Supplemental material

Supplementary Table 1. Psychotropic medications included in the study

Category	Drug name
Lithium	Lithium carbonate
	Lithium sulphate
Antipsychotics	Amisulpride
	Aripiprazole
	Asenapine
	Chlorpromazine
	Clopenthixol
	Clozapine
	Droperidol
	Fluphenazine
	Flupentixol
	Haloperidol
	Lurasidone
	Molindone
	Olanzapine
	Paliperidone
	Pericyazine
	Perphenazine
	Pimozide
	Quetiapine
	Risperidone
	Sertindole
	Sulpiride
	Thioridazine
	Trifluoperazine
	Ziprasidone
	Zuclopenthixol
Mood stabilizing antiepileptics	Carbamazepine
	Lamotrigine
	Valproate sodium
Antidepressants	Amineptine
	Amitriptyline
	Clomipramine
	Dothiepin
	Doxepin
	Imipramine
	Maprotiline
	Mianserin
	Motival
	Nortriptyline
	Protriptyline
	Trazodone
	Trimipramine
	Moclobemide
	Phenelzine
	Citalopram
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
	Agomelatine
	Bupropion
	Desvenlafaxine
	Milnacipran

	Mirtazapine
	Nefazodone
	Oxitriptan
	Venlafaxine
	Vortioxetine
	Duloxetine
	Tianeptine
Benzodiazepine derivatives	Flunitrazepam
	Flurazepam
	Lormetazepam
	Midazolam
	Nitrazepam
	Temazepam
	Triazolam
	Alprazolam
	Bromazepam
	Chlordiazepoxide
	Diazepam
	Lorazepam
	Prazepam
	Pinazepam
	Clobazam
	Clonazepam
	Dipotassium clorazepate
	Loprazolam
	Estazolam
	Quazepam
	Oxazepam

Supplementary Table 2. Selection criteria of traumatic injuries cases at the emergency room setting in public hospitals in Hong Kong

In Hong Kong, it is a compulsory standard procedure that the clinicians and trauma nurses at the emergency room settings in the public hospitals to identify the traumatic injuries cases based on the National Trauma Data Standard Patient Inclusion Criteria by the American College of Surgeons Committee on Trauma (American College of Surgeons Committee on Trauma, 2019).

Inclusion criteria 1: at least one of the following injury diagnostic codes	
Description	ICD-10-CM codes
Types of injuries: 1. Open wound 2. Fracture 3. Dislocation and sprain of joints and ligaments 4. Injury of nerve 5. Injury to blood vessels 6. Injury to muscle, fascia and tendon, internal organs 7. Crushing injury 8. Avulsion and traumatic amputation 9. Other and unspecified injuries Injuries to different body parts, including: 1. Head 2. Neck 3. Thorax 4. Abdomen, lower back, lumbar spine, pelvis and external genitals, 5. Shoulders and upper arm, 6. Elbow and forearm, 7. Wrist, hand and fingers 8. Hip and thigh 9. Knee and lower leg 10. Ankle and foot	S00-S99 with 7th character modifiers of A, B, or C only
Injuries involving multiple body regions	T07
Injury of unspecified body region	T14
Burns and corrosions of external body surface, eyes and internal organs, specified by site	T20-T28 with 7th character modifier of A only (burns by specific body parts – initial encounter)
Burns and corrosions of multiple and unspecified body regions	T30-T32 (burn by TBSA percentages)
Traumatic compartment syndrome of different body parts	T79.A1-T79.A9 with 7th character modifier of A only (Traumatic Compartment Syndrome – initial encounter)
Inclusion criteria 2: hospital admission or death	
• Hospital admission diagnosis defined by trauma registry inclusion criteria; or • Patient transfer from one hospital to another hospital; or • Death resulting from the traumatic injury	--
Exclusion criteria 1: Superficial injuries	
Superficial injuries of different body parts	S00, S10, S20, S30, S40, S50, S60, S70, S80, S90

Reference

American College of Surgeons Committee on Trauma. (2019). National Trauma Data Standard Data Dictionary 2019 Admissions. Retrieved from https://www.facs.org/~/media/files/quality%20programs/trauma/ntdb/ntds/data%20dictionaries/ntdb_data_dictionary_2019_revision.ashx

Supplementary Table 3. Description of sensitivity analyses

Several sensitivity analyses were planned to test the validity and robustness of the initial study results.

No.	Sensitivity analysis	Details
1	Redefining the start of the observation period to 1st January 2001, the 18th birthday of the individual, the date of the patient entering the database, or the first observed date of bipolar disorder diagnosis, whichever was later	Individuals might receive less medical attention before the diagnosis of bipolar disorder and the prescribing pattern might be different.
2	Removing patients who died during the observation period	Since traumatic injuries carry high risk of mortality, the observation period could be censored as a direct result of the traumatic injuries, causing bias to the results in both directions (under- or over-estimating the benefits of pharmacological treatment). A total of 702 patients with ER admissions due to traumatic injuries died during the observation period but there were no clustering of death shortly after the events. This will assess the effect of death on the results.
3	Removing patients with exposure to pharmacological treatment of bipolar disorder before the start of the observation period	As the self-controlled case series compared the incidence within an individual, included individuals were not necessary to be incident users of the treatment. This will assess this potential effect.
4	Removing patients with schizophrenia diagnosis (ICD-9-CM: 295) between the database inception and the end of observation period	Since there is some debate as to whether schizophrenia and bipolar disorder can be truly comorbid, removing patients who ever received schizophrenia diagnosis can ensure the patients who were truly diagnosed with bipolar disorder.
5	Redefining the study cohort by 1) including patients who had at least 2 hospitalization record with a diagnosis of bipolar disorder and 2) excluding those who had more than 1 schizophrenia related hospitalization record	A previous validation study, which validated the diagnosis of bipolar disorder in Swedish national registry, suggested the use of search algorithm based on at least 2 inpatient episodes of bipolar disorder and exclude patients with more than 1 inpatient episode of schizophrenia could improve sensitivity and specificity (Sellgren, Landén, Lichtenstein, Hultman, & Långström, 2011). To ensure patients included in our cohort were diagnosed with bipolar disorder, we applied the same criteria to define the study cohort.
6	Removing patients with event happening on the first day of treatment	As the exact time of the event is not available in the database, it is difficult to determine if the event occurred before or after the treatment initiation.
7	Adjusting for age, concurrent use of antidepressants, benzodiazepine derivatives. hypnotics and anxiolytics as time-varying confounders	As a previous study found an association between the risk of road accidents and use of anxiolytics (Ravera, van Rein, de Gier, & de Jong-van den Berg, 2011), it is possible that hypnotics and anxiolytics affect cognitive ability and hence causes traumatic injuries due to road accidents.
8	Adjusting for age, concurrent use of antidepressants and benzodiazepine derivatives, doses of treatment agents as time-varying confounders	Since varying dose of mood stabilizing treatment infers the changing severity of illness of bipolar disorder and changing dose of mood stabilizing treatment might also affect the prescribing of treatment regimen, doses of mood stabilizing agents can be a possible confounder. To examine the effect of dose, we calculated the sum of total doses within the same exposure period using the ratio of prescribed daily dose to defined

		daily dose and the duration of exposure period. Then we further separated the exposure periods (for both acute and maintenance treatment) into low and high doses (above or below the median).
9	Different drug non-adherence scenarios	Each exposed period was further extended by adding 1 to 10 weeks after the end of an exposed period to assess this effect.
10	Computing E-value, which is defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome to nullify the observed association.	Since there might be some time-varying unmeasured confounding factors which might potentially cause bias to the results, an E-value can quantify the minimum strength of association that an unmeasured confounder could have to affect the observed results.

References

Ravera, S., van Rein, N., de Gier, J. J., & de Jong-van den Berg, L. T. (2011). Road traffic accidents and psychotropic medication use in The Netherlands: a case-control study. *British Journal of Clinical Pharmacology, 72*(3), 505-513. doi:10.1111/j.1365-2125.2011.03994.x

Sellgren, C., Landén, M., Lichtenstein, P., Hultman, C. M., & Långström, N. (2011). Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatrica Scandinavica, 124*(6), 447-453. doi:10.1111/j.1600-0447.2011.01747.x

Supplementary Table 4. Results of subgroup analysis

Risk periods	No. of events	Patient years	Crude incidence (per 100 patient-years)	Adjusted IRR[a] (95% CI)	P-value
Lithium					
Baseline[b]	4461	71455.31	6.24	1.00	--
Pre-exposure period	31	127.24	24.36	1.27 (0.87-1.87)	0.2166
Acute treatment	41	633.68	6.47	0.67 (0.48-0.94)	0.0208
Maintenance treatment	480	9734.97	4.93	0.81 (0.70-0.94)	0.0046
Post-exposure period	27	303.39	8.90	1.20 (0.80-1.78)	0.3811
Antipsychotics					
Baseline[b]	2929	45466.13	6.37	1.00	--
Pre-exposure period	130	354.54	36.67	3.74 (3.04-4.58)	<.0001
Acute treatment	213	2264.49	9.41	1.43 (1.20-1.70)	<.0001
Maintenance treatment	1683	33006.27	5.10	1.00 (0.90-1.10)	0.9631
Post-exposure period	85	1163.15	7.31	1.16 (0.91-1.47)	0.2359
Mood stabilizing antiepileptics (i.e. valproate, carbamazepine and lamotrigine)					
Baseline[b]	3610	55258.02	6.53	1.00	--
Pre-exposure period	71	286.95	24.74	1.90 (1.46-2.47)	<.0001
Acute treatment	140	1674.49	8.36	1.17 (0.95-1.43)	0.1343
Maintenance treatment	1173	24269.04	4.83	0.99 (0.90-1.10)	0.9218
Post-exposure period	46	766.08	6.00	1.00 (0.73-1.38)	0.9835
Other medications adjusted (as time-varying factor)					
Antidepressants during treatment	934	16187.31	5.77	1.08 (0.98-1.20)	0.1288
No antidepressants	4106	66067.27	6.21	1.00	--
Benzodiazepine derivatives during treatment	878	14845.54	5.91	1.27 (1.15-1.41)	<.0001
No benzodiazepine derivatives	4162	67409.04	6.17	1.00	--

[a]All estimates are adjusted for age in one-year age band and concurrent use of antidepressants, benzodiazepine derivatives, and/or different classes of treatment agents (i.e. lithium, antipsychotics, mood stabilizing antiepileptics).

[b]When stratifying by drug classes, baseline period refers to unexposed period to study drug class.

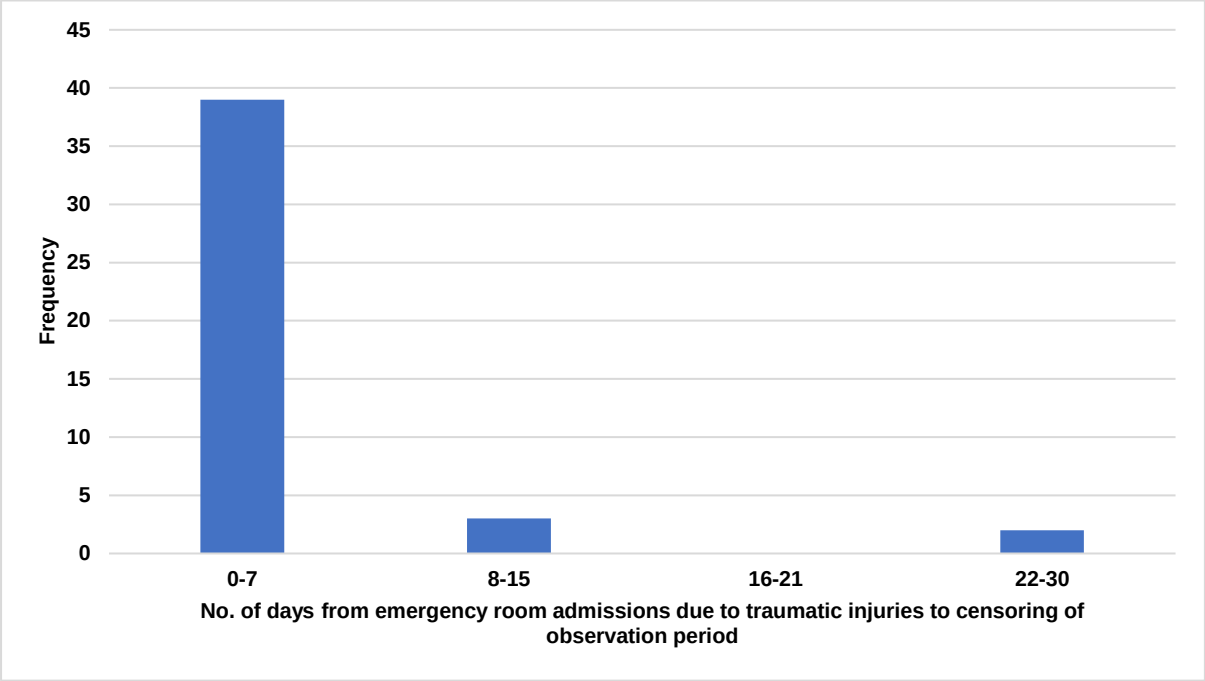
Abbreviations: CI=confidence interval; IRR=incidence rate ratio

Supplementary Table 5. Results of sex stratified analysis

	No. of events	Adjusted IRR[a] (95% CI)	P-value
Males (n=1919)			
Baseline	963	1.00	--
Pre-exposure period	66	5.49 (4.24-7.11)	<0.0001
Acute treatment	96	1.56 (1.23-1.97)	<0.0001
Maintenance treatment	764	0.95 (0.81-1.11)	0.52
Post-exposure period	30	1.12 (0.77-1.64)	0.54
Females (n=3121)			
Baseline	1480	1.00	--
Pre-exposure period	67	3.72 (2.90-4.78)	0.001
Acute treatment	142	1.38 (1.14-1.67)	0.001
Maintenance treatment	1365	0.98 (0.87-1.11)	0.79
Post-exposure period	67	1.48 (1.15-1.91)	0.002

[a]All estimates are adjusted for age in one-year age band and concurrent use of antidepressants and/or benzodiazepine derivatives.

Abbreviations: CI=confidence interval; ER=emergency room; IRR=incidence rate ratio



Supplementary Figure 1. Distribution of patients who died within 30 days after the first emergency room admissions due to traumatic injuries

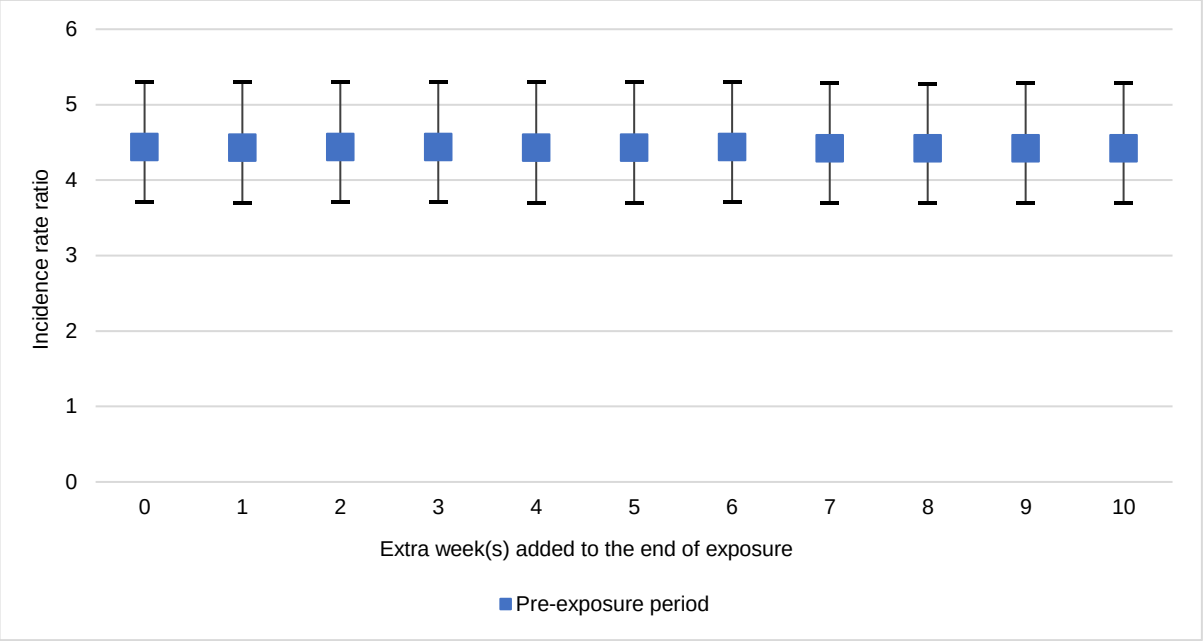
Supplementary Table 6. Results from sensitivity analyses

	No. of events	Adjusted IRR[a] (95% CI)	P-value
Sensitivity analysis 1: Study started on 1st January 2001, the 18th birthday of the individual, the date of the patient entering the database, or the first observed date of bipolar disorder diagnosis, whichever was later. (n=2634)			
Baseline	537	1.00	--
Pre-exposure period	28	4.57 (3.08-6.77)	<0.0001
Acute treatment	182	1.56 (1.28-1.91)	<0.0001
Maintenance treatment	1817	1.07 (0.92-1.25)	0.37
Post-exposure period	70	1.51 (1.16-1.96)	0.002
Sensitivity analysis 2: Removing patients who died during the observation period (n=4338)			
Baseline	2215	1.00	--
Pre-exposure period	111	4.39 (3.61-5.34)	<0.0001
Acute treatment	198	1.35 (1.14-1.58)	<0.0001
Maintenance treatment	1737	0.88 (0.80-0.98)	0.02
Post-exposure period	77	1.22 (0.96-1.54)	0.10
Sensitivity analysis 3: Restricting the cohort to incident users of treatment of mood stabilizers and/or antipsychotics (n=4843)			
Baseline	2420	1.00	--
Pre-exposure period	130	4.47 (3.73-5.36)	<0.0001
Acute treatment	233	1.48 (1.28 -1.72)	<0.0001
Maintenance treatment	1966	0.96 (0.87-1.05)	0.36
Post-exposure period	94	1.37 (1.10-1.69)	0.004
Sensitivity analysis 4: Removing patients with schizophrenia between the database inception and the end of observation period (n=4365)			
Baseline	2248	1.00	--
Pre-exposure period	120	4.65 (3.85-5.62)	<0.0001
Acute treatment	208	1.55 (1.32-1.82)	<0.0001
Maintenance treatment	1705	0.97 (0.87-1.07)	0.53
Post-exposure period	84	1.42 (1.14-1.78)	0.002
Sensitivity analysis 5: Redefining the study cohort by 1) including patients who had at least 2 hospitalization record with a diagnosis of bipolar disorder and 2) excluding those who had more than 1 schizophrenia related hospitalization record (n=2384)			
Baseline	891	1.00	--
Pre-exposure period	64	4.35 (3.35-5.65)	<0.0001
Acute treatment	129	1.35 (1.10-1.66)	0.0045
Maintenance treatment	1246	0.96 (0.84-1.10)	0.5687
Post-exposure period	54	1.39 (1.04-1.85)	0.0247
Sensitivity analysis 6: Removing patients in which the event happened on the first day of treatment (n=5017)			
Baseline	2443	1.00	--
Pre-exposure period	133	4.42 (3.69-5.28)	<0.0001
Acute treatment	215	1.29 (1.32-1.82)	0.0001
Maintenance treatment	2129	0.96 (0.87-1.05)	0.37
Post-exposure period	97	1.33 (1.08-1.64)	0.007
Sensitivity analysis 7: Adjusted for age, concurrent use of antidepressants, benzodiazepine derivatives. hypnotics and anxiolytics as time-varying confounders (n=5040)			
Baseline	2443	1.00	--
Pre-exposure period	133	4.41 (3.69-5.28)	<0.0001
Acute treatment	238	1.41 (1.21-1.63)	<0.0001
Maintenance treatment	2129	0.95 (0.86-1.05)	0.2904

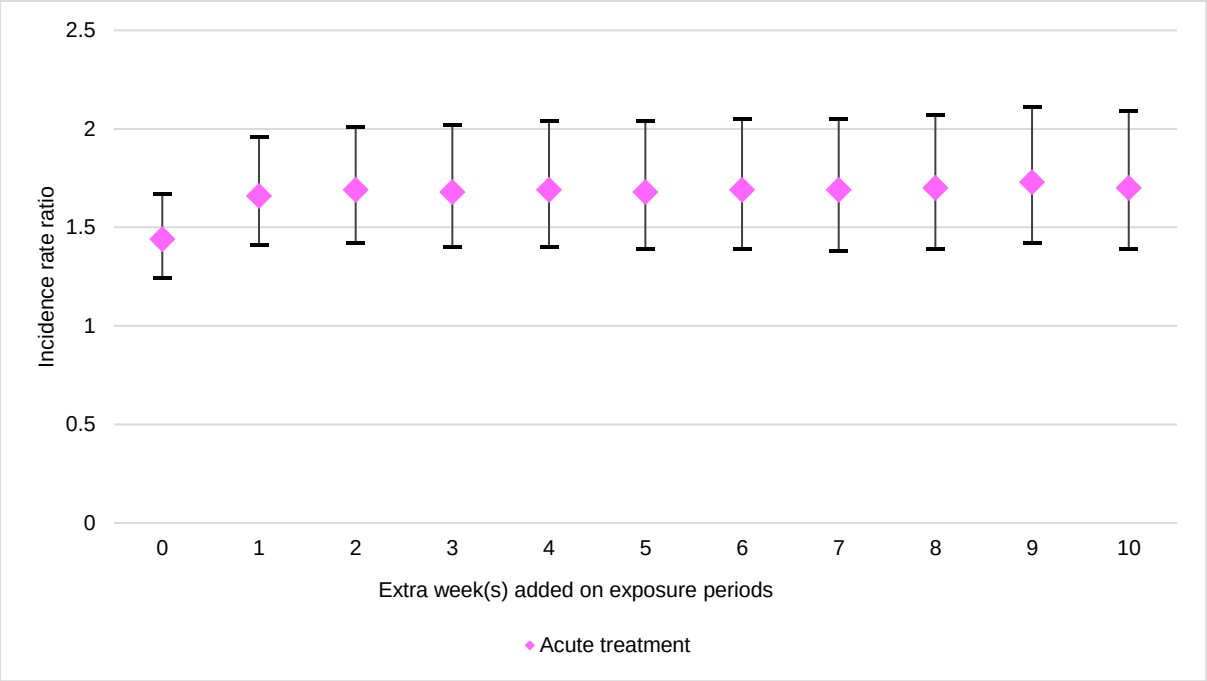
Post-exposure period	97	1.34 (1.09-1.66)	0.0061
Sensitivity analysis 8: Adjusted for age, concurrent use of antidepressants and benzodiazepine derivatives, doses of treatment agents as time-varying confounders (n=5040)			
Baseline	2443	1.00	--
Pre-exposure period	133	4.43 (3.70-5.30)	<0.0001
Acute treatment: low dose	167	1.41 (1.19-1.67)	<0.0001
Acute treatment: high dose	71	1.51 (1.18-1.95)	0.0012
Maintenance treatment: low dose	254	1.11 (0.96-1.30)	0.1618
Maintenance treatment: high dose	1875	0.94 (0.85-1.04)	0.2288
Post-exposure period	97	1.34 (1.09-1.66)	0.00061

[a]All estimates are adjusted for age in one-year age band and concurrent use of antidepressants and/or benzodiazepine derivatives.

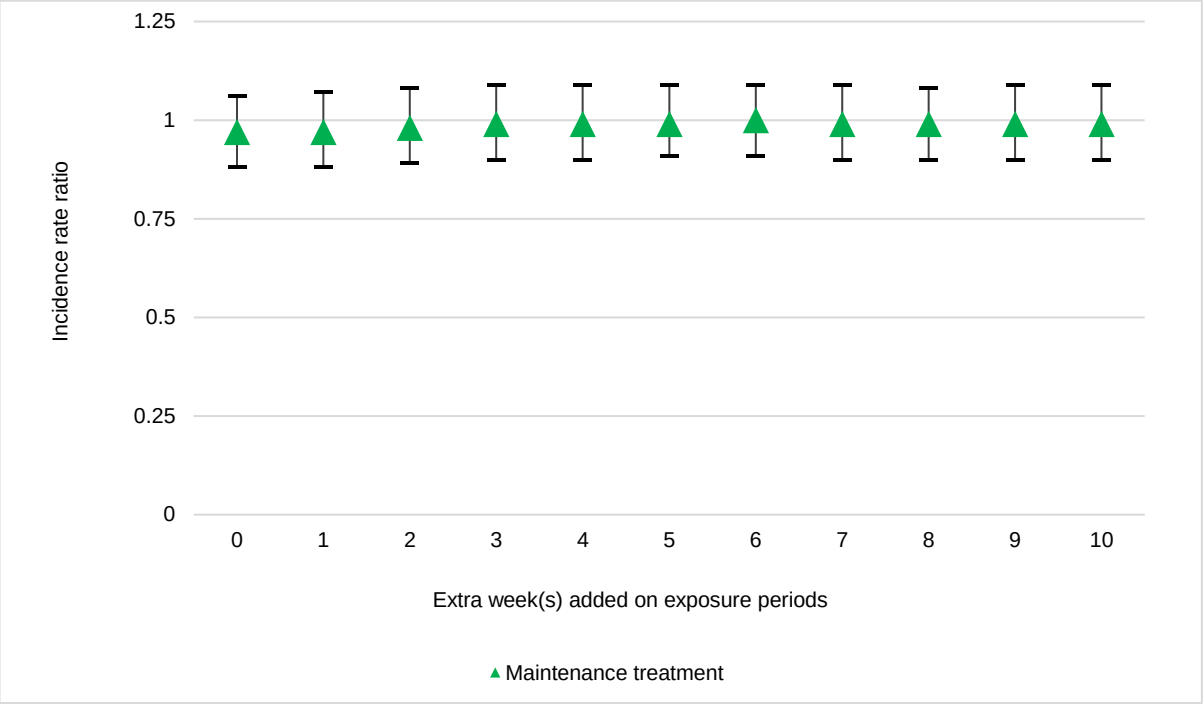
Abbreviations: CI=confidence interval; ER=emergency room; IRR=incidence rate ratio



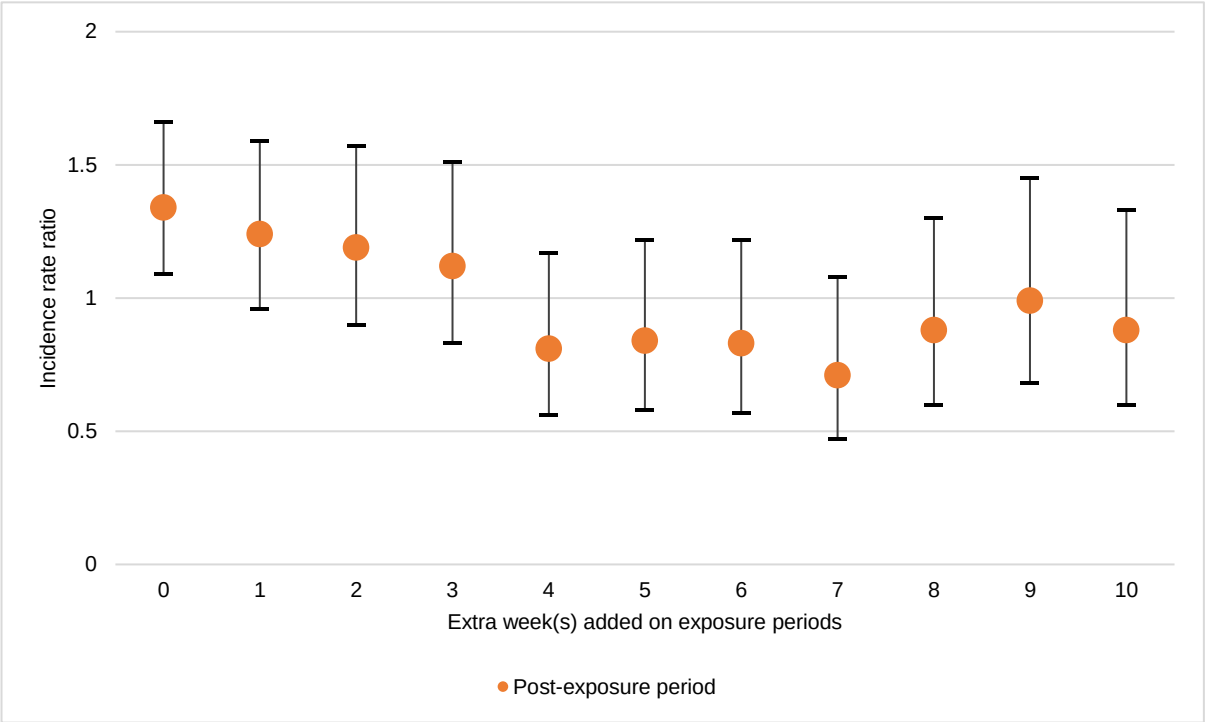
Supplementary Figure 2. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the pre-exposure period



Supplementary Figure 3. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the acute treatment



Supplementary Figure 4. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the maintenance treatment



Supplementary Figure 5. Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio of emergency room admissions due to traumatic injuries in the post-exposure period

Supplementary Table 7. Results from E-value analysis

Risk windows	Adjusted IRR (95% CI)	E-value (lower CI)
Acute treatment	1.44 (1.24-1.67)	2.24 (1.79)
Maintenance treatment	0.97 (0.88-1.06)	--
Direct comparison of maintenance treatment with pre-exposure period	0.22 (0.18-0.26)	8.56 (7.15)
Direct comparison of maintenance treatment with acute treatment	0.67 (0.59-0.77)	2.35 (1.92)
Direct comparison of maintenance treatment with post-exposure period	0.72 (0.58-0.89)	2.12 (1.5)

In our main analysis, the IRR (95% CI) for ER admissions due to traumatic injuries with the acute treatment was 1.44 (1.24-1.67). The E-value for the result point estimate was 2.24 with the lower confidence interval was 1.79 in an IRR scale. This result indicated that our observed increase in the risk of ER admissions due to traumatic injuries during the acute treatment could be explained away by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 2.24 each; the confidence interval could be moved to include 1.00 (i.e. no association) by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 1.79-fold each, with the existing confounders that were already accounted for, but weaker confounding could not do so.

During maintenance treatment, the IRR for ER admissions due to traumatic injuries did not reach statistical significance so the E-value was not calculated.

The E-value for the result point estimates of the direct comparison of different risk windows with the maintenance treatment for the ER admissions due to traumatic injuries were calculated. Similar to the main analysis, the calculated E-value (from 2.12 to 8.56) and lower confidence interval (from 1.5 to 7.15) explained the minimum strength of an unmeasured time-varying confounder that would nullify the observed decreased risk of ER admissions due to traumatic injuries with the use of pharmacological treatment of BPD.

Therefore, it is unlikely that an unmeasured time-varying confounder with this large magnitude of an association with both receiving pharmacological treatment of BPD and risk of ER admissions due to traumatic injuries exists, as such magnitude is much larger than those risk factors for ER admissions due to traumatic injuries, in particular age, concurrent use of psychotropic medications, for which we have already controlled for in the analyses. Therefore, our result is unlikely to have been due to an unmeasured time-varying confounder and this further supports the validity of our result.