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RESEARCH REPORT

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Previous psychiatric hospitalizations as risk factors for single and multiple future alcohol-related hospitalizations in patients with alcohol use disorders

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Abstract

Background and aims: People with alcohol use disorder (AUD) often have co-occurring psychiatric conditions. The association between psychiatric conditions and AUD relapse has not yet been fully explored. This study aimed to quantify different psychiatric comorbidities as risk factors for first and multiple AUD rehospitalizations in patients already hospitalized once for AUD.

Methods: We used a nation-wide routine health-care database in Scotland, UK, between 2010 and 2019. Individuals with a first hospitalization for AUD (codes F10.0-9 in the ICD-10 codes) were checked for previous hospitalizations where the main or co-occurring cause was a psychiatric condition (any other F0-F99 code in ICD-10). The final cohort included 23 529 patients, 18 620 of whom did not have a history of any other psychiatric comorbidity. First, individuals with a history of any previous psychiatric hospitalization were grouped and compared with those without on the basis of time to AUD rehospitalization. Then, individuals with different histories of psychiatric hospitalization were compared with each other. Cox and Prentice, Williams and Peterson gap-time models were used for single and multiple AUD rehospitalizations, respectively.

Results: The AUD rehospitalization rate in individuals with a previous psychiatric hospitalization was 8% higher compared with those without [hazard ratio (HR) = 1.08, 95% confidence interval (CI) = 1.01–1.14]. The difference in rehospitalization rate reduced following the first rehospitalization (HR at second rehospitalization from first: 0.95, 95% CI = 0.87–1.04 and HR at third rehospitalization from second: 0.94, 95% CI = 0.84–1.07). Mood disorders and neurotic, stress-related and somatoform disorders were associated with a 54% (HR = 1.54, 95% CI = 1.38–1.72) and 39% (HR = 1.39, 95% CI = 1.17–1.66) increase in the risk of a first AUD rehospitalization. Other conditions, such as disorders due to psychoactive substance use or schizophrenia, were associated with decreases in future AUD rehospitalization (HR = 0.89, 95% CI = 0.82–0.97 and HR = 0.82, 95% CI = 0.58–1.16, respectively).

Conclusions: Patients with AUD appear to have different rates of AUD rehospitalization based on different co-occurring psychiatric conditions. Addiction-related characteristics

may be more relevant risk indicators for multiple AUD readmission than psychiatric comorbidities.

KEYWORDS
Alcohol dependence, alcohol use disorder, comorbidities, mental health, multiple failure survival analysis, observational study, Prentice Williams and Peterson model, psychiatric disorders, relapse, routine health-care data

INTRODUCTION

The vulnerability of an individual to a specific substance use disorder, such as alcohol use disorder (AUD), is due to a combination of biological, physiological and developmental risk factors [1]. Specifically, for AUD, it has been shown how genetics (e.g. variations in a large number of genes [1, 2]) and the environmental and social context (e.g. social support and peer pressure [3, 4]) can be associated with addiction. Other relevant factors for AUD are personality [5] and comorbidities (i.e. the presence of additional conditions co-occurring with AUD) [6].

People with AUD often present with co-occurring psychiatric conditions [7]. The NESARC-III survey, a nationally representative study on the adult population in the United States, found that mental disorders were more prevalent in those with severe AUD. Furthermore, those mental disorders were themselves more severe [8]. This effect was more pronounced in borderline, antisocial and avoidant disorders. Other studies have shown associations between anxiety and mood disorders with the presence of any AUD [7, 9].

The relationship between AUD and other psychiatric disorders is complex and bidirectional, with alcohol use as both a cause and effect of other psychiatric symptomatology. Specifically, there are studies indicating that psychiatric disorders may trigger other risk factors for AUDs [6, 9]. In contrast, other research found that AUDs could induce psychiatric syndromes, mainly due to the effects that functioning AUD may have on psychological function [6, 10]. Moreover, self-medication, which is the use of alcohol (or other substances) to manage the symptoms caused by other conditions, may create or strengthen the association between the use disorder and psychiatric morbidity.

Beyond incident AUD, another important factor for the impact of psychiatric comorbidities is relapse. Relapse can be defined as the recurrence of problematic alcohol use after a period of improvement [11]. Relapses can be triggered by numerous factors and can be partly explained by the compulsive nature of addiction itself. Previous studies have shown how long-term relapse rates can vary between 42.9 and 60.5% based on receiving treatment for AUD [12]. Therefore, relapse to AUD during or after remission and detoxication constitutes a significant public health concern. Different psychiatric conditions could lead to different experiences of withdrawal symptoms, but also different desires or cravings after remission; thus, they could have different associations with risk of relapses.

While there is evidence of an association between specific comorbidities and AUD, and the additional barriers to recovery experienced by AUD patients [13], there is limited research on how the type of psychiatric comorbidity may affect the risk of AUD relapse. Previous literature reviews [14, 15] found heterogeneous results for the role of psychiatric comorbidities on the risk of relapse. This was probably due to studies being limited to specific populations and comorbidities and inconsistencies in how relapses were defined and measured [15]. Beyond these limitations, these studies usually have either small sample size or poor follow-up—a particular challenge in this area of research, as relapses may not occur for several years.

In observational studies using routine health-care data, relapse is typically more difficult to detect. In particular, as mild AUDs are often undiagnosed and untreated, hospital records are more likely to detect severe AUD episodes (those requiring hospitalizations) or incidental AUD diagnoses. Therefore, while observational studies using routine health-care records are unlikely to capture the full chronological relapse history of all individuals, they are likely to identify the most important clinical cases. Moreover, although studies using routine health-care data may present more challenges in precisely measuring AUD relapses, they usually have longer follow-up periods and a larger sample size, suggesting stronger external validity of their findings.

By using a routine health-care database, this study aims to describe patients hospitalized due to AUD with different psychiatric comorbidities and to quantify such comorbidities as risk factors for AUD rehospitalization. Epidemiological studies typically estimate only the time to the first outcome event [16] (e.g. rehospitalization). In this study, we estimated both first and multiple AUD rehospitalizations, allowing assessment of whether the effect of comorbidities changed in further AUD episodes. We used a nation-wide database of individuals with hospitalizations due to AUD in Scotland, UK between 2010 and 2019.

METHODS

Cohort identification

This study used the General/Acute and Inpatient Day Case (SMR01) data set [17], which collects patient-level data for all episodes of hospital inpatient and day case hospitalizations from hospitals in Scotland. We identified our cohort by selecting all patients aged more than 18 years who had AUD as the main reason for their hospitalization between January 2010 and March 2019. We selected only patients with the first hospitalization for AUD in the last 10 years, by screening back 10 years in the hospital records. Diagnoses were recorded in the SMR01 data set using the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10 [18]); all

codes under the category 'mental and behavioural disorders due to the use of alcohol' (codes F10.0-9) were identified as AUD. There were no changes to the diagnosis classification throughout the study period.

We then obtained previous hospitalizations related to psychiatric conditions from hospital records up to 10 years prior to the first AUD episode. Comorbidities were identified as previous hospitalizations with a psychiatric condition (any F0-F99 code in ICD-10, but excluding codes F10.0–9) as either the main or co-occurring cause. Events of interest were subsequent hospitalizations with AUD coded as the main cause of hospitalization.

The final cohort included 23 529 patients, 18 620 of whom did not have a history of any other psychiatric comorbidity. We first compared individuals with and without a history of previous psychiatric hospitalizations. Successively, to allow head-to-head comparisons of the impact of each psychiatric diagnosis on AUD rehospitalizations, individuals with more than one kind of previous psychiatric diagnosis were removed. We then divided patients into five subgroups based on the ICD-10 mental and behavioural disorders diagnosis received in a previous hospitalization: OMD (organic mental disorders, identified with F0 codes in the ICD-10 classification), PSU (mental and behavioural disorders due to psychoactive substance use—excluding alcohol, codes F11–19), SSDD (schizophrenia, schizotypal and delusional disorders, code F2), MD (mood disorders, code F3) and NSSD (neurotic, stress-related and somatoform disorders, code F4). Figure 1 describes the different comorbidity groups identified by this cohort.

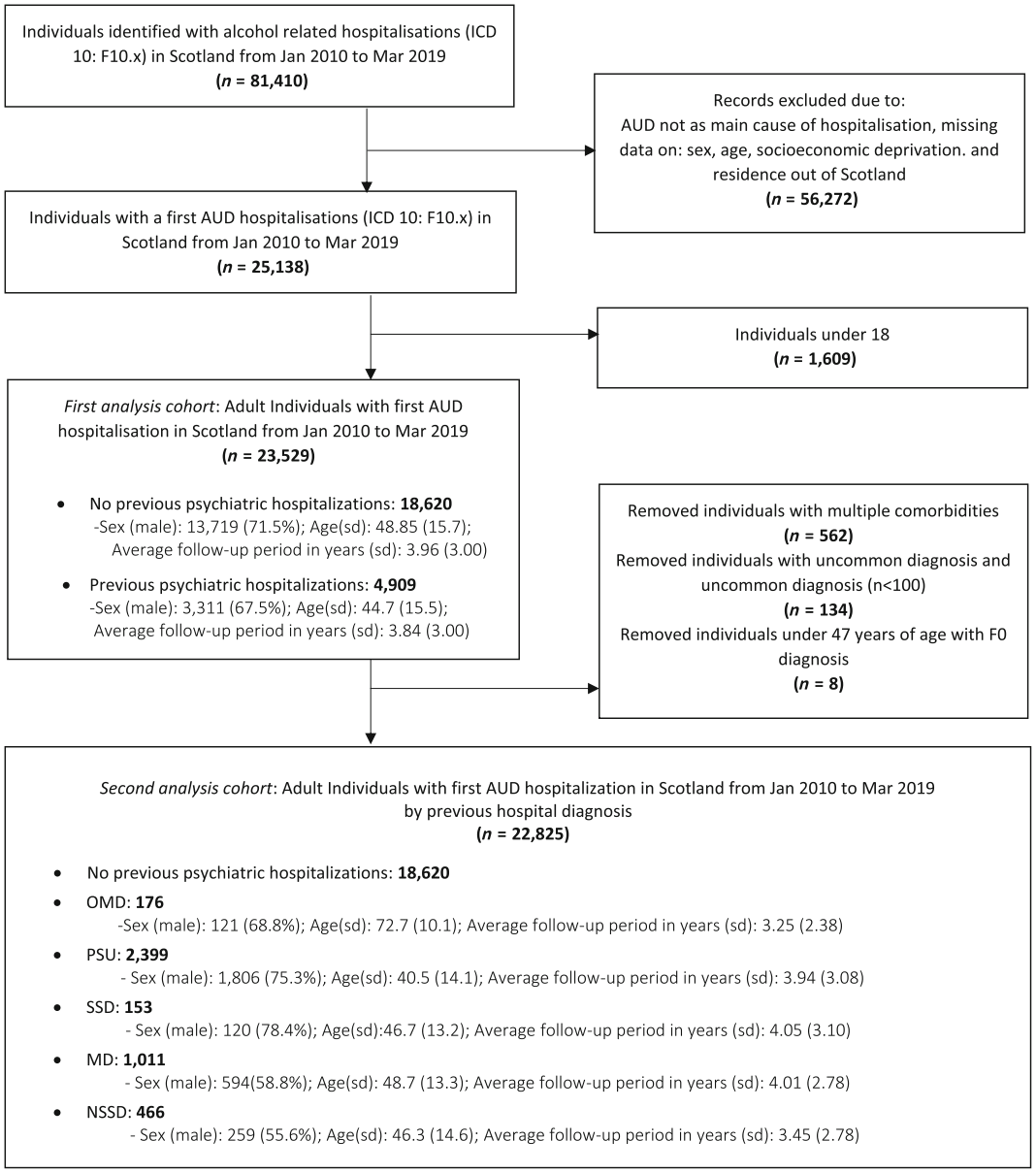

FIGURE 1 Cohort identification. MD = mood (affective) disorders; NSSD = neurotic, stress-related and somatoform disorders; OMD = organic, including symptomatic, mental disorders; PSU = mental and behavioural disorders due to psychoactive substance use—different than alcohol; SSD = schizophrenia, schizotypal and delusional disorders.

There were multiple different previous psychiatric hospitalizations in this cohort. Therefore, to ensure sufficient statistical power in this second analysis, only previous psychiatric conditions with more than 100 patients were considered.

In the OMD group, mainly composed of individuals with dementia, the distribution of age was left-skewed (see supporting information), with the few individuals aged less than 50 years having almost no rehospitalizations. Therefore, there was only a partial overlap in the distribution of age between the OMD and the reference group (those with no history of previous comorbidity). As data based-inference is only valid for the region of overlap [19], we restricted the comparison between the reference and OMD groups to an older subset, building a separate regression. This subset consisted of individuals aged more than 47 years, representing the vast majority (97%) of individuals experiencing rehospitalizations and including 95% of the original OMD group.

Analysis

Descriptive statistics on the number of rehospitalizations and prescriptions were calculated.

As therapies may influence relapse rates, we linked patients with any prescription received for alcohol withdrawal or dependence using the prescribing national data sets from Scotland [20]. We then used prescriptions for AUD as a proxy to identify if the individual was receiving therapy. By detecting whether patients received AUD prescriptions before or after their first AUD hospitalization and by identifying variations in prescribing rates among comorbidities, we aimed to provide complementary information to explain differences in rehospitalization rates. Prescriptions were those included within the National Institute for Health and Care Excellence (NICE) treatment summary for alcohol dependence [21]. For assisted alcohol withdrawal, medications were chlordiazepoxide, diazepam, carbamazepine, clomethiazole and lorazepam; for alcohol dependence, medications were acamprosate, disulfiram, naltrexone and nalmefene. Based on this, we created four variables representing prescriptions to include in our models differing by indication (withdrawal or dependence) and timing (received before or after the first AUD hospitalization). It is worth noting that while most of the medications for alcohol dependence are exclusively for AUD patients, medications for symptoms of withdrawal from alcohol are also often used for other conditions such as anxiety, mood disorders or others.

Survival models were used to estimate the association between the risk of AUD rehospitalization and previous hospitalizations related to other psychiatric reasons. We initially ran models comparing individuals without comorbidities with all those who had experienced at least one. We then compared individuals without comorbidities with all the diagnostic subgroups.

We assessed the time to first AUD rehospitalization using Cox regression. We then assessed the time to multiple AUD rehospitalizations using the Prentice, Williams and Peterson gap-time model (PWP-GT). PWP-GT models assume that recurrent events within the individual are related: individuals are not at risk for the n^{th} AUD hospitalization until they experience their $(n\text{-}1)^{th}$ [22, 23]. As PWP-GT models require a large number of study subjects for every failure time [22, 23], based on the number of subjects experiencing multiple AUD hospitalizations, we set the maximum number of rehospitalizations at three. Both Cox and PWP-GT models were then fitted with and without prescription covariates. Results and goodness of fit were compared. Separate models using death as a competing risk event were also fitted using both cause-specific hazard and Fine and Gray methodologies. Cox regressions of time to second rehospitalization (from the first) and time to third rehospitalization (from the second) were also performed to provide a more comprehensive interpretation of when multiple AUD hospitalizations occur.

As 3–15% of participants had prescriptions for alcohol dependence before their first AUD hospitalization (Table 1), a minority of our patients had already received some sort of treatment for alcohol (e.g. in primary care) prior to their first hospitalization. This confirmed that 'hospitalizations' identified only the most severe AUD episodes. To generalize our conclusions, we ran a sensitivity analysis on participants without any alcohol-dependent or withdrawal prescriptions before their first hospitalization.

There were differences in size, number of events and potential confounders between subgroup cohorts. To account for this, we used covariate adjustment, as this method is preferred to propensity score methods, especially when comparator groups have small sizes (e.g. close to 150) [24]. Model covariates were prescriptions and previous comorbidities and baseline characteristics. Patients' baseline characteristics were: sex, age, Scottish index of multiple deprivation [25] and health board location. Prescriptions between hospitalizations were presented as time-varying covariates and baseline characteristics were time-invariant covariates. There was no pre-registered analysis plan for this study, so findings should be considered explorative.

RESULTS

Descriptive analysis

The percentage of patients without psychiatric comorbidities and at least one AUD rehospitalization was 28% (Table 1). This was similar to the individuals with a history of psychiatric comorbidities (27%). However, there were differences between subgroups. The OMD subgroup had the lowest percentage of individuals experiencing at least one (17%) or more (3%) rehospitalizations. MD had the highest occurrence rate throughout all subgroups, with 33% of the patients experiencing at least one rehospitalization and 16% experiencing further rehospitalizations. Death was not the main cause of censoring in any of the groups, but it was most prevalent in the OMD group (43%). This was considerably higher than all other comparators (Table 1) (Figure 1).

More than a third of the overall cohort had already received prescriptions with a potential indication for withdrawal and/or dependence prior to the first hospitalization. Individuals with a history of

TABLE 1 Number of AUD rehospitalization and prescriptions prior and after first AUD hospitalization.

	No previous hospitalization s related to psychiatric disorders (*n* = 18 620)		Previous OMD (organic, including symptomatic, mental disorders) hospitalization s (*n* = 176)			Previous PSU (mental, behavioural disorders due to psychoactive substance use—different than alcohol) hospitalizations (*n* = 2339)		Previous SSD (Schizophrenia, schizotypal and delusional disorders) hospitalizations (*n* = 153)		Previous MD (mood [affective] disorders) hospitalizations (*n* = 1011)		Previous NSSD hospitalizations (neurotic, stress-related and somatoform disorders) (*n* = 466)		All previous mental health diagnosis aggregated (including subgroup categories not included in the analysis and multiple diagnoses) (*n* = 4909)	
No. of AUD rehospitalizations															
0	13 315		72%	146	83%	1796	75%	121	79%	678	67%	341	73%	3175	73%
At least 1	5305		28%	30	17%	603	25%	32	21%	333	33%	125	27%	1136	27%
> 1	2599		14%	5	3%	268	11%	16	10%	165	16%	62	13%	609	12%
Number of deaths during follow-up period		3821 (21%)		75 (43%)			413 (17%)		32 (21%)		152 (15%)		52 (11%)		856 (17%)
Prescriptions															
Prior to first AUD hospitalization indication for the following															
Alcohol dependence	1778		10%	<5	<3%	206	9%	16	10%	171	17%	68	15%	483	11%
Alcohol withdrawal	5252		28%	38	21%	697	29%	51	33%	397	39%	216	46%	1448	33%
Dep and/or with dep	5837		31%	39	22%	777	33%	57	37%	454	45%	235	50%	1888	37%
Cumulative prescriptions after first AUD hospitalization until third AUD relapse															
Alcohol dependence	2745		15%	11	6%	282	12%	16	10%	276	27%	94	20%	556	11%
Alcohol withdrawal	5635		30%	59	34%	732	31%	60	39%	409	40%	208	45%	1711	35%
Dep and/or with dep	6888		37%	68	38%	857	36%	66	43%	527	52%	244	52%	2098	43%

Note: Due to disclosure restrictions, in the case of fewer than five events, '< 5 was reported.

Abbreviations: AUD = alcohol use disorder; MD = mood disorders; NSSD = neurotic, stress-related and somatoform disorder; OMD = organic mental disorders; PSU = previous hospital diagnoses of other substance use; SSD = schizophrenia, schizotypal and delusional disorders; Dep = dependence.

TABLE 2 Models on first and multiple AUD rehospitalizations.

	Hazard ratio	*P*-value	95% confidence interval	
First AUD rehospitalization				
No previous psychiatric hospitalization versus any previous psychiatric hospitalization				
Any previous hospitalization	1.075	0.020	1.011	1.142
Prescriptions				
Dep prescriptions pre-first event	0.599	< 0.001	0.514	0.698
With prescriptions pre-first event	0.586	< 0.001	0.544	0.632
Dep prescriptions post-first event	0.242	< 0.001	0.202	0.299
With prescriptions post-first event	0.144	< 0.001	0.128	0.162
Analysis by hospital diagnosis				
No previous psychiatric hospitalization	–	–	–	–
OMD[a]	1.033	0.861	0.717	1.486
PSU	0.891	0.008	0.817	0.970
SSD	0.821	0.266	0.580	1.162
MD	1.541	< 0.001	1.378	1.722
NSSD	1.393	< 0.001	1.165	1.664
Prescriptions				
Dep prescriptions pre-first event	0.660	< 0.001	0.570	0.764
With prescriptions pre-first event	0.567	< 0.001	0.525	0.612
Dep prescriptions post-first event	0.255	< 0.001	0.214	0.304
With prescriptions post-first event	0.139	< 0.001	0.124	0.158
Multiple AUD rehospitalization				
No previous psychiatric hospitalization versus any previous psychiatric hospitalization				
Any previous hospitalization	1.025	0.297	0.979	1.074
Prescriptions				
Dep prescriptions pre-first event	0.514	< 0.001	0.458	0.577
With prescriptions pre-first event	0.522	< 0.001	0.493	0.553
Dep prescriptions post-first event	0.218	< 0.001	0.190	0.252
With prescriptions post-first event	0.134	< 0.001	0.122	0.148
Analysis by hospital diagnosis				
No previous psychiatric hospitalization				
OMD[a]	0.796	0.171	0.574	1.103
PSU	0.833	< 0.001	0.777	0.886
SSD	0.844	0.206	0.577	0.977
MD	1.470	< 0.001	1.084	1.281
NSSD	1.344	< 0.001	0.895	1.170
Prescriptions				
Dep prescriptions pre-first event	0.521	< 0.001	0.464	0.584
with prescriptions pre-first event	0.518	< 0.001	0.488	0.550
Dep prescriptions post-first event	0.226	< 0.001	0.197	0.260
With prescriptions post-first event	0.131	< 0.001	0.119	0.145

Note: All models adjusted for sex, age, Scottish index of multiple deprivation and Scottish health board location.
Abbreviations: MD = mood (affective) disorders; NSSD = neurotic, stress-related and somatoform disorders; OMD = organic, including symptomatic, mental disorders; PSU = mental and behavioural disorders due to psychoactive substance use—different than alcohol; SSD = schizophrenia, schizotypal and delusional disorders; Dep = dependence.
[a]Results from a separated regression, comparing only a restricted sample of control and OMD population

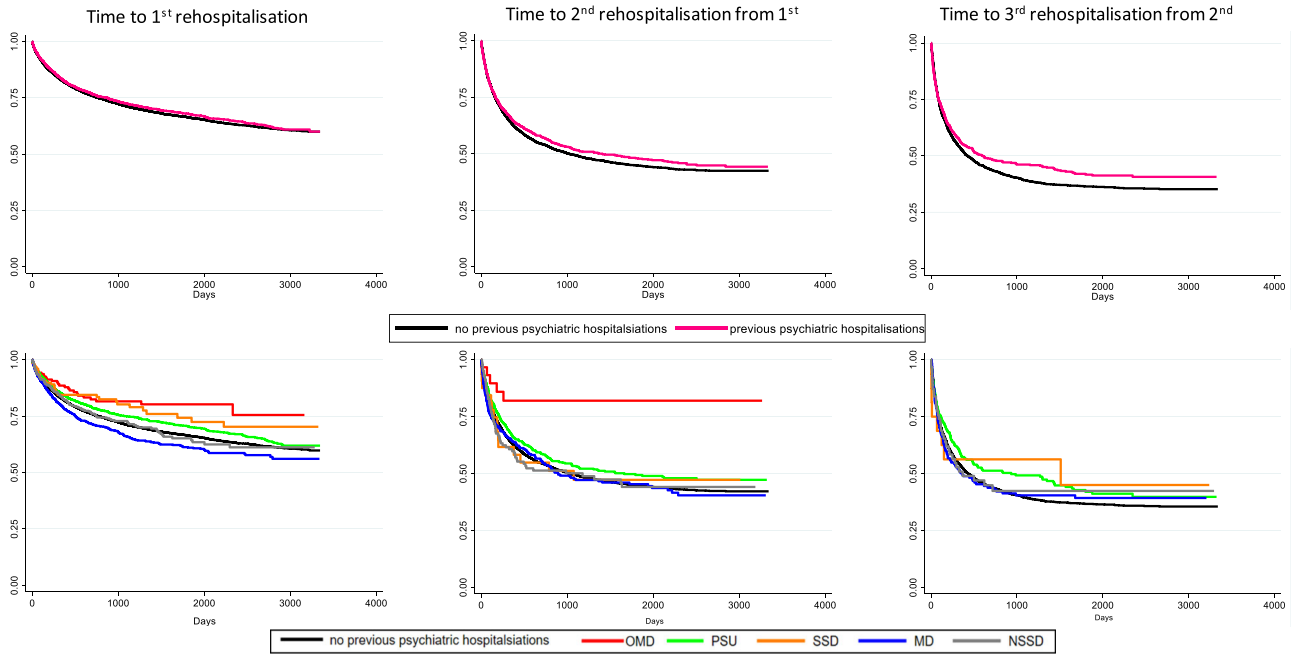

FIGURE 2 Kaplan–Meier curves of time to first, second and third rehospitalization from the previous one. Upper row: comparison between any previous psychiatric hospitalization and lack of previous psychiatric hospitalizations. Lower row: comparison across different previous psychiatric diagnosis at the hospital. Due to disclosure restrictions, the right panel of the second row does not include OMD, as at the end of the observation period there were fewer than five individuals at risk. MD = mood (affective) disorders; NSSD = neurotic, stress-related and somatoform disorders; OMD = organic, including symptomatic, mental disorders; PSU = mental and behavioural disorders due to psychoactive substance use—different than alcohol; SSD = schizophrenia, schizotypal and delusional disorders.

psychiatric hospitalizations had a higher rate of prescriptions (37 versus 31%). MD and NSSD subgroups had the highest prescription rates (45 and 50%, respectively) (Table 1). While the prescription rates increased after the first AUD hospitalization throughout all subgroups, these patterns remained. The subgroup with the lowest prescription rate after a first AUD was PSU (36%).

Inferential analysis

Time to first AUD rehospitalization

The presence of a previous psychiatric hospitalization increased the risk of future AUD rehospitalizations by 8% [hazard ratio (HR) = 1.08, 95% confidence interval (CI) = 1.01–1.14]. Within the subgroups, a history of PSU or SSD hospitalization was associated with a decreased risk of AUD relapse compared to those with no previous mental health hospitalizations. In contrast, MD and NSSD were associated with an increased risk (Table 2). Individuals with a previous MD diagnosis had the highest risk of rehospitalization among all groups: a 54% increased risk of AUD rehospitalization compared to those with no previous psychiatric hospitalizations (HR = 1.54, 95% CI = 1.38–1.72). Furthermore, those with a previous NSSD diagnosis had a 39% increased risk of readmission (HR = 1.39, 95% CI = 1.17–1.66). In contrast, individuals with a history of PSU had a 11% decreased in risk of rehospitalization (HR = 0.89, 95% CI = 0.82–0.97).

Multiple AUD rehospitalizations

When considering all subsequent AUD readmissions, all co-occurring diagnoses were associated with a relatively lower risk of recurrent AUD rehospitalization (except for SSD) (Table 2). This implies that the likelihood of relapse decelerates after the first event in all groups compared to the reference group. The median survival time reduced with the number of relapses among all categories (Figure 2).

There was an improvement in statistical goodness of fit for both single and multiple rehospitalization models after including prescriptions for alcohol dependence or withdrawal (models without prescriptions in the Supporting information). Single failure Cox models from first to second rehospitalization and from second to third rehospitalization had a lower point estimate of the hazard ratio of AUD rehospitalization for individuals with previous psychiatric diagnoses compared to time to first readmission (HR at first rehospitalization: 1.08 P = 0.03, HR at second rehospitalization from first: 0.95, 95% CI = 0.87–1.04, HR at third rehospitalization from second: 0.94, 95% CI = 0.84–1.07). This was also shown in the subgroup analysis: either groups initially associated with a higher (MD, NSSD and OMD) or lower (PSU and SSD) risk of AUD hospital readmission had a lower relative risk after the first AUD rehospitalization (see supporting information). Models estimating time to first rehospitalization, accounting for competing risk of death, were not substantially different to those used in the main analysis (models reported in the supporting information).

DISCUSSION

This is the first study, to our knowledge, that has used a large-scale national data set to compare the risk associated with previous psychiatric hospitalizations on future AUD hospitalizations. We found that, in patients with AUD, a previous psychiatric hospital diagnosis increased the risk of a future AUD rehospitalization by 8%. In particular, diagnoses such as mood disorders (MD) or neurotic, stress-related and somatoform disorders (NSSD) were associated with a 54 and 39% increase in the risk of individuals with an AUD hospitalization having their first AUD rehospitalization. In contrast, individuals with previous hospital diagnoses of other substance use (PSU) were associated with an 11% decrease in the risk of the first AUD readmission. Individuals with previous hospitalizations for OMD or SSD did not show a significant difference in the risk of first AUD rehospitalization with a population without history of psychiatric hospitalizations.

Overall, the time to successive multiple AUD readmission decreased after the first AUD rehospitalization. This may be because the risk set for further rehospitalizations was composed of individuals who had already severely relapsed (requiring a hospitalization), and therefore at greater risk of similar episodes. However, in our assessment of multiple AUD rehospitalizations by subgroups, the relative risk of hospitalization decreased for people with previous psychiatric admissions (with the exception of SSD). The relative risk also decreased for groups initially associated with an increase in the risk of rehospitalization (MD and NSSD), indicating that the difference between patients who already had a higher risk and those without any psychiatric comorbidity is reduced with the number of severe AUD events. This was also confirmed in single Cox regressions analysing time to further rehospitalizations (see Supporting information and Fig. 2). This may have multiple interpretations. One explanation could be that in individuals with multiple severe AUD events and a history of mental health comorbidities, other risk factors (such as family history, personality and the environment) could become more relevant in establishing the chronic pattern of AUD. This would be in accordance with previous studies illustrating that vulnerability and addiction-related characteristics are more relevant risk factors for co-occurring alcohol dependence than anxiety/depression-related traits [26]. Alternatively, the decrease in rehospitalization rates over time for people with mental health comorbidities could be due to more active follow-up. This would be consistent with the finding that most of the comorbid groups have a higher rate of prescription (Table 1). While we must acknowledge the limitations of routine hospital data in detecting all AUD relapses (see later), our findings could have implications for the patterns of the most severe AUD episodes and relapses.

Mood disorders (MD) and neurotic, stress-related disorders (NSSD) were the two conditions with the highest rate of single and multiple rehospitalization compared to the rest of the co-occurring psychopathologies analysed in this study. Depression and anxiety had already been found to be more prevalent in the AUD population [9, 26] as well as relevant risk factors for AUD [26]. Further, these two co-occurring conditions share with AUD prevalent risk factors such as stress (a common symptom in NSSD) [14, 27] and depressive symptoms (common in MD) [15] associated with the propensity of relapse to addiction in general (i.e. not necessarily related to alcohol).

We found a significant relationship between the NSSD group and AUD rehospitalization. This is in disagreement with studies using the same approach to define comorbidity (life-time diagnoses) and in line with studies identifying comorbidities if close in time with the relapse episode (28) [15]. The literature regarding anxiety and AUD relapse is heterogeneous, as the overlap between AUD and anxiety disorder symptoms can lead to misleading diagnoses when the two comorbidities are assessed close to each other [15]. Our study is based on life-time hospital diagnoses up to 10 years before the first AUD severe event, which should ensure the distinction between the two diagnoses. We found a 40 and 34% increase in the risk of first and multiple AUD rehospitalizations for patients with NSSD (which include anxiety).

While some studies have highlighted the high rates of AUD among individuals with schizophrenia [28], to the best of our knowledge there are no studies which have examined alcohol-related hospitalizations or relapses. In our analysis, individuals in group SSD (including schizophrenia diagnoses) did not have an AUD rehospitalization rate significantly different from a population without a history of psychiatric disorders.

Individuals with a history of other substance disorders were associated with a lower risk of AUD readmission than the rest of the population. One possible interpretation could be that the reducing rate is linked to the higher psychological and physical dependence of other substances different than alcohol [29] which drive future hospitalizations, while alcohol may be only a secondary or marginal contributor.

The OMD group did not have significant differences at time to first rehospitalization, compared with a population without previous psychiatric hospitalizations. In contrast, OMD had significant differences in time to second hospitalization and with the greatest change between the two models (single versus multiple rehospitalization) throughout all subgroups. This subgroup also had the sharpest increase of any prescribed medications after a first hospitalization (Table 1). This could be associated with an increase in other complementary and specific care pathways for these patients (e.g. residential homes or care providers) after the first severe episodes characterized by close supervision that would limit alcohol consumption. Alternatively, the development of organic disorders which can reduce motivation and activity could be the leading factor in reducing alcohol consumption. However, different characteristics in this group, such as a significantly higher age at baseline, higher percentage of death and a low number of AUD rehospitalization after the first episode, may limit the comparison with this group. However, the restricted comparison we developed for this group, based on the region of overlap, should have levelled out different baseline characteristics. Competing risk analysis supported our findings.

Certainly, the most robust conclusions of this study can be drawn for groups who had the highest number of events in our study period, as well as a longer follow-up period (PSU, MD and NSSD). Conversely, studies with greater samples or more targeted studies are needed for

individuals with organic mental disorders (OMD) or schizophrenia (SSD) to provide more conclusive findings on multiple severe episodes or hospitalizations.

Strengths and limitations

This study has highlighted the importance of adjusting regression models for therapies received by individuals when comparing different populations in observational studies, as different conditions may induce or require distinct levels of treatments [indeed, the rate of AUD-related prescriptions after the first AUD hospitalization varied among individuals with different psychiatric diagnoses (Table 1)]. While we recognize that psychological interventions are a key part of alcohol treatment, we were only able to obtain access to data on prescriptions. We demonstrated that prescriptions included as time-varying covariates in both single and multiple rehospitalization survival models were significant and increased the goodness of fit, generating substantial differences in terms of coefficient size and statistical significance compared with models not including them (Supporting information).

The main strength of this study was the simultaneous comparison of different psychiatric comorbidities with AUD on the risk of experiencing future AUD episodes using a single large patient cohort. Although the use of routine health-care data meant that we were not able to detect all individuals' chronological relapses we were probably able to identify the most severe AUD episodes, and we had a consistent method to recognize them among all psychiatric diagnoses. In contrast, smaller clinical studies that can identify relapses more precisely usually have smaller samples, allowing fewer comorbidity comparisons within the study. Furthermore, the definition of relapses varies among small studies [15], limiting comparison of different conditions between studies.

There were also several limitations in our study. First, prescriptions of some medications for withdrawal, such as benzodiazepines, could also be given for other psychiatric conditions. By including them separately, together with prescriptions exclusively used for alcohol dependence, we aimed to reduce this confounding effect. Secondly, some individuals with a history of mental health comorbidities may have had a greater chance of being rehospitalized for AUD in psychiatric hospitals. However, the overall low occurrence of AUD-related hospitalizations in Scottish psychiatric hospitals (6%) [30] should not be a major source of bias in our analysis. Another limitation of our study may be the potentially low accuracy of mental health diagnoses in general acute hospitalizations. This may have led to misclassification of diagnosis with some overlapping symptoms (e.g. MD and NSSD). However, we found similar findings for such groups supported by theoretical affinity in their relationship with AUD [26]. Several epidemiological studies in this area [7, 9] which have analysed subcategories of AUD (e.g. withdrawal, dependence and amnestic syndrome) argue that they have different dynamics. We aggregated all F10.x diagnoses into a single category to increase the statistical power of certain groups, as well as to overcome possible misdiagnoses at hospital admission within the AUD groups.

CONCLUSION

A history of previous psychiatric hospitalization increased the risk of a first AUD readmission in patients already hospitalized once for AUD. However, the effect differed among psychiatric conditions: PSU had a lower risk of AUD rehospitalization, while MD and NSSD had a higher risk. Overall, in patients with a history of previous psychiatric diagnoses the risk of future multiple AUD rehospitalization diminishes after the first AUD readmission compared to individuals without psychiatric comorbidities. This could suggest that addiction-related characteristics are more relevant risk indicators for recurring AUD episodes requiring hospitalizations than psychiatric comorbidities.

AUTHOR CONTRIBUTIONS

Francesco Manca: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). **James Lewsey:** Methodology (supporting); supervision (lead); writing—review and editing (equal).

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DECLARATION OF INTERESTS

The study was self-funded. Both authors report no financial relationships with commercial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were available from the Scottish National Safe Haven. Restrictions apply to the availability of these data, which were used under license for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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