**Supplement**

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**e-Table 1**. Baseline characteristics and incident risk of alcohol dependence in patients with bipolar disorder (cohort: January 1, 1999, to December 31, 2012; *n* = 21 777) relative to the comparison controls, stratified by sex

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Bipolar cohort | Follow-up Duration | Incident Alcohol Dependence | Contributed Person-years | Crude Incidencea | Comparison controls | Follow-up Duration | Incident Alcohol Dependence | Contributed Person-years | Crude Incidencea | aIRRb | 95% CI | *P* |
| Men | N | Mean (SD), y | n |  |  | N | Mean (SD), y | n |  |  |  |  |  |
| Agec, y |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <18 | 219 | 6.4 (3.9) | 6 | 1391 | 431.3 | 876 | 6.5 (3.8) | 6 | 5661 | 106.0 | 4.07 | 1.31-12.62 | 0.015 |
| 18-29 | 5811 | 4.9 (3.9) | 251 | 28266 | 888.0 | 23244 | 5.2 (3.9) | 166 | 119846 | 138.5 | 6.41 | 5.27-7.80 | <.001 |
| 30-39 | 1760 | 5.6 (4.2) | 271 | 9871 | 2745.4 | 7040 | 6.7 (4.0) | 128 | 47263 | 270.8 | 10.14 | 8.22-12.51 | <.001 |
| 40-49 | 1635 | 5.5 (4.1) | 229 | 8994 | 2546.1 | 6540 | 6.7 (3.9) | 99 | 43745 | 226.3 | 11.25 | 8.89-14.24 | <.001 |
| 50-59 | 1265 | 5.0 (3.7) | 112 | 6281 | 1783.2 | 5060 | 5.9 (3.7) | 65 | 29761 | 218.4 | 8.16 | 6.01-11.08 | <.001 |
| ≥60 | 444 | 4.9 (3.7) | 26 | 2154 | 1207.1 | 1176 | 5.9 (4.0) | 17 | 10412 | 163.3 | 7.39 | 4.01-13.62 | <.001 |
| Total | 11134 | 5.1 (4.0) | 895 | 56959 | 1571.3 | 43936 | 5.8 (4.0) | 481 | 256687 | 187.4 | 8.39 | 7.51-9.37 | <.001 |
| Women |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <18 | 241 | 6.3 (3.9) | 2 | 1507 | 132.7 | 964 | 6.3 (3.9) | 0 | 6077 | 0.0 | - | - | - |
| 18-29 | 2833 | 6.3 (3.9) | 93 | 17900 | 519.6 | 11332 | 6.5 (3.8) | 30 | 73751 | 40.7 | 12.77 | 8.46-19.28 | <.001 |
| 30-39 | 2832 | 6.1 (3.9) | 137 | 17184 | 797.3 | 11328 | 6.4 (3.8) | 50 | 72635 | 68.8 | 11.58 | 8.38-16.01 | <.001 |
| 40-49 | 2467 | 5.7 (3.9) | 90 | 13988 | 643.4 | 9868 | 6.1 (3.8) | 28 | 60115 | 46.6 | 13.81 | 9.04-21.11 | <.001 |
| 50-59 | 1812 | 5.4 (3.7) | 36 | 9759 | 368.9 | 7248 | 5.9 (3.8) | 9 | 42473 | 21.2 | 17.41 | 8.39-36.14 | <.001 |
| ≥60 | 472 | 5.4 (3.8) | 8 | 2536 | 315.5 | 1888 | 5.9 (4.0) | 0 | 11159 | 0.0 | - | - | - |
| Total | 10657 | 5.9 (3.9) | 366 | 62873 | 582.1 | 42628 | 6.2 (3.8) | 117 | 266211 | 44.0 | 13.25 | 10.76-16.31 | <.001 |

\**P* < .05; \*\**P* < .01; aIncidence: incident number/100 000 person-years; b Estimated using Poisson regression model.

Abbreviation: aIRR = adjusted incidence rate ratio; cIndicates age when bipolar disorder was newly diagnosed between January 1, 1999, and December 31, 2012

**e-Figure 1.** Study flow diagram for the sensitivity analysis

The selected individuals (*n* = 9,989,196)

Any patient who was an outpatient or inpatient, or visited emergency) with a consistent diagnosis of bipolar disorder (ICD-9-CM codes 296.0-296.16, 296.4-296.81, 296.89) between January 1, 1999, and December 31, 2012 (*n* = 7241)

Nationwide National Health Insurance Research Database (1996-2013)

N = 1 000 000 representatives

Excluding ever diagnosed with schizophrenia (ICD-9-CM code 295.\*\*) in the study cohort between January 1, 1999, and December 31, 2013 (*n* = 10804)

Excluding inpatient, outpatient, and emergency patients that had alcohol dependence (ICD-9-CM code 303.\*\*) or alcohol psychosis (ICD-9-CM code 291.\*\*) before firstly diagnosed as bipolar disorder (baseline) (*n* = 406)

Bipolar cohort (*n* = 6835)

Cases with incident alcohol dependence (ICD-9-CM coded 291.\*\* and 303.\*\*; *n* = 158) after the baseline

Patients aged between 15 and 65 years (*n* = 5619)

Age- and sex-matched comparison controls with the ratio of 1:4 randomly selected from the general population (*n*=22476)

Controls with incident alcohol dependence (*n*=119)

Calculate the adjusted incidence rate ratio (aIRR)

**e-Table 2.** Sensitivity analysis of baseline characteristics and incident risk of alcohol dependence among patients with bipolar disorder who were outpatients or inpatients, or visited the emergency relative to the corresponding comparison controls

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Bipolar cohort | Follow-up Duration | Incident Alcohol Dependence | Contributed Person-years | Crude Incidencea | Comparison controls | Follow-up Duration | Incident Alcohol Dependence | Contributed Person-years | Crude Incidencea | aIRRb | 95% CI | *P* |
| Agec, y | N | Mean (SD), y | n |  |  | N | Mean (SD), y | n |  |  |  |  |  |
| <18 | 150 | 5.9 (3.8) | 3 | 881 | 340.5 | 600 | 5.9 (3.7) | 1 | 3525 | 28.4 | 12.00 | 1.25-115.40 | 0.031 |
| 18-29 | 1344 | 6.1 (3.6) | 38 | 8232 | 461.6 | 5376 | 6.2 (3.6) | 25 | 33492 | 74.6 | 6.18 | 3.73-10.24 | <.001 |
| 30-39 | 1206 | 6.2 (4.1) | 54 | 7453 | 724.5 | 4824 | 6.4 (3.9) | 29 | 31008 | 93.5 | 7.75 | 4.93-12.16 | <.001 |
| 40-49 | 1305 | 6.6 (4.0) | 46 | 8663 | 531.0 | 5220 | 6.9 (3.9) | 31 | 35834 | 86.5 | 6.14 | 3.89-9.68 | <.001 |
| 50-59 | 1117 | 6.2 (4.0) | 13 | 6865 | 189.4 | 4468 | 6.3 (4.0) | 21 | 28264 | 74.3 | 2.55 | 1.28-5.09 | 0.008 |
| ≥60 | 497 | 6.6 (4.4) | 4 | 3281 | 121.9 | 1988 | 6.9 (4.3) | 12 | 13647 | 87.9 | 1.39 | 0.45-4.30 | 0.571 |
| Total | 5619 | 6.3 (4.0) | 158 | 35376 | 446.6 | 22476 | 6.5 (3.9) | 119 | 145770 | 81.6 | 5.47 | 4.31-6.94 | <.001 |

\**P* < .05; \*\**P* < .01

aIncidence: incident number/100 000 person-years

b Estimated using Poisson regression model.

Abbreviation: aIRR = adjusted incidence rate ratio.

cIndicates age when bipolar disorder was diagnosed between January 1, 1999, and December 31, 2012

**e-Table 3.** Univariate analysis of physical comorbidities in patients with bipolar disorder who had alcohol dependence and controls derived from a nationwide bipolar cohort from 2001 to 2012

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic N (%) | Case(*n* = 1261) | Controls(*n* = 5044) | Unadjusted risk ratioa | 95% CI | *P* value |
|  | N (%) | N (%) |  |  |  |
| Cardiovascular disease | 348 (27.6) | 1033 (20.5) | 1.53 | 1.32-1.77 | <.0001 |
| Diabetes mellitus | 103 (8.2) | 439 (8.7) | 0.93 | 0.74-1.17 | 0.5316 |
| Cerebrovascular disease | 37 (2.9) | 88 (1.7) | 1.72 | 1.16-2.54 | 0.0070 |
| Chronic hepatic disease | 318 (25.2) | 439 (8.7) | 3.66 | 3.10-4.33 | <.0001 |
| Cancer | 32 (2.5) | 75 (1.5) | 1.74 | 1.14-2.65 | 0.0103 |
| Pneumonia | 61 (4.8) | 136 (2.7) | 1.84 | 1.35-2.51 | 0.0001 |
| COPD | 90 (7.1) | 260 (5.2) | 1.42 | 1.11-1.82 | 0.0006 |
| Upper respiratory tract infection | 205 (16.3) | 900 (17.8) | 0.89 | 0.76-1.06 | 0.1825 |
| Delirium+ | 38 (3.0) | 18 (0.4) | 8.44 | 4.82-14.80 | <.0001 |

aEstimated using univariate conditional logistic regression, \**P* < .05, \*\**P* < .01, \*\*\**P* < .001

+ Based on ICD-9-CM codes including presenile dementia with delirium, senile dementia with delirium, arteriosclerotic dementia with delirium, alcohol withdrawal delirium, drug-induced delirium, acute delirium, and subacute delirium

**e-Table 4.** Univariate analysis of psychiatric comorbidities in patients with bipolar disorder who had alcohol dependence and controls derived from a nationwide bipolar cohort from 2001 to 2012

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic N (%) | Case(*n* = 1261) | Controls(*n* = 5044) | Unadjusted risk ratioa | 95% CI | *P* value |
| **Psychiatric Comorbidity** | N (%) | N (%) |  |  |  |
|  |  |  |  |  |  |
| Any psychiatric disorder | 1073 (85.1) | 4028 (79.9) | 1.46 | 1.23-1.74 | <.0001 |
| Dementia | 71 (5.6) | 165 (3.3) | 1.77 | 1.33-2.36 | <.0001 |
| Drug-induced mental disorders  | 247 (19.6) | 225 (4.5) | 5.33 | 4.37-6.51 | <.0001 |
| Depressive disorder | 508 (40.3) | 1056 (20.9) | 2.62 | 2.29-3.01 | <.0001 |
| Anxiety disorder | 327 (25.9) | 710 (14.1) | 2.14 | 1.84-2.49 | <.0001 |
| Personality disorder  | 143 (11.3) | 202 (4.0) | 3.14 | 2.50-3.95 | <.0001 |
| Adjustment reaction | 101 (8.0) | 175 (3.5) | 2.62 | 2.00-3.42 | <.0001 |
| Hyperactivity disorder | 6 (0.5) | 20 (0.4) | 1.20 | 0.48-2.99 | 0.6952 |
| Intellectual Disabilities | 19 (1.5) | 97 (1.9) | 0.77 | 0.47-1.28 | 0.3182 |
| Sleep disorder | 452 (35.8) | 1180 (23.4) | 1.86 | 1.62-2.12 | <.0001 |

a Estimated using univariate conditional logistic regression

**e-Table 5.** Distribution of the use of concomitant medications in patients with bipolar disorder who had alcohol dependence and controls derived from a nationwide bipolar cohort from 2001 to 2012

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic N (%) | Case(*n* = 1261)  | Controls(*n* = 5044)  | Unadjusted risk ratioa | 95% CI | *P* value |
|  | N (%) | N (%) |  |  |  |
| **Concomitant drugs** |  |  |  |  |  |
| Cardiovascular drugs |  |  |  |  |  |
| Antihypertensive agents | 34 (2.7) | 135 (2.7) | 1.01 | 0.69-1.48 | 0.9685 |
| Beta-blocking agents | 58 (4.6) | 1614 (32.0) | 1.83 | 1.61-2.08 | <.0001 |
| Calcium channel blockers | 192 (15.2) | 455 (9.0) | 1.89 | 1.57-2.29 | <.0001 |
| Agents acting on the renin-angiotensin system | 99 (7.9) | 318 (6.3) | 1.29 | 1.01-1.65 | 0.0408 |
| Lipid modifying agents | 99 (7.9) | 331 (6.6) | 1.22 | 0.96-1.55 | 0.0985 |
|  |  |  |  |  |  |
| Respiratory drugs++ | 984 (78.0) | 3607 (71.5) | 1.42 | 1.23-1.65 | <.0001 |
| Antidiabetic drugs  | 83 (6.6) | 346 (6.9) | 0.96 | 0.74-1.23 | 0.7214 |
| Antithrombotic agents | 110 (8.7) | 298 (5.9) | 1.56 | 1.23-1.98 | 0.0002 |
| Corticosteroids for systemic use | 340 (27.0) | 1032 (20.5) | 1.43 | 1.24-1.65 | <.0001 |
| Anti-Parkinson drugs | 481 (38.1) | 1706 (33.8) | 1.23 | 1.08-1.40 | 0.0026 |
|  |  |  |  |  |  |
| Mood stabilizers | 905 (71.8) | 3207 (63.6) | 1.48 | 1.29-1.70 | <.0001 |
|  Lithium | 332 (26.3) | 1609 (31.9) | 0.75 | 0.65-0.87 | <.0001 |
|  Valproic acid | 683 (54.2) | 1957 (38.8) | 1.89 | 1.66-2.14 | <.0001 |
|  Carbamazepine | 164 (13.0) | 554 (11.0) | 1.24 | 1.02-1.50 | 0.0343 |
|  Lamotrigine | 103 (8.2) | 351 (7.0) | 1.20 | 0.95-1.51 | 0.1305 |
|  |  |  |  |  |  |
| Antipsychotics | 1070 (84.9) | 3101 (61.5) | 3.73 | 3.15-4.42 | <.0001 |
| Antidepressants | 913 (72.4) | 2007 (39.8) | 4.14 | 3.59-4.76 | <.0001 |
|  |  |  |  |  |  |
| Benzodiazepines | 1231 (97.6) | 3768 (74.7) | 15.08 | 10.4-21.86 | <.0001 |
| Short acting | 939 (74.5) | 2252 (44.7) | 3.66 | 3.18-4.21 | <.0001 |
| Intermediate | 1180 (93.6) | 3078 (61.0) | 10.10 | 7.97-12.8 | <.0001 |
| Long acting | 1221 (96.8) | 3612 (71.6) | 12.97 | 9.38-17.93 | <.0001 |
|  |  |  |  |  |  |

aEstimated using univariate conditional logistic regression, \**P* < .05, \*\**P* < .01, \*\*\**P* < .001

++ Based on ATC codes including those for nasal preparations, throat preparations, drugs for obstructive airway diseases, cough and cold preparations, antihistamines for systemic use, and other respiratory system products

Mood stabilizers included lithium, valproic acid, carbamazepine, and lamotrigine, which are among standard medications for the treatment of bipolar disorder.