# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eMethods

*Sensitivity analyses of the association between bipolar disorder and osteoporosis*

First, in order to test for outcome misclassification, we repeated the Cox proportional hazard regression described above restricting the outcome to "osteoporosis with pathological fracture" (ICD-10: M80). Second, as the bipolar disorder cohort consists of both incident patients (those having received the incident diagnosis of bipolar disorder on or after their 40$^{th}$ birthday) and prevalent patients (those having received the incident bipolar disorder diagnosis before turning 40 years), we repeated the Cox proportional hazard regression after stratifying on incident/prevalent status, using the osteoporosis definition from the main analysis as outcome.

*Sensitivity analyses of lithium treatment for bipolar disorder and the risk of developing osteoporosis*

These sensitivity analyses involved the exact same modifications as outlined above under "*Sensitivity analyses of the association between bipolar disorder and osteoporosis"*

**eTable 1: Definition of variables based on Anatomical Therapeutic Chemical (ATC-codes) and International Classification of Diseases 10 (ICD-10) codes.**

| | |
|---|---|
| **Mental disorders:** | |
| Schizophrenia and schizoaffective disorder | ICD-10: F20, F25 |
| Bipolar disorder | ICD-10: F30-31 |
| Eating disorder | ICD-10: F50 |
| | |
| **Medications:** | |
| Lithium | ATC: N05AN01 |
| Antipsychotics | ATC: N05A (excluding N05AN01)* |
| Valproate | ATC: N03AG01 |
| Lamotrigine | ATC: N03AX09 |
| Systemic corticosteroids | ATC: H02AB |
| Sedative medications (benzodiazepines and hypnotics) | ATC: N05BA and N05C |
| | |
| **Osteoporosis:** | |
| Osteoporosis with a pathological fracture | ICD-10: M80 |
| Osteoporosis without a pathological fracture | ICD-10: M81 |
| Osteoporosis in other disease | ICD-10:M82 |
| Medication used against osteoporosis | ATC: M05B |
| | |
| **Charlson Comorbidity Index:** | |
| Myocardial infarction | ICD-10: I21-I23 |
| Congestive Heart failure | ICD-10: I50, I11.0, I13.0, I13.2 |
| Peripheral vascular disease | ICD-10: I70-I74, I77 |
| Cerebrovascular disease | ICD-10: I60-I69, G45, G46 |
| Dementia | ICD-10: F00-F03, F05.1, G30 |
| Chronic pulmonary disease | ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 |
| Connective tissue disease | ICD-10: M05, M06, M08, M09, M30-M36, D86 |
| Ulcer disease | ICD-10: K22.1, K25-K28 |
| Mild liver disease | ICD-10: B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0 |
| Hemiplegia | ICD-10: G81, G82 |
| Moderate to severe renal disease | ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61 |
| Any tumor | ICD-10: C00-C75 |
| Leukemia | ICD-10: C91-C95 |
| Lymphoma | ICD-10: C81-C85, C88, C90, C96 |
| Moderate to severe liver disease | ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 |
| Metastatic solid tumor | ICD-10: C76-C80 |
| AIDS | ICD-10: B21-B24 |

* Distribution of users of the specific antipsychotics (first redeemed prescription of an antipsychotic: N05AA01): (chlorpromazine): 15; N05AA02 (levomepromazine): 615; N05AA03+N05AA04 (promazine+acepromazine): 6; N05AB02 (fluphenazine): 16; N05AB03 (perphenazine): 329; N05AB04 (prochlorprenazine): 18; N05AC01 (periciazine): 16; N05AC02 (thioridazine): 53; N05AD01 (haloperidol): 693; N05AD03+N05AD05 (melperone+pipamperone): 73; N05AE03 (sertindole): 9; N05AE04 (ziprasidone): 176; N05AE05 (lurasidone): 6; N05AF01 (flupentixol): 334; N05AF03 (chlorprotixene): 1,770; N05AF05 (zuclopentixol): 1,315; N05AG02 (pimozide): 44; N05AG03 (penfluriol): 18; N05AH02 (clozapine): 38; N05AH03 (olanzapine): 3,512; N05AH04 (quetiapine): 5,603; N05AH05 (asenapine): 13; N05AL01 (sulpiride): 43; N05AL05 (amisulpride): 27; N05AX08 (risperidone): 1,388; N05AX12 (aripiprazole): 704; N05AX13 (paliperidone): 30.

**eTable 2: Baseline characteristics of the patients with bipolar disorder and the age- and sex-matched reference individuals, stratified by sex.**

| | Reference individuals (N=114,560) | | Individuals with bipolar disorder | |
|---|---|---|---|---|
| **Characteristics** | **Male (N=49,725)** | **Female (N=64,835)** | **Male (N=9,945)** | **Female (N=12,967)** |
| **Age, median (IQR)** | 50.7 (41.5-60.4) | 50.1 (41.0-61.5) | 50.7 (41.6-60.4) | 50.1 (41.0-61.5) |
| **Female, N (%)** | X | X | X | X |
| **Charlson Comorbidity index** | | | | |
| 0 | 46,175 (92.9%) | 60,452 (93.2%) | 8,424 (84.7%) | 11,194 (86.3%) |
| 1 | 2,690 (5.4%) | 3,518 (5.4%) | 1,090 (11.0%) | 1,345 (10.4%) |
| 2 | 860 (1.7%) | 865 (1.3%) | 431 (4.3%) | 428 (3.3%) |
| | | | | |
| **Type of Charlson Comorbidity** | | | | |
| Acute myocardial infaction | 286 (0.6%) | 185 (0.3%) | 88 (0.9%) | 62 (0.5%) |
| Congestive heart failure | 313 (0.6%) | 246 (0.4%) | 132 (1.3%) | 107 (0.8%) |
| Peripheral vascular disease | 319 (0.6%) | 295 (0.5%) | 104 (1.0%) | 78 (0.6%) |
| Cerebrovascular disease | 538 (1.1%) | 566 (0.9%) | 306 (3.1%) | 298 (2.3%) |
| Dementia | 85 (0.2%) | 122 (1.2%) | 93 (0.9%) | 98 (0.8%) |
| Pulmonary disease | 560 (1.1%) | 866 (1.3%) | 246 (2.5%) | 435 (3.6%) |
| Connective tissue disorder | 163 (0.3%) | 446 (0.7%) | 46 (0.5%) | 145 (1.1%) |
| Ulcer | 185 (0.4%) | 235 (0.4%) | 105 (1.1%) | 105 (0.8%) |
| Mild liver disease | 144 (0.3%) | 143 (0.2%) | 127 (1.3%) | 99 (0.8%) |
| Paraplegia | 33 (0.1%) | 30 (0.0%) | 12 (0.1%) | 9 (0.1%) |
| Diabetes | 630 (1.3%) | 634 (1.0%) | 300 (3.0%) | 316 (2.4%) |
| Diabetes with complication | 322 (0.6%) | 276 (0.4%) | 132 (1.3%) | 127 (1.0%) |
| Renal disease | 188 (0.4%) | 151 (0.2%) | 102 (1.0%) | 115 (0.9%) |
| Solid tumor | 718 (1.4%) | 1,097 (1.7%) | 214 (2.2%) | 277 (2.1%) |
| Leukemia | 31 (0.1%) | 24 (0.0%) | 10 (0.1%) | 11 (0.1%) |
| Lymphoma | 62 (0.1%) | 57 (0.1%) | 19 (0.2%) | 19 (0.1%) |
| Severe liver disease | 33 (0.1%) | 27 (0.0%) | 32 (0.3%) | 22 (0.2%) |
| Metastatic tumor | 73 (0.1%) | 118 (0.2%) | 30 (0.3%) | 30 (0.2%) |
| Aids | 27 (0.1%) | 25 (0.0%) | 26 (0.3%) | 5 (0.0%) |
| **Eating disorder** | 0 (0.0%) | 5 (0.0%) | X | X |
| **Prior medication** | | | | |
| Systemic corticosteroids | 603 (1.2%) | 940 (1.4%) | 158 (1.6%) | 290 (2.2%) |
| Sedatives | 3,289 (6.6%) | 8,234 (12.7%) | 4,377 (44.0%) | 6,990 (53.9%) |

X = Too few cases to report due to the risk of identification of individuals.

**eTable 3: Association between bipolar disorder and osteoporosis stratified by incident/prevalent bipolar disorder status**

| INCIDENT | Number of individuals with osteoporosis | Incidence rate per 1,000 years of follow-up (95%CI) | Hazard rate ratio (95%CI)* |
|---|---|---|---|
| **Individuals with incident bipolar disorder (4,937)** | 85 | 2.52 (2.04-3.12) | 1.26 (1.00-1.60) |
| **Age- and sex-matched reference individuals (24,685)** | 358 | 2.05 (1.84-2.27) | 1.00 (ref.) |

| PREVALENT | Number of individuals with osteoporosis | Incidence rate per 1,000 years of follow-up (95%CI) | Hazard rate ratio (95%CI)* |
|---|---|---|---|
| **Individuals with prevalent bipolar disorder (17,975)** | 1500 | 10.11 (9.61-10.63) | 1.14 (1.08-1.21) |
| **Age- and sex-matched reference individuals (89,875)** | 7788 | 9.09 (8.89-9.30) | 1.00 (ref.) |

*Unadjusted (matched on age and sex).

**eTable 4: Association between bipolar disorder and osteoporotic fractures**

| | Number of individuals with osteoporosis | Incidence rate per 1,000 years of follow-up (95%CI) | Hazard rate ratio (95%CI)* |
|---|---|---|---|
| **Individuals with bipolar disorder** | 274 | 1.45 (1.29-1.63) | 1.36 (1.19-1.55) |
| **Age- and sex-matched reference individuals** | 1,208 | 1.13 (1.06-1.19) | 1.00 (ref.) |

*Unadjusted (matched on age and sex).

**eTable 5: Association between bipolar disorder and osteoporosis stratified by sex**

| | Number of individuals with osteoporosis | Follow-up time | Incidence rate per 1,000 years follow-up (95%CI) | Hazard rate ratio (95% CI) |
|---|---|---|---|---|
| **Females** | | | | |
| Patients with bipolar disorder | 1,253 | 104,393.29 | 12.00 (11.36-12.69) | **1.07 (1.01-1.13)** |
| Age- and sex-matched reference individuals | 6,743 | 583,800.87 | 11.55 (11.28-11.83) | 1.00 (ref) |
| **Males** | | | | |
| Patients with bipolar disorder | 332 | 77,770.995 | 4.27 (3.83-4.75) | **1.42 (1.26-1.60)** |
| Age- and sex matched reference individuals | 1,403 | 447,729.94 | 3.13 (2.97-3.30) | 1.00 (ref) |

Statistically significant results are marked in **bold**.

**eTable 6: Association between bipolar disorder and osteoporosis stratified by incident/prevalent bipolar disorder status**

| | Unadjusted<br>Hazard rate ratio (95%CI) | Partly adjusted[a]<br>Hazard rate ratio (95%CI) | Fully adjusted[b]<br>Hazard rate ratio (95%CI) |
|---|---|---|---|
| **LITHIUM** | | | |
| **Incident (N=1,402)** | | | |
| Treatment duration model[c] | **0.33 (0.13-0.82)** | **0.35 (0.13-0.92)** | **0.35 (0.13-0.94)** |
| Intention-to-treat model[d] | 0.65 (0.40-1.06) | 0.70 (0.42-1.18) | 0.70 (0.42-1.19) |
| **Prevalent (N=7,348)** | | | |
| Treatment duration model[c] | **0.63 (0.54-0.73)** | **0.62 (0.53-0.72)** | **0.63 (0.55-0.74)** |
| Intention-to-treat model[d] | **0.77 (0.69-0.86)** | **0.76 (0.69-0.85)** | **0.78 (0.70-0.87)** |
| **ANTIPSYCHOTICS** | | | |
| **Incident (N=2,861)** | | | |
| Treatment duration model[c] | 0.98 (0.56-1.69) | 1.00 (0.56-1.79) | 0.93 (0.51-1.70) |
| Intention-to-treat model[d] | 0.91 (0.59-1.42) | 0.87 (0.55-1.39) | 0.77 (0.47-1.26) |
| **Prevalent (N=14,003)** | | | |
| Treatment duration model[c] | **1.17 (1.02-1.35)** | 1.11 (0.96-1.28) | 1.08 (0.94-1.25) |
| Intention-to-treat model[d] | 1.08 (0.96-1.22) | 1.06 (0.94-1.20) | 1.04 (0.93-1.18) |
| **VALPROATE** | | | |
| **Incident (N=610)** | | | |
| Treatment duration model[c] | 1.75 (0.84-3.65) | 2.03 (0.81-5.09) | 1.98 (0.79-4.97) |
| Intention-to-treat model[d] | 1.09 (0.60-1.97) | 1.43 (0.71-2.89) | 1.38 (0.68-2.79) |
| **Prevalent (3,243)** | | | |
| Treatment duration model[c] | **1.37 (1.14-1.66)** | 1.12 (0.93-1.36) | 1.14 (0.94-1.38) |
| Intention-to-treat model[d] | **1.24 (1.09-1.42)** | 1.12 (0.98-1.27) | 1.13 (0.99-1.29) |
| **LAMOTRIGINE** | | | |
| **Incident (N=1,573)** | | | |
| Treatment duration model[c] | 0.55 (0.23-1.23) | 0.97 (0.39-2.56) | 0.92 (0.36-2.35) |
| Intention-to-treat model[d] | 0.67 (0.39-1.14) | 0.82 (0.45-1.50) | 0.75 (0.41-1.39) |
| **Prevalent (N=6,015)** | | | |
| Treatment duration model[c] | 1.09 (0.93-1.27) | 1.08 (0.92-1.26) | 1.09 (0.93-1.27) |
| Intention-to-treat model[d] | 1.06 (0.95-1.19) | 1.07 (0.96-1.20) | 1.08 (0.96-1.21) |

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, Charlson Comorbidity Index, use of systemic corticosteroids, use of sedative medication and eating disorder diagnosis.

[c] Users were followed until treatment discontinuation (6 months after last prescription), osteoporosis, death, or January 1, 2019, whichever came first.

[d] Users were followed until osteoporosis, death, or January 1, 2019, whichever came first. Statistically significant results are marked in **bold**.

**eTable 7: The association between lithium, antipsychotic, valproate and lamotrigine treatment of bipolar disorder and the risk of osteoporotic fractures.**

| | Unadjusted<br>Hazard rate ratio (95%CI) | Partly adjusted[a]<br>Hazard rate ratio (95%CI) | Fully adjusted[b]<br>Hazard rate ratio (95%CI) |
|---|---|---|---|
| **LITHIUM** | | | |
| Treatment duration model[c] | **0.48 (0.32-0.73)** | **0.43 (0.29-0.65)** | **0.45 (0.30-0.68)** |
| Intention-to-treat model[d] | **0.77 (0.60-0.98)** | **0.71 (0.55-0.91)** | **0.73 (0.57-0.93)** |
| **ANTIPSYCHOTICS** | | | |
| Treatment duration model[c] | **1.26 (0.89-1.79)** | 1.00 (0.71-1.43) | 0.98 (0.69-1.39) |
| Intention-to-treat model[d] | **1.32 (0.99-1.76)** | 1.12 (0.84-1.51) | 1.11 (0.83-1.48) |
| **VALPROATE** | | | |
| Treatment duration model[c] | **1.26 (0.78-2.01)** | 0.79 (0.49-1.28) | 0.83 (0.52-1.34) |
| Intention-to-treat model[d] | **1.26 (0.93-1.70)** | 0.97 (0.71-1.32) | 0.99 (0.73-1.35) |
| **LAMOTRIGINE** | | | |
| Treatment duration model[c] | 0.93 (0.63-1.37) | 0.81 (0.55-1.20) | 0.81 (0.55-1.19) |
| Intention-to-treat model[d] | 1.02 (0.78-1.33) | 0.97 (0.74-1.27) | 0.97 (0.74-1.28) |

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, Charlson Comorbidity Index, use of systemic corticosteroids, use of sedative medication and eating disorder diagnosis.

[c] Users were followed until treatment discontinuation (6 months after last prescription), osteoporosis, death, or January 1, 2019, whichever came first.

[d] Users were followed until osteoporosis, death, or January 1, 2019, whichever came first. Statistically significant results are marked in **bold**.

**eTable 8: Sex-stratified associations between lithium, antipsychotic, valproate and lamotrigine treatment of bipolar disorder and the risk of osteoporosis**

| | Unadjusted<br>Hazard rate ratio (95%CI) | Partly adjusted[a]<br>Hazard rate ratio (95%CI) | Fully adjusted[b]<br>Hazard rate ratio (95%CI) |
|---|---|---|---|
| **LITHIUM** | | | |
| **Females** | | | |
| Treatment duration model[c] | **0.68 (0.57-0.799** | **0.62 (0.53-0.73)** | **0.64 (0.54-0.75)** |
| Intention-to-treat model[d] | **0.86 (0.77-0.97)** | **0.81 (0.72-0.91)** | **0.82 (0.73-0.92)** |
| **Males** | | | |
| Treatment duration model[c] | **0.56 (0.40-0.79)** | **0.52 (0.37-0.73)** | **0.55 (0.39-0.77)** |
| Intention-to-treat model[d] | **0.66 (0.52-0.83)** | **0.62 (0.49-0.78)** | **0.65 (0.52-0.82)** |
| **ANTIPSYCHOTICS** | | | |
| **Females** | | | |
| Treatment duration model[c] | 1.07 (0.92-1.25) | 0.97 (0.83-1.13) | 0.95 (0.81-1.11) |
| Intention-to-treat model[d] | 1.07 (0.94-1.21) | 0.99 (0.87-1.13) | 0.97 (0.85-1.11) |
| **Males** | | | |
| Treatment duration model[c] | **1.57 (1.17-2.10)** | **1.35 (1.01-1.81)** | 1.31 (0.98-1.76) |
| Intention-to-treat model[d] | **1.30 (1.02-1.66)** | 1.14 (0.89-1.46) | 1.13 (0.88-1.45) |
| **VALPROATE** | | | |
| **Females** | | | |
| Treatment duration model[c] | **1.44 (1.18-1.78)** | 1.16 (0.94-1.43) | 1.19 (0.96-1.46) |
| Intention-to-treat model[d] | **1.25 (1.09-1.45)** | 1.11 (0.96-1.29) | 1.13 (0.98-1.31) |
| **Males** | | | |
| Treatment duration model[c] | 1.43 (0.96-2.12) | 1.09 (0.73-1.63) | 1.10 (0.74-1.64) |
| Intention-to-treat model[d] | **1.34 (1.02-1.76)** | 1.13 (0.86-1.49) | 1.13 (0.86-1.49) |
| **LAMOTRIGINE** | | | |
| **Females** | | | |
| Treatment duration model[c] | 0.92 (0.78-1.10) | 0.96 (0.81-1.14) | 0.97 (0.82-1.15) |
| Intention-to-treat model[d] | 0.98 (0.87-1.11) | 1.03 (0.91-1.17) | 1.03 (0.91-1.17) |
| **Males** | | | |
| Treatment duration model[c] | 1.19 (0.85-1.67) | 1.08 (0.78-1.51) | 1.10 (0.78-1.53) |
| Intention-to-treat model[d] | 0.99 (0.76-1.27) | 0.92 (0.71-1.18) | 0.93 (0.72-1.20) |

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, Charlson Comorbidity Index, use of systemic corticosteroids, use of sedative medication and eating disorder diagnosis

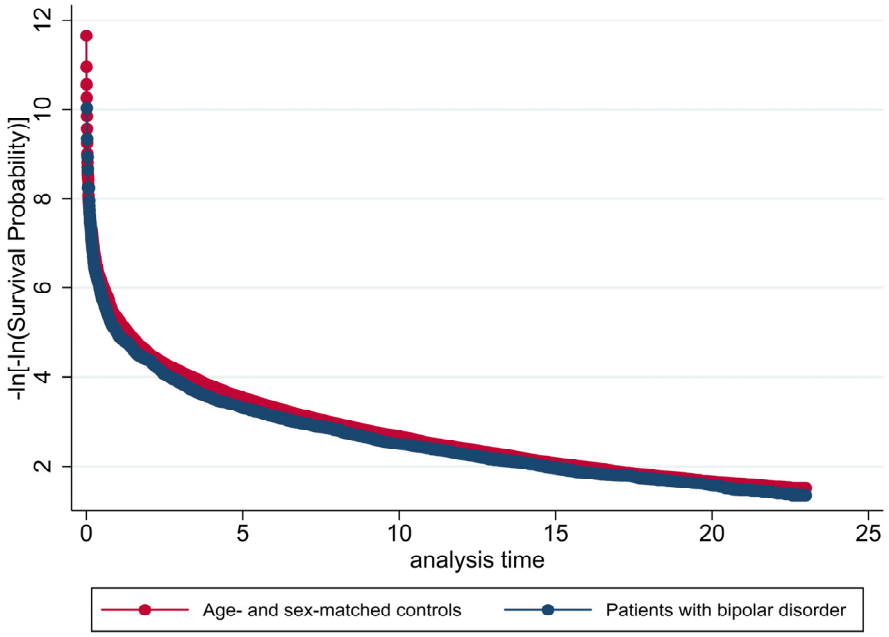
[c] Users were followed until treatment discontinuation (6 months after last prescription), osteoporosis, death, or January 1, 2019, whichever came first.

[d] Users were followed until osteoporosis, death, or January 1, 2019, whichever came first.

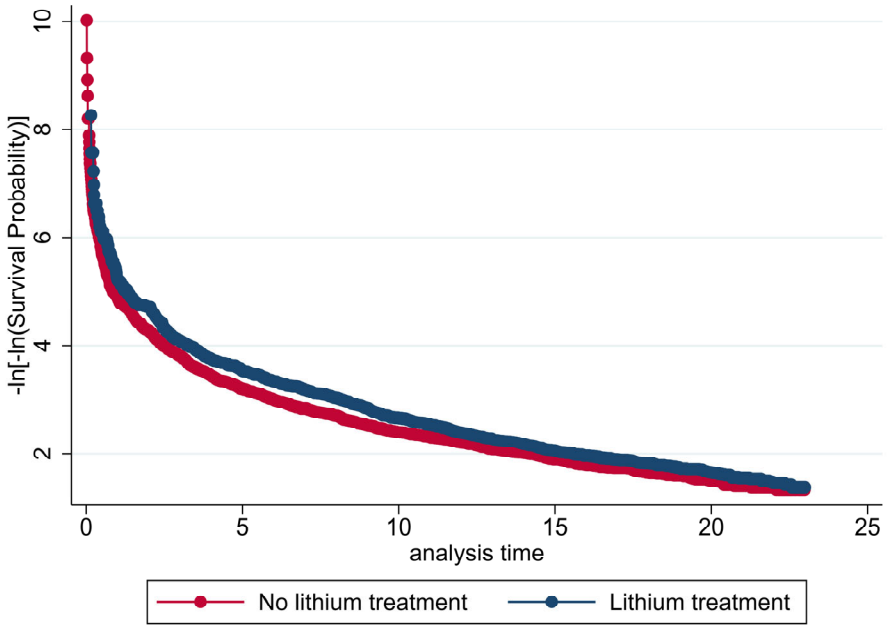
Statistically significant results are marked in **bold**.

**eFigure 1: Log-log survival functions (time to osteoporosis) confirming proportional hazards**

**A. For patients with bipolar disorder and age- and sex-matched reference individuals.**



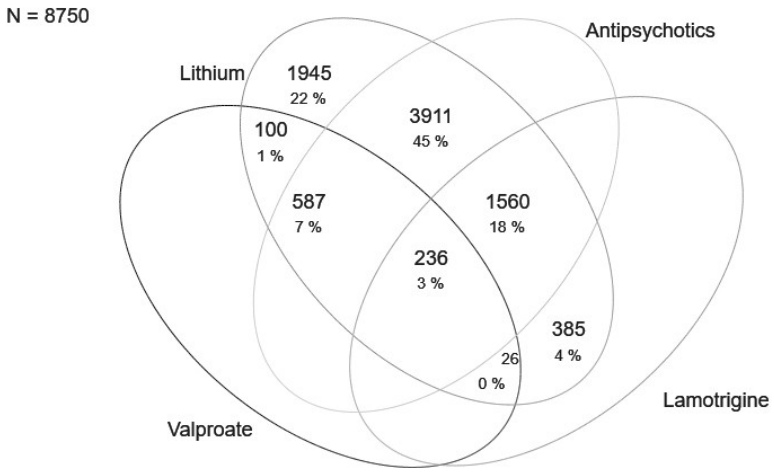

**A. For patients with bipolar disorder receiving lithium and not receiving lithium, respectively***



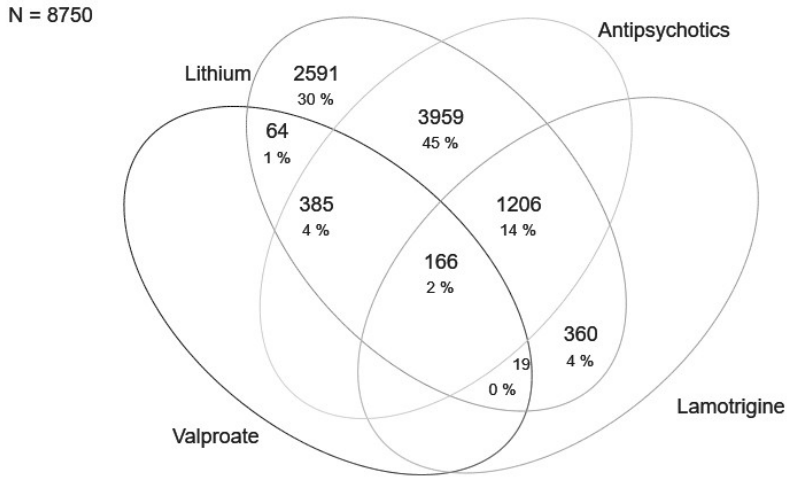

*The proportional hazards assumption was also met for the other medications (plots not shown).

**eFigure 2: Venn diagrams among the 8,750 individuals treated with lithium showing the overlap with other treatments during the time from 1) lithium initiation until 6 months after the last lithium prescription (model 1) and 2) from lithium initiation until the last prescription (model 2).**

**Model 1:**

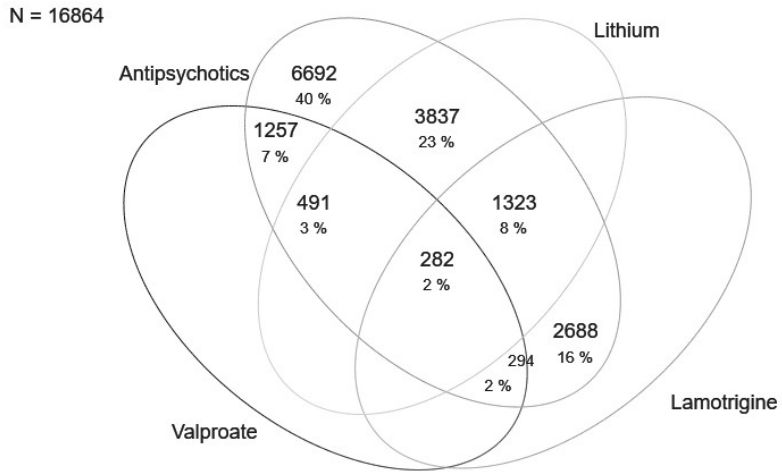



**Model 2:**

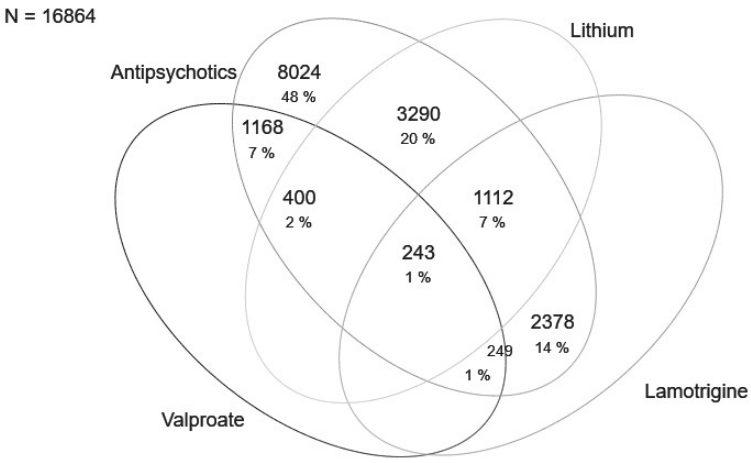


**eFigure 3: Venn diagrams among the 16,864 individuals treated with antipsychotics showing the overlap with other treatments during the time from 1) antipsychotic initiation until 6 months after the last lithium prescription (model 1) and 2) from antipsychotic initiation until the last prescription (model 2).**

**Model 1:**

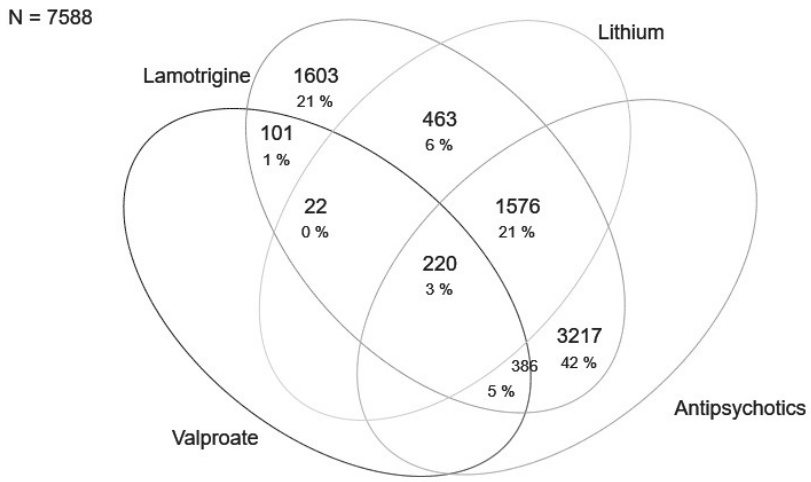



**Model 2:**

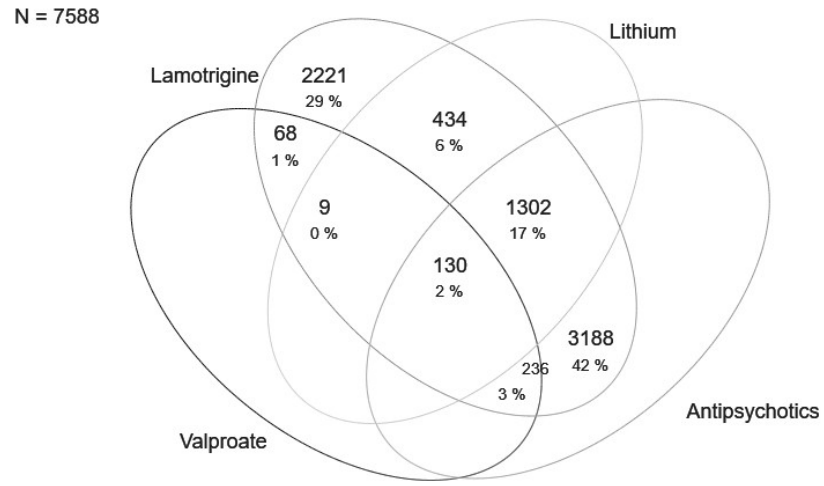


**eFigure 4: Venn diagrams among the 7,588 individuals treated with lamotrigine showing the overlap with other treatments during the time from 1) lamotrigine initiation until 6 months after the last lithium prescription (model 1) and 2) from lamotrigine initiation until the last prescription (model 2).**

**Model 1:**

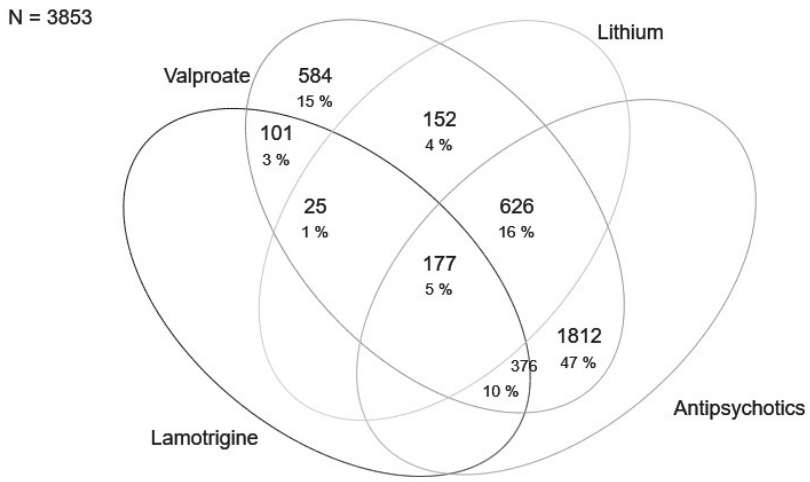



**Model 2:**

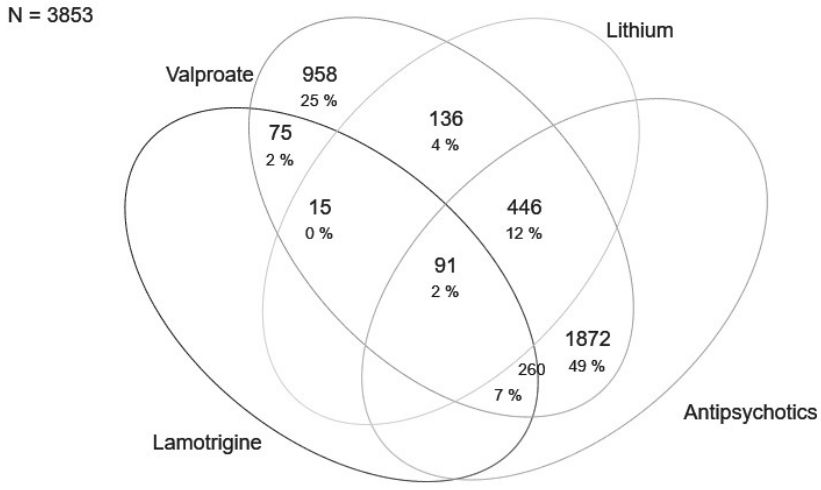


**eFigure 5: Venn diagrams among the 3,853 individuals treated with valproate showing the overlap with other treatments during the time from 1) valproate initiation until 6 months after the last lithium prescription (model 1) and 2) from valproate initiation until the last prescription (model 2).**

**Model 1:**

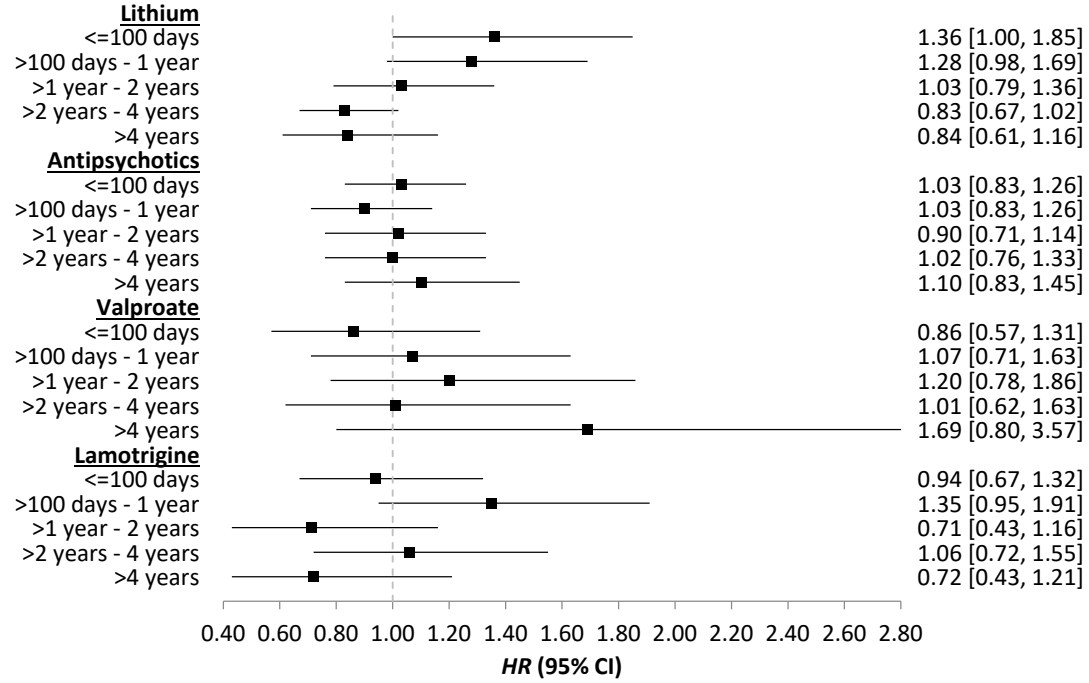



**Model 2:**

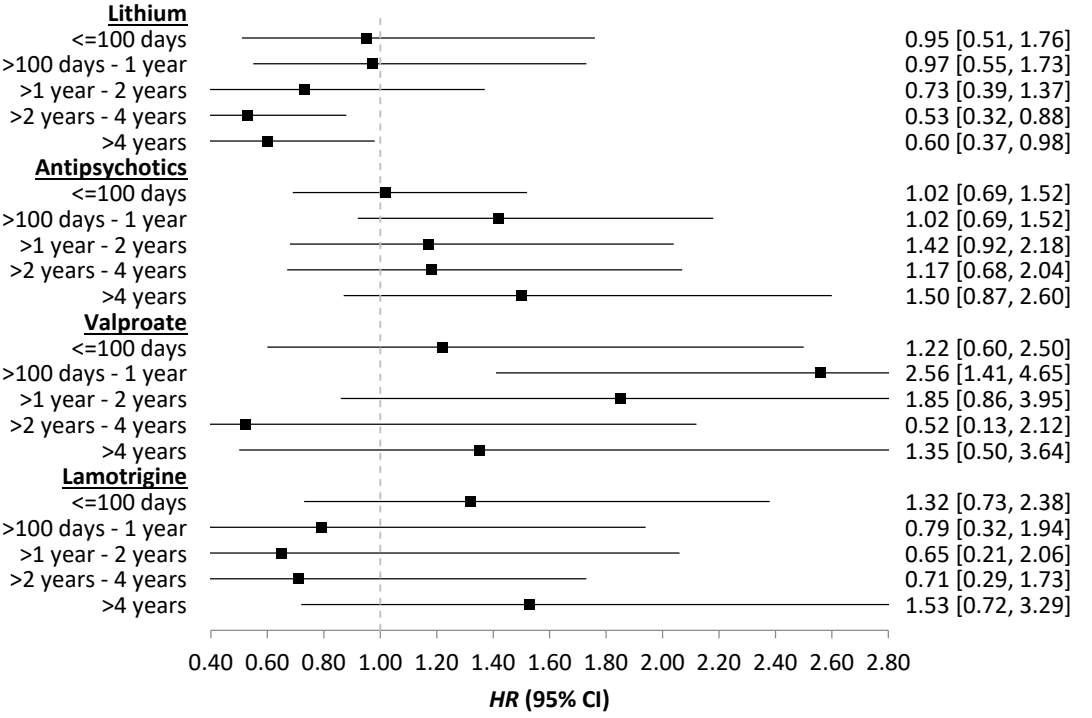


**eFigure 6: Sex-stratified association between the duration of lithium, antipsychotic, valproate and lamotrigine treatment of bipolar disorder and the risk of osteoporosis.**

**A) Females**




**B) Males**



Patients with bipolar disorder with an index date in the period from January 1, 1996 to January 1, 2010 were included in this analysis. The number of treatment days was calculated based on the period going from the index date and five years forward. The patients were then followed from the date five year after the index date, until osteoporosis, death, or January 1, 2019, whichever came first. The incidence rates of osteoporosis were compared between patients that received treatment (corresponding to the duration intervals outlined in the figure) and patients who that did not, stratified on treatment duration. The Hazard Rate Ratios were adjusted for age, sex, Charlson Comorbidity Index, use of systemic corticosteroids, use of sedative medication and eating disorder diagnosis.