# Supplementary Methods

## TriNetX network

This section provides an expanded version of our previous description of the network.1,2

*Legal and ethical status*

TriNetX’s Analytics network is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law which protects the privacy and security of healthcare data. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert, refreshed in December 2020, supersedes the need for TriNetX’s previous waiver from the Western Institutional Review Board (IRB). The network contains data that are provided by participating Health Care Organizations (HCOs), each of which represents and warrants that it has all necessary rights, consents, approvals and authority to provide the data to TriNetX under a Business Associate Agreement (BAA), so long as their name remains anonymous as a data source and their data are utilized for research purposes. The data shared through the TriNetX Platform are attenuated to ensure that they do not include sufficient information to facilitate the determination of which HCO contributed which specific information about a patient.

*Acquisition of data, quality control, and other procedures*

The data are stored onboard a TriNetX appliance – a physical server residing at the institution’s data centre or a virtual hosted appliance. The TriNetX platform is a fleet of these appliances connected into a federated network able to broadcast queries to each appliance. Results are subsequently collected and aggregated.

Once the data are sent to the network, they are mapped to a standard and controlled set of clinical terminologies and undergo a data quality assessment including ‘data cleaning’ that rejects records which do not meet the TriNetX quality standards. HIPAA compliance of the clinical patient data is achieved using de-identification. Different data modalities are available in the network. They include demographics (coded to HL7 version 3 administrative standards), diagnoses (represented by ICD-10-CM codes), procedures (coded in ICD-10-PCS or CPT), measurements (coded to LOINC), and clinical drugs (represented as VA class and/or RxNorm). While extensive information is provided about patients’ diagnoses and procedures, other variables (such as socioeconomic and lifetime factors are not comprehensively represented).

The data from a typical HCO generally go back around 7 years, with some going back 13 years. The data are continuously updated. HCOs update their data at various times, with most refreshing every 1, 2, or 4 weeks.

The data come primarily (>93%) from HCOs in the USA, with the remainder coming from India, Australia, Malaysia, Taiwan, Spain, UK, and Bulgaria. As noted above, to comply with legal frameworks and ethical guidelines guarding against data re-identification, the identity of participating HCOs and their individual contribution to each dataset are not disclosed to researchers.

Data quality assessment followed a standardised strategy wherein the data are reviewed for conformance (adherence to specified standards and formats), completeness (quantifying data presence or absence) and plausibility (believability of the data from a clinical perspective). There are pre-defined metrics for each of the above assessment categories. Results for these metrics are visualised and reviewed for each new site that joins the network as well as on an ongoing basis. Any identified issue is communicated to the data provider and resolved before continuing data collection.

The basic formatting of contributed data is also checked (e.g. to ensure that dates are properly represented). Records are checked against a list of required fields (e.g., patient identifier) and rejects those records for which the required information is missing. Referential integrity checking is done to ensure that data spanning multiple database tables can be successfully joined together. As the data are refreshed, changes in volume of data over time is monitored to ensure data validity. At least one non-demographic fact for each patient is required for them to be counted in the dataset. Patient records with only demographics information are discarded.

The software also undergoes quality control. The engineers testing the software are independent from the engineers developing it. Each test code is checked by two independent testing engineers. Each piece of software is tested extensively against a range of synthetic data (i.e. generated for the purpose of testing) for which the expected output is established independently. If the software fails to return this output, then the software is deemed to have failed the test and is examined and modified accordingly. For statistical software (including that used for propensity score matching, for Kaplan-Meier analysis, etc), an additional quality control step is implemented. Two independent codes are written in two different programming languages (typically R and python) and the statistical results are compared. If discrepancies are identified, then the codes are deemed to have failed the test and are examined and modified accordingly. All the code is reviewed independently by another engineer.

The test strategy follows three levels of granularity:

1. Unit tests: These test specific blocks, or units, of code that perform specific actions (e.g. querying the database).
2. Integration tests: These ensure that different components are working together correctly.
3. End-to-end tests: These tests run the entire system and check the final output.

*Some comments on advantages and disadvantages of EHR data*

One advantage of EHR data, like those in TriNetX, over insurance claim data is that both insured and uninsured patients are included. An advantage of EHR data over survey data is that they represent the diagnostic rates in the population presenting to healthcare facilities. This provides an accurate account of the burden of specific diagnoses on healthcare systems. However, there are also limitations inherent to research using electronic health records,3–5 including TriNetX:

1. Patients with acute or post-acute sequelae of COVID-19 but were not diagnosed are not included leading to underestimation of actual incidences.
2. Despite the matching and use of various comparison cohorts, there may well be residual confounding, particularly related to social and economic factors which are not well captured in EHR networks and which might influence outcomes post COVID-19.
3. We do not know which diagnoses were made in primary or secondary care or specialist facilities, nor by whom.
4. A patient may be seen in different HCOs for different parts of their care, and if one HCO is not part of the federated network then part of their medical records may not be available. Using a network of HCOs (rather than a single HCO) limits this possibility but does not fully remove it.
5. How long a symptom/diagnosis persists is difficult to assess using EHR data as this is not typically coded. As a result, we can comment on incidence of new cases but cannot assess the duration of clinical features.
6. Since the data are presented as they are recorded, we cannot be sure that there has not been mis-recording of information, adding a degree of noise to the data.
7. Historical data before the start of EHRs (or the addition of an HCO to the network) may well be incomplete.

## Definition of cohorts

In the primary analysis, the cohorts were defined based on a recorded serum lithium level (between 0.5 and 1.0 mmol/L for the primary cohort of interest, and between 0.05 and 0.5 for the control cohort). Serum lithium level was encoded as LOINC code 14334-7 in patients’ EHR. A secondary control cohort was defined as those taking valproate (RxNorml code 40254) who did not have a diagnosis of epilepsy (ICD-10 code G40). This secondary control cohort was compared to those with a high lithium level (as defined above) who did not have a diagnosis of epilepsy.

Other cohorts were defined in the robustness analysis, as described in the main manuscript. The specific codes used were as follows:

1. To identify patients who were not vaccinated before or within 6 months after the index lithium level, we excluded from both the primary cohort of interest and the control cohort all those with any of the following codes present in their EHR before or within 6 months of their recorded lithium level:

	1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use
	2. Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted; first dose
	3. Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted; second dose
	4. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage, for intramuscular use
	5. Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage; first dose
	6. Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage; second dose
	7. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x10^10 viral particles/0.5mL dosage, for intramuscular use
	8. Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x10^10 viral particles/0.5mL dosage, single dose
	9. SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein
	10. SARS-CoV-2 (COVID-19) vaccine
2. To identify those with a diagnosis of bipolar disorder, the ICD-10 code F31 had to be present within the patient’s EHR.

## Definition of covariates

To reduce the effect of confounding on associations, cohorts were matched for established or suspected risk factors for COVID-196–9 and for established risk factors for COVID-19 death10 (taken to be risk factors of a more severe COVID-19 illness). These were the covariates used in our previous studies.1,2,11 In this study, in addition to these covariates, cohorts were also matched for common indication for lithium therapy (namely specific mood disorders and personality disorders), and for possible concurrent medications which are known to be associated with different incidence or outcomes of COVID-19, namely antidepressants and fluvoxamine in particular, and antipsychotics and clozapine in particular. The following confounding factors were therefore included (with ICD-10/VA Class/RxNorm codes in brackets):

1. **Age** at the time of diagnosis.
2. **Sex** coded as female, male, or other.
3. **Race** encoded as 6 separate dichotomous variables: White (2106-3), Black or African American (2054-5), American Indian or Alaska Native (1002-5), Asian (2028-9), Native Hawaiian or Other Pacific Islander (2076-8), or Unknown Race (2131-1).
4. **Ethnicity** encoded as Hispanic or Latino (2135-2), Not Hispanic or Latino (2186-5), or Unknown Ethnicity.
5. **Socioeconomic deprivation** encoded as the ICD-10 code for Problems related to housing and economic circumstances (Z59).
6. **Obesity** encoded as one dichotomous variable and one categorical variable: Overweight and obesity (E66) and body mass index (categorised into < 25 kg/m2, 25-30 kg/m2, ≥ 30 kg/m2 which are the WHO thresholds for not obese, pre-obese, and obesity).
7. **Hypertension** encoded as 2 dichotomous and 2 categorical variables: Hypertensive diseases (I10-I16), the now deprecated version that was used until 2018 Hypertension diseases (I10-I15), measurements of systolic blood pressure (categorised into < 140mmHg, 140-160mmHg, and ≥ 160mmHg), and diastolic blood pressure (categorised into < 90mmHg, 90-100mmHg, and ≥ 100mmHg). The blood pressure categories correspond to the absence of hypertension, stage 1 hypertension, and stage 2 (and over) hypertension as per the NICE guidelines.
8. **Diabetes** **mellitus** encoded as 2 dichotomous variables: Type 1 diabetes mellitus (E10) and Type 2 diabetes mellitus (E11).
9. **Chronic lower respiratory diseases** encoded by each sub-category of the corresponding ICD-10 group: Bronchitis, not specified as acute or chronic (J40), Simple and mucopurulent chronic bronchitis (J41), Unspecified chronic bronchitis (J42), Emphysema (J43), Other chronic obstructive pulmonary disease (J44), Asthma (J45), Bronchiectasis (J47).
10. **Nicotine dependence** encoded as the corresponding ICD-10 diagnosis (F17.2).
11. **Substance use disorders** encoded as the ICD-10 code for mental and behavioural disorders due to psychoactive substance use (F10-F19).
12. **Psychotic disorders** encoded as the ICD-10 code for schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20-F29).
13. **Mood disorders** encoded as a single variable (as well as individual codes, see below) with any of the ICD-10 code for mood disorders (F30-F39).
14. **Manic episode** (F30)
15. **Bipolar disorder** (F31)
16. **Major depressive disorder, single episode** (F32)
17. **Major depressive disorder, recurrent** (F33)
18. **Persistent mood disorders** (F34)
19. **Unspecified mood disorder** (F39)
20. **Anxiety disorders** encoded as the ICD-10 code for anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48)
21. **Personality disorders** encoded as disorders of adult personality and behavior (F60-F69)
22. **Heart diseases** encoded as 2 categorical variables: Ischaemic heart disease (I20-I25) and Other forms of heart disease (I30-I52).
23. **Chronic kidney disease** encoded as 2 dichotomous variables: Chronic kidney disease (N18) and Hypertensive chronic kidney disease (I12).
24. **Chronic liver disease** encoded as 8 categorical variables: Alcoholic liver disease (K70), Hepatic failure, not elsewhere classified (K72), Chronic hepatitis, not elsewhere classified (K73), Fibrosis and cirrhosis of liver (K74), Fatty (change of) liver, not elsewhere classified (K76.0), Chronic passive congestion of liver (K76.1), Portal hypertension (K76.6), Other specified diseases of liver (K76.8).
25. **Stroke** encoded as the dichotomous variable Cerebral infarction (I63) .
26. **Dementia** encoded as 6 dichotomous variables: Vascular dementia (F01), Dementia in other diseases classified elsewhere (F02), Unspecified dementia (F03), Alzheimer's disease (G30), Frontotemporal dementia (G31.0), and Dementia with Lewy bodies (G31.83).
27. **Cancer and haematological cancer in particular** encoded as 2 dichotomous variables: Neoplasms (C00-D49) and Malignant neoplasms of lymphoid, hematopoietic and related tissue (C81-C96).
28. **Organ transplant** encoded as 2 dichotomous variables: Renal Transplantation Procedures and Liver Transplantation Procedures.
29. **Rheumatoid arthritis** encoded as 2 dichotomous variables: Rheumatoid arthritis with rheumatoid factor (M05) and Other rheumatoid arthritis (M06).
30. **Lupus** encoded as a dichotomous variable corresponding ICD-10 code (M32).
31. **Psoriasis** encoded as a dichotomous variable corresponding ICD-10 code (L40).
32. **Disorders involving an immune mechanism** encoded as a dichotomous variable “Certain disorders involving the immune mechanism” (D80-D89).
33. **Antipsychotics** as a class, encoded as VA Class CN700
34. **Clozapine** encoded as RxNorm 2626
35. **Antidepressants** as a class, encoded as VA Class CN600
36. **Fluvoxamine** encoded as RxNorm 42355

Each individual code was considered a confounding factor in and of itself so that matching was achieved for each of them individually. For instance, matching was achieved for each subcategory (and not just for the whole category) of chronic lower respiratory diseases. For variables representing diagnoses and socioeconomic deprivation, an individual was considered positive if the diagnostic was recorded at least once in their health record before the index event. For categorical variables representing measurements (i.e. BMI and blood pressures), all available measurements for all individuals were used and propensity score matching sought to define cohorts with similar numbers of measurements falling into each category.

## Definition of outcomes

The primary outcome was a composite of confirmed COVID-19 diagnosis or positive PCR test for SARS-CoV-2, as defined below.

1. A confirmed diagnosis of COVID-19 was defined as the presence of ICD-10 code U07.1 in the patient’ EHR.
2. A positive PCR test for SARS-CoV-2 was defined as any of the following:
	1. Positive SARS-CoV-2 RNA in Respiratory specimen
	2. Positive SARS-CoV-2 RNA in Unspecified specimen
	3. Positive SARS-CoV-2 N gene in Respiratory specimen
	4. Positive SARS-CoV-2 N gene in Unspecified specimen
	5. Positive SARS-CoV-2 RdRp gene in Respiratory specimen
	6. Positive SARS-CoV-2 E gene in Respiratory specimen
	7. Positive SARS-CoV-2 E gene in Unspecified specimen
	8. Positive SARS-CoV-2 RNA panel in Respiratory specimen
	9. Positive SARS-CoV-2 RNA panel in Unspecified specimen
	10. Positive SARS-CoV-2 RNA in Nasopharynx
	11. Positive SARS coronavirus 2 and related RNA
	12. Positive SARS-related coronavirus RNA in Respiratory specimen
	13. Positive SARS coronavirus 2 ORF1ab in Respiratory specimen

A secondary outcome was another respiratory tract infection (ICD-10 codes J00-J22). The negative control (skin infection) was coded as L00-L08.

## Details on analysis of concurrent antidepressant use

Lithium levels might reflect patients’ compliance with medications in general. Because many patients in our sample were receiving concurrent prescriptions of antidepressants, it is possible that the results are in part driven by antidepressant use rather than lithium levels (even though cohorts were matched for past or concurrent antidepressant use). To test this possibility, we compared individuals on lithium who were also taking antidepressants to individuals on lithium who were not.

If indeed the difference between the cohorts with the high and low lithium levels is a mere reflection of the fact that patients with higher levels were more likely to take antidepressants, then we ought to see an even larger difference when comparing patients on lithium who take vs. those who do not take antidepressants regardless of lithium level. In a robustness analysis, we tested this possibility by comparing two cohorts. Both cohorts had a lithium level measured between 0.05 and 1.0 on or after January 19, 2020 and/or had lithium recorded as a medication in their EHR (inclusion of the latter further increases statistical power to detect any difference). The first cohort also had an antidepressant recorded in their medication on or after January 19, 2020, while the second cohort had no antidepressant recorded during that period.

The two cohorts were matched in the same way as in the primary analysis resulting in 8329 individual in each cohort. The hazard ratio for the composite endpoint of confirmed COVID-19 diagnosis or positive PCR test for SARS-CoV-2 was calculated. A hazard ratio significantly lower than 1 would indicate a possible confounding effect of concurrent antidepressant use on our findings.

Of note, this analysis was preferred over an alternative analysis in which patients who also had antidepressants recorded in their EHR were simply excluded from both cohorts. This is because the overlap between lithium and antidepressant prescribing is such that excluding them results in much smaller cohorts (n=3341 in each cohort after matching).

This results in lack of statistical power, which can be demonstrated empirically by repeatedly sampling individuals at random from the primary cohorts to create sub-cohorts of size 3341. Because these cohorts are created by randomly sampling from the main cohort, they lead, on average, to the same magnitude of effect of interest as in the primary analysis. We can then estimate statistical power to detect such an effect with the reduced sample size by calculating the frequency of significant findings among the randomly sampled cohorts. In doing so with 1000 randomly sampled cohorts, we note a statistical power of 14.5%.

Conducting this alternative analysis was done for completeness. Given its lack of statistical power, it provides meaningful information only if the 95% confidence interval of the HR does not contain the HR from the primary analysis (which would suggest that concurrent antidepressant use explains a substantial part of the results).

## Details on statistical analyses

*Implementation details of propensity score matching*

In propensity score matching, the propensity score was calculated using a logistic regression (implemented by the function LogisticRegression of the scikit-learn package in Python 3.7) including each of the covariates mentioned above. To eliminate the influence of ordering of records, the order of the records in the covariate matrix were randomised before matching.

*Testing proportional hazards*

The assumption that the hazards were proportional when accounting for the two phases was tested using the generalized Schoenfeld approach12 implemented in the cox.zph function of the survival package (version 3.2.3) in R.

*E-value*

The E-value allows to quantify the sensitivity of the findings to unmeasured confounders. Specifically, an E-value of *x*, implies that any unmeasured confounder needs to be associated with both the exposure and the outcome of interest with a relative risk of *x*-fold each to explain away the observed association. We used the computation of approximate E-Value for HR with rare (< 15%) outcomes as recommended.13

# Supplementary Tables

**Supplementary Table 1** – Characteristics of the unmatched and matched cohorts with high (0.5-1.0 mmol/L) and low (0.05-0.5 mmol/L) serum lithium level. SMD = Standardised Mean Difference.

|  |  |  |
| --- | --- | --- |
|  | **Before matching** | **After matching** |
|  | **High level** | **Low level** | **SMD** | **High level** | **Low level** | **SMD** |
| Number | 14008 | 12546 | - | 11791 | 11791 | - |
| DEMOGRAPHICS |  |  |  |  |  |  |
| Age; mean (SD); y | 43.3 (17.7) | 41.6 (17.4) | 0.1 | 42.0 (17.4) | 42.0 (17.4) | 0.003 |
| Sex; n (%) |  |  |  |  |  |  |
|  Female | 7767 (55.4) | 6798 (54.2) | 0.03 | 6452 (54.7) | 6434 (54.6) | 0.003 |
|  Male | 6234 (44.5) | 5740 (45.8) | 0.03 | 5333 (45.2) | 5351 (45.4) | 0.003 |
|  Other | 10 (0.07) | 10 (0.08) | 0.003 | 10 (0.09) | 10 (0.09) | 0 |
| Race; n (%) |  |  |  |  |  |  |
|  White | 10836 (77.4) | 9223 (73.5) | 0.09 | 8837 (74.9) | 8856 (75.1) | 0.004 |
|  Black or African American | 1155 (8.2) | 1254 (10.0) | 0.06 | 1102 (9.3) | 1096 (9.3) | 0.002 |
|  Asian | 254 (1.8) | 212 (1.7) | 0.009 | 208 (1.8) | 205 (1.7) | 0.002 |
|  American Indian or Alaska Native | 59 (0.4) | 72 (0.6) | 0.02 | 58 (0.5) | 61 (0.5) | 0.004 |
|  Native Hawaiian or Other Pacific Islander | 20 (0.1) | 20 (0.2) | 0.004 | 19 (0.2) | 17 (0.1) | 0.004 |
|  Unknown | 1684 (12.0) | 1765 (14.1) | 0.06 | 1567 (13.3) | 1556 (13.2) | 0.003 |
| Ethnicity; n (%) |  |  |  |  |  |  |
|  Hispanic or Latino | 896 (6.4) | 954 (7.6) | 0.05 | 837 (7.1) | 840 (7.1) | 0.001 |
|  Not Hispanic of Latino | 10054 (71.8) | 8668 (69.1) | 0.06 | 8254 (70.0) | 8269 (70.1) | 0.003 |
|  Unknown | 3058 (21.8) | 2924 (23.3) | 0.04 | 2700 (22.9) | 2682 (22.7) | 0.004 |
| Socioeconomic deprivation; n (%) | 791 (5.6) | 795 (6.3) | 0.03 | 722 (6.1) | 725 (6.1) | 0.001 |
| COMORBIDITIES; n (%) |  |  |  |  |  |  |
| Overweight and obesity | 3253 (23.2) | 2859 (22.8) | 0.01 | 2704 (22.9) | 2696 (22.9) | 0.002 |
| Hypertensive disease | 4108 (29.3) | 3558 (28.4) | 0.02 | 3379 (28.7) | 3360 (28.5) | 0.004 |
| Diabetes mellitus |  |  |  |  |  |  |
|  Type 1 diabetes mellitus | 246 (1.8) | 222 (1.8) | 0.001 | 212 (1.8) | 212 (1.8) | 0 |
|  Type 2 diabetes mellitus | 1873 (13.4) | 1580 (12.6) | 0.02 | 1516 (12.9) | 1508 (12.8) | 0.002 |
| Chronic lower respiratory diseases |  |  |  |  |  |  |
|  Bronchitis; not specified as acute or chronic | 723 (5.2) | 595 (4.7) | 0.02 | 584 (5.0) | 566 (4.8) | 0.007 |
|  Simple and mucopurulent chronic bronchitis | 69 (0.5) | 52 (0.4) | 0.01 | 49 (0.4) | 51 (0.4) | 0.003 |
|  Unspecified chronic bronchitis | 75 (0.5) | 63 (0.5) | 0.005 | 64 (0.5) | 59 (0.5) | 0.006 |
|  Emphysema | 220 (1.6) | 197 (1.6) | 2.00E-05 | 181 (1.5) | 185 (1.6) | 0.003 |
|  Other chronic obstructive pulmonary disease | 808 (5.8) | 678 (5.4) | 0.02 | 660 (5.6) | 650 (5.5) | 0.004 |
|  Asthma | 2001 (14.3) | 1802 (14.4) | 0.002 | 1709 (14.5) | 1704 (14.5) | 0.001 |
|  Bronchiectasis | 43 (0.3) | 43 (0.3) | 0.006 | 40 (0.3) | 37 (0.3) | 0.004 |
| Nicotine dependence | 3330 (23.8) | 3156 (25.2) | 0.03 | 2912 (24.7) | 2913 (24.7) | 2.00E-04 |
| Psychiatric comorbidities |  |  |  |  |  |  |
|  Substance misuse | 5363 (38.3) | 5086 (40.5) | 0.05 | 4696 (39.8) | 4693 (39.8) | 5.00E-04 |
|  Psychotic disorders | 3835 (27.4) | 3504 (27.9) | 0.01 | 3287 (27.9) | 3292 (27.9) | 9.00E-04 |
|  Mood disorders | 11666 (83.3) | 10219 (81.5) | 0.05 | 9611 (81.5) | 9643 (81.8) | 0.007 |
|  Manic episode | 1307 (9.3) | 964 (7.7) | 0.06 | 973 (8.3) | 947 (8.0) | 0.008 |
|  Bipolar disorder | 9586 (68.4) | 7812 (62.3) | 0.1 | 7580 (64.3) | 7586 (64.3) | 0.001 |
|  Major depressive disorder; single episode | 5253 (37.5) | 5088 (40.6) | 0.06 | 4661 (39.5) | 4646 (39.4) | 0.003 |
|  Major depressive disorder; recurrent | 2979 (21.3) | 2943 (23.5) | 0.05 | 2664 (22.6) | 2683 (22.8) | 0.004 |
|  Persistent mood disorder | 990 (7.1) | 938 (7.5) | 0.02 | 874 (7.4) | 867 (7.4) | 0.002 |
|  Unspecified mood disorder | 2130 (15.2) | 1928 (15.4) | 0.004 | 1816 (15.4) | 1802 (15.3) | 0.003 |
|  Anxiety disorders | 7916 (56.5) | 7198 (57.4) | 0.02 | 6742 (57.2) | 6726 (57.0) | 0.003 |
|  Personality disorders | 2225 (15.9) | 2033 (16.2) | 0.009 | 1903 (16.1) | 1904 (16.1) | 2.00E-04 |
| Heart disease |  |  |  |  |  |  |
|  Ischemic heart diseases | 848 (6.1) | 783 (6.2) | 0.008 | 738 (6.3) | 729 (6.2) | 0.003 |
|  Other forms of heart disease | 2797 (20.0) | 2499 (19.9) | 0.001 | 2351 (19.9) | 2333 (19.8) | 0.004 |
| Chronic kidney diseases |  |  |  |  |  |  |
|  Chronic kidney disease (CKD) | 829 (5.9) | 580 (4.6) | 0.06 | 579 (4.9) | 563 (4.8) | 0.006 |
|  Hypertensive chronic kidney disease | 325 (2.3) | 234 (1.9) | 0.03 | 229 (1.9) | 226 (1.9) | 0.002 |
| Chronic liver disease |  |  |  |  |  |  |
|  Alcoholic liver disease | 92 (0.7) | 113 (0.9) | 0.03 | 90 (0.8) | 88 (0.7) | 0.002 |
|  Hepatic failure; not elsewhere classified | 94 (0.7) | 113 (0.9) | 0.03 | 90 (0.8) | 91 (0.8) | 0.001 |
|  Chronic hepatitis; not elsewhere classified | 32 (0.2) | 27 (0.2) | 0.003 | 27 (0.2) | 26 (0.2) | 0.002 |
|  Fibrosis and cirrhosis of liver | 160 (1.1) | 169 (1.3) | 0.02 | 147 (1.2) | 152 (1.3) | 0.004 |
|  Fatty (change of) liver; not elsewhere classified | 633 (4.5) | 589 (4.7) | 0.008 | 540 (4.6) | 543 (4.6) | 0.001 |
|  Chronic passive congestion of liver | 55 (0.4) | 53 (0.4) | 0.005 | 44 (0.4) | 47 (0.4) | 0.004 |
|  Portal hypertension | 60 (0.4) | 60 (0.5) | 0.007 | 54 (0.5) | 54 (0.5) | 0 |
|  Other specified diseases of liver | 355 (2.5) | 346 (2.8) | 0.01 | 312 (2.6) | 319 (2.7) | 0.004 |
| Cerebral infarction | 314 (2.2) | 257 (2.0) | 0.01 | 254 (2.2) | 246 (2.1) | 0.005 |
| Dementia |  |  |  |  |  |  |
|  Vascular dementia | 114 (0.8) | 93 (0.7) | 0.008 | 93 (0.8) | 89 (0.8) | 0.004 |
|  Dementia in other diseases classified elsewhere | 172 (1.2) | 130 (1.0) | 0.02 | 131 (1.1) | 127 (1.1) | 0.003 |
|  Unspecified dementia | 277 (2.0) | 210 (1.7) | 0.02 | 212 (1.8) | 206 (1.7) | 0.004 |
|  Alzheimer disease | 85 (0.6) | 59 (0.5) | 0.02 | 63 (0.5) | 59 (0.5) | 0.005 |
|  Frontotemporal dementia | 17 (0.1) | 10 (0.08) | 0.01 | 14 (0.1) | 10 (0.09) | 0.01 |
|  Dementia with Lewy bodies | 25 (0.2) | 18 (0.1) | 0.009 | 19 (0.2) | 18 (0.2) | 0.002 |
| Neoplasms |  |  |  |  |  |  |
|  Neoplasms (any) | 2819 (20.1) | 2286 (18.2) | 0.05 | 2199 (18.6) | 2190 (18.6) | 0.002 |
|  Haematological malignancy | 101 (0.7) | 103 (0.8) | 0.01 | 92 (0.8) | 91 (0.8) | 0.001 |
| Organ transplant |  |  |  |  |  |  |
|  Renal Transplantation Procedures | 10 (0.07) | 10 (0.08) | 0.003 | 10 (0.09) | 10 (0.09) | 0 |
|  Liver Transplantation Procedures | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) | NA |
| Psoriasis | 294 (2.1) | 212 (1.7) | 0.03 | 216 (1.8) | 205 (1.7) | 0.007 |
| Rheumatoid arthritis |  |  |  |  |  |  |
|  Rheumatoid arthritis with rheumatoid factor | 39 (0.3) | 28 (0.2) | 0.01 | 31 (0.3) | 28 (0.2) | 0.005 |
|  Other rheumatoid arthritis | 174 (1.2) | 146 (1.2) | 0.007 | 139 (1.2) | 139 (1.2) | 0 |
| Systemic lupus erythematosus (SLE) | 73 (0.5) | 57 (0.5) | 0.01 | 57 (0.5) | 57 (0.5) | 0 |
| Disorders involving the immune mechanism | 239 (1.7) | 230 (1.8) | 0.01 | 213 (1.8) | 214 (1.8) | 6.00E-04 |
| MEDICATIONS; n (%) |  |  |  |  |  |  |
|  Antipsychotics | 9698 (69.2) | 8548 (68.1) | 0.02 | 8067 (68.4) | 8076 (68.5) | 0.002 |
|  Clozapine | 584 (4.2) | 447 (3.6) | 0.03 | 441 (3.7) | 433 (3.7) | 0.004 |
|  Antidepressants | 8901 (63.5) | 8261 (65.8) | 0.05 | 7712 (65.4) | 7675 (65.1) | 0.007 |
|  Fluvoxamine | 261 (1.9) | 221 (1.8) | 0.008 | 220 (1.9) | 213 (1.8) | 0.004 |

**Supplementary Table 2** – Characteristics of the matched cohorts with high serum lithium level (0.5-1.0 mmol/L) and those taking valproate. SMD = Standardised Mean Difference.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Lithium (high)** | **Valproate** | **SMD** |
| Number | 13346 | 13346 | - |
| DEMOGRAPHICS |  |  |  |
| Age; mean (SD); y | 43.4 (17.7) | 43.2 (17.7) | 0.01 |
| Sex; n (%) |  |  |  |
|  Female | 7405 (55.5) | 7206 (54.0) | 0.03 |
|  Male | 5934 (44.5) | 6134 (46.0) | 0.03 |
|  Other | 10 (0.07) | 10 (0.07) | 0 |
| Race; n (%) |  |  |  |
|  White | 10289 (77.1) | 10145 (76.0) | 0.03 |
|  Black or African American | 1078 (8.1) | 1074 (8.0) | 0.001 |
|  Asian | 242 (1.8) | 226 (1.7) | 0.009 |
|  American Indian or Alaska Native | 57 (0.4) | 65 (0.5) | 0.009 |
|  Native Hawaiian or Other Pacific Islander | 19 (0.1) | 17 (0.1) | 0.004 |
|  Unknown | 1661 (12.4) | 1819 (13.6) | 0.04 |
| Ethnicity; n (%) |  |  |  |
|  Hispanic or Latino | 854 (6.4) | 776 (5.8) | 0.02 |
|  Not Hispanic of Latino | 9442 (70.7) | 9086 (68.1) | 0.06 |
|  Unknown | 3050 (22.9) | 3484 (26.1) | 0.08 |
| Socioeconomic deprivation; n (%) | 713 (5.3) | 752 (5.6) | 0.01 |
| COMORBIDITIES; n (%) |  |  |  |
| Overweight and obesity | 2983 (22.4) | 2911 (21.8) | 0.01 |
| Hypertensive disease | 3784 (28.4) | 3693 (27.7) | 0.02 |
| Diabetes mellitus |  |  |  |
|  Type 1 diabetes mellitus | 224 (1.7) | 230 (1.7) | 0.003 |
|  Type 2 diabetes mellitus | 1725 (12.9) | 1739 (13.0) | 0.003 |
| Chronic lower respiratory diseases |  |  |  |
|  Bronchitis; not specified as acute or chronic | 664 (5.0) | 657 (4.9) | 0.002 |
|  Simple and mucopurulent chronic bronchitis | 64 (0.5) | 72 (0.5) | 0.008 |
|  Unspecified chronic bronchitis | 68 (0.5) | 73 (0.5) | 0.005 |
|  Emphysema | 194 (1.5) | 217 (1.6) | 0.01 |
|  Other chronic obstructive pulmonary disease | 709 (5.3) | 739 (5.5) | 0.01 |
|  Asthma | 1827 (13.7) | 1791 (13.4) | 0.008 |
|  Bronchiectasis | 37 (0.3) | 37 (0.3) | 0 |
| Nicotine dependence | 3089 (23.1) | 3199 (24.0) | 0.02 |
| Psychiatric comorbidities |  |  |  |
|  Substance misuse | 5028 (37.7) | 5143 (38.5) | 0.02 |
|  Psychotic disorders | 3501 (26.2) | 3685 (27.6) | 0.03 |
|  Mood disorders | 11044 (82.8) | 11060 (82.9) | 0.003 |
|  Manic episode | 1197 (9.0) | 1223 (9.2) | 0.007 |
|  Bipolar disorder | 9065 (67.9) | 9161 (68.6) | 0.02 |
|  Major depressive disorder; single episode | 4851 (36.3) | 4794 (35.9) | 0.009 |
|  Major depressive disorder; recurrent | 2758 (20.7) | 2764 (20.7) | 0.001 |
|  Persistent mood disorder | 908 (6.8) | 933 (7.0) | 0.007 |
|  Unspecified mood disorder | 1894 (14.2) | 1920 (14.4) | 0.006 |
|  Anxiety disorders | 7360 (55.1) | 7331 (54.9) | 0.004 |
|  Personality disorders | 1970 (14.8) | 2042 (15.3) | 0.02 |
| Heart disease |  |  |  |
|  Ischemic heart diseases | 759 (5.7) | 775 (5.8) | 0.005 |
|  Other forms of heart disease | 2534 (19.0) | 2513 (18.8) | 0.004 |
| Chronic kidney diseases |  |  |  |
|  Chronic kidney disease (CKD) | 766 (5.7) | 742 (5.6) | 0.008 |
|  Hypertensive chronic kidney disease | 303 (2.3) | 326 (2.4) | 0.01 |
| Chronic liver disease |  |  |  |
|  Alcoholic liver disease | 78 (0.6) | 81 (0.6) | 0.003 |
|  Hepatic failure; not elsewhere classified | 79 (0.6) | 77 (0.6) | 0.002 |
|  Chronic hepatitis; not elsewhere classified | 29 (0.2) | 37 (0.3) | 0.01 |
|  Fibrosis and cirrhosis of liver | 140 (1.0) | 138 (1.0) | 0.001 |
|  Fatty (change of) liver; not elsewhere classified | 567 (4.2) | 534 (4.0) | 0.01 |
|  Chronic passive congestion of liver | 49 (0.4) | 48 (0.4) | 0.001 |
|  Portal hypertension | 48 (0.4) | 54 (0.4) | 0.007 |
|  Other specified diseases of liver | 318 (2.4) | 306 (2.3) | 0.006 |
| Cerebral infarction | 250 (1.9) | 246 (1.8) | 0.002 |
| Dementia |  |  |  |
|  Vascular dementia | 84 (0.6) | 88 (0.7) | 0.004 |
|  Dementia in other diseases classified elsewhere | 145 (1.1) | 149 (1.1) | 0.003 |
|  Unspecified dementia | 244 (1.8) | 243 (1.8) | 6.00E-04 |
|  Alzheimer disease | 67 (0.5) | 67 (0.5) | 0 |
|  Frontotemporal dementia | 11 (0.08) | 14 (0.1) | 0.007 |
|  Dementia with Lewy bodies | 24 (0.2) | 24 (0.2) | 0 |
| Neoplasms |  |  |  |
|  Neoplasms (any) | 2610 (19.6) | 2419 (18.1) | 0.04 |
|  Haematological malignancy | 90 (0.7) | 84 (0.6) | 0.006 |
| Organ transplant |  |  |  |
|  Renal Transplantation Procedures | 10 (0.07) | 10 (0.07) | 0 |
|  Liver Transplantation Procedures | 0 (0.0) | 10 (0.07) | 0.04 |
| Psoriasis | 266 (2.0) | 243 (1.8) | 0.01 |
| Rheumatoid arthritis |  |  |  |
|  Rheumatoid arthritis with rheumatoid factor | 38 (0.3) | 35 (0.3) | 0.004 |
|  Other rheumatoid arthritis | 166 (1.2) | 153 (1.1) | 0.009 |
| Systemic lupus erythematosus (SLE) | 63 (0.5) | 69 (0.5) | 0.006 |
| Disorders involving the immune mechanism | 202 (1.5) | 198 (1.5) | 0.002 |
| MEDICATIONS; n (%) |  |  |  |
|  Antipsychotics | 9125 (68.4) | 9179 (68.8) | 0.009 |
|  Clozapine | 490 (3.7) | 554 (4.2) | 0.02 |
|  Antidepressants | 8401 (62.9) | 8278 (62.0) | 0.02 |
|  Fluvoxamine | 230 (1.7) | 242 (1.8) | 0.007 |

**Supplementary Table 3** – Characteristics of the matched cohorts with consistently high (0.5-1.0 mmol/L) and consistently low (0.05-0.5 mmol/L) serum lithium level (i.e. with no lithium level outside the respective range within 6 months of the index level). SMD = Standardised Mean Difference.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **High level** | **Low level** | **SMD** |
| Number | 6448 | 6448 | - |
| DEMOGRAPHICS |  |  |  |
| Age; mean (SD); y | 41.8 (17.4) | 41.8 (17.3) | 0.001 |
| Sex; n (%) |  |  |  |
|  Female | 3523 (54.6) | 3522 (54.6) | 3.00E-04 |
|  Male | 2920 (45.3) | 2920 (45.3) | 0 |
|  Other | 10 (0.2) | 10 (0.2) | 0 |
| Race; n (%) |  |  |  |
|  White | 4892 (75.9) | 4899 (76.0) | 0.003 |
|  Black or African American | 536 (8.3) | 545 (8.5) | 0.005 |
|  Asian | 114 (1.8) | 116 (1.8) | 0.002 |
|  American Indian or Alaska Native | 32 (0.5) | 32 (0.5) | 0 |
|  Native Hawaiian or Other Pacific Islander | 10 (0.2) | 10 (0.2) | 0 |
|  Unknown | 868 (13.5) | 849 (13.2) | 0.009 |
| Ethnicity; n (%) |  |  |  |
|  Hispanic or Latino | 499 (7.7) | 507 (7.9) | 0.005 |
|  Not Hispanic of Latino | 4845 (75.1) | 4820 (74.8) | 0.009 |
|  Unknown | 1104 (17.1) | 1121 (17.4) | 0.007 |
| Socioeconomic deprivation; n (%) | 362 (5.6) | 366 (5.7) | 0.003 |
| COMORBIDITIES; n (%) |  |  |  |
| Overweight and obesity | 1449 (22.5) | 1438 (22.3) | 0.004 |
| Hypertensive disease | 1805 (28.0) | 1778 (27.6) | 0.009 |
| Diabetes mellitus |  |  |  |
|  Type 1 diabetes mellitus | 97 (1.5) | 99 (1.5) | 0.003 |
|  Type 2 diabetes mellitus | 751 (11.6) | 741 (11.5) | 0.005 |
| Chronic lower respiratory diseases |  |  |  |
|  Bronchitis; not specified as acute or chronic | 288 (4.5) | 282 (4.4) | 0.005 |
|  Simple and mucopurulent chronic bronchitis | 29 (0.5) | 28 (0.4) | 0.002 |
|  Unspecified chronic bronchitis | 29 (0.5) | 29 (0.5) | 0 |
|  Emphysema | 89 (1.4) | 92 (1.4) | 0.004 |
|  Other chronic obstructive pulmonary disease | 319 (4.9) | 318 (4.9) | 7.00E-04 |
|  Asthma | 906 (14.1) | 909 (14.1) | 0.001 |
|  Bronchiectasis | 13 (0.2) | 17 (0.3) | 0.01 |
| Nicotine dependence | 1540 (23.9) | 1551 (24.1) | 0.004 |
| Psychiatric comorbidities |  |  |  |
|  Substance misuse | 2466 (38.2) | 2496 (38.7) | 0.01 |
|  Psychotic disorders | 1537 (23.8) | 1542 (23.9) | 0.002 |
|  Mood disorders | 5262 (81.6) | 5279 (81.9) | 0.007 |
|  Manic episode | 406 (6.3) | 410 (6.4) | 0.003 |
|  Bipolar disorder | 4018 (62.3) | 4039 (62.6) | 0.007 |
|  Major depressive disorder; single episode | 2586 (40.1) | 2555 (39.6) | 0.01 |
|  Major depressive disorder; recurrent | 1441 (22.3) | 1415 (21.9) | 0.01 |
|  Persistent mood disorder | 463 (7.2) | 462 (7.2) | 6.00E-04 |
|  Unspecified mood disorder | 929 (14.4) | 919 (14.3) | 0.004 |
|  Anxiety disorders | 3609 (56.0) | 3612 (56.0) | 9.00E-04 |
|  Personality disorders | 969 (15.0) | 971 (15.1) | 9.00E-04 |
| Heart disease |  |  |  |
|  Ischemic heart diseases | 394 (6.1) | 386 (6.0) | 0.005 |
|  Other forms of heart disease | 1229 (19.1) | 1190 (18.5) | 0.02 |
| Chronic kidney diseases |  |  |  |
|  Chronic kidney disease (CKD) | 270 (4.2) | 256 (4.0) | 0.01 |
|  Hypertensive chronic kidney disease | 107 (1.7) | 103 (1.6) | 0.005 |
| Chronic liver disease |  |  |  |
|  Alcoholic liver disease | 45 (0.7) | 50 (0.8) | 0.009 |
|  Hepatic failure; not elsewhere classified | 46 (0.7) | 45 (0.7) | 0.002 |
|  Chronic hepatitis; not elsewhere classified | 16 (0.2) | 13 (0.2) | 0.01 |
|  Fibrosis and cirrhosis of liver | 75 (1.2) | 78 (1.2) | 0.004 |
|  Fatty (change of) liver; not elsewhere classified | 262 (4.1) | 262 (4.1) | 0 |
|  Chronic passive congestion of liver | 23 (0.4) | 22 (0.3) | 0.003 |
|  Portal hypertension | 27 (0.4) | 28 (0.4) | 0.002 |
|  Other specified diseases of liver | 149 (2.3) | 141 (2.2) | 0.008 |
| Cerebral infarction | 127 (2.0) | 117 (1.8) | 0.01 |
| Dementia |  |  |  |
|  Vascular dementia | 30 (0.5) | 28 (0.4) | 0.005 |
|  Dementia in other diseases classified elsewhere | 56 (0.9) | 55 (0.9) | 0.002 |
|  Unspecified dementia | 92 (1.4) | 87 (1.3) | 0.007 |
|  Alzheimer disease | 30 (0.5) | 25 (0.4) | 0.01 |
|  Frontotemporal dementia | 10 (0.2) | 10 (0.2) | 0 |
|  Dementia with Lewy bodies | 10 (0.2) | 10 (0.2) | 0 |
| Neoplasms |  |  |  |
|  Neoplasms (any) | 1164 (18.1) | 1180 (18.3) | 0.006 |
|  Haematological malignancy | 52 (0.8) | 51 (0.8) | 0.002 |
| Organ transplant |  |  |  |
|  Renal Transplantation Procedures | 0 (0.0) | 0 (0.0) | NA |
|  Liver Transplantation Procedures | 0 (0.0) | 0 (0.0) | NA |
| Psoriasis | 107 (1.7) | 106 (1.6) | 0.001 |
| Rheumatoid arthritis |  |  |  |
|  Rheumatoid arthritis with rheumatoid factor | 15 (0.2) | 18 (0.3) | 0.009 |
|  Other rheumatoid arthritis | 78 (1.2) | 84 (1.3) | 0.008 |
| Systemic lupus erythematosus (SLE) | 32 (0.5) | 29 (0.5) | 0.007 |
| Disorders involving the immune mechanism | 113 (1.8) | 110 (1.7) | 0.004 |
| MEDICATIONS; n (%) |  |  |  |
|  Antipsychotics | 4219 (65.4) | 4220 (65.4) | 3.00E-04 |
|  Clozapine | 182 (2.8) | 175 (2.7) | 0.007 |
|  Antidepressants | 4172 (64.7) | 4176 (64.8) | 0.001 |
|  Fluvoxamine | 112 (1.7) | 107 (1.7) | 0.006 |

**Supplementary Table 4** – Characteristics of the matched cohorts with high (0.5-1.0 mmol/L) and low (0.05-0.5 mmol/L) serum lithium level who did not receive a COVID-19 vaccine before or in the 6 months after the index lithium level. SMD = Standardised Mean Difference.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **High level** | **Low level** | **SMD** |
| Number | 11508 | 11508 | - |
| DEMOGRAPHICS |  |  |  |
| Age; mean (SD); y | 41.8 (17.4) | 42.0 (17.4) | 0.01 |
| Sex; n (%) |  |  |  |
|  Female | 6289 (54.6) | 6258 (54.4) | 0.005 |
|  Male | 5212 (45.3) | 5243 (45.6) | 0.005 |
|  Other | 10 (0.09) | 10 (0.09) | 0 |
| Race; n (%) |  |  |  |
|  White | 8588 (74.6) | 8582 (74.6) | 0.001 |
|  Black or African American | 1070 (9.3) | 1079 (9.4) | 0.003 |
|  Asian | 191 (1.7) | 195 (1.7) | 0.003 |
|  American Indian or Alaska Native | 57 (0.5) | 56 (0.5) | 0.001 |
|  Native Hawaiian or Other Pacific Islander | 16 (0.1) | 17 (0.1) | 0.002 |
|  Unknown | 1586 (13.8) | 1579 (13.7) | 0.002 |
| Ethnicity; n (%) |  |  |  |
|  Hispanic or Latino | 815 (7.1) | 813 (7.1) | 7.00E-04 |
|  Not Hispanic of Latino | 7954 (69.1) | 7971 (69.3) | 0.003 |
|  Unknown | 2739 (23.8) | 2724 (23.7) | 0.003 |
| Socioeconomic deprivation; n (%) | 679 (5.9) | 683 (5.9) | 0.001 |
| COMORBIDITIES; n (%) |  |  |  |
| Overweight and obesity | 2567 (22.3) | 2545 (22.1) | 0.005 |
| Hypertensive disease | 3216 (27.9) | 3209 (27.9) | 0.001 |
| Diabetes mellitus |  |  |  |
|  Type 1 diabetes mellitus | 204 (1.8) | 202 (1.8) | 0.001 |
|  Type 2 diabetes mellitus | 1446 (12.6) | 1435 (12.5) | 0.003 |
| Chronic lower respiratory diseases |  |  |  |
|  Bronchitis; not specified as acute or chronic | 533 (4.6) | 543 (4.7) | 0.004 |
|  Simple and mucopurulent chronic bronchitis | 34 (0.3) | 45 (0.4) | 0.02 |
|  Unspecified chronic bronchitis | 57 (0.5) | 56 (0.5) | 0.001 |
|  Emphysema | 168 (1.5) | 173 (1.5) | 0.004 |
|  Other chronic obstructive pulmonary disease | 616 (5.4) | 624 (5.4) | 0.003 |
|  Asthma | 1625 (14.1) | 1614 (14.0) | 0.003 |
|  Bronchiectasis | 34 (0.3) | 35 (0.3) | 0.002 |
| Nicotine dependence | 2850 (24.8) | 2842 (24.7) | 0.002 |
| Psychiatric comorbidities |  |  |  |
|  Substance misuse | 4564 (39.7) | 4547 (39.5) | 0.003 |
|  Psychotic disorders | 3183 (27.7) | 3176 (27.6) | 0.001 |
|  Mood disorders | 9332 (81.1) | 9341 (81.2) | 0.002 |
|  Manic episode | 941 (8.2) | 899 (7.8) | 0.01 |
|  Bipolar disorder | 7377 (64.1) | 7393 (64.2) | 0.003 |
|  Major depressive disorder; single episode | 4451 (38.7) | 4422 (38.4) | 0.005 |
|  Major depressive disorder; recurrent | 2531 (22.0) | 2491 (21.6) | 0.008 |
|  Persistent mood disorder | 824 (7.2) | 813 (7.1) | 0.004 |
|  Unspecified mood disorder | 1744 (15.2) | 1724 (15.0) | 0.005 |
|  Anxiety disorders | 6508 (56.6) | 6460 (56.1) | 0.008 |
|  Personality disorders | 1853 (16.1) | 1810 (15.7) | 0.01 |
| Heart disease |  |  |  |
|  Ischemic heart diseases | 705 (6.1) | 719 (6.2) | 0.005 |
|  Other forms of heart disease | 2226 (19.3) | 2251 (19.6) | 0.005 |
| Chronic kidney diseases |  |  |  |
|  Chronic kidney disease (CKD) | 559 (4.9) | 545 (4.7) | 0.006 |
|  Hypertensive chronic kidney disease | 220 (1.9) | 217 (1.9) | 0.002 |
| Chronic liver disease |  |  |  |
|  Alcoholic liver disease | 82 (0.7) | 83 (0.7) | 0.001 |
|  Hepatic failure; not elsewhere classified | 83 (0.7) | 86 (0.7) | 0.003 |
|  Chronic hepatitis; not elsewhere classified | 25 (0.2) | 24 (0.2) | 0.002 |
|  Fibrosis and cirrhosis of liver | 136 (1.2) | 145 (1.3) | 0.007 |
|  Fatty (change of) liver; not elsewhere classified | 516 (4.5) | 518 (4.5) | 8.00E-04 |
|  Chronic passive congestion of liver | 45 (0.4) | 46 (0.4) | 0.001 |
|  Portal hypertension | 48 (0.4) | 50 (0.4) | 0.003 |
|  Other specified diseases of liver | 288 (2.5) | 290 (2.5) | 0.001 |
| Cerebral infarction | 228 (2.0) | 237 (2.1) | 0.006 |
| Dementia |  |  |  |
|  Vascular dementia | 83 (0.7) | 83 (0.7) | 0 |
|  Dementia in other diseases classified elsewhere | 116 (1.0) | 118 (1.0) | 0.002 |
|  Unspecified dementia | 200 (1.7) | 202 (1.8) | 0.001 |
|  Alzheimer disease | 60 (0.5) | 55 (0.5) | 0.006 |
|  Frontotemporal dementia | 12 (0.1) | 10 (0.09) | 0.006 |
|  Dementia with Lewy bodies | 13 (0.1) | 15 (0.1) | 0.005 |
| Neoplasms |  |  |  |
|  Neoplasms (any) | 2068 (18.0) | 2056 (17.9) | 0.003 |
|  Haematological malignancy | 87 (0.8) | 78 (0.7) | 0.009 |
| Organ transplant |  |  |  |
|  Renal Transplantation Procedures | 10 (0.09) | 0 (0.0) | 0.04 |
|  Liver Transplantation Procedures | 0 (0.0) | 0 (0.0) | NA |
| Psoriasis | 206 (1.8) | 192 (1.7) | 0.009 |
| Rheumatoid arthritis |  |  |  |
|  Rheumatoid arthritis with rheumatoid factor | 19 (0.2) | 25 (0.2) | 0.01 |
|  Other rheumatoid arthritis | 126 (1.1) | 129 (1.1) | 0.002 |
| Systemic lupus erythematosus (SLE) | 53 (0.5) | 53 (0.5) | 0 |
| Disorders involving the immune mechanism | 199 (1.7) | 204 (1.8) | 0.003 |
| MEDICATIONS; n (%) |  |  |  |
|  Antipsychotics | 7888 (68.5) | 7830 (68.0) | 0.01 |
|  Clozapine | 408 (3.5) | 413 (3.6) | 0.002 |
|  Antidepressants | 7429 (64.6) | 7399 (64.3) | 0.005 |
|  Fluvoxamine | 201 (1.7) | 193 (1.7) | 0.005 |

**Supplementary Table 5** – Characteristics of the matched cohorts with high (0.5-1.0 mmol/L) and low (0.05-0.5 mmol/L) serum lithium level who had a diagnosis of bipolar disorder. SMD = Standardised Mean Difference.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **High** | **Low** | **SMD** |
| Number | 7607 | 7607 | - |
| DEMOGRAPHICS |  |  |  |
| Age; mean (SD); y | 42.8 (17.1) | 42.9 (17.1) | 0.005 |
| Sex; n (%) |  |  |  |
|  Female | 4276 (56.2) | 4279 (56.3) | 8.00E-04 |
|  Male | 3329 (43.8) | 3327 (43.7) | 5.00E-04 |
|  Other | 10 (0.1) | 10 (0.1) | 0 |
| Race; n (%) |  |  |  |
|  White | 5839 (76.8) | 5847 (76.9) | 0.002 |
|  Black or African American | 665 (8.7) | 663 (8.7) | 9.00E-04 |
|  Asian | 144 (1.9) | 141 (1.9) | 0.003 |
|  American Indian or Alaska Native | 33 (0.4) | 35 (0.5) | 0.004 |
|  Native Hawaiian or Other Pacific Islander | 11 (0.1) | 10 (0.1) | 0.004 |
|  Unknown | 915 (12.0) | 911 (12.0) | 0.002 |
| Ethnicity; n (%) |  |  |  |
|  Hispanic or Latino | 600 (7.9) | 595 (7.8) | 0.002 |
|  Not Hispanic of Latino | 5842 (76.8) | 5849 (76.9) | 0.002 |
|  Unknown | 1165 (15.3) | 1163 (15.3) | 7.00E-04 |
| Socioeconomic deprivation; n (%) | 577 (7.6) | 577 (7.6) | 0 |
| COMORBIDITIES; n (%) |  |  |  |
| Overweight and obesity | 2039 (26.8) | 2026 (26.6) | 0.004 |
| Hypertensive disease | 2500 (32.9) | 2511 (33.0) | 0.003 |
| Diabetes mellitus |  |  |  |
|  Type 1 diabetes mellitus | 166 (2.2) | 156 (2.1) | 0.009 |
|  Type 2 diabetes mellitus | 1117 (14.7) | 1115 (14.7) | 7.00E-04 |
| Chronic lower respiratory diseases |  |  |  |
|  Bronchitis; not specified as acute or chronic | 421 (5.5) | 437 (5.7) | 0.009 |
|  Simple and mucopurulent chronic bronchitis | 40 (0.5) | 41 (0.5) | 0.002 |
|  Unspecified chronic bronchitis | 46 (0.6) | 49 (0.6) | 0.005 |
|  Emphysema | 146 (1.9) | 149 (2.0) | 0.003 |
|  Other chronic obstructive pulmonary disease | 515 (6.8) | 525 (6.9) | 0.005 |
|  Asthma | 1291 (17.0) | 1297 (17.1) | 0.002 |
|  Bronchiectasis | 33 (0.4) | 32 (0.4) | 0.002 |
| Nicotine dependence | 2309 (30.4) | 2314 (30.4) | 0.001 |
| Psychiatric comorbidities |  |  |  |
|  Substance misuse | 3591 (47.2) | 3607 (47.4) | 0.004 |
|  Psychotic disorders | 2287 (30.1) | 2285 (30.0) | 6.00E-04 |
|  Mood disorders | 7409 (97.4) | 7407 (97.4) | 0.002 |
|  Manic episode | 889 (11.7) | 855 (11.2) | 0.01 |
|  Bipolar disorder | 7206 (94.7) | 7206 (94.7) | 0 |
|  Major depressive disorder; single episode | 3213 (42.2) | 3195 (42.0) | 0.005 |
|  Major depressive disorder; recurrent | 1665 (21.9) | 1668 (21.9) | 0.001 |
|  Persistent mood disorder | 556 (7.3) | 554 (7.3) | 0.001 |
|  Unspecified mood disorder | 1374 (18.1) | 1366 (18.0) | 0.003 |
|  Anxiety disorders | 4871 (64.0) | 4864 (63.9) | 0.002 |
|  Personality disorders | 1377 (18.1) | 1367 (18.0) | 0.003 |
| Heart disease |  |  |  |
|  Ischemic heart diseases | 579 (7.6) | 584 (7.7) | 0.002 |
|  Other forms of heart disease | 1776 (23.3) | 1759 (23.1) | 0.005 |
| Chronic kidney diseases |  |  |  |
|  Chronic kidney disease (CKD) | 449 (5.9) | 451 (5.9) | 0.001 |
|  Hypertensive chronic kidney disease | 194 (2.5) | 200 (2.6) | 0.005 |
| Chronic liver disease |  |  |  |
|  Alcoholic liver disease | 75 (1.0) | 74 (1.0) | 0.001 |
|  Hepatic failure; not elsewhere classified | 68 (0.9) | 74 (1.0) | 0.008 |
|  Chronic hepatitis; not elsewhere classified | 17 (0.2) | 20 (0.3) | 0.008 |
|  Fibrosis and cirrhosis of liver | 114 (1.5) | 109 (1.4) | 0.005 |
|  Fatty (change of) liver; not elsewhere classified | 418 (5.5) | 424 (5.6) | 0.003 |
|  Chronic passive congestion of liver | 34 (0.4) | 36 (0.5) | 0.004 |
|  Portal hypertension | 44 (0.6) | 41 (0.5) | 0.005 |
|  Other specified diseases of liver | 247 (3.2) | 249 (3.3) | 0.001 |
| Cerebral infarction | 186 (2.4) | 184 (2.4) | 0.002 |
| Dementia |  |  |  |
|  Vascular dementia | 74 (1.0) | 67 (0.9) | 0.01 |
|  Dementia in other diseases classified elsewhere | 97 (1.3) | 93 (1.2) | 0.005 |
|  Unspecified dementia | 159 (2.1) | 149 (2.0) | 0.009 |
|  Alzheimer disease | 48 (0.6) | 42 (0.6) | 0.01 |
|  Frontotemporal dementia | 10 (0.1) | 10 (0.1) | 0 |
|  Dementia with Lewy bodies | 15 (0.2) | 13 (0.2) | 0.006 |
| Neoplasms |  |  |  |
|  Neoplasms (any) | 1658 (21.8) | 1675 (22.0) | 0.005 |
|  Haematological malignancy | 73 (1.0) | 70 (0.9) | 0.004 |
| Organ transplant |  |  |  |
|  Renal Transplantation Procedures | 10 (0.1) | 10 (0.1) | 0 |
|  Liver Transplantation Procedures | 0 (0.0) | 0 (0.0) | NA |
| Psoriasis | 152 (2.0) | 164 (2.2) | 0.01 |
| Rheumatoid arthritis |  |  |  |
|  Rheumatoid arthritis with rheumatoid factor | 17 (0.2) | 18 (0.2) | 0.003 |
|  Other rheumatoid arthritis | 112 (1.5) | 114 (1.5) | 0.002 |
| Systemic lupus erythematosus (SLE) | 38 (0.5) | 41 (0.5) | 0.005 |
| Disorders involving the immune mechanism | 155 (2.0) | 149 (2.0) | 0.006 |
| MEDICATIONS; n (%) |  |  |  |
|  Antipsychotics | 5695 (74.9) | 5682 (74.7) | 0.004 |
|  Clozapine | 261 (3.4) | 250 (3.3) | 0.008 |
|  Antidepressants | 5294 (69.6) | 5306 (69.8) | 0.003 |
|  Fluvoxamine | 134 (1.8) | 133 (1.7) | 0.001 |

# Supplementary Figures



**Supplementary Fig. 1** Kaplan-Meier curves for the other outcomes between the cohorts with high vs. low serum level. The shaded areas around the curves represent the 95% confidence intervals.



**Supplementary Fig. 2** Kaplan-Meier curves comparing the incidence of the primary outcome (i.e. composite of COVID-19 diagnosis or positive PCR test for SARS-CoV-2) in the secondary analysis and robustness analyses, namely when comparing high serum lithium level to valproate prescription (top left), comparing cohorts who had consistently high vs. consistently low lithium level (top right), comparing cohorts with high vs. low serum lithium level who did not receive a COVID-19 vaccine before and up to 6 months after the index lithium level (bottom left), and comparing individuals with high vs. low serum lithium level who had a recorded diagnosis of bipolar disorder (bottom right). The shaded areas around the curves represent the 95% confidence intervals.

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