Benzodiazepine and z-drug prescribing in critical care survivors and the risk of rehospitalisation or death due to falls/trauma and due to any cause: a retrospective matched cohort study using the UK Clinical Practice Research Datalink

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Abstract:

Purpose: Benzodiazepines and z-drugs are often prescribed to critical care survivors due to high prevalence of mental health problems and insomnia. However, their safety has not been studied in this population.

Methods: Retrospective cohort study of 28,678 adult critical care survivors hospitalised in 2010 and 2018: 4844 prescribed benzodiazepines or z-drugs, matched to 23,834 unexposed survivors using UK Clinical Practice Research Datalink linked datasets. Multivariable stratified Cox regression was used to estimate the adjusted hazards ratio (adjHR) with 95% confidence intervals (CI) of community benzodiazepine/z-drug prescribing and falls/trauma-related events, as well as all-cause 30-day rehospitalisation or death. We performed subgroup analyses on patients without pre-critical care admission prescription of benzodiazepines/z-drugs ('treatment-naïve'), and sensitivity analyses excluding patients receiving palliative care after discharge.

Results: Prescription of benzodiazepines or z-drugs showed no conclusive evidence of increased risk of falls/trauma-related events in the whole cohort (adjHR 1.27; 95%CI:0.76-2.14) or in treatment-naïve individuals (adjHR 1.79; 95%CI: 0.61-5.26), because estimates lacked precision due to low event rates. For all-cause rehospitalisation or death, benzodiazepines/z-drugs were associated with increased risk (whole cohort adjHR 1.24, 95%CI:1.14-1.36; treatment-naïve adjHR 1.66, 95%CI:1.49-1.86). However, after excluding patients treated for palliative care, the association persisted only in treatment-naïve individuals (whole cohort adjHR 1.08, 95%CI:0.98-1.19; treatment-naïve adjHR 1.42, 95%CI:1.25-1.62).

Conclusions: Community benzodiazepine and z-drug prescribing was associated with increased risk of all-cause, but not falls/trauma-related, rehospitalisations and deaths in critical care survivors who had not been prescribed these before hospitalisation. Clinicians should balance the possible benefits with the likely harms of prescribing these drugs in this potentially vulnerable patient group.

Keywords (4): benzodiazepines, hypnotics and sedatives, pharmacoepidemiology, critical care

Conflicts of interest: All authors declare no conflicts of interest.

Take home message: Benzodiazepines and z-drugs are often prescribed to critical care survivors due to high prevalence of mental health problems and insomnia. However, this study found an increased risk of all-cause rehospitalisation and death with their prescriptions in patients not prescribed these medicines before critical care hospitalisation.

140 character Tweet: In critical care survivors, new benzodiazepines and z-drug prescriptions are associated with increased risk of rehospitalisation and death.

Introduction:

Survivors of critical illness often experience new or worsened physical and mental health issues, making them a more vulnerable patient group.[1–4] Conditions such as anxiety,[5] posttraumatic stress disorder (PTSD),[6] and sleep disturbances[7] reportedly affect over half of critical care survivors within the first months after hospital discharge – conditions frequently associated with decreased quality of life, and increased morbidity and mortality.[8] Moreover, anxiety and PTSD can exacerbate sleep disorders and vice versa.[9–12] Benzodiazepines (e.g., diazepam) and z-drug hypnotics (e.g., zopiclone, zolpidem) are widely prescribed to minimise anxiety symptoms and sleep disorders.[8, 11, 13–15] Adverse events such as falls, fractures, road traffic accidents, dependency, respiratory depression, and death are known to be associated with benzodiazepines and z-drugs.[8, 16–20] Whether benzodiazepines and z-drugs increase the risk of adverse events in critical care survivors has not been established, despite many patients receiving prescriptions.[21–23] Survivors of critical illness may have newly acquired co-morbidities, polypharmacy and organ dysfunction, increasing their vulnerability to adverse drug events.[3, 24, 25]

We aimed to estimate the risk of benzodiazepine and z-drug prescribing on adverse outcomes for critical care survivors in the 90 days after hospital discharge. Adverse outcomes were defined as rehospitalisation or death due to falls or trauma-related events as well as rehospitalisation or death due to any cause.

Methods

Study design, setting, participants

This study was a retrospective matched cohort study. It was a secondary analysis of data obtained for a larger study investigating multimorbidity.[26] The multimorbidity study was limited to two annual cohorts (2010 and 2018) of all patients aged 18 years and over registered with a United Kingdom primary care practice contributing to the Clinical Practice Research Datalink (CPRD) Aurum database[27] on either January 1,

2010 or January 1, 2018. The study population for the study presented here was restricted to adults who had a hospitalisation with critical care admission in the same calendar year as their cohort and who were discharged from hospital alive (the "index hospitalisation"). Only the first hospitalisation event was included for patients with more than one hospitalisation with critical care. There was no restriction on length of critical care stay for inclusion in the study population. Patients were excluded if their data did not meet minimum data quality standards or had opted out of data sharing with CPRD (Figure 1).

Benzodiazepine or z-drug exposure

We used risk-set sampling: patients who received any community benzodiazepine or z-drug prescription within 90 days from index hospital discharge were matched with up to five patients who did not receive any community benzodiazepine or z-drug prescription within the same time-period. Patients were matched on days from hospital discharge to prescription ("match date" in those not prescribed), primary care practice, and cohort year, provided that no rehospitalisation [or death] occurred prior to the prescription or match date. Unexposed matches were censored if they subsequently received a community benzodiazepine or z-drug prescription. For the treatment-naïve analyses, only patients who had not received a community prescription for benzodiazepines or z-drugs within 180 days prior to index hospitalisation were included. In-hospital benzodiazepine or z-drug exposures were not available from these data sources and "treatment-naïve" patients may have been commenced these drugs in hospital.

Data sources and linkage

We were provided the following datasets linked by anonymised patient identifier: CPRD Aurum (primary care data including community prescriptions), Hospital Episode Statistics Admitted Patient Care (HES APC, hospitalisation data including the critical care dataset), Office for National Statistics (ONS, national death registration data), and Index of Multiple Deprivation (IMD, socioeconomic data). Almost all emergency hospital

and critical care is provided by the National Health Service (NHS) in the UK and recorded in these datasets. All NHS patients must register with a single primary care practice which acts as a gatekeeper to specialist services. Primary care practices undertake all community prescribing. Specialist drugs prescribed and dispensed in hospital outpatient settings (such as biologics) are variably recorded in the primary care record, but these prescriptions constitute a very small proportion of overall prescriptions issued. ONS comprises all national mortality data, a legal requirement in the UK. For details on these data sources, see references.[28–30] CPRD approved data access for this study (protocol reference 23_002860[31]), and oversees all aspects of information governance, ethics and confidentiality for studies accessing anonymised healthcare data held by CPRD.

Outcomes: Patients were followed up for 30 days after their first prescription after discharge (exposed) or corresponding match date (unexposed) for outcome assessment (Figure 2). We chose this follow-up period as the risk of adverse outcomes with benzodiazepines and z-drug hypnotics is typically highest shortly after initiation.[32–34] The two pre-specified outcomes of interest were: 1) a composite outcome of rehospitalisation or death due to falls or trauma-related events; and 2) a composite outcome of rehospitalisation or death due to any cause. Falls or trauma-related rehospitalisation or death were categorised by International Classification of Diseases - Tenth Edition (ICD-10) codes R29.6 (rehospitalisation only), S*, T07*, T14*, V*, W00*, and W01* coded in any hospital diagnosis or cause of death position [35–37].

Confounders: Sociodemographic factors included sex, age, ethnicity, and socioeconomic status (based on 2019 IMD quintiles of the patient's postcode). We derived variables including patients' baseline comorbidity count, prescription history of benzodiazepines or z-drugs, opioids, and gabapentinoids, number of prior hospitalisations and number of prior primary care consultations. The number of baseline comorbidities was modified from the Elixhauser-defined list of comorbidities[38] using all available ICD-10 hospital diagnosis codes[39, 40] and UK

Read codes (primary care diagnosis codes, Appendix) prior to index hospitalisation. We modified the Elixhauser comorbidity count by removing the mental health diagnoses which were instead included as individual binary co-variates (psychoses, alcohol dependence, and substance dependence). We additionally removed depression from the Elixhauser count and included a binary covariate for 'depression or anxiety' based on all available hospital and primary care data. Lastly, we created two additional binary covariates at time of index hospital admission to include in the models: history of insomnia (based on primary care practice data), and history of hospitalisation due to falls (ICD-10 diagnosis codes R29.6, W0*, W1). History of opioids and gabapentinoids were included as potential confounders given their association with increased risk of falls or trauma in older patients.[15, 41]

Critical care hospitalisation factors included year (2010 or 2018), mode of hospital admission, primary hospital diagnosis, critical care unit type, total number of organ systems supported (cardiovascular, respiratory, and/or renal support), out-of-hours discharge from critical care unit (discharge between 22:00 and 08:00 of last stay for those with more than one), and total hospital length of stay (in days). Primary diagnosis for critical care hospitalisation was categorised into ten categories defined by hospital ICD-10 codes: circulatory (I00-I99), neoplasms (C00-D49), digestive (K00-K95), respiratory (J00-J99), injury or poisoning (S00-T88), musculoskeletal (M00-M99), genitourinary (N00-N99), infectious (A00-B99), symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99), and all other conditions.[23]

Statistical methods

Patient characteristics were reported using proportions or medians with interquartile ranges (IQR). Associations between benzodiazepine or z-drug prescription and outcomes were evaluated using multivariable stratified Cox proportional hazard models (stratified by matched set). For the falls or trauma-related outcomes, we performed a cause-specific analysis where all other causes of rehospitalisation or deaths were treated as competing risks. No violations of proportional hazards assumptions were

observed on Schoenfeld plots. Adjusted hazards ratios (HR) with 95% confidence intervals (CI) were estimated for the exposure-outcome after adjusting for confounders using the *finalfit* package. Multiple imputation was performed for patients with missing data (7.6% of study population) using the *mice* package. All analyses were performed using R version 4.1.1. For the treatment-naïve group, the matched sets for all exposed patients were removed if they had received a prescription for a benzodiazepine or z-drug in 180 days prior to critical care hospitalisation. Any remaining matched set without an exposed patient were removed from analyses (also for sensitivity analyses). To assess if one medication class had a stronger association with outcomes, we separated patients by the medication class they were prescribed (benzodiazepines, z-drugs, or both), and multivariable stratified Cox proportional hazard models were repeated for the full matched cohort and the treatment-naïve group.

Sensitivity analyses

We conducted several sensitivity analyses. We explored our primary analysis after stratifying the study population by year of hospital admission to assess changes in exposure and outcomes rates between the two cohorts. Furthermore, we conducted a series of sensitivity analyses excluding patients who may have been receiving palliative care in the community after hospital discharge. First, we excluded patients who died in the first 30 days after index hospital discharge – both in the full matched cohort and the treatment-naïve group. Second, we used a broader definition and excluded patients who received any primary care diagnoses indicating palliative care (Appendix) or prescriptions associated with palliative and end-of-life care within 90 days of hospital discharge. Palliative care prescriptions were selected after consulting clinical experts and relevant literature [42] and comprised the following medications: injectable morphine, diamorphine, midazolam, levomepromazine, hyoscine, and haloperidol (excluding depot injections). Lastly, we conducted a sensitivity analysis after excluding patients who received a prescription for midazolam (all routes) from hospital discharge through the observation period.

Results

Among 58,784 survivors of critical illness, 6376 patients (12.2%; 95%CI: 11.9–12.4) were prescribed a benzodiazepine or z-drug within 90 days of index hospital discharge (Supplemental Table S1). Of these, 4853 (8.3%; 95%CI: 8.0–8.5) patients received a prescription prior to rehospitalisation and 4844 patients (50.2% female) were matched to 23,834 unexposed patients (43.3% female) by days from hospital discharge, primary care practice, and year (Table 1). The median days to prescription (or match date in the unexposed) was 11 days (IQR 4-25 days). The median age of those exposed was 64 years (IQR 51 – 74) versus 66 years (53–75) and most patients were of white ethnicity (91%). The most common main condition for index hospitalisation was circulatory disease (28%), followed by neoplasms (20%) (Supplemental Table S2). Most critically ill patients (70.4%) were cared for in a general/medical/surgical critical care unit while 19.5% were cared for in a cardio/thoracic critical care unit. A higher proportion of exposed patients received a prescription for opioids prior to hospitalisation (49% exposed versus 28% unexposed). The median hospital length of stay was 9 days (IQR 6-18 days). Of all benzodiazepines and z-drug prescriptions within 90 days, zopiclone was the most commonly prescribed drug (37.2%), followed by diazepam (26.3%), temazepam (11.6%), lorazepam (5.8%), clonazepam (4.9%), nitrazepam (3.9%), zolpidem (3.6%), midazolam (2.8%), clobazam (2.3%), or other (<1% each).

Among the matched patients, 14.9% (4260/28,678) had received one or more benzodiazepine or z-drug prescription within 180 days prior to index hospitalisation and were excluded from the treatment-naïve group. For the treatment-naïve group analyses, 2880 match sets without an exposed patient were excluded from analyses leaving 1964 exposed patients matched to 9099 unexposed patients (Table 1).

Risk of falls or trauma-related rehospitalisation or death

Among exposed patients, 1.3% (62/4844) had a fall or trauma-related rehospitalisation or death within 30 days of prescription, compared to 0.8% (179/23,834) of the unexposed matches (Figure 3). The adjusted HR for falls or trauma-related outcomes was 1.27 (95%CI: 0.76-2.14) in the exposed group compared to unexposed matches

(Table 2). Among treatment-naïve survivors, 0.9% of exposed and 0.7% of unexposed survivors had a fall or trauma-related rehospitalisation (adjusted HR 1.79; 95%CI: 0.61-5.26). These estimates lacked precision due to low event rates.

Risk of all-cause rehospitalisation or death

Of the exposed patients, 24.0% (1164/4844) were rehospitalised or died within 30 days of their prescription date versus 16.5% (3930/23,834) within 30 days of the match date in the unexposed matches. The adjusted HR was 1.24 (95%CI: 1.14-1.36) for the exposed compared to unexposed matches (Table 2). Among treatment-naïve survivors, the adjusted HR was 1.66 for those prescribed benzodiazepines or z-drugs compared to unexposed naïve matches (95%CI: 1.49-1.86).

Benzodiazepine versus z-drugs

Patients prescribed benzodiazepines had an adjusted HR of 1.32 (95%CI: 1.18-1.48) for all-cause rehospitalisation or death when compared to their unexposed matches (Table 2). The magnitude of association was greater when restricted to treatment-naïve patients (adjusted HR 2.08; 95%CI: 1.77-2.44). For patients prescribed z-drugs, the adjusted HR was 1.16 (95%CI: 1.04-1.31) for all-cause rehospitalisation or death when compared to their unexposed matches, and 1.35 (95%CI: 1.15-1.58) among treatment-naïve matches. Patients were infrequently prescribed benzodiazepines and z-drugs together, with resulting risk estimates with low precision (Table 2). Reflecting small numbers of outcomes, there were no statistically significant associations between individual drug classes and falls or trauma-related rehospitalisation or death (Table 2).

Sensitivity analyses

Analyses stratified by year of hospital admission found similar incidences (Supplemental Table S3) and associations (Supplemental Table S4). Excluding patients who died within 30 days of index discharge (n=274 from the full matched cohort and

n=125 from the treatment-naïve group) [and any match sets without an exposed patient] found similar associations as the primary analysis (Supplemental Table S5). Excluding patients with a primary care diagnosis of palliative care or prescription for palliative injectables within 90 days of hospital discharge (n=713 from the full matched cohort and n=390 from the treatment-naïve group), attenuated associations so that only the all-cause outcome in the treatment-naïve group remained statistically significant (adjusted HR: 1.42 (95%CI: 1.25-1.62), Supplemental Table S6). Lastly, excluding patients prescribed midazolam from hospital discharge through the observation window (n=252 from the full matched cohort and n=171 from the treatment-naïve group) found similar results as when we excluded patients with a primary care diagnosis or prescription for palliative care, reflecting the fact that the majority of midazolam prescriptions were likely for a palliative indication (Supplemental Table S7).

Discussion

One in eight critical care survivors received a prescription for a benzodiazepine or z-drug in primary care within 90 days of index hospital discharge. There was no conclusive evidence that prescription of benzodiazepines or z-drugs was associated with increased risk of falls or trauma-related events, because estimates lacked precision due to low event rates and did not reach statistical significance. The risk of all-cause rehospitalisation or death was increased with benzodiazepine or z-drug prescription in the 30 days after prescription or match date (24.0% in exposed versus 16.5% unexposed), which persisted after controlling for confounding. However, sensitivity analyses excluding patients treated for palliative care after hospital discharge demonstrated that this finding was only consistent in treatment-naïve survivors. When analyses were stratified by medication class, benzodiazepines showed a greater magnitude of association with outcomes compared with z-drugs. The magnitude of associations between benzodiazepine or z-drug prescription and adverse outcomes was more pronounced among the subgroup of treatment-naïve patients for all analyses.

Previous studies have reported prescription rates of benzodiazepine or z-drug prescriptions after critical illness. A recent study from Sweden assessed benzodiazepine prescriptions for 18 months following critical care hospital discharge from 2010 to 2017, but excluded patients that died in the first three months.[43] They found that 7% of adult critical care survivors received a dispensed benzodiazepine prescription during the first three months after hospital discharge. This proportion initially reduced and then plateaued during follow-up, to around 5% of critical care survivors during months seven to 18 after hospital discharge. Our work in the Lothian region of Scotland found that 6.5% of treatment-naïve adult critical care survivors were prescribed an anxiolytic or hypnotic within 90 days of hospital discharge (most of which were benzodiazepines or z-drugs). [23] A recent study of critical care survivors aged 65 years and over from Ontario, Canada found that 3.5% were dispensed a new benzodiazepine and 1.1% non-benzodiazepine sedative within seven days after hospital discharge.[22]

Systematic reviews and meta-analyses have consistently demonstrated a significant increased risk of falls, fractures, and road traffic accidents with benzodiazepine and z-drug prescribing [17, 18, 34, 44] but most of these studies focused on older adults in the community setting. While our study demonstrated short-term risk of rehospitalisation or death with benzodiazepine or z-drug prescribing in all critical care survivors, this increased risk is explained, at least in part, by patients receiving palliative care. However, in treatment-naïve survivors prescribed benzodiazepines or z-drugs, the risk of all-cause outcomes persisted even after excluding patients treated for palliative care in sensitivity analyses. Co-prescription of other central nervous system suppressing medication could have an additive effect, although we included gabapentinoids and opioids as potential confounders for this reason. When z-drugs were first licensed they were marketed as a safer alternative, but studies suggest that z-drugs have no less risk of adverse events than benzodiazepines.[45, 46] Potential explanations for the observed increased risk of benzodiazepines compared to z-drugs in our study include pharmacokinetic differences (long half-life and active metabolites) of diazepam, the most commonly prescribed benzodiazepine in our study, compared to zopiclone (short

half-life and largely inactive metabolites)[46], the most commonly prescribed z-drug in our study. Previous research suggest that benzodiazepines cause greater central nervous system and respiratory depression compared to z-drugs.[45] The increased risk of rehospitalisation or death among treatment-naïve survivors is consistent with research which found benzodiazepines to have the highest risk of adverse events within the first two weeks of initiation compared to continuous use.[32] This is also reasonable according to the concept of "depletion of susceptibles"[47] - where the risk of adverse events is lower in prevalent users as they have tolerated the medication well enough to continue. However, our primary analysis did not exclude prevalent users due to the nature of physiologic changes associated with critical illness – even if a patient tolerated benzodiazepines or z-drugs in the past, this does not mean that they would tolerate it after a critical illness.

Our study has several strengths. This study is among the first to examine the risk of adverse outcomes associated with benzodiazepine or z-drug prescribing in population-based adult survivors of critical illness after adjustment for multiple confounders. Our ability to include all adult patients without restriction maximises generalisability to all critical care survivors, and is uncommon when compared to other published psychotropic prescribing studies.[21, 22] Another strength of our study is that we matched on days from hospital discharge, as this is an important time-varying indicator of vulnerability in this population (e.g., the longer a patient is from their index hospital discharge without rehospitalisation, the more recovered they are likely to be). Lastly, our data sources are fit-for-purpose for pharmacoepidemiologic studies. The CPRD Aurum database includes routinely collected data and prescriptions from primary care practices. Almost all prescriptions in the UK come from primary care practices (including medicines initiated/recommended by specialists), making misclassification of prescriptions minimal.

Our study has a number of limitations. We assessed only falls or trauma-related outcomes that resulted in hospitalisation or death and did not consider such events

that may have occurred without a healthcare visit or treated as an outpatient. This likely explains the low frequency of falls or trauma-related outcomes, which did not allow for precision in the risk estimates (which would have strengthened the inference between benzodiazepine and z-drug prescribing and adverse outcomes). As we identified this possibility *a priori*, we included all-cause outcomes in our study protocol. This study was restricted to data from patients admitted to hospital with critical care in calendar years 2010 and 2018, with follow up through 2011 and 2019, respectively. While changes in practice may have occurred from then until present, we did not observe differences in baseline characteristics or associations between the two cohorts in our stratified analyses. Additionally, by studying cohorts with follow-up periods occurring before the start of the COVID-19 pandemic, we hope to mitigate the influences of COVID-19 on the findings. We used IMD as an indicator for socioeconomic status, however, this was based on IMD data from 2019. Given that neighbourhood deprivation may change over time, residual confounding may have affected the 2010 cohort. We elected to observe initial prescribing for up to 90 days understanding that the further from hospital discharge a patient is prescribed, the likelihood that it is related to the critical care event may reduce. However, previous studies investigating post-critical care sequelae have demonstrated that critical care survivors experience persisting risk of health problems in the months after hospital discharge.[7, 48] Next, while HES APC includes high quality hospital data, it lacks in-hospital prescribing data, so that patients who received a supply of benzodiazepines or z-drugs from the hospital at the time of discharge would be misclassified as unexposed if there was no subsequent prescription from their primary care provider. However, this misclassification of unexposed patients would bias results towards the null. Additionally, past studies have shown that patients starting benzodiazepines or z-drugs in hospital are frequently re-prescribed these medicines again in the community shortly after hospital discharge.[22, 49–53] We included gabapentinoids and opioids as confounders, although other central nervous systems suppressing medication classes exist and may have affected the adverse outcomes findings. Lastly, we did not explore the indication for benzodiazepine or z-drug prescriptions in this study. Our recent work has found that almost half of patients prescribed benzodiazepines or z-drugs within 90 days of critical illness did not have a

coded diagnosis of depression, anxiety, or insomnia, making the true indication difficult to assess in these data.[54]

Our findings have implications for clinical practice and policy. Firstly, continuing improvements in critical care practice to minimise the incidence of mental health disorders post-discharge are required.[55] Where prescribing is necessary, recently discharged critical care survivors should be recognised as particularly vulnerable to adverse events, because of newly acquired morbidities and impaired physical function. Efforts to minimise exposure to benzodiazepines and z-drugs should focus on addressing any modifiable factors such as pain. If medications are deemed necessary, then a risk to benefit approach is required, adopting best practices in medication selection and indication (e.g. antidepressants or z-drugs over benzodiazepines). This approach should be based on minimising medication exposure (dose and duration) and be individualised to the patient's post-critical care physiological, co-morbidity and polypharmacy considerations. Clinicians should consider the effectiveness of non-pharmacological therapies, such as cognitive behavioural therapy, or alternative drugs with safer profiles like certain antidepressants or melatonin, in this vulnerable patient population.

Conclusion

This study has demonstrated an increased risk of all-cause, but not falls or trauma-related, rehospitalisation and death outcomes associated with community benzodiazepine and z-drug prescribing in critical care survivors who had not been prescribed these before hospitalisation. Clinicians should balance the possible benefits with the likely harms of prescribing these medicines in potentially vulnerable critical care survivors.

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Study protocol and programming code is available by request.

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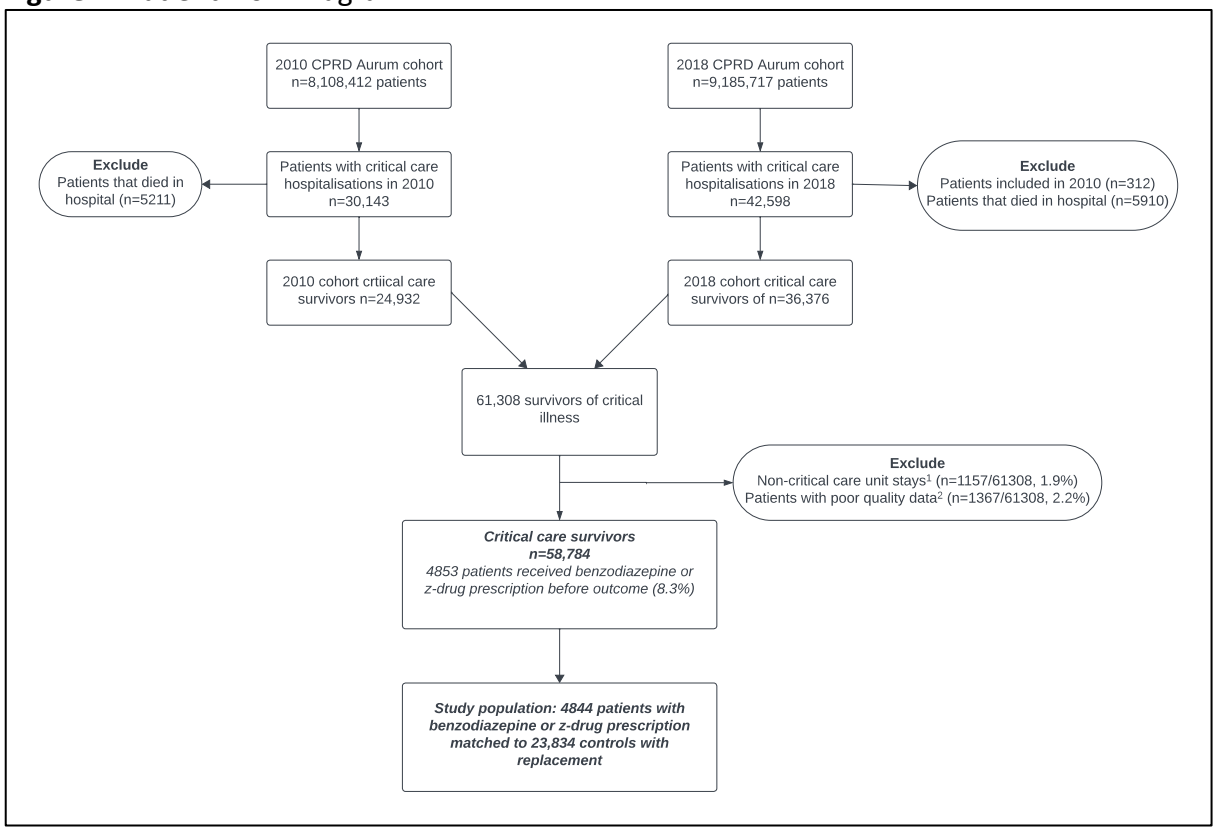
Benzodiazepine and z-drug prescribing in critical care survivors and the risk of rehospitalisation or death due to falls/trauma and due to any cause: a retrospective matched cohort study using the UK Clinical Practice Research Datalink

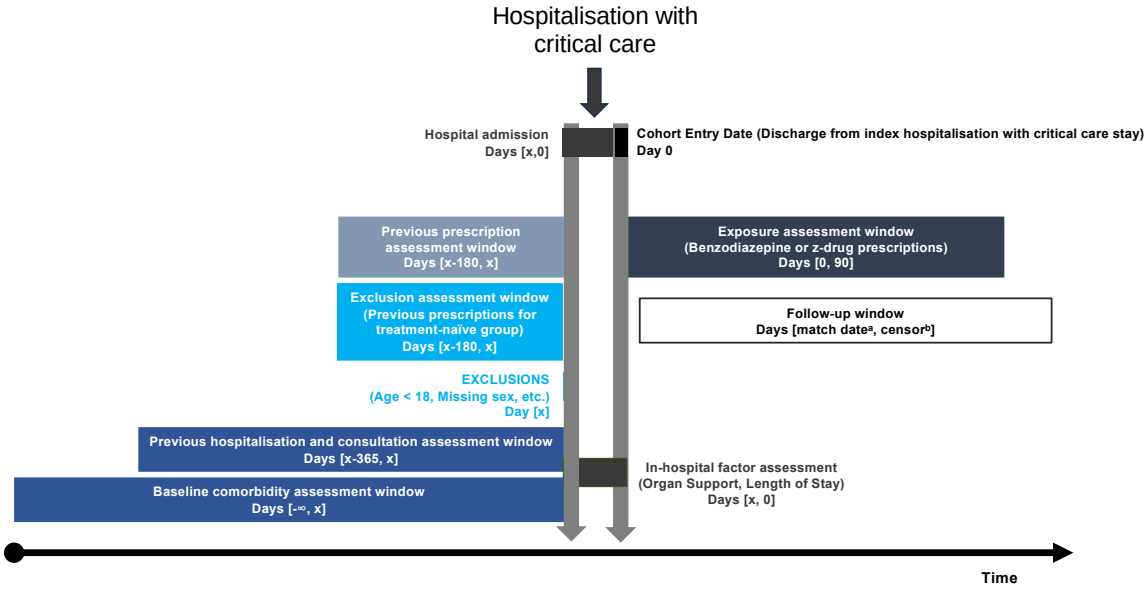
Figure 1. Patient Flow Diagram



CPRD: Clinical Practice Research Datalink

[1]*Non-critical care unit stays* were patients who were provided critical care outside a typical unit (e.g., ward). [2]*Patients with poor quality data* included those missing sex, age, primary care practice identifier, hospital discharge date, or as recommended by the data manager.

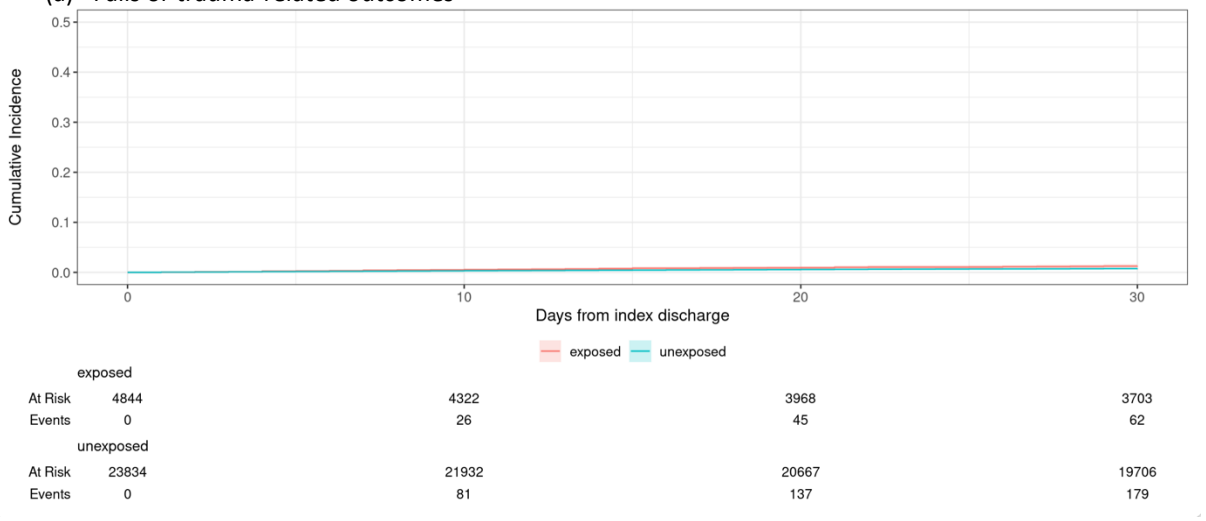
Figure 2. Study diagram



a. Comparator risk-set matched on days from cohort entry, primary care practice, and year.
b. Earliest of outcome, 30 days of follow-up or end of study period.

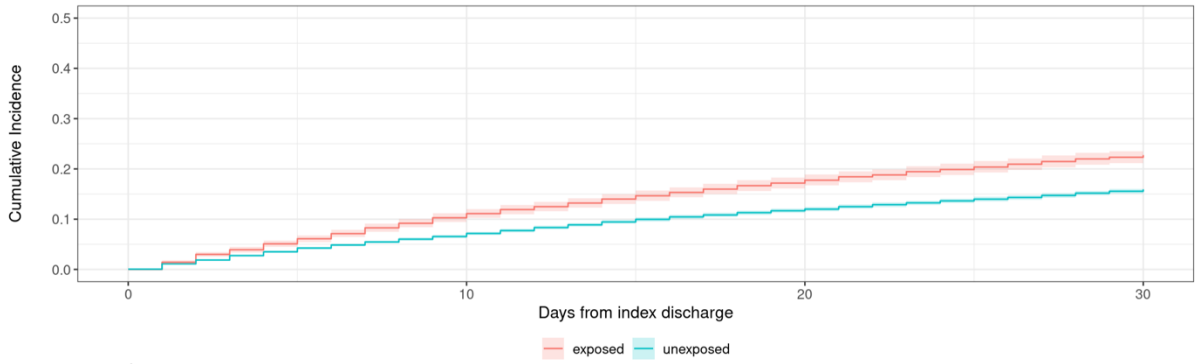
Figure 3. Cumulative incidence plots of falls or trauma-related rehospitalisation or death (*a*), and all-cause rehospitalisation or death (*b*).

(a) Falls or trauma-related outcomes



exposed				
At Risk	4844	4322	3968	3703
Events	0	26	45	62
unexposed				
At Risk	23834	21932	20667	19706
Events	0	81	137	179

(b) All-cause outcomes



exposed				
At Risk	4844	4322	3968	3703
Events	0	538	860	1102
unexposed				
At Risk	23834	21932	20667	19706
Events	13	1686	2825	3751

Table 1. Matched study population sociodemographic, comorbidity, and hospital characteristics, *left*, and matched treatment-naïve group, *right*.

		All matched patients (n=28,678)		Treatment-naïve matched (n=11,063)	
Characteristic	**Levels**	**Unexposed**	**Benzodiazepine or z-drug exposed**	**Unexposed**	**Benzodiazepine or z-drug exposed**
Sex	Male	13517 (56.7)	2414 (49.8)	5282 (58.1)	1186 (60.4)
	Female	10317 (43.3)	2430 (50.2)	3817 (41.9)	778 (39.6)
Age	Median (IQR)	66.0 (53.0 to 75.0)	64.0 (51.0 to 74.0)	66.0 (53.0 to 75.0)	65.0 (53.0 to 75.0)
Ethnicity	White	21600 (90.6)	4509 (93.1)	8253 (90.7)	1815 (92.4)
	Asian	954 (4.0)	167 (3.4)	384 (4.2)	78 (4.0)
	Black	689 (2.9)	81 (1.7)	254 (2.8)	42 (2.1)
	Mixed	126 (0.5)	24 (0.5)	34 (0.4)	7 (0.4)
	Other	323 (1.4)	45 (0.9)	112 (1.2)	16 (0.8)
	Missing	142 (0.6)	18 (0.4)	62 (0.7)	6 (0.3)
IMD quintile	5, Most deprived	5040 (21.1)	1200 (24.8)	1794 (19.7)	400 (20.4)
	4	4705 (19.7)	927 (19.1)	1773 (19.5)	366 (18.6)
	3	4552 (19.1)	900 (18.6)	1743 (19.2)	371 (18.9)
	2	4752 (19.9)	937 (19.3)	1902 (20.9)	424 (21.6)
	1, Least deprived	4754 (19.9)	875 (18.1)	1877 (20.6)	401 (20.4)
	Missing	31 (0.1)	<10 (<0.01)	10 (0.1)	2 (0.1)
Elixhauser comorbidity count[1] (median (IQR))		2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)
History of insomnia		1913 (8.0)	1304 (26.9)	628 (6.9)	300 (15.3)
History of falls		2465 (10.3)	809 (16.7)	854 (9.4)	201 (10.2)
History of anxiety or depression		7500 (31.5)	2716 (56.1)	2655 (29.2)	791 (40.3)
History of psychoses		435 (1.8)	270 (5.6)	122 (1.3)	54 (2.7)
History of alcohol dependence		2682 (11.3)	1015 (21.0)	944 (10.4)	303 (15.4)
History of substance dependence		528 (2.2)	419 (8.6)	172 (1.9)	66 (3.4)
History of benzodiazepine or z-drug prescription		1380 (5.8)	2880 (59.5)		
History of opioid prescription		6627 (27.8)	2385 (49.2)	2368 (26.0)	696 (35.4)
History of gabapentinoids prescription		1412 (5.9)	738 (15.2)	482 (5.3)	132 (6.7)
No. hospital admissions (median (IQR)/year)		1.0 (0.0 to 2.0)	1.0 (0.0 to 3.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)
No. primary care consultations (median (IQR)/year)		8.0 (2.0 to 14.0)	11.0 (5.0 to 20.0)	7.0 (2.0 to 14.0)	9.0 (3.0 to 16.0)
Year of hospital admission	2010	11773 (49.4)	2415 (49.9)	4542 (49.9)	994 (50.6)
	2018	12061 (50.6)	2429 (50.1)	4557 (50.1)	970 (49.4)
Hospital admission method	Elective	11365 (47.7)	2047 (42.3)	4407 (48.4)	864 (44.0)
	Emergency	10895 (45.7)	2573 (53.1)	4080 (44.8)	970 (49.4)
	Transfer/Other	1573 (6.6)	224 (4.6)	612 (6.7)	130 (6.6)
	Missing	1 (<0.01)	0 (0.0)	0 (0.0)	0 (0.0)
Critical care unit type	Gen/Med/Surg	16668 (69.9)	3518 (72.6)	6304 (69.3)	1255 (63.9)
	Cardiothoracic	4717 (19.8)	873 (18.0)	1888 (20.7)	489 (24.9)
	Neuro	864 (3.6)	179 (3.7)	336 (3.7)	87 (4.4)
	Other	754 (3.2)	81 (1.7)	276 (3.0)	30 (1.5)
	Missing	831 (3.5)	193 (4.0)	295 (3.2)	103 (5.2)
Total organ systems supported	None	1947 (8.2)	356 (7.3)	723 (7.9)	121 (6.2)
	1	6911 (29.0)	1315 (27.1)	2642 (29.0)	472 (24.0)
	2	12469 (52.3)	2623 (54.1)	4815 (52.9)	1123 (57.2)
	3	843 (3.5)	192 (4.0)	315 (3.5)	90 (4.6)
	Missing	1664 (7.0)	358 (7.4)	604 (6.6)	158 (8.0)
Out of hours critical care discharge	Yes	3558 (14.9)	779 (16.1)	1392 (15.3)	310 (15.8)
	Missing	831 (3.5)	193 (4.0)	295 (3.2)	103 (5.2)
Critical care length of stay (median (IQR) days)		2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)
Hospital length of stay (median (IQR) days)		9.0 (5.0 to 17.0)	10.0 (6.0 to 20.0)	9.0 (5.0 to 17.0)	11.0 (6.0 to 22.0)
Days to match date (median (IQR))		11.0 (4.0 to 25.0)	11.0 (4.0 to 25.0)	12.0 (5.0 to 31.0)	12.0 (5.0 to 31.0)

[1] Modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical.

Table 2. Benzodiazepine or z-drug prescription after hospital discharge in adult critical care survivors and the association with rehospitalisation or death within 30 days of prescription or match date.

Exposure	N (%)	N (%) with outcome in follow-up window	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Matched cohort: falls or trauma-related outcome					
Unexposed	23834 (83.1)	179 (0.8)	Ref	Ref	Ref
Benzodiazepine or z-drug exposed	4844 (16.9)	62 (1.3)	1.76 (1.32-2.35, p<0.001)	1.02 (0.59-1.78, p=0.943)	1.27 (0.76-2.14, p=0.364)
Matched cohort: all-cause outcome					
Unexposed	23834 (83.1)	3930 (16.5)	Ref	Ref	Ref
Benzodiazepine or z-drug exposed	4844 (16.9)	1164 (24.0)	1.51 (1.41-1.61, p<0.001)	1.22 (1.12-1.34, p<0.001)	1.24 (1.14-1.36, p<0.001)
Treatment-naïve matched cohort: falls or trauma-related outcome					
Unexposed	9099 (82.2)	65 (0.7)	Ref	Ref	Ref
Benzodiazepine or z-drug exposed	1964 (17.8)	17 (0.9)	1.29 (0.75-2.19, p=0.357)	1.51 (0.45-5.03, p=0.501)	1.79 (0.61-5.26, p=0.279)
Treatment-naïve matched cohort: all-cause outcome					
Unexposed	9099 (82.2)	1413 (15.5)	Ref	Ref	Ref
Benzodiazepine or z-drug exposed	1964 (17.8)	496 (25.3)	1.73 (1.56-1.91, p<0.001)	1.64 (1.46-1.85, p<0.001)	1.66 (1.49-1.86, p<0.001)
Matched cohort: falls or trauma-related outcome					
Unexposed	23834 (83.1)	179 (0.8)	Ref	Ref	Ref
Benzodiazepine exposed	2444 (8.5)	36 (1.5)	2.07 (1.44-2.95, p<0.001)	1.10 (0.53-2.29, p=0.794)	1.37 (0.69-2.73, p=0.360)
Z-drug exposed	2242 (7.8)	19 (0.8)	1.15 (0.71-1.84, p=0.573)	0.81 (0.38-1.72, p=0.580)	1.07 (0.54-2.11, p=0.845)
Benzodiazepine and z-drug exposed	158 (0.6)	7 (4.4)	1.15 (0.71-1.84, p=0.573)	0.81 (0.38-1.72, p=0.580)	3.52 (0.81-15.28, p=0.093)
Matched cohort: all-cause outcome					
Unexposed	23834 (83.1)	3930 (16.5)	Ref	Ref	Ref
Benzodiazepine exposed	2444 (8.5)	643 (26.3)	1.68 (1.55-1.83, p<0.001)	1.31 (1.16-1.48, p<0.001)	1.32 (1.18-1.48, p<0.001)
Z-drug exposed	2242 (7.8)	480 (21.4)	1.32 (1.20-1.45, p<0.001)	1.14 (1.01-1.29, p=0.032)	1.16 (1.04-1.31, p=0.010)
Benzodiazepine and z-drug exposed	158 (0.6)	41 (25.9)	1.62 (1.19-2.20, p=0.002)	1.22 (0.82-1.81, p=0.327)	1.22 (0.84-1.79, p=0.295)
Treatment-naïve matched cohort: falls or trauma-related outcome					
Unexposed	9099 (82.2)	65 (0.7)	Ref	Ref	Ref
Benzodiazepine exposed	806 (7.3)	9 (1.1)	1.74 (0.87-3.50, p=0.118)	5.72 (0.66-49.77, p=0.114)	4.68 (0.67-32.49, p=0.115)
Z-drug exposed	1138 (10.3)	7 (0.6)	0.88 (0.40-1.92, p=0.751)	0.53 (0.09-3.11, p=0.485)	0.96 (0.23-3.97, p=0.951)
Benzodiazepine and z-drug exposed	20 (0.2)	<5 (<25.0)	8.04 (1.11-57.91, p=0.039)	10.38 (0.18-590.37, p=0.256)	14.57 (0.18-1154.8, p=0.223)
Treatment-naïve matched cohort: all-cause outcome					
Unexposed	9099 (82.2)	1413 (15.5)	Ref	Ref	Ref
Benzodiazepine exposed	806 (7.3)	258 (32.0)	2.30 (2.01-2.63, p<0.001)	2.08 (1.76-2.47, p<0.001)	2.08 (1.77-2.44, p<0.001)
Z-drug exposed	1138 (10.3)	230 (20.2)	1.33 (1.16-1.53, p<0.001)	1.30 (1.10-1.54, p=0.002)	1.35 (1.15-1.58, p<0.001)
Benzodiazepine and z-drug exposed	20 (0.2)	8 (40.0)	2.96 (1.48-5.92, p=0.002)	2.93 (1.04-8.24, p=0.041)	2.78 (1.08-7.18, p=0.034)

[1]Adjusted models were adjusted for sex, age, ethnicity, socioeconomic status, baseline comorbidity count, history of psychoses, alcohol dependence, substance dependence, depression or anxiety, insomnia, and hospitalisations due to falls, prescription history of benzodiazepines/z-drugs, opioids, gabapentinoids, number of prior hospitalisations and primary care consultations, year of critical care hospitalisation, primary hospital diagnosis, critical care unit type, total number of organ systems supported, out-of-hours discharge from critical care, and total hospital length of stay (in days).

Benzodiazepine and z-drug prescribing in critical care survivors and the risk of rehospitalisation or death due to falls/trauma and due to any cause: a retrospective matched cohort study using the UK Clinical Practice Research Datalink

Elizabeth T. Mansi, Christopher T. Rentsch, Richard S. Bourne, Annie Jeffery, Bruce Guthrie, Nazir I. Lone

Supplementary Materials

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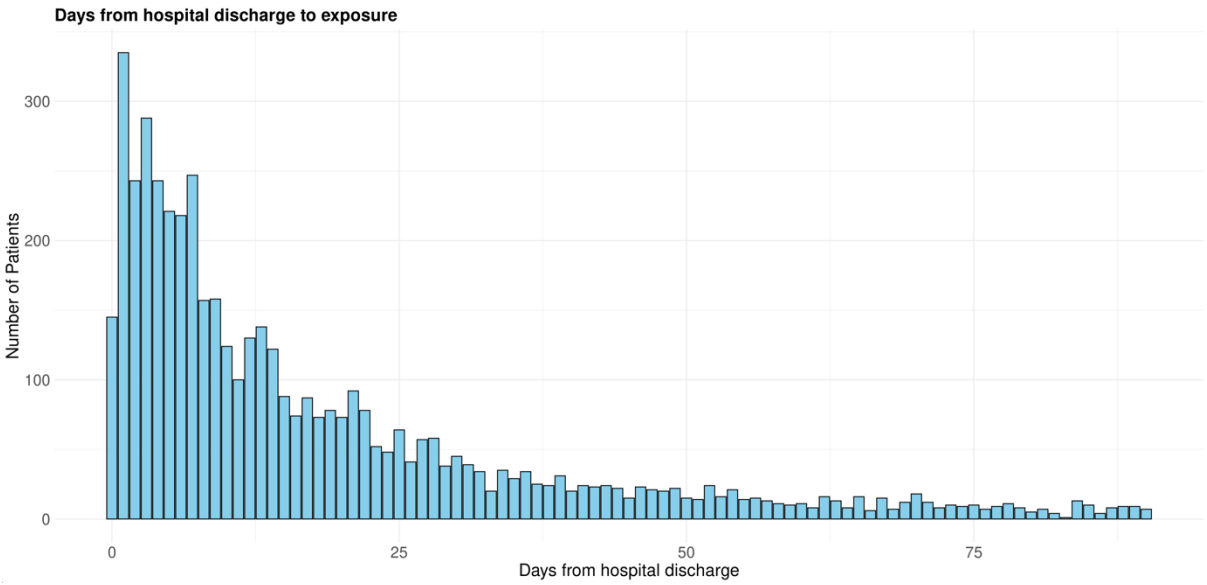
Supplemental Figure S1. Days to first prescription from hospital discharge in exposed critical care survivors (n=4844).



Supplemental Table S1. Patient characteristics of all possible study participants before matching, stratified by benzodiazepine or z-drug exposure within 90 days of discharge.

		All n=58,784 (%)	**Unexposed** n=52,408 (%)	**Benzodiazepine or z-drug exposed[1]** n=6376 (%)
Sex	Male Female	33056 (56.2) 25728 (43.8)	29891 (57.0) 22517 (43.0)	3165 (49.6) 3211 (50.4)
Age	Median (IQR)	65.0 (52.0 to 75.0)	66.0 (52.0 to 75.0)	64.0 (51.0 to 74.0)
Age group	18-49 50-64 65-79 80+	12464 (21.2) 15764 (26.8) 22381 (38.1) 8175 (13.9)	11045 (21.1) 13898 (26.5) 20069 (38.3) 7396 (14.1)	1419 (22.3) 1866 (29.3) 2312 (36.3) 779 (12.2)
Ethnicity	White Asian Black Mixed Other Missing	52055 (88.6) 3078 (5.2) 2158 (3.7) 345 (0.6) 902 (1.5) 246 (0.4)	46126 (88.0) 2847 (5.4) 2054 (3.9) 315 (0.6) 844 (1.6) 222 (0.4)	5929 (93.0) 231 (3.6) 104 (1.6) 30 (0.5) 58 (0.9) 24 (0.4)
IMD quintile	5, Most deprived 4 3 2 1, Least deprived Missing	12825 (21.8) 12160 (20.7) 11275 (19.2) 11421 (19.4) 11012 (18.7) 91 (0.2)	11263 (21.5) 10909 (20.8) 10084 (19.2) 10193 (19.4) 9875 (18.8) 84 (0.2)	1562 (24.5) 1251 (19.6) 1191 (18.7) 1228 (19.3) 1137 (17.8) 7 (0.1)
Modified Elixhauser comorbidity count[2]	Median (IQR)	3.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	3.0 (1.8 to 4.0)
History of insomnia		5943 (10.1)	4299 (8.2)	1644 (25.8)
History of falls		7258 (12.3)	6198 (11.8)	1060 (16.6)
History of anxiety or depression		20387 (34.7)	16832 (32.1)	3555 (55.8)
History of psychoses		1508 (2.6)	1145 (2.2)	363 (5.7)
History of alcohol dependence		7670 (13.0)	6364 (12.1)	1306 (20.5)
History of substance dependence		1866 (3.2)	1334 (2.5)	532 (8.3)
History of benzodiazepine or z-drug prescription		6383 (10.9)	2753 (5.3)	3630 (56.9)
History of opioid prescription		17560 (29.9)	14422 (27.5)	3138 (49.2)
History of gabapentinoid prescription		4324 (7.4)	3350 (6.4)	974 (15.3)
Number hospital admissions (1 year)	Number hospital admissions (1 year)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 3.0)
Number primary care consultations (1 year)	Median (IQR)	8.0 (3.0 to 15.0)	8.0 (3.0 to 14.0)	11.0 (5.0 to 20.0)
Year of hospital admission	2010 2018	23998 (40.8) 34786 (59.2)	20859 (39.8) 31549 (60.2)	3139 (49.2) 3237 (50.8)
Hospital admission method	Elective Emergency Transfer/Other Missing	25896 (44.1) 28780 (49.0) 4105 (7.0) <10 (<0.01)	23275 (44.4) 25324 (48.3) 3806 (7.3) <10 (<0.01)	2621 (41.1) 3456 (54.2) 299 (4.7) 0 (0.0)
Primary condition at index hospitalisation	Circulatory Neoplasms Digestive Respiratory Injury Musculoskeletal Genitourinary Infectious Abnormal findings[3] Other	16278 (27.7) 11425 (19.4) 6413 (10.9) 5481 (9.3) 5772 (9.8) 2429 (4.1) 2009 (3.4) 1763 (3.0) 1459 (2.5) 5755 (9.8)	14813 (28.3) 10122 (19.3) 5728 (10.9) 4717 (9.0) 4975 (9.5) 2146 (4.1) 1807 (3.4) 1572 (3.0) 1264 (2.4) 5264 (10.0)	1465 (23.0) 1303 (20.4) 685 (10.7) 764 (12.0) 797 (12.5) 283 (4.4) 202 (3.2) 191 (3.0) 195 (3.1) 491 (7.7)
Critical care unit type	Gen/Med/Surg Cardio/Thoracic Neuro Other Missing	40895 (69.6) 11127 (18.9) 2487 (4.2) 2139 (3.6) 2136 (3.6)	36231 (69.1) 10055 (19.2) 2231 (4.3) 2016 (3.8) 1875 (3.6)	4664 (73.1) 1072 (16.8) 256 (4.0) 123 (1.9) 261 (4.1)

Cardiovascular support	Basic Advanced Missing	36628 (62.3) 11367 (19.3) 2768 (4.7)	32557 (62.1) 10288 (19.6) 2440 (4.7)	4071 (63.8) 1079 (16.9) 328 (5.1)
Respiratory support	Basic Advanced Missing	17977 (30.6) 18440 (31.4) 3373 (5.7)	15861 (30.3) 16432 (31.4) 2994 (5.7)	2116 (33.2) 2008 (31.5) 379 (5.9)
Renal support	 Missing	3058 (5.2) 4134 (7.0)	2705 (5.2) 3662 (7.0)	353 (5.5) 472 (7.4)
Total organ systems supported	None 1 2 3 Missing	4743 (8.1) 16809 (28.6) 30698 (52.2) 2345 (4.0) 4189 (7.1)	4280 (8.2) 15041 (28.7) 27307 (52.1) 2069 (3.9) 3711 (7.1)	463 (7.3) 1768 (27.7) 3391 (53.2) 276 (4.3) 478 (7.5)
Out of hours critical care discharge	 Missing	8777 (14.9) 2136 (3.6)	7764 (14.8) 1875 (3.6)	1013 (15.9) 261 (4.1)
Critical care length of stay (days)	Median (IQR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)
Hospital length of stay	Median (IQR)	9.0 (6.0 to 19.0)	9.0 (5.0 to 18.0)	10.0 (6.0 to 20.0)

[1]within 90 days of critical care hospital discharge. [2]modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. [3]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
IMD: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical

Supplemental Table S2. Additional characteristics for matched study population, *left*, and matched treatment-naïve group, *right*.

		All matched patients (n=28,678)		Treatment-naïve matched (n=11,063)	
Characteristic	**Levels**	**Unexposed**	**Benzodiazepine or z-drug exposed**	**Unexposed**	**Benzodiazepine or z-drug exposed**
Primary condition at index hospitalisation	Circulatory	6834 (28.7)	1160 (23.9)	2699 (29.7)	640 (32.6)
	Neoplasms	4778 (20.0)	929 (19.2)	1825 (20.1)	428 (21.8)
	Digestive	2568 (10.8)	521 (10.8)	959 (10.5)	192 (9.8)
	Respiratory	2256 (9.5)	593 (12.2)	826 (9.1)	151 (7.7)
	Injury	2159 (9.1)	602 (12.4)	804 (8.8)	203 (10.3)
	Musculoskeletal	1065 (4.5)	247 (5.1)	410 (4.5)	86 (4.4)
	Genitourinary	697 (2.9)	139 (2.9)	254 (2.8)	42 (2.1)
	Infectious	596 (2.5)	135 (2.8)	225 (2.5)	39 (2.0)
	Abnormal findings[1]	565 (2.4)	145 (3.0)	210 (2.3)	60 (3.1)
	Other	2316 (9.7)	373 (7.7)	887 (9.7)	123 (6.3)
Cardiovascular support	Basic	14907 (62.5)	3083 (63.6)	5639 (62.0)	1163 (59.2)
	Advanced	4611 (19.3)	847 (17.5)	1840 (20.2)	471 (24.0)
	Missing	1061 (4.5)	243 (5.0)	396 (4.4)	122 (6.2)
Respiratory support	Basic	7419 (31.1)	1610 (33.2)	2829 (31.1)	582 (29.6)
	Advanced	7377 (31.0)	1559 (32.2)	2875 (31.6)	732 (37.3)
	Missing	1310 (5.5)	280 (5.8)	474 (5.2)	133 (6.8)
Renal support		1019 (4.3)	228 (4.7)	375 (4.1)	101 (5.1)
	Missing	1640 (6.9)	357 (7.4)	596 (6.6)	158 (8.0)

[1] Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

Supplemental Table S3. Patient characteristics, exposure, and outcomes for the matched study population characteristics (*left)* and matched treatment-naïve group (*right),* stratified by year of hospital admission.

		2010 n=14,188 (%)	**2018** n=14,490 (%)	**Treatment-naïve 2010** n=5536 (%)	**Treatment-naïve 2018** n=5527 (%)
Sex	Male	7976 (56.2)	7955 (54.9)	3283 (59.3)	3185 (57.6)
	Female	6212 (43.8)	6535 (45.1)	2253 (40.7)	2342 (42.4)
Age	Median (IQR)	65.0 (53.0 to 75.0)	65.0 (53.0 to 75.0)	66.0 (54.0 to 75.0)	66.0 (53.0 to 75.0)
Age group	18-49	2921 (20.6)	2963 (20.4)	1098 (19.8)	1077 (19.5)
	50-64	3903 (27.5)	3992 (27.6)	1493 (27.0)	1501 (27.2)
	65-79	5475 (38.6)	5532 (38.2)	2196 (39.7)	2156 (39.0)
	80+	1889 (13.3)	2003 (13.8)	749 (13.5)	793 (14.3)
Ethnicity	White	13127 (92.5)	12982 (89.6)	5123 (92.5)	4945 (89.5)
	Asian	460 (3.2)	661 (4.6)	200 (3.6)	262 (4.7)
	Black	321 (2.3)	449 (3.1)	121 (2.2)	175 (3.2)
	Mixed	60 (0.4)	90 (0.6)	19 (0.3)	22 (0.4)
	Other	141 (1.0)	227 (1.6)	47 (0.8)	81 (1.5)
	Missing	79 (0.6)	81 (0.6)	26 (0.5)	42 (0.8)
IMD quintile	5, Most deprived	3025 (21.3)	3215 (22.2)	1061 (19.2)	1133 (20.5)
	4	2693 (19.0)	2939 (20.3)	1040 (18.8)	1099 (19.9)
	3	2717 (19.1)	2735 (18.9)	1057 (19.1)	1057 (19.1)
	2	2900 (20.4)	2789 (19.2)	1215 (21.9)	1111 (20.1)
	1, Least deprived	2824 (19.9)	2805 (19.4)	1153 (20.8)	1125 (20.4)
	Missing	29 (0.2)	7 (0.0)	10 (0.2)	2 (0.0)
Modified Elixhauser comorbidity count[1]	Median (IQR)	2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)
History of insomnia		1371 (9.7)	1846 (12.7)	370 (6.7)	558 (10.1)
History of falls		1217 (8.6)	2057 (14.2)	388 (7.0)	667 (12.1)
History of anxiety or depression		4341 (30.6)	5875 (40.5)	1451 (26.2)	1995 (36.1)
History of psychoses		269 (1.9)	436 (3.0)	71 (1.3)	105 (1.9)
History of alcohol dependence		1410 (9.9)	2287 (15.8)	452 (8.2)	795 (14.4)
History of substance dependence		307 (2.2)	640 (4.4)	62 (1.1)	176 (3.2)
History of benzodiazepine or z-drug prescription		2176 (15.3)	2084 (14.4)	NA	NA
History of opioid prescription		4642 (32.7)	4370 (30.2)	1616 (29.2)	1448 (26.2)
History of gabapentinoid prescription		612 (4.3)	1538 (10.6)	180 (3.3)	434 (7.9)
Number hospital admissions (1 year)	Median (IQR)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)
Number primary care consultations (1 year)	Median (IQR)	7.0 (1.0 to 15.0)	9.0 (4.0 to 15.0)	7.0 (1.0 to 14.0)	8.0 (4.0 to 14.0)
Hospital admission method	Elective	7101 (50.0)	6311 (43.6)	2848 (51.4)	2423 (43.8)
	Emergency	6143 (43.3)	7325 (50.6)	2300 (41.5)	2750 (49.8)
	Transfer/Other	943 (6.6)	854 (5.9)	388 (7.0)	354 (6.4)
	Missing	<10 (<0.01)			
Primary condition at index hospitalisation	Circulatory	4125 (29.1)	3869 (26.7)	1724 (31.1)	1615 (29.2)
	Neoplasms	2886 (20.3)	2821 (19.5)	1161 (21.0)	1092 (19.8)
	Digestive	1511 (10.6)	1578 (10.9)	555 (10.0)	596 (10.8)
	Respiratory	1362 (9.6)	1487 (10.3)	482 (8.7)	495 (9.0)
	Injury	1365 (9.6)	1396 (9.6)	489 (8.8)	518 (9.4)
	Musculoskeletal	674 (4.8)	638 (4.4)	253 (4.6)	243 (4.4)
	Genitourinary	413 (2.9)	423 (2.9)	145 (2.6)	151 (2.7)
	Infectious	169 (1.2)	562 (3.9)	63 (1.1)	201 (3.6)
	Abnormal findings[2]	412 (2.9)	298 (2.1)	159 (2.9)	111 (2.0)
	Other	1271 (9.0)	1418 (9.8)	505 (9.1)	505 (9.1)
Critical care unit type	Gen/Med/Surg	9940 (70.1)	10246 (70.7)	3725 (67.3)	3834 (69.4)
	Cardio/Thoracic	2853 (20.1)	2737 (18.9)	1266 (22.9)	1111 (20.1)
	Neuro	467 (3.3)	576 (4.0)	184 (3.3)	239 (4.3)
	Other	294 (2.1)	541 (3.7)	113 (2.0)	193 (3.5)
	Missing	634 (4.5)	390 (2.7)	248 (4.5)	150 (2.7)

Cardiovascular support	Basic Advanced Missing	8580 (60.5) 2902 (20.5) 739 (5.2)	9410 (64.9) 2556 (17.6) 565 (3.9)	3287 (59.4) 1240 (22.4) 289 (5.2)	3515 (63.6) 1071 (19.4) 229 (4.1)
Respiratory support	Basic Advanced Missing	4483 (31.6) 4500 (31.7) 898 (6.3)	4546 (31.4) 4436 (30.6) 692 (4.8)	1682 (30.4) 1847 (33.4) 338 (6.1)	1729 (31.3) 1760 (31.8) 269 (4.9)
Renal support	 Missing	711 (5.0) 1233 (8.7)	536 (3.7) 764 (5.3)	296 (5.3) 455 (8.2)	180 (3.3) 299 (5.4)
Total organ systems supported	None 1 2 3 Missing	1160 (8.2) 3843 (27.1) 7322 (51.6) 627 (4.4) 1236 (8.7)	1143 (7.9) 4383 (30.2) 7770 (53.6) 408 (2.8) 786 (5.4)	415 (7.5) 1522 (27.5) 2880 (52.0) 261 (4.7) 458 (8.3)	429 (7.8) 1592 (28.8) 3058 (55.3) 144 (2.6) 304 (5.5)
Out of hours critical care discharge	 Missing	2349 (16.6) 634 (4.5)	1988 (13.7) 390 (2.7)	966 (17.4) 248 (4.5)	736 (13.3) 150 (2.7)
Critical care length of stay (days)	Median (IQR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)
Hospital length of stay	Median (IQR)	10.0 (6.0 to 19.0)	9.0 (5.0 to 17.0)	10.0 (6.0 to 19.0)	9.0 (5.0 to 17.0)
Days to prescription (or match date)	Median (IQR)	11.0 (4.0 to 25.0)	11.0 (4.0 to 25.0)	11.0 (4.0 to 29.0)	13.0 (5.0 to 34.0)
Benzodiazepine or z-drug exposure	Exposed Unexposed	2415 (17.0) 11773 (83.0)	2429 (16.8) 12061 (83.2)	994 (18.0) 4542 (82.0)	970 (17.6) 4557 (82.4)
Falls or trauma-related outcomes[3]		75 (0.5)	166 (1.1)	28 (0.5)	54 (1.0)
All-cause outcomes[3]		2474 (17.4)	2620 (18.1)	959 (17.3)	950 (17.2)

[1]Modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis; [2]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified; [3]rehospitalisation or death within 30 days of match date

IQR: interquartile range; *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical

Supplemental Table S4. Benzodiazepine or z-drug prescription (exposure) after hospital discharge in adult critical care survivors and the association with rehospitalisation or death within 30 days of prescription or match date, stratified by year of hospital admission.

Exposure	N (%)	N (%) with outcome in follow-up window	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
2010 Matched cohort: falls or trauma-related outcome					
Unexposed	11773 (83.0)	57 (0.5)	Reference	Reference	
Exposed	2415 (17.0)	18 (0.7)	1.60 (0.94-2.71, p=0.084)	1.60 (0.46-5.61, p=0.463)	1.63 (0.44-6.01, p=0.455)
2010 Matched cohort: all-cause outcome					
Unexposed	11773 (83.0)	1902 (16.2)	Reference	Reference	Reference
Exposed	2415 (17.0)	572 (23.7)	1.52 (1.38-1.67, p<0.001)	1.24 (1.09-1.42, p=0.001)	1.25 (1.11-1.42, p<0.001)
2010 Treatment-naive cohort: falls or trauma-related outcome					
Unexposed	4542 (82.0)	22 (0.5)	Reference	*Insufficient outcomes for multivariable analysis.*	*Insufficient outcomes for multivariable analysis.*
Exposed	994 (18.0)	6 (0.6)	1.32 (0.54-3.26, p=0.544)		
2010 Treatment-naive cohort: all-cause outcome					
Unexposed	4542 (82.0)	710 (15.6)	Reference	Reference	Reference
Exposed	994 (18.0)	249 (25.1)	1.70 (1.47-1.96, p<0.001)	1.65 (1.39-1.96, p<0.001)	1.67 (1.42-1.95, p<0.001)
2018 Matched cohort: falls or trauma-related outcome					
Unexposed	12061 (83.2)	122 (1.0)	Reference	Reference	Reference
Exposed	2429 (16.8)	44 (1.8)	1.85 (1.31-2.61, p<0.001)	1.02 (0.50-2.07, p=0.965)	1.34 (0.70-2.54, p=0.372)
2018 Matched cohort: all-cause outcome					
Unexposed	12061 (83.2)	2028 (16.8)	Reference	Reference	Reference
Exposed	2429 (16.8)	592 (24.4)	1.50 (1.37-1.64, p<0.001)	1.23 (1.08-1.41, p=0.002)	1.25 (1.10-1.42, p=0.001)
2018 Treatment-naive cohort: falls or trauma-related outcome					
Unexposed	4557 (82.4)	43 (0.9)	Reference	*Insufficient outcomes for multivariable analysis.*	*Insufficient outcomes for multivariable analysis.*
Exposed	970 (17.6)	11 (1.1)	1.28 (0.66-2.47, p=0.471)		
2018 Treatment-naive cohort: all-cause outcome					
Unexposed	4557 (82.4)	703 (15.4)	Reference	Reference	Reference
Exposed	970 (17.6)	247 (25.5)	1.75 (1.52-2.03, p<0.001)	1.68 (1.42-1.99, p<0.001)	1.69 (1.44-1.99, p<0.001)

HR: hazard ratio; *CI:* confidence interval

[1]Adjusted models were adjusted for sex, age, ethnicity, socioeconomic status, baseline comorbidity count, history of psychoses, alcohol dependence, substance dependence, depression or anxiety, insomnia, andhospitalisations due to falls, prescription history of benzodiazepines/z-drugs, opioids, gabapentinoids, number of prior hospitalisations and primary care consultations, year of critical care hospitalisation, primary hospital diagnosis, critical care unit type, total number of organ systems supported, out-of-hours discharge from critical care, and total hospital length of stay (in days).

Supplemental Table S5. Sensitivity analysis. Benzodiazepine or z-drug prescription (exposure) after hospital discharge in adults surviving critical illness *for at least 30 days after index hospital discharge* and the association with all-cause rehospitalisation or death within 30 days of prescription or match date.

Exposure	N (%)	N (%) with outcome in follow-up window	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Matched cohort: falls or trauma-related outcome					
Unexposed Exposed	23097 (83.0) 4725 (17.0)	163 (0.7) 58 (1.2)	Reference 1.78 (1.32-2.40, p<0.001)	Reference 1.09 (0.62-1.92, p=0.759)	Reference 1.36 (0.80-2.32, p=0.260)
Matched cohort: all-cause outcome					
Unexposed Exposed	23097 (83.0) 4725 (17.0)	3673 (15.9) 1045 (22.1)	Reference 1.42 (1.33-1.52, p<0.001)	Reference 1.14 (1.03-1.26, p=0.009)	Reference 1.15 (1.05-1.26, p=0.003)
Treatment-naïve matched cohort: falls or trauma-related outcome					
Unexposed Exposed	8683 (82.2) 1886 (17.8)	57 (0.7) 15 (0.8)	Reference 1.26 (0.71-2.22, p=0.433)	Reference 1.47 (0.39-5.53, p=0.570)	Reference 2.22 (0.70-7.01, p=0.168)
Treatment-naïve matched cohort: all-cause outcome					
Unexposed Exposed	8683 (82.2) 1886 (17.8)	1306 (15.0) 418 (22.2)	Reference 1.53 (1.37-1.71, p<0.001)	Reference 1.48 (1.31-1.68, p<0.001)	Reference 1.50 (1.33-1.69, p<0.001)

HR: hazard ratio; *CI:* confidence interval

[1]Adjusted models were adjusted for sex, age, ethnicity, socioeconomic status, baseline comorbidity count, history of psychoses, alcohol dependence, substance dependence, depression or anxiety, insomnia, and hospitalisations due to falls, prescription history of benzodiazepines/z-drugs, opioids, gabapentinoids, number of prior hospitalisations and primary care consultations, year of critical care hospitalisation, primary hospital diagnosis, critical care unit type, total number of organ systems supported, out-of-hours discharge from critical care, and total hospital length of stay (in days).

Supplemental Table S6. Sensitivity analysis. Benzodiazepine or z-drug prescription after hospital discharge in adults surviving critical illness and the association with all-cause rehospitalisation or death within 30 days of prescription or match date, excluding patients with palliative care diagnoses or treatments within 90 days of hospital discharge.

Exposure	N (%)	N (%) with outcome in follow-up window	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Matched cohort: falls or trauma-related outcome					
Unexposed Exposed	21548 (82.9) 4460 (17.1)	156 (0.7) 56 (1.3)	Reference 1.76 (1.30-2.39, p<0.001)	Reference 1.05 (0.57-1.92, p=0.880)	Reference 1.27 (0.72-2.25, p=0.414)
Matched cohort: all-cause outcome					
Unexposed Exposed	21548 (82.9) 4460 (17.1)	3516 (16.3) 944 (21.2)	Reference 1.35 (1.26-1.45, p<0.001)	Reference 1.07 (0.96-1.19, p=0.217)	Reference 1.08 (0.98-1.19, p=0.121)
Treatment-naïve matched cohort: falls or trauma-related outcome					
Unexposed Exposed	7817 (82.0) 1721 (18.0)	54 (0.7) 14 (0.8)	Reference 1.20 (0.67-2.16, p=0.540)	Reference 0.57 (0.12-2.60, p=0.465)	Reference 1.36 (0.40-4.66, p=0.607)
Treatment-naïve matched cohort: all-cause outcome					
Unexposed Exposed	7817 (82.0) 1721 (18.0)	1174 (15.0) 342 (19.8)	Reference 1.35 (1.20-1.53, p<0.001)	Reference 1.39 (1.21-1.60, p<0.001)	Reference 1.42 (1.25-1.62, p<0.001)

HR: hazard ratio; *CI:* confidence interval

[1]Adjusted models were adjusted for sex, age, ethnicity, socioeconomic status, baseline comorbidity count, history of psychoses, alcohol dependence, substance dependence, depression or anxiety, insomnia, and hospitalisations due to falls, prescription history of benzodiazepines/z-drugs, opioids, gabapentinoids, number of prior hospitalisations and primary care consultations, year of critical care hospitalisation, primary hospital diagnosis, critical care unit type, total number of organ systems supported, out-of-hours discharge from critical care, and total hospital length of stay (in days).

Supplemental Table S7. Sensitivity analysis. Benzodiazepine or z-drug prescription after hospital discharge in adults surviving critical illness and the association with all-cause rehospitalisation or death within 30 days of prescription or match date, excluding patients who received a prescription for midazolam from hospital discharge through observation window.

Exposure	N (%)	N (%) with outcome in follow-up window	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Matched cohort: falls or trauma-related outcome					
Unexposed Exposed	22620 (83.1) 4599 (16.9)	169 (0.7) 58 (1.3)	Reference 1.76 (1.30-2.39, p<0.001)	Reference 1.05 (0.57-1.92, p=0.880)	Reference 1.27 (0.72-2.25, p=0.414)
Matched cohort: all-cause outcome					
Unexposed Exposed	22620 (83.1) 4599 (16.9)	3733 (16.5) 1009 (21.9)	Reference 1.35 (1.26-1.45, p<0.001)	Reference 1.07 (0.96-1.19, p=0.217)	Reference 1.08 (0.98-1.19, p=0.121)
Treatment-naïve matched cohort: falls or trauma-related outcome					
Unexposed Exposed	8326 (82.2) 1801 (17.8)	59 (0.7) 15 (0.8)	Reference 1.20 (0.67-2.16, p=0.540)	Reference 0.57 (0.12-2.60, p=0.465)	Reference 1.36 (0.40-4.66, p=0.607)
Treatment-naïve matched cohort: all-cause outcome					
Unexposed Exposed	8326 (82.2) 1801 (17.8)	1299 (15.6) 380 (21.1)	Reference 1.35 (1.20-1.53, p<0.001)	Reference 1.39 (1.21-1.60, p<0.001)	Reference 1.42 (1.25-1.62, p<0.001)

HR: hazard ratio; *CI:* confidence interval

[1]Adjusted models were adjusted for sex, age, ethnicity, socioeconomic status, baseline comorbidity count, history of psychoses, alcohol dependence, substance dependence, depression or anxiety, insomnia, and hospitalisations due to falls, prescription history of benzodiazepines/z-drugs, opioids, gabapentinoids, number of prior hospitalisations and primary care consultations, year of critical care hospitalisation, primary hospital diagnosis, critical care unit type, total number of organ systems supported, out-of-hours discharge from critical care, and total hospital length of stay (in days).

Supplemental Table S8. Matched study population with count of outcomes occurring in the 30-day window, stratified by exposure.

Outcomes	**Benzodiazepine or z-drug exposed (n=4844)** N (%)	**Unexposed (n=23,834)** N (%)
Falls or trauma-related rehospitalisation	61 (1.3)	176 (0.74)
All-cause rehospitalisation	1031 (21.3)	3813 (16.0)
Falls or trauma-related deaths	<5 (<0.1)	5 (0.02)
All-cause deaths	190 (3.9)	212 (0.89)

Supplemental Table S9. Benzodiazepine or z-drug prescription after hospital discharge in matched adult critical care survivors and the association with falls or trauma-related rehospitalisation or death within 30 days of prescription or match date.

Patient Characteristic	Level	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Benzodiazepine or z-drug exposure	Unexposed	Reference	Reference	Reference
	Exposed	1.76 (1.32-2.35, p<0.001)	1.02 (0.59-1.78, p=0.943)	1.27 (0.76-2.14, p=0.364)
Sex	Male	Reference	Reference	Reference
	Female	1.11 (0.86-1.42, p=0.434)	0.76 (0.51-1.13, p=0.175)	0.81 (0.56-1.17, p=0.266)
Age		1.03 (1.02-1.04, p<0.001)	1.02 (1.01-1.04, p=0.002)	1.02 (1.01-1.04, p=0.001)
Ethnicity	White	Reference	Reference	Reference
	Asian	0.41 (0.15-1.11, p=0.080)	0.33 (0.07-1.50, p=0.152)	0.42 (0.11-1.56, p=0.194)
	Black, Mixed, Other	0.71 (0.35-1.43, p=0.339)	0.64 (0.22-1.90, p=0.423)	0.94 (0.35-2.53, p=0.901)
IMD quintile	5, Most deprived	Reference	Reference	Reference
	4	1.14 (0.81-1.62, p=0.450)	1.26 (0.66-2.40, p=0.477)	1.41 (0.78-2.56, p=0.257)
	3	0.70 (0.47-1.05, p=0.081)	0.87 (0.43-1.76, p=0.704)	0.80 (0.41-1.55, p=0.498)
	2	0.70 (0.47-1.04, p=0.078)	0.85 (0.39-1.81, p=0.666)	0.95 (0.47-1.89, p=0.873)
	1, Least deprived	0.65 (0.43-0.98, p=0.040)	0.86 (0.37-2.01, p=0.731)	0.85 (0.39-1.87, p=0.681)
Elixhauser comorbidity count[2]		1.21 (1.15-1.28, p<0.001)	1.08 (0.98-1.18, p=0.145)	1.09 (0.99-1.19, p=0.078)
History of insomnia	No	Reference	Reference	Reference
	Yes	1.64 (1.17-2.29, p=0.004)	1.20 (0.67-2.16, p=0.539)	1.22 (0.70-2.12, p=0.479)
History of falls	No	Reference	Reference	Reference
	Yes	5.93 (4.59-7.65, p<0.001)	4.02 (2.44-6.64, p<0.001)	3.66 (2.31-5.81, p<0.001)
History of anxiety or depression	No	Reference	Reference	Reference
	Yes	1.82 (1.41-2.34, p<0.001)	1.23 (0.81-1.88, p=0.326)	1.17 (0.79-1.73, p=0.437)
History of psychoses	No	Reference	Reference	Reference
	Yes	1.93 (1.05-3.54, p=0.033)	0.89 (0.33-2.41, p=0.813)	0.78 (0.30-2.03, p=0.602)
History of alcohol dependence	No	Reference	Reference	Reference
	Yes	1.98 (1.46-2.68, p<0.001)	1.21 (0.72-2.02, p=0.477)	1.13 (0.70-1.82, p=0.627)
History of substance dependence	No	Reference	Reference	Reference
	Yes	2.12 (1.28-3.52, p=0.004)	1.00 (0.41-2.44, p=0.996)	1.02 (0.43-2.40, p=0.963)
History of benzodiazepine or z-drug prescription	No	Reference	Reference	Reference
	Yes	2.04 (1.52-2.72, p<0.001)	1.50 (0.80-2.80, p=0.205)	1.20 (0.66-2.18, p=0.541)
History of opioid prescription	No	Reference	Reference	Reference
	Yes	1.63 (1.26-2.11, p<0.001)	1.09 (0.71-1.68, p=0.693)	1.13 (0.76-1.68, p=0.538)
History of gabapentinoids prescription	No	Reference	Reference	Reference
	Yes	2.80 (2.02-3.90, p<0.001)	0.91 (0.49-1.67, p=0.758)	0.99 (0.57-1.72, p=0.979)
No. hospital admissions		1.02 (1.01-1.03, p=0.001)	1.03 (1.00-1.06, p=0.054)	1.04 (1.01-1.07, p=0.009)
No. primary care consultations		1.02 (1.02-1.03, p<0.001)	1.01 (1.00-1.03, p=0.097)	1.01 (1.00-1.03, p=0.115)
Hospital admission method	Elective	Reference	Reference	Reference
	Emergency	3.93 (2.87-5.38, p<0.001)	2.45 (1.42-4.22, p=0.001)	2.53 (1.53-4.19, p<0.001)
	Transfer/Other	0.77 (0.30-1.92, p=0.569)	0.46 (0.12-1.74, p=0.253)	0.49 (0.15-1.56, p=0.224)

Primary condition at index hospitalisation	Circulatory	Reference	Reference	Reference
	Infectious	2.35 (1.15-4.81, p=0.020)	1.09 (0.35-3.44, p=0.879)	0.82 (0.28-2.40, p=0.716)
	Neoplasms	0.83 (0.51-1.36, p=0.468)	1.26 (0.61-2.60, p=0.526)	1.17 (0.59-2.31, p=0.645)
	Respiratory	1.85 (1.15-2.97, p=0.011)	1.09 (0.50-2.38, p=0.823)	1.38 (0.67-2.83, p=0.376)
	Digestive	1.23 (0.72-2.08, p=0.445)	0.81 (0.37-1.76, p=0.596)	0.73 (0.35-1.51, p=0.390)
	Musculoskeletal	0.95 (0.43-2.10, p=0.894)	1.06 (0.33-3.47, p=0.917)	0.92 (0.30-2.79, p=0.885)
	Genitourinary	2.82 (1.49-5.33, p=0.001)	1.92 (0.66-5.57, p=0.229)	1.44 (0.56-3.67, p=0.444)
	Abnormal Findings[3]	1.86 (0.84-4.13, p=0.127)	1.16 (0.39-3.47, p=0.794)	1.63 (0.59-4.52, p=0.346)
	Injury	4.67 (3.21-6.80, p<0.001)	3.67 (1.84-7.32, p<0.001)	3.37 (1.81-6.30, p<0.001)
	Other	1.22 (0.70-2.11, p=0.483)	1.42 (0.63-3.21, p=0.393)	1.19 (0.54-2.61, p=0.660)
Critical care unit type	Gen/Med/Surg	Reference	Reference	Reference
	Cardio/Thoracic	0.30 (0.19-0.50, p<0.001)	0.63 (0.30-1.33, p=0.226)	0.63 (0.30-1.31, p=0.209)
	Neuro	0.79 (0.39-1.60, p=0.509)	0.87 (0.34-2.25, p=0.778)	0.87 (0.35-2.17, p=0.767)
	Other	0.37 (0.12-1.15, p=0.085)	0.15 (0.03-0.90, p=0.037)	0.12 (0.02-0.73, p=0.022)
Total organ systems supported	None	Reference	Reference	Reference
	1	0.67 (0.42-1.07, p=0.093)	0.49 (0.23-1.04, p=0.063)	0.46 (0.23-0.94, p=0.033)
	2	0.73 (0.47-1.12, p=0.147)	0.56 (0.27-1.16, p=0.117)	0.50 (0.25-1.01, p=0.052)
	3	1.11 (0.56-2.22, p=0.758)	0.98 (0.32-3.02, p=0.969)	0.77 (0.27-2.20, p=0.622)
Out of hours critical care discharge	No	Reference	Reference	Reference
	Yes	1.14 (0.81-1.61, p=0.465)	1.35 (0.78-2.34, p=0.287)	1.20 (0.71-2.02, p=0.504)
Hospital length of stay (days)		1.01 (1.00-1.01, p<0.001)	1.01 (1.00-1.02, p=0.013)	1.01 (1.00-1.02, p=0.014)
strata(caseID)		-	-	

[1]Adjusted models were adjusted for all other variables presented in this table.
[2]modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. [3]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
HR: hazard ratio; *CI:* confidence interval; *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical

Supplemental Table S10. Benzodiazepine or z-drug prescription after hospital discharge in matched adult critical care survivors and the association with all-cause rehospitalisation or death within 30 days of prescription or match date.

Patient Characteristic	Level	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Benzodiazepine or z-drug exposure	Unexposed	Reference	Reference	Reference
	Exposed	1.51 (1.41-1.61, p<0.001)	1.22 (1.12-1.34, p<0.001)	1.24 (1.14-1.36, p<0.001)
Sex	Male	Reference	Reference	Reference
	Female	1.03 (0.98-1.09, p=0.246)	0.96 (0.89-1.02, p=0.195)	0.95 (0.89-1.01, p=0.108)
Age		1.00 (1.00-1.01, p<0.001)	1.00 (1.00-1.00, p=0.223)	1.00 (1.00-1.00, p=0.284)
Ethnicity	White	Reference	Reference	Reference
	Asian	1.02 (0.89-1.18, p=0.769)	0.96 (0.80-1.16, p=0.705)	0.97 (0.81-1.16, p=0.749)
	Black, Mixed, Other	0.89 (0.77-1.02, p=0.093)	0.87 (0.73-1.04, p=0.128)	0.86 (0.72-1.02, p=0.086)
IMD quintile	5, Most deprived	Reference	Reference	Reference
	4	1.06 (0.97-1.15, p=0.193)	1.10 (0.99-1.23, p=0.086)	1.12 (1.01-1.25, p=0.034)
	3	0.97 (0.89-1.05, p=0.440)	1.04 (0.92-1.17, p=0.579)	1.04 (0.92-1.16, p=0.555)
	2	0.93 (0.85-1.01, p=0.104)	0.91 (0.80-1.03, p=0.146)	0.96 (0.85-1.09, p=0.561)
	1, Least deprived	0.94 (0.86-1.02, p=0.140)	1.02 (0.88-1.17, p=0.829)	1.06 (0.93-1.21, p=0.384)
Elixhauser comorbidity count[2]		1.08 (1.07-1.10, p<0.001)	1.05 (1.03-1.07, p<0.001)	1.05 (1.03-1.07, p<0.001)
History of insomnia	No	Reference	Reference	Reference
	Yes	1.09 (1.01-1.19, p=0.037)	0.86 (0.77-0.96, p=0.008)	0.87 (0.78-0.96, p=0.008)
History of falls	No	Reference	Reference	Reference
	Yes	1.38 (1.28-1.49, p<0.001)	1.17 (1.06-1.30, p=0.003)	1.17 (1.06-1.29, p=0.001)
History of anxiety or depression	No	Reference	Reference	Reference
	Yes	1.14 (1.08-1.21, p<0.001)	1.00 (0.92-1.08, p=0.971)	0.99 (0.92-1.07, p=0.855)
History of psychoses	No	Reference	Reference	Reference
	Yes	1.08 (0.91-1.29, p=0.369)	0.94 (0.76-1.16, p=0.552)	0.93 (0.76-1.14, p=0.463)
History of alcohol dependence	No	Reference	Reference	Reference
	Yes	1.16 (1.08-1.26, p<0.001)	1.03 (0.93-1.14, p=0.563)	1.01 (0.92-1.11, p=0.838)
History of substance dependence	No	Reference	Reference	Reference
	Yes	1.16 (1.00-1.34, p=0.049)	0.93 (0.77-1.12, p=0.448)	0.87 (0.72-1.04, p=0.131)
History of benzodiazepine or z-drug prescription	No	Reference	Reference	Reference
	Yes	1.58 (1.47-1.69, p<0.001)	1.20 (1.07-1.34, p=0.001)	1.19 (1.08-1.32, p=0.001)
History of opioid prescription	No	Reference	Reference	Reference
	Yes	1.38 (1.30-1.46, p<0.001)	1.09 (1.01-1.18, p=0.026)	1.10 (1.03-1.19, p=0.007)
History of gabapentinoids prescription	No	Reference	Reference	Reference
	Yes	1.44 (1.32-1.58, p<0.001)	1.10 (0.97-1.24, p=0.133)	1.15 (1.03-1.29, p=0.017)
No. hospital admissions		1.02 (1.02-1.02, p<0.001)	1.04 (1.03-1.05, p<0.001)	1.04 (1.03-1.05, p<0.001)
No. primary care consultations		1.02 (1.01-1.02, p<0.001)	1.01 (1.01-1.01, p<0.001)	1.01 (1.01-1.01, p<0.001)
Hospital admission method	Elective	Reference	Reference	Reference
	Emergency	1.28 (1.21-1.35, p<0.001)	1.47 (1.35-1.60, p<0.001)	1.48 (1.36-1.61, p<0.001)
	Transfer/Other	0.92 (0.81-1.04, p=0.175)	1.20 (1.02-1.42, p=0.028)	1.24 (1.07-1.45, p=0.005)
Primary condition	Circulatory	Reference	Reference	Reference

at index hospitalisation	Infectious	1.57 (1.32-1.86, p<0.001)	0.99 (0.79-1.22, p=0.891)	0.98 (0.80-1.21, p=0.878)
	Neoplasms	1.86 (1.72-2.02, p<0.001)	1.85 (1.65-2.06, p<0.001)	1.87 (1.68-2.07, p<0.001)
	Respiratory	1.51 (1.37-1.68, p<0.001)	1.06 (0.92-1.21, p=0.421)	1.06 (0.93-1.20, p=0.395)
	Digestive	1.58 (1.43-1.74, p<0.001)	1.23 (1.08-1.40, p=0.002)	1.21 (1.07-1.37, p=0.003)
	Musculoskeletal	0.81 (0.69-0.97, p=0.018)	0.77 (0.62-0.94, p=0.013)	0.73 (0.60-0.90, p=0.002)
	Genitourinary	2.01 (1.74-2.33, p<0.001)	1.42 (1.16-1.74, p=0.001)	1.38 (1.14-1.67, p=0.001)
	Abnormal Findings[3]	1.66 (1.40-1.96, p<0.001)	1.26 (1.02-1.56, p=0.030)	1.28 (1.05-1.57, p=0.016)
	Injury	1.04 (0.93-1.17, p=0.499)	0.84 (0.72-0.98, p=0.022)	0.82 (0.72-0.95, p=0.007)
	Other	0.99 (0.88-1.12, p=0.875)	0.83 (0.71-0.97, p=0.019)	0.86 (0.75-1.00, p=0.051)
Critical care unit type	Gen/Med/Surg	Reference	Reference	Reference
	Cardio/Thoracic	0.74 (0.68-0.80, p<0.001)	0.93 (0.83-1.03, p=0.166)	0.93 (0.84-1.04, p=0.198)
	Neuro	0.94 (0.81-1.09, p=0.384)	1.00 (0.84-1.20, p=0.986)	1.01 (0.85-1.20, p=0.896)
	Other	0.89 (0.75-1.06, p=0.184)	0.90 (0.73-1.12, p=0.356)	0.92 (0.75-1.14, p=0.439)
Total organ systems supported	None	Reference	Reference	Reference
	1	1.12 (1.00-1.26, p=0.042)	0.89 (0.78-1.02, p=0.108)	0.89 (0.78-1.02, p=0.104)
	2	1.04 (0.94-1.16, p=0.431)	0.88 (0.77-1.01, p=0.071)	0.89 (0.78-1.02, p=0.088)
	3	1.35 (1.15-1.59, p<0.001)	0.98 (0.79-1.20, p=0.813)	0.97 (0.78-1.20, p=0.760)
Out of hours critical care discharge	No	Reference	Reference	Reference
	Yes	1.03 (0.95-1.11, p=0.491)	1.04 (0.94-1.15, p=0.432)	1.01 (0.92-1.11, p=0.771)
Hospital length of stay (days)		1.00 (1.00-1.00, p<0.001)	1.00 (1.00-1.00, p<0.001)	1.00 (1.00-1.00, p<0.001)
strata(caseID)		-	-	

[1]Adjusted models were adjusted for all other variables presented in this table.
[2]modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. [3]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
HR: hazard ratio; *CI:* confidence interval; *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical

Supplemental Table S11. Benzodiazepine or z-drug prescription after hospital discharge in treatment-naïve matched adult critical care survivors and the association with falls or trauma-related rehospitalisation or death within 30 days of prescription or match date.

Patient Characteristic	Level	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Benzodiazepine or z-drug exposure	Unexposed	Reference	Reference	Reference
	Exposed	1.29 (0.75-2.19, p=0.357)	1.51 (0.45-5.03, p=0.501)	1.79 (0.61-5.26, p=0.279)
Sex	Male	Reference	Reference	Reference
	Female	1.48 (0.96-2.28, p=0.076)	1.79 (0.65-4.93, p=0.263)	1.48 (0.58-3.77, p=0.404)
Age		1.03 (1.01-1.05, p<0.001)	1.02 (0.98-1.06, p=0.272)	1.02 (0.98-1.05, p=0.375)
Ethnicity	White	Reference	Reference	Reference
	Asian	0.89 (0.28-2.82, p=0.843)	0.37 (0.02-6.45, p=0.496)	0.44 (0.04-4.56, p=0.481)
	Black, Mixed, Other	0.87 (0.28-2.77, p=0.819)	3.09 (0.22-43.32, p=0.402)	2.33 (0.20-26.65, p=0.487)
IMD quintile	5, Most deprived	Reference	Reference	Reference
	4	1.57 (0.82-3.02, p=0.172)	14.63 (1.98-107.81, p=0.008)	9.71 (1.54-61.12, p=0.017)
	3	0.76 (0.35-1.65, p=0.487)	0.74 (0.10-5.48, p=0.772)	0.55 (0.08-3.56, p=0.520)
	2	0.98 (0.49-1.99, p=0.966)	4.94 (0.69-35.35, p=0.112)	3.50 (0.55-22.39, p=0.180)
	1, Least deprived	1.08 (0.54-2.16, p=0.830)	3.07 (0.29-32.76, p=0.353)	1.66 (0.18-15.01, p=0.642)
Elixhauser comorbidity count[2]		1.25 (1.14-1.36, p<0.001)	1.13 (0.86-1.49, p=0.392)	1.17 (0.90-1.51, p=0.230)
History of insomnia	No	Reference	Reference	Reference
	Yes	1.85 (1.00-3.42, p=0.048)	5.07 (0.86-29.90, p=0.073)	4.78 (0.90-25.56, p=0.066)
History of falls	No	Reference	Reference	Reference
	Yes	8.56 (5.54-13.21, p<0.001)	26.87 (4.30-167.82, p<0.001)	15.32 (3.40-69.02, p=0.001)
History of anxiety or depression	No	Reference	Reference	Reference
	Yes	2.02 (1.31-3.12, p=0.001)	1.70 (0.57-5.10, p=0.344)	1.63 (0.61-4.38, p=0.325)
History of psychoses	No	Reference	Reference	Reference
	Yes	4.06 (1.64-10.02, p=0.002)	15.09 (0.68-336.36, p=0.087)	10.32 (0.51-207.59, p=0.124)
History of alcohol dependence	No	Reference	Reference	Reference
	Yes	1.78 (1.02-3.12, p=0.043)	1.07 (0.23-4.92, p=0.928)	0.81 (0.21-3.11, p=0.757)
History of substance dependence	No	Reference	Reference	Reference
	Yes	2.28 (0.83-6.23, p=0.108)	0.21 (0.01-4.24, p=0.311)	0.52 (0.03-7.70, p=0.625)
History of opioid prescription	No	Reference	Reference	Reference
	Yes	2.32 (1.50-3.58, p<0.001)	1.31 (0.46-3.73, p=0.610)	1.27 (0.48-3.35, p=0.623)
History of gabapentinoids prescription	No	Reference	Reference	Reference
	Yes	2.21 (1.10-4.41, p=0.025)	0.12 (0.01-1.32, p=0.083)	0.07 (0.01-0.59, p=0.015)
No. hospital admissions		1.02 (1.00-1.04, p=0.017)	1.00 (0.91-1.11, p=0.926)	1.00 (0.91-1.10, p=0.983)
No. primary care consultations		1.03 (1.02-1.04, p<0.001)	1.07 (1.00-1.14, p=0.036)	1.08 (1.02-1.14, p=0.011)
Hospital admission method	Elective	Reference	Reference	Reference
	Emergency	4.68 (2.67-8.20, p<0.001)	6.22 (1.71-22.66, p=0.006)	8.74 (2.48-30.82, p=0.001)
	Transfer/Other	0.95 (0.22-4.16, p=0.948)	1.74 (0.15-20.01, p=0.657)	1.38 (0.13-14.07, p=0.783)
Primary condition	Circulatory	Reference	Reference	Reference

at index hospitalisation	Infectious	3.09 (1.04-9.18, p=0.042)	0.16 (0.01-2.09, p=0.162)	0.14 (0.01-1.58, p=0.109)
	Neoplasms	0.91 (0.42-1.99, p=0.815)	0.87 (0.14-5.54, p=0.885)	0.81 (0.15-4.30, p=0.800)
	Respiratory	1.87 (0.83-4.19, p=0.130)	0.66 (0.12-3.62, p=0.630)	0.73 (0.15-3.65, p=0.694)
	Digestive	1.07 (0.42-2.71, p=0.891)	1.22 (0.18-8.23, p=0.838)	0.69 (0.12-3.86, p=0.662)
	Musculoskeletal	0.76 (0.18-3.30, p=0.715)	0.04 (0.00-1.69, p=0.091)	0.07 (0.00-2.70, p=0.151)
	Genitourinary	2.81 (0.95-8.37, p=0.063)	2.86 (0.20-41.40, p=0.441)	2.34 (0.21-26.49, p=0.482)
	Abnormal Findings[3]	1.53 (0.35-6.60, p=0.572)	0.72 (0.03-15.86, p=0.832)	3.54 (0.36-35.12, p=0.272)
	Injury	4.64 (2.49-8.63, p<0.001)	10.51 (1.76-62.76, p=0.010)	11.97 (2.26-63.39, p=0.005)
	Other	0.77 (0.26-2.30, p=0.644)	0.18 (0.02-1.71, p=0.136)	0.25 (0.03-2.11, p=0.197)
Critical care unit type	Gen/Med/Surg	Reference	Reference	Reference
	Cardio/Thoracic	0.35 (0.16-0.76, p=0.008)	0.46 (0.08-2.83, p=0.404)	0.60 (0.12-3.02, p=0.527)
	Neuro	1.41 (0.57-3.51, p=0.456)	0.74 (0.06-9.32, p=0.816)	0.88 (0.12-6.61, p=0.898)
	Other	0.39 (0.05-2.80, p=0.348)	0.47 (0.01-15.30, p=0.672)	0.51 (0.02-15.28, p=0.690)
Total organ systems supported	None	Reference	Reference	Reference
	1	0.69 (0.27-1.79, p=0.450)	1.55 (0.19-12.90, p=0.687)	1.13 (0.12-10.34, p=0.910)
	2	1.13 (0.48-2.64, p=0.781)	5.13 (0.78-33.86, p=0.089)	2.49 (0.43-14.49, p=0.301)
	3	1.48 (0.42-5.23, p=0.546)	19.09 (0.88-414.52, p=0.060)	2.07 (0.13-32.81, p=0.597)
Out of hours critical care discharge	No	Reference	Reference	Reference
	Yes	1.41 (0.81-2.45, p=0.221)	2.00 (0.49-8.27, p=0.337)	2.13 (0.57-7.93, p=0.250)
Hospital length of stay (days)		1.01 (1.00-1.01, p=0.002)	1.00 (0.98-1.02, p=0.984)	1.01 (0.99-1.03, p=0.221)
strata(caseID)			-	

[1]Adjusted models were adjusted for all other variables presented in this table.
[2]modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. [3]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
HR: hazard ratio; *CI:* confidence interval; *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical

Supplemental Table S12. Benzodiazepine or z-drug prescription after hospital discharge in treatment-naïve matched adult critical care survivors and the association with all-cause rehospitalisation or death within 30 days of prescription or match date.

Patient Characteristic	Level	Unadjusted HR, Complete case analysis (95% CI, p-value)	[1]Adjusted HR, Complete case analysis (95%CI, p-value)	[1]Adjusted HR, with multiple imputation (95% CI, p-value)
Benzodiazepine or z-drug exposure	Unexposed	Reference	Reference	Reference
	Exposed	1.73 (1.56-1.91, p<0.001)	1.64 (1.46-1.85, p<0.001)	1.66 (1.49-1.86, p<0.001)
Sex	Male	Reference	Reference	Reference
	Female	1.04 (0.95-1.14, p=0.385)	0.97 (0.86-1.08, p=0.562)	0.97 (0.87-1.08, p=0.575)
Age		1.01 (1.00-1.01, p<0.001)	1.00 (1.00-1.01, p=0.387)	1.00 (1.00-1.01, p=0.405)
Ethnicity	White	Reference	Reference	Reference
	Asian	1.13 (0.91-1.40, p=0.268)	1.03 (0.76-1.40, p=0.832)	1.02 (0.76-1.36, p=0.888)
	Black, Mixed, Other	0.92 (0.73-1.16, p=0.478)	0.98 (0.72-1.33, p=0.900)	0.92 (0.68-1.24, p=0.576)
IMD quintile	5, Most deprived	Reference	Reference	Reference
	4	1.01 (0.88-1.16, p=0.852)	0.96 (0.79-1.16, p=0.640)	0.99 (0.83-1.19, p=0.944)
	3	0.94 (0.82-1.09, p=0.414)	0.91 (0.74-1.12, p=0.364)	0.91 (0.74-1.10, p=0.325)
	2	0.80 (0.69-0.92, p=0.002)	0.65 (0.53-0.81, p<0.001)	0.72 (0.59-0.88, p=0.001)
	1, Least deprived	0.90 (0.78-1.03, p=0.139)	0.84 (0.67-1.06, p=0.141)	0.87 (0.70-1.08, p=0.198)
Elixhauser comorbidity count[2]		1.08 (1.06-1.11, p<0.001)	1.05 (1.02-1.08, p=0.002)	1.05 (1.02-1.08, p=0.002)
History of insomnia	No	Reference	Reference	Reference
	Yes	0.91 (0.77-1.07, p=0.265)	0.76 (0.62-0.94, p=0.012)	0.76 (0.62-0.93, p=0.008)
History of falls	No	Reference	Reference	Reference
	Yes	1.43 (1.25-1.64, p<0.001)	1.30 (1.08-1.56, p=0.006)	1.32 (1.11-1.57, p=0.002)
History of anxiety or depression	No	Reference	Reference	Reference
	Yes	1.10 (1.00-1.21, p=0.046)	1.08 (0.95-1.23, p=0.243)	1.07 (0.95-1.21, p=0.291)
History of psychoses	No	Reference	Reference	Reference
	Yes	1.17 (0.84-1.63, p=0.365)	1.03 (0.68-1.56, p=0.897)	1.02 (0.68-1.53, p=0.906)
History of alcohol dependence	No	Reference	Reference	Reference
	Yes	1.17 (1.02-1.33, p=0.024)	0.99 (0.83-1.18, p=0.888)	0.96 (0.81-1.14, p=0.679)
History of substance dependence	No	Reference	Reference	Reference
	Yes	0.76 (0.53-1.07, p=0.120)	0.69 (0.45-1.05, p=0.083)	0.64 (0.42-0.97, p=0.038)
History of opioid prescription	No	Reference	Reference	Reference
	Yes	1.33 (1.21-1.46, p<0.001)	1.02 (0.90-1.16, p=0.745)	1.02 (0.91-1.16, p=0.711)
History of gabapentinoids prescription	No	Reference	Reference	Reference
	Yes	1.42 (1.19-1.68, p<0.001)	1.14 (0.91-1.43, p=0.264)	1.23 (0.99-1.53, p=0.062)
No. hospital admissions		1.02 (1.02-1.03, p<0.001)	1.06 (1.04-1.07, p<0.001)	1.06 (1.04-1.07, p<0.001)
No. primary care consultations		1.02 (1.01-1.02, p<0.001)	1.01 (1.01-1.02, p<0.001)	1.01 (1.01-1.02, p<0.001)
Hospital admission method	Elective	Reference	Reference	Reference
	Emergency	1.37 (1.25-1.51, p<0.001)	1.57 (1.36-1.82, p<0.001)	1.58 (1.38-1.81, p<0.001)
	Transfer/Other	0.93 (0.76-1.15, p=0.512)	1.34 (1.03-1.74, p=0.029)	1.29 (1.01-1.66, p=0.041)
Primary condition	Circulatory	Reference	Reference	Reference
	Infectious	1.58 (1.19-2.11, p=0.002)	0.96 (0.67-1.38, p=0.823)	0.95 (0.68-1.35, p=0.791)

at index hospitalisation	Neoplasms	1.96 (1.73-2.22, p<0.001)	1.98 (1.66-2.37, p<0.001)	1.99 (1.67-2.36, p<0.001)
	Respiratory	1.53 (1.29-1.81, p<0.001)	1.00 (0.79-1.25, p=0.968)	1.03 (0.83-1.27, p=0.822)
	Digestive	1.63 (1.39-1.90, p<0.001)	1.34 (1.08-1.66, p=0.008)	1.30 (1.06-1.59, p=0.012)
	Musculoskeletal	0.59 (0.43-0.81, p=0.001)	0.54 (0.37-0.79, p=0.002)	0.51 (0.35-0.74, p<0.001)
	Genitourinary	1.88 (1.46-2.42, p<0.001)	1.44 (1.02-2.04, p=0.038)	1.38 (1.00-1.92, p=0.053)
	Abnormal Findings[3]	1.80 (1.38-2.36, p<0.001)	1.39 (0.99-1.96, p=0.059)	1.50 (1.08-2.08, p=0.015)
	Injury	0.99 (0.82-1.21, p=0.955)	0.93 (0.72-1.20, p=0.570)	0.89 (0.70-1.13, p=0.343)
	Other	1.00 (0.83-1.22, p=0.973)	0.91 (0.70-1.18, p=0.469)	0.95 (0.75-1.22, p=0.710)
Critical care unit type	Gen/Med/Surg	Reference	Reference	Reference
	Cardio/Thoracic	0.75 (0.67-0.85, p<0.001)	0.97 (0.81-1.15, p=0.723)	0.96 (0.81-1.13, p=0.626)
	Neuro	0.94 (0.74-1.19, p=0.599)	0.97 (0.72-1.29, p=0.814)	0.98 (0.74-1.30, p=0.877)
	Other	0.78 (0.58-1.05, p=0.099)	0.79 (0.53-1.16, p=0.231)	0.84 (0.57-1.22, p=0.355)
Total organ systems supported	None	Reference	Reference	Reference
	1	1.21 (1.00-1.46, p=0.046)	0.95 (0.75-1.20, p=0.644)	0.91 (0.72-1.14, p=0.396)
	2	1.06 (0.89-1.27, p=0.513)	0.87 (0.69-1.10, p=0.240)	0.86 (0.69-1.07, p=0.181)
	3	1.52 (1.16-1.98, p=0.002)	1.00 (0.70-1.41, p=0.984)	0.95 (0.67-1.35, p=0.774)
Out of hours critical care discharge	No	Reference	Reference	Reference
	Yes	1.09 (0.96-1.23, p=0.178)	1.16 (0.99-1.36, p=0.072)	1.12 (0.96-1.31, p=0.149)
Hospital length of stay (days)		1.00 (1.00-1.01, p<0.001)	1.00 (1.00-1.01, p=0.028)	1.00 (1.00-1.00, p=0.105)
strata(caseID)		-	-	

[1]Adjusted models were adjusted for all other variables presented in this table.
[2]modified by removing four mental health conditions (depression, psychoses, alcohol dependence, substance dependence) for individual analysis. [3]symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
HR: hazard ratio; *CI:* confidence interval; *IMD*: index of multiple deprivation; *Gen/Med/Surg:* General/Medical/Surgical