497 (2.7)	54 (2.7)	0%	45 (2.3)	54 (2.7)	3%
20+	119 (0.6)	12 (0.6)	0%	11 (0.6)	11 (0.6)	0%
Healthcare utilization[j]						
GP/FP visits						

0-4	6079 (32.5)	465 (23.4)	20%	519 (26.4)	465 (23.6)	6%
5-9	4951 (26.5)	607 (30.6)	9%	573 (29.1)	602 (30.6)	3%
10-14	3143 (16.8)	417 (21)	11%	348 (17.7)	415 (21.1)	9%
15-19	1607 (8.6)	200 (10.1)	5%	210 (10.7)	196 (10)	2%
20+	2913 (15.6)	295 (14.9)	2%	317 (16.1)	289 (14.7)	4%
Internist visits						
0	14095 (75.4)	1406 (70.9)	10%	1421 (72.2)	1398 (71.1)	2%
1	2155 (11.5)	268 (13.5)	6%	251 (12.8)	267 (13.6)	2%
2	824 (4.4)	95 (4.8)	2%	102 (5.2)	94 (4.8)	2%
3+	1619 (8.7)	215 (10.8)	7%	193 (9.8)	208 (10.6)	3%
Cardiologist visits						
0	12719 (68)	1156 (58.3)	20%	1173 (59.6)	1152 (58.6)	2%
1	3300 (17.7)	385 (19.4)	45	379 (19.3)	385 (19.6)	1%
2	1186 (6.3)	182 (9.2)	11%	161 (8.2)	180 (9.2)	4%
3+	1488 (8)	261 (13.2)	17%	254 (12.9)	250 (12.7)	1%
Geriatrician visits						
0	17964 (96.1)	1894 (95.5)	3%	1880 (95.6)	1879 (95.5)	0%
1	329 (1.8)	29 (1.5)	2%	41 (2.1)	28 (1.4)	5%
2	132 (0.7)	24 (1.2)	5%	16 (0.8)	23 (1.2)	4%
3+	268 (1.4)	37 (1.9)	4%	30 (1.5)	37 (1.9)	3%
Nephrologist visits						
0	17882 (95.7)	1860 (93.8)	9%	1842 (93.6)	1846 (93.8)	1%
1	457 (2.4)	73 (3.7)	8%	61 (3.1)	71 (3.6)	3%
2	182 (1)	27 (1.4)	4%	40 (2)	26 (1.3)	5%
3+	172 (0.9)	24 (1.2)	3%	24 (1.2)	24 (1.2)	0%

Neurologist visits						
0	16768 (89.7)	1729 (87.1)	8%	1726 (87.7)	1715 (87.2)	2%
1	1000 (5.3)	123 (6.2)	4%	125 (6.4)	123 (6.3)	0%
2	445 (2.4)	67 (3.4)	6%	53 (2.7)	67 (3.4)	4%
3+	480 (2.6)	65 (3.3)	4%	63 (3.2)	62 (3.2)	0%
Psychiatrist visits						
0	7836 (41.9)	924 (46.6)	9%	825 (41.9)	917 (46.6)	9%
1	1185 (6.3)	122 (6.1)	1%	136 (6.9)	119 (6)	4%
2	961 (5.1)	114 (5.7)	3%	94 (4.8)	113 (5.7)	4%
3+	8711 (46.6)	824 (41.5)	10%	912 (46.4)	818 (41.6)	10%
Number of hospitalizations						
0	15603 (83.5)	1599 (80.6)	8%	1583 (80.5)	1592 (80.9)	1%
1	2098 (11.32)	269 (13.6)	7%	258 (13.1)	262 (13.3)	1%
2	592 (3.2)	76 (3.8)	3%	67 (3.4)	74 (3.8)	2%
3+	400 (2.1)	40 (2)	1%	59 (3)	39 (2)	6%
Number of emergency departments visits						
0	10543 (56.4)	1097 (55.3)	2%	1088 (55.3)	1089 (55.4)	0%
1	3716 (19.9)	434 (21.9)	5%	423 (21.5)	429 (21.8)	1%
2	1838 (9.8)	185 (9.3)	2%	191 (9.7)	184 (9.4)	1%
3+	2596 (13.9)	268 (13.5)	1%	265 (13.5)	265 (13.5)	0%
Calcium test	3675 (19.7)	374 (18.9)	2%	382 (19.4)	367 (18.7)	2%
Lithium test	11463 (61.3)	1366 (68.9)	16%	1366 (69.4)	1350 (68.6)	2%
Serum creatinine test	13960 (74.7)	1641 (82.7)	20%	1629 (82.8)	1625 (82.6)	1%
TSH test	12727 (68.1)	1459 (73.5)	12%	1461 (74.3)	1446 (73.5)	2%
At home physician services	923 (4.9)	83 (4.2)	3%	79 (4)	83 (4.2)	1%

Bone mineral density test	1147 (6.1)	138 (7)	4%	156 (7.9)	136 (6.9)	4%
Cardiac catheterization	75 (0.4)	58 (2.9)	20%	37 (1.9)	50 (2.5)	4%
Cardiac stress test	1171 (6.3)	244 (12.3)	21%	247 (12.6)	237 (12)	2%
Carotid ultrasound	367 (2)	90 (4.5)	14%	82 (4.2)	88 (4.5)	1%
Chest Xray	5652 (30.2)	720 (36.3)	13%	669 (34)	707 (35.9)	4%
Cataract	379 (2)	50 (2.5)	3%	55 (2.8)	50 (2.5)	2%
Cervical cancer screening	1322 (7.1)	160 (8.1)	4%	168 (8.5)	160 (8.1)	1%
Colorectal cancer screening	2336 (12.5)	305 (15.4)	8%	284 (14.4)	302 (15.4)	3%
Cholesterol test	8566 (45.8)	1201 (60.5)	30%	1176 (59.8)	1186 (60.3)	1%
CT abdomen	1316 (7)	121 (6.1)	4%	138 (7)	120 (6.1)	4%
CT extremities	126 (0.7)	11 (0.6)	1%	11 (0.6)	11 (0.6)	0%
CT head	2648 (14.2)	308 (15.5)	4%	318 (16.2)	303 (15.4)	2%
CT neck	229 (1.2)	20 (1)	2%	16 (0.8)	20 (1)	2%
CT pelvis	1232 (6.6)	116 (5.8)	3%	120 (6.1)	115 (5.8)	1%
CT spine	324 (1.7)	34 (1.7)	0%	26 (1.3)	34 (1.7)	3%
CT thorax	1055 (5.6)	108 (5.4)	1%	118 (6)	105 (5.3)	3%
Echocardiography	1604 (8.6)	365 (18.4)	29%	361 (18.4)	351 (17.8)	2%
Electroencephalography	288 (1.5)	45 (2.3)	6%	33 (1.7)	44 (2.2)	4%
Flu shot	5433 (29.1)	840 (42.3)	28%	851 (43.3)	831 (42.2)	2%
Cytoscopy	583 (3.1)	76 (3.8)	4%	73 (3.7)	75 (3.8)	1%
Hearing test	557 (3)	80 (4)	5%	75 (3.8)	78 (4)	1%
Mammography	2109 (11.3)	202 (10.2)	4%	196 (10)	202 (10.3)	1%
Prostate specific antigen (PSA) test	680 (3.6)	80 (4)	2%	60 (3.1)	77 (3.9)	4%
Holter monitoring	675 (3.6)	128 (6.5)	13%	121 (6.2)	126 (6.4)	1%
Parathyroid hormone testing	586 (3.1)	83 (4.2)	6%	92 (4.7)	82 (4.2)	2%

Pulmonary function test	1207 (6.5)	166 (8.4)	7%	166 (8.4)	163 (8.3)	0%
Urinalysis	7870 (42.1)	970 (48.9)	14%	991 (50.4)	963 (49)	3%
Osmolality	50 (0.3)	9 (0.5)	3%	11 (0.6)	8 (0.4)	3%
Laboratory measurement[k]						
Baseline eGFR[l]						
Not available[m]	8653 (46.3)	1123 (56.6)	21%	1115 (56.7)	1111 (56.5)	0%
< 30 mL/min/1.73 m^2	107 (0.6)	11 (0.6)	0%	12 (0.6)	11 (0.6)	0%
30 ≤ 45 mL/min/1.73 m^2	424 (2.3)	53 (2.7)	3%	42 (2.1)	53 (2.7)	4%
45 ≤ 60 mL/min/1.73 m^2	1279 (6.8)	132 (6.7)	0%	126 (6.4)	130 (6.6)	1%
60 ≤ 90 mL/min/1.73 m^2	4988 (26.7)	423 (21.3)	13%	401 (20.4)	420 (21.4)	2%
90+ mL/min/1.73 m^2	3242 (17.3)	242 (12.2)	14%	271 (13.8)	242 (12.3)	4%
Serum lithium level[n]						
Not available	10616 (56.8)	1250 (63)	13%	1232 (62.6)	1238 (62.9)	1%
0 ≤ 0.6 mmol/L	3418 (18.3)	308 (15.5)	7%	310 (15.8)	306 (15.6)	1%
0.6 ≤1 mmol/L	3796 (20.3)	334 (16.8)	9%	347 (17.6)	331 (16.8)	2%
1 ≤1.5 mmol/L	803 (4.3)	85 (4.3)	0%	75 (3.8)	85 (4.3)	3%

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CT = computed tomography, GP/FP = general practitioner/family physician, TSH = thyroid stimulating hormone, eGFR = estimated glomerular filtration rate, LHIN = Local Health Integration Network, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation

[a] Data are presented as the number (percentage) of patients unless otherwise reported.

[b] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

[c] Rural residence was defined as a population of < 10,000 people. Residential information was not available for 6 (0.2%) ACEI/ARB users and 48 (0.3%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into the "No" category during matching.

[d] Income was categorized into fifths of average neighbourhood income on the index date. Income was not available for 14 (0.5%) ACEI/ARB users and 94 (0.5%) non-ACEI/ARB users in the unmatched cohort. Missing values in the unmatched cohort were re-classified into income

quintile 3 during matching.

[e] LHIN refers to health authorities responsible for the regional administration of public healthcare services in Ontario.

[f] Comorbid conditions in the five years preceding the index date were considered.

[g]This indicates a history of previous lithium toxicity within one year prior to the index date. Since There is inter-individual variability in patients' sensitivity, and tolerance to lithium (94) and patients could experience lithium toxicity while having therapeutic lithium levels (95, 96), a previous lithium toxicity may be an indicator of being more sensitive or intolerable to lithium. Therefore, we tried to match this variable that could impact the outcome in the comparison groups.

[h] Charlson comorbidity index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.

[i] Baseline medication use in the 120 days preceding the index date was considered. Renin-inhibitors are not included in the table since they were used by less than six patients in each group.

[j] Health care utilization in the one year preceding the index date was considered.

[k] Most recent laboratory test values in a 365–day period before the cohort entry date.

[l]eGFR was calculated using the CKD-EPI equation that does not consider race, for patients with available SCr.

[m] These patients either not checked SCr within one year prior to the index date, or the lab that checked their SCr was not linked with OLIS.

[n] For levels between 1.5 and 2 mmol/L and higher than 2 mmol/L, there were less than 6 patients in each cell.

Appendix I. Baseline characteristics of chronic lithium users ≥ 66 years old, who were or were not newly dispensed an ACEI/ARB before and after matching[a]

Variables	Unmatched			Matched		
	non-ACEI/ARB users (n = 8,433)	ACEI/ARB users (n = 1,410)	Standardized difference	non-ACEI/ARB users (n = 1,389)	ACEI/ARB users (n = 1,389)	Standardized difference[b]
Demographics						
Age, mean (SD), years	74.0 (6.8)	73.3 (6.1)	11%	73.2 (6.2)	73.3 (6.1)	1%
Women	5122 (60.7)	809 (57.4)	7%	805 (58)	800 (57.6)	1%
Year of cohort entry						
2002	592 (7)	102 (7.2)	1%	96 (6.9)	100 (7.2)	1%
2003	545 (6.5)	101 (7.2)	3%	94 (6.8)	100 (7.2)	2%
2004	432 (5.1)	113 (8)	12%	125 (9)	112 (8.1)	3%
2005	387 (4.6)	87 (6.2)	7%	85 (6.1)	86 (6.2)	0%
2006	300 (3.6)	93 (6.6)	14%	72 (5.2)	89 (6.4)	5%
2007	327 (3.9)	79 (5.6)	8%	76 (5.5)	77 (5.5)	0%
2008	312 (3.7)	80 (5.7)	9%	82 (5.9)	79 (5.7)	1%
2009	305 (3.6)	86 (6.1)	12%	78 (5.6)	83 (6)	2%
2010	307 (3.6)	65 (4.6)	5%	55 (4)	62 (4.5)	2%
2011	290 (3.4)	66 (4.7)	7%	76 (5.5)	65 (4.7)	4%
2012	285 (3.4)	64 (4.5)	6%	63 (4.5)	63 (4.5)	0%
2013	334 (4)	61 (4.3)	2%	59 (4.2)	61 (4.4)	1%
2014	347 (4.1)	55 (3.9)	1%	61 (4.4)	55 (4)	2%
2015	366 (4.3)	54 (3.8)	3%	64 (4.6)	54 (3.9)	3%
2016	395 (4.7)	65 (4.6)	0%	55 (4)	65 (4.7)	3%

2017	456 (5.4)	52 (3.7)	8%	39 (2.8)	51 (3.7)	5%
2018	493 (5.8)	59 (4.2)	7%	56 (4)	59 (4.2)	1%
2019	589 (7)	55 (3.9)	14%	68 (4.9)	55 (4)	4%
2020	625 (7.4)	42 (3)	20%	47 (3.4)	42 (3)	2%
2021	746 (8.8)	31 (2.2)	29%	38 (2.7)	31 (2.2)	3%
Rural residence[c]	1131 (13.4)	204 (14.5)	3%	198 (14.3)	202 (14.5)	1%
Long-term care	1392 (16.5)	83 (5.9)	34%	72 (5.2)	83 (6)	3%
Income quintiled						
1	1798 (21.3)	293 (20.8)	1%	284 (20.4)	290 (20.9)	1%
2	1723 (20.4)	285 (20.2)	0%	273 (19.7)	280 (20.2)	1%
3	1661 (19.7)	275 (19.5)	1%	266 (19.2)	273 (19.7)	1%
4	1534 (18.2)	276 (19.6)	4%	303 (21.8)	270 (19.4)	6%
5	1717 (20.4)	281 (19.9)	1%	263 (18.9)	276 (19.9)	3%
LHINe						
1	404 (4.8)	88 (6.2)	6%	88 (6.3)	88 (6.3)	0%
2	756 (9)	131 (9.3)	1%	117 (8.4)	129 (9.3)	3%
3	465 (5.5)	68 (4.8)	3%	73 (5.3)	67 (4.8)	2%
4	1253 (14.9)	204 (14.5)	1%	164 (11.8)	200 (14.4)	8%
5	204 (2.4)	50 (3.5)	7%	41 (3)	48 (3.5)	3%
6	397 (4.7)	66 (4.7)	0%	78 (5.6)	64 (4.6)	5%
7	851 (10.1)	121 (8.6)	5%	136 (9.8)	120 (8.6)	4%
8	754 (8.9)	146 (10.4)	5%	133 (9.6)	143 (10.3)	2%
9	691 (8.2)	114 (8.1)	0%	118 (8.5)	114 (8.2)	1%
10	527 (6.2)	74 (5.2)	4%	86 (6.2)	72 (5.2)	4%
11	1235 (14.6)	190 (13.5)	3%	207 (14.9)	188 (13.5)	4%

12	334 (4)	51 (3.6)	2%	51 (3.7)	50 (3.6)	1%
13	410 (4.9)	78 (5.5)	3%	74 (5.3)	78 (5.6)	1%
14	152 (1.8)	29 (2.1)	2%	23 (1.7)	28 (2)	2%
Lithium prescriber's information						
General practitioner	4275 (50.7)	756 (53.6)	6%	725 (52.2)	742 (53.4)	2%
Psychiatrist	2371 (28.1)	380 (27)	2%	369 (26.6)	377 (27.1)	1%
Other	1787 (21.2)	274 (19.4)	4%	295 (21.2)	270 (19.4)	4%
Comorbiditiesf						
Acute kidney injury	373 (4.4)	67 (4.8)	2%	67 (4.8)	65 (4.7)	0%
Alcoholism	391 (4.6)	56 (4)	3%	48 (3.5)	54 (3.9)	2%
Angina	899 (10.7)	245 (17.4)	19%	204 (14.7)	231 (16.6)	5%
Atrial fibrillation/flutter	309 (3.7)	48 (3.4)	2%	63 (4.5)	47 (3.4)	6%
Bipolar disorder	5752 (68.2)	960 (68.1)	0%	954 (68.7)	944 (68)	2%
Chronic kidney disease	677 (8)	154 (10.9)	10%	157 (11.3)	152 (10.9)	1%
Chronic liver disease	324 (3.8)	49 (3.5)	2%	57 (4.1)	47 (3.4)	4%
Chronic obstructive pulmonary disease	2117 (25.1)	359 (25.5)	1%	351 (25.3)	353 (25.4)	0%
Cirrhosis	197 (2.3)	33 (2.3)	0%	35 (2.5)	31 (2.2)	2%
Coronary artery disease	1421 (16.9)	350 (24.8)	20%	346 (24.9)	333 (24)	2%
Dementia	2969 (35.2)	359 (25.5)	21%	370 (26.6)	354 (25.5)	3%
Diabetes Mellitus	943 (11.2)	331 (23.5)	33%	305 (22)	322 (23.2)	3%
Glaucoma	575 (6.8)	89 (6.3)	2%	75 (5.4)	88 (6.3)	4%
Major hemorrhage	414 (4.9)	63 (4.5)	2%	56 (4)	63 (4.5)	2%
Congestive heart failure	663 (7.9)	139 (9.9)	7%	130 (9.4)	132 (9.5)	0%
Hyperparathyroidism	39 (0.5)	7 (0.5)	0%	7 (0.5)	7 (0.5)	0%
Hypertension	2303 (27.3)	571 (40.5)	28%	567 (40.8)	554 (39.9)	2%

Hypokalemia	222 (2.6)	23 (1.6)	7%	37 (2.7)	23 (1.7)	7%
Hyponatremia	2964 (35.1)	505 (35.8)	1%	464 (33.4)	490 (35.3)	4%
Hypothyroidism	1541 (18.3)	256 (18.2)	0%	253 (18.2)	255 (18.4)	1%
Hypercalcemia	90 (1.1)	17 (1.2)	1%	14 (1)	17 (1.2)	2%
Lithium toxicity at baseline[g]	630 (7.5)	116 (8.2)	3%	95 (6.8)	113 (8.1)	5%
Migraine	400 (4.7)	73 (5.2)	2%	74 (5.3)	72 (5.2)	0%
Myocardial infarction	139 (1.6)	48 (3.4)	12%	37 (2.7)	44 (3.2)	3%
Obesity	463 (5.5)	119 (8.4)	11%	122 (8.8)	115 (8.3)	2%
Parkinson's disease	888 (10.5)	131 (9.3)	4%	136 (9.8)	127 (9.1)	2%
Peripheral vascular disease	70 (0.8)	16 (1.1)	3%	11 (0.8)	15 (1.1)	3%
Schizophrenia	3028 (35.9)	453 (32.1)	8%	428 (30.8)	448 (32.3)	3%
Seizure	139 (1.6)	11 (0.8)	7%	14 (1)	10 (0.7)	3%
Ischemic stroke	154 (1.8)	45 (3.2)	9%	18 (1.3)	45 (3.2)	13%
Transient ischemic attack	74 (0.9)	14 (1)	1%	7 (0.5)	13 (0.9)	5%
Depression	4193 (49.7)	612 (43.4)	13%	625 (45)	605 (43.6)	3%
Ventricular arrhythmia	1920 (22.8)	286 (20.3)	6%	268 (19.3)	280 (20.2)	2%
Inflammatory bowel disease	57 (0.7)	7 (0.5)	3%	14 (1)	7 (0.5)	6%
Leukemia	134 (1.6)	22 (1.6)	0%	20 (1.4)	22 (1.6)	2%
Cancer	2754 (32.7)	465 (33)	1%	447 (32.2)	460 (33.1)	2%
Prostatic hyperplasia	1078 (12.8)	192 (13.6)	2%	197 (14.2)	187 (13.5)	2%
Prostatitis	293 (3.5)	42 (3)	3%	61 (4.4)	40 (2.9)	8%
Hypotension	195 (2.3)	29 (2.1)	1%	34 (2.4)	26 (1.9)	3%
Rhabdomyolysis	130 (1.5)	18 (1.3)	2%	17 (1.2)	17 (1.2)	0%
Multiple sclerosis	53 (0.6)	7 (0.5)	1%	6 (0.4)	7 (0.5)	1%
Urinary retention	257 (3)	38 (2.7)	2%	34 (2.4)	37 (2.7)	2%

Sepsis	143 (1.7)	25 (1.8)	1%	19 (1.4)	25 (1.8)	3%
Tremor	54 (0.6)	7 (0.5)	1%	8 (0.6)	7 (0.5)	1%
Osteoarthritis	1144 (13.6)	138 (9.8)	12%	172 (12.4)	137 (9.9)	8%
Raynaud's syndrome	361 (4.3)	67 (4.8)	2%	72 (5.2)	66 (4.8)	2%
Gout	295 (3.5)	65 (4.6)	6%	42 (3)	62 (4.5)	8%
Charlson comorbidity indexh						
0	6800 (80.6)	1093 (77.5)	8%	1130 (81.4)	1079 (77.7)	9%
1	754 (8.9)	139 (9.9)	3%	107 (7.7)	138 (9.9)	8%
2	480 (5.7)	93 (6.6)	4%	78 (5.6)	90 (6.5)	4%
3+	399 (4.7)	85 (6)	6%	74 (5.3)	82 (5.9)	3%
Medication use[i]						
Alpha-adrenergic blocking agents	170 (2)	32 (2.3)	2%	19 (1.4)	32 (2.3)	7%
Platelet reducing agents	229 (2.7)	56 (4)	7%	44 (3.2)	52 (3.7)	3%
Antibiotics	1915 (22.7)	342 (24.3)	4%	294 (21.2)	339 (24.4)	8%
Anticonvulsants	599 (7.1)	72 (5.1)	8%	77 (5.5)	72 (5.2)	1%
Antipsychotics	3704 (43.9)	444 (31.5)	26%	491 (35.3)	441 (31.7)	8%
Antiarrhythmic agents	34 (0.4)	9 (0.6)	3%	11 (0.8)	7 (0.5)	4%
Aspirin	250 (3)	72 (5.1)	11%	74 (5.3)	70 (5)	1%
Benzodiazepines	2808 (33.3)	409 (29)	9%	407 (29.3)	402 (28.9)	1%
Calcium channel blockers	1002 (11.9)	289 (20.5)	24%	279 (20.1)	279 (20.1)	0%
Vitamin k antagonists	207 (2.5)	16 (1.1)	11%	10 (0.7)	16 (1.2)	5%
Loop diuretics	461 (5.5)	118 (8.4)	11%	123 (8.9)	113 (8.1)	3%
Thiazide diuretics	389 (4.6)	152 (10.8)	23%	153 (11)	146 (10.5)	2%
Potassium-sparing diuretics	84 (1)	25 (1.8)	7%	22 (1.6)	24 (1.7)	1%
Tricyclic antidepressants	2770 (32.8)	374 (26.5)	14%	373 (26.9)	367 (26.4)	1%

Digoxin	109 (1.3)	20 (1.4)	1%	19 (1.4)	19 (1.4)	0%
Iron preparations	459 (5.4)	60 (4.3)	5%	66 (4.8)	59 (4.2)	3%
H2 receptor antagonist	416 (4.9)	78 (5.5)	3%	67 (4.8)	77 (5.5)	3%
Cholinergic blocking agents	527 (6.2)	66 (4.7)	7%	80 (5.8)	65 (4.7)	5%
Corticosteroids	584 (6.9)	120 (8.5)	6%	110 (7.9)	118 (8.5)	2%
Beta-adrenergic agonists	879 (10.4)	140 (9.9)	2%	123 (8.9)	137 (9.9)	3%
NSAIDs	855 (10.1)	170 (12.1)	6%	171 (12.3)	166 (12)	1%
Alkalinizing agents	96 (1.1)	9 (0.6)	5%	6 (0.4)	9 (0.6)	3%
Selective serotonin reuptake inhibitors	2818 (33.4)	413 (29.3)	9%	419 (30.2)	412 (29.7)	1%
Statins	2220 (26.3)	526 (37.3)	24%	518 (37.3)	511 (36.8)	1%
Typical antipsychotics	579 (6.9)	87 (6.2)	3%	64 (4.6)	86 (6.2)	7%
Vasodilator antihypertensive drugs	258 (3.1)	89 (6.3)	15%	65 (4.7)	82 (5.9)	5%
Warfarin	255 (3)	49 (3.5)	3%	65 (4.7)	46 (3.3)	7%
Cholinesterase inhibitors	451 (5.3)	56 (4)	6%	56 (4)	56 (4)	0%
Overactive bladder drugs	360 (4.3)	78 (5.5)	6%	58 (4.2)	78 (5.6)	6%
Levothyroxine	2432 (28.8)	388 (27.5)	3%	384 (27.6)	382 (27.5)	0%
Number of unique drug names						
0-4	2219 (26.3)	369 (26.2)	0%	388 (27.9)	367 (26.4)	3%
5-9	3920 (46.5)	678 (48.1)	3%	640 (46.1)	665 (47.9)	4%
10-14	1715 (20.3)	281 (19.9)	1%	282 (20.3)	277 (19.9)	1%
15-19	466 (5.5)	68 (4.8)	3%	68 (4.9)	68 (4.9)	0%
20+	113 (1.3)	14 (1)	3%	11 (0.8)	12 (0.9)	1%
Healthcare utilizationj						
GP/FP visits						
0-4	2299 (27.3)	299 (21.2)	14%	343 (24.7)	297 (21.4)	8%

5-9	2203 (26.1)	459 (32.6)	14%	399 (28.7)	451 (32.5)	8%
10-14	1560 (18.5)	289 (20.5)	5%	271 (19.5)	285 (20.5)	3%
15-19	767 (9.1)	144 (10.2)	4%	139 (10)	142 (10.2)	1%
20+	1604 (19)	219 (15.5)	9%	237 (17.1)	214 (15.4)	5%
Internist visits						
0	6222 (73.8)	1001 (71)	6%	1003 (72.2)	990 (71.3)	2%
1	993 (11.8)	183 (13)	4%	170 (12.2)	180 (13)	2%
2	397 (4.7)	65 (4.6)	0%	72 (5.2)	64 (4.6)	3%
3+	821 (9.7)	161 (11.4)	6%	144 (10.4)	155 (11.2)	3%
Cardiologist visits						
0	5343 (63.4)	776 (55)	17%	805 (58)	774 (55.7)	5%
1	1603 (19)	272 (19.3)	1%	278 (20)	271 (19.5)	1%
2	631 (7.5)	139 (9.9)	9%	101 (7.3)	138 (9.9)	9%
3+	856 (10.2)	223 (15.8)	17%	205 (14.8)	206 (14.8)	0%
Geriatrician visits						
0	7869 (93.3)	1330 (94.3)	4%	1314 (94.6)	1314 (94.6)	0%
1	235 (2.8)	26 (1.8)	7%	34 (2.4)	25 (1.8)	4%
2	101 (1.2)	21 (1.5)	3%	11 (0.8)	19 (1.4)	6%
3+	228 (2.7)	33 (2.3)	3%	30 (2.2)	31 (2.2)	0%
Nephrologist visits						
0	7990 (94.7)	1301 (92.3)	10%	1280 (92.2)	1282 (92.3)	0%
1	244 (2.9)	55 (3.9)	6%	59 (4.2)	55 (4)	1%
2	95 (1.1)	28 (2)	7%	24 (1.7)	28 (2)	2%
3+	104 (1.2)	26 (1.8)	5%	26 (1.9)	24 (1.7)	2%
Neurologist visits						

0	7434 (88.2)	1225 (86.9)	4%	1211 (87.2)	1207 (86.9)	1%
1	491 (5.8)	95 (6.7)	4%	91 (6.6)	94 (6.8)	1%
2	236 (2.8)	41 (2.9)	1%	43 (3.1)	40 (2.9)	1%
3+	272 (3.2)	49 (3.5)	2%	44 (3.2)	48 (3.5)	2%
Psychiatrist visits						
0	3983 (47.2)	734 (52.1)	10%	691 (49.7)	723 (52.1)	5%
1	516 (6.1)	83 (5.9)	1%	82 (5.9)	79 (5.7)	1%
2	420 (5)	85 (6)	4%	77 (5.5)	84 (6)	2%
3+	3514 (41.7)	508 (36)	12%	539 (38.8)	503 (36.2)	5%
Number of hospitalizations						
0	6818 (80.8)	1119 (79.4)	4%	1139 (82)	1111 (80)	5%
1	1120 (13.3)	204 (14.5)	3%	169 (12.2)	196 (14.1)	6%
2	300 (3.6)	59 (4.2)	3%	45 (3.2)	58 (4.2)	5%
3+	195 (2.3)	28 (2)	2%	36 (2.6)	24 (1.7)	6%
Number of emergency departments visits						
0	4944 (58.6)	808 (57.3)	3%	842 (60.6)	798 (57.5)	6%
1	1698 (20.1)	306 (21.7)	4%	266 (19.2)	302 (21.7)	6%
2	831 (9.9)	137 (9.7)	1%	122 (8.8)	135 (9.7)	3%
3+	960 (11.4)	159 (11.3)	0%	159 (11.4)	154 (11.1)	1%
Calcium test	2063 (24.5)	304 (21.6)	7%	303 (21.8)	298 (21.5)	1%
Lithium test	5655 (67.1)	995 (70.6)	8%	960 (69.1)	977 (70.3)	3%
Serum creatinine test	6767 (80.2)	1181 (83.8)	9%	1167 (84)	1161 (83.6)	1%
TSH test	6085 (72.2)	1049 (74.4)	5%	1029 (74.1)	1033 (74.4)	1%
At home physician services	620 (7.4)	77 (5.5)	8%	65 (4.7)	76 (5.5)	4%
Bone mineral density test	667 (7.9)	130 (9.2)	5%	139 (10)	128 (9.2)	3%

Cardiac catheterization	35 (0.4)	40 (2.8)	19%	25 (1.8)	26 (1.9)	1%
Cardiac stress test	541 (6.4)	186 (13.2)	23%	163 (11.7)	173 (12.5)	2%
Carotid ultrasound	239 (2.8)	67 (4.8)	10%	73 (5.3)	65 (4.7)	3%
Chest Xray	2889 (34.3)	531 (37.7)	7%	506 (36.4)	515 (37.1)	1%
Cataract	289 (3.4)	58 (4.1)	4%	60 (4.3)	56 (4)	2%
Cervical cancer screening	372 (4.4)	79 (5.6)	6%	75 (5.4)	77 (5.5)	0%
Colorectal cancer screening	1068 (12.7)	211 (15)	7%	225 (16.2)	210 (15.1)	3%
Cholesterol test	3735 (44.3)	828 (58.7)	29%	825 (59.4)	810 (58.3)	2%
CT abdomen	659 (7.8)	98 (7)	3%	93 (6.7)	97 (7)	1%
CT extremities	63 (0.7)	9 (0.6)	1%	14 (1)	9 (0.6)	4%
CT head	1483 (17.6)	245 (17.4)	1%	254 (18.3)	242 (17.4)	2%
CT neck	113 (1.3)	13 (0.9)	4%	20 (1.4)	13 (0.9)	5%
CT pelvis	629 (7.5)	95 (6.7)	3%	91 (6.6)	94 (6.8)	1%
CT spine	152 (1.8)	28 (2)	1%	26 (1.9)	28 (2)	1%
CT thorax	546 (6.5)	77 (5.5)	4%	85 (6.1)	76 (5.5)	3%
Echocardiography	902 (10.7)	294 (20.9)	28%	275 (19.8)	276 (19.9)	0%
Electroencephalography	124 (1.5)	22 (1.6)	1%	21 (1.5)	21 (1.5)	0%
Flu shot	3074 (36.5)	717 (50.9)	29%	722 (52)	702 (50.5)	3%
Cytoscopy	356 (4.2)	65 (4.6)	2%	57 (4.1)	64 (4.6)	2%
Hearing test	321 (3.8)	80 (5.7)	9%	57 (4.1)	75 (5.4)	6%
Mammography	917 (10.9)	155 (11)	0%	174 (12.5)	154 (11.1)	4%
Prostate specific antigen (PSA) test	247 (2.9)	50 (3.5)	3%	41 (3)	50 (3.6)	3%
Holter monitoring	409 (4.8)	104 (7.4)	11%	101 (7.3)	101 (7.3)	0%
Parathyroid hormone testing	317 (3.8)	78 (5.5)	8%	85 (6.1)	78 (5.6)	2%
Pulmonary function test	543 (6.4)	130 (9.2)	10%	120 (8.6)	125 (9)	1%

Urinalysis	3847 (45.6)	706 (50.1)	9%	706 (50.8)	697 (50.2)	1%
Laboratory measurementk						
Baseline eGFRl						
Not available[m]	3890 (46.1)	777 (55.1)	18%	752 (54.1)	763 (54.9)	2%
< 30 mL/min/1.73 m^2	70 (0.8)	18 (1.3)	5%	21 (1.5)	18 (1.3)	2%
30 ≤ 45 mL/min/1.73 m^2	308 (3.7)	55 (3.9)	1%	44 (3.2)	53 (3.8)	3%
45 ≤ 60 mL/min/1.73 m^2	841 (10)	122 (8.7)	4%	118 (8.5)	120 (8.6)	0%
60 ≤ 90 mL/min/1.73 m^2	2474 (29.3)	340 (24.1)	12%	346 (24.9)	337 (24.3)	1%
90+ mL/min/1.73 m^2	850 (10.1)	98 (7)	11%	108 (7.8)	98 (7.1)	3%
Serum lithium level[n]						
Not available	4790 (56.8)	868 (61.6)	10%	844 (60.8)	854 (61.5)	1%
0 ≤ 0.6 mmol/L	1768 (21)	251 (17.8)	8%	251 (18.1)	248 (17.9)	1%
0.6 ≤1 mmol/L	1582 (18.8)	228 (16.2)	7%	235 (16.9)	224 (16.1)	2%
1 ≤1.5 mmol/L	280 (3.3)	60 (4.3)	5%	57 (4.1)	60 (4.3)	1%

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CT = computed tomography, GP/FP = general practitioner/family physician, TSH = thyroid stimulating hormone, eGFR = estimated glomerular filtration rate, LHIN = Local Health Integration Network, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation

[a] Data are presented as the number (percentage) of patients unless otherwise reported.

[b] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

[c] Rural residence was defined as a population of < 10,000 people. Missing values in the unmatched cohort were re-classified into the "No" category during matching.

[d] Income was categorized into fifths of average neighbourhood income on the index date. Missing values in the unmatched cohort were re-classified into income quintile 3 during matching.

[e] LHIN refers to health authorities responsible for the regional administration of public healthcare services in Ontario.

[f] Comorbid conditions in the five years preceding the index date were considered.

[g] This indicates a history of previous lithium toxicity within one year prior to the index date. Since There is inter-individual variability in patients' sensitivity, and tolerance to lithium (94) and patients could experience lithium toxicity while having therapeutic lithium levels (95, 96), a previous

lithium toxicity may be an indicator of being more sensitive or intolerable to lithium. Therefore, we tried to match this variable that could impact the outcome in the comparison groups.

[h] Charlson comorbidity index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.

[i] Baseline medication use in the 120 days preceding the index date was considered. Renin-inhibitors are not included in the table since they were used by less than six patients in each group.

[j] Health care utilization in the one year preceding the index date was considered.

[k] Most recent laboratory test values in a 365–day period before the cohort entry date.

[l] eGFR was calculated using the CKD-EPI equation that does not consider race, for patients with available SCr.

[m] These patients either did not check SCr within one year prior to the index date, or the lab that checked their SCr was not linked with OLIS.

[n] For levels between 1.5 and 2 mmol/L and higher than 2 mmol/L, there were less than 6 patients in each cell.

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Publications:

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