Longitudinal assessment of the effect of cannabis use on hospital readmission rates in early psychosis: A 6-year follow-up in an inpatient cohort

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ABSTRACT

Cannabis is the most commonly used illicit drug in psychosis patients and has been identified as a risk factor for relapse and subsequent hospital readmission, having substantial economic implications. To clarify the contribution of cannabis consumption to hospital readmission, a consecutive inpatient cohort of 161 early psychosis patients was included into the study. Data on cannabis use at admission and number of hospital readmissions and length of stay (LOS, number of inpatient days) in a 6-year follow-up was extracted from clinical notes. 62.4% of the patients had lifetime cannabis use. Their admission lasted on average 54.3 ± 75 days and over the following 6 years patients had 2.2 ± 2.8 hospital readmissions, for a total of 197.4 ± 331.5 days. Cannabis use significantly predicted the number of hospital readmissions and LOS in the following 6 years, the latter remaining significant after adjusting for use of other substance. Cannabis-using patients of male gender and Black ethnicity had a longer LOS at follow-up compared to female patients and other ethnic groups, respectively. Having a history of cannabis use when admitted to an early intervention inpatient unit for psychosis is associated with a higher number of subsequent hospital readmissions and a longer LOS, especially in male and Black patients.

1. Introduction

In recent years, more attention has been paid to the public health impact of cannabis use, especially by young adults (Hall and Lynskey, 2016) with evidence of a growing prevalence of regular cannabis use worldwide, with approximately 200 million users (National Academies of Sciences, 2017). Convergent and replicated findings indicate that cannabis use can induce psychotic symptoms (Henquet et al., 2005; Skinner et al., 2011; van Gastel et al., 2012) and increase the risk of developing a psychotic disorder (Colizzi and Murray, 2018; Moore et al., 2007; Radhakrishnan et al., 2014; Sami et al., 2017), especially in young and vulnerable individuals with a history of heavy use (Colizzi et al., 2015a, b). This is in line with experimental evidence that acute administration of delta-9-tetrahydrocannabinol (Δ9-THC) as well as cannabinoid agonists, including phytocannabinoids and synthetic cannabinoids, induce transient psychosis-like symptoms and cognitive impairments in individuals at clinical high-risk to develop a psychotic disorder (Vadhan et al., 2017) as well as healthy individuals (Bhattacharyya et al., 2009; D'Souza et al., 2004; Sherif et al., 2016). Recent evidence indicates that almost one in two patients with cannabis-induced psychosis develops schizophrenia or bipolar disorder, being the highest rate of conversion to a severe psychiatric disorder among patients with a substance-induced psychosis (Starzer et al., 2018). However, whether the association between cannabis and psychosis is causal in nature is still debated (Ksir and Hart, 2016a, 2016b; Schoeler et al., 2016b). Cannabis is also the most commonly used illicit drug in patients with established psychosis (Moore et al., 2012) and its use is especially high in young people presenting with their first episode of psychosis (Patel et al., 2016). Research evidence suggests that continued cannabis use after the onset

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of psychosis predicts poor disease outcome (Linszen et al., 1994), as also confirmed by a recent meta-analysis (Schoeler et al., 2016a). More specifically, cannabis use has been shown to exacerbate psychotic symptoms (Ouellet-Plamondon et al., 2017; Schoeler et al., 2016a; Seddon et al., 2016), increase risk of non-remission (Colizzi et al., 2016) and cause relapse (Patel et al., 2016; Schoeler et al., 2016c) in a dose-dependent manner (Schoeler et al., 2016d). Moreover, cannabis represents a risk factor for both poor medication adherence (Colizzi et al., 2016; Foglia et al., 2017; Schoeler et al., 2017a), antipsychotic treatment-failure (Patel et al., 2016; Wilson and Bhattacharyya, 2016) and dropout from treatment (Miller et al., 2009) and the association between cannabis use and poor outcome in psychosis may be mediated by its effects on medication non-adherence (Colizzi et al., 2016; Schoeler et al., 2017b) and treatment failure (Patel et al., 2016). Cannabis-associated psychosis relapse may have substantial economic implications in light of the potential subsequent need for hospital care (Knapp et al., 2009). Within the first 2 years after the onset of either affective or non-affective psychosis up to 50% of patients experience a relapse which results in hospital readmission, with the risk exceeding 80% by the 8th year of illness (Alvarez-Jimenez et al., 2012).

Several studies have investigated the effect of cannabis use on risk of relapse and hospitalization in incident cohorts of psychosis patients (Schoeler et al., 2016a). On the other hand, only limited research has specifically evaluated the effects of cannabis use on psychosis outcome in inpatient cohorts (Foti et al., 2010; Rylander et al., 2017; San et al., 2013). Specifically, one study assessed relapse rates during a 1-year follow-up in an inpatient cohort of schizophrenia spectrum disorder patients with long and varying duration of illness (ranging from ≤5 years to >20 years), indicating that cannabis consumption was a risk factor for relapse (San et al., 2013). Another study followed up for 1 month patients admitted to hospital with psychotic symptoms, finding that, compared to patients testing negative for the presence of the active metabolite of cannabis 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC−COOH), those acutely intoxicated with cannabis required a shorter inpatient psychiatric hospitalization. However, the groups did not differ in terms of readmission rates, presentation to psychiatric emergency services, or symptom severity at follow-up (Rylander et al., 2017). One more study followed up schizophrenia spectrum disorder patients for 10 years after their first admission, suggesting an adverse course of psychotic symptoms in cannabis-using patients (Foti et al., 2010). Collectively, the interpretation of these findings is challenging in light of methodological heterogeneity between the studies in terms of outcome variable (relapse, hospital readmission, or symptom course), follow-up (from 1 month to 10 years), and illness stage (first presentation, chronic psychosis) or severity (acute drug-induced psychosis, established psychosis). Also, these studies investigated the contributing impact of other illicit drugs on psychosis outcome. In particular, Foti et al. indicated that cannabis use is associated with an adverse course of psychotic symptoms even after controlling for stimulant and cocaine use (Foti et al., 2010). Rylander et al. found that patients testing negative for cannabis and patients with a urine toxicology screen positive for cannabis do not differ in terms of positivity for other stimulants, including cocaine, amphetamine, and opioids (Rylander et al., 2017). Interestingly, San et al. indicated that consumption of cocaine, and not heroin, is a risk factor for psychosis relapse independent of cannabis use (San et al., 2013). Conversely, these studies didn't take into account the potential confounding effect of other common substances such as alcohol (Foti et al., 2010; San et al., 2013) and/ or tobacco (Foti et al., 2010; Rylander et al., 2017; San et al., 2013). Alcohol and tobacco have been identified as a significant problem in people with schizophrenia (Bouza et al., 2010) and meta-analytic evidence indicates that tobacco use represented a risk factor for psychosis (Gurillo et al., 2015). Thus, the association between alcohol and tobacco use on one hand and psychosis outcome on the other merits further examination.

Therefore, in a consecutive inpatient cohort of patients admitted for psychosis to a specialist Early Intervention inpatient Unit within a 1-year period, we obtained information from clinical records on current admission, past medical history, and cannabis as well as other substance use. Information on clinical outcome in terms of subsequent inpatient care, such as the number of readmissions and days spent in hospital over a 6-year follow-up period was also extracted from electronic clinical notes. This study design allowed us to mitigate the potential confounding effects of short follow-up (Baeza et al., 2009), high attrition rate (Potthoff, 2017), and illness stage or severity (Schoeler et al., 2016a). Therefore, the strength of our study was the ability to examine the following hypothesis: cannabis use in patients with early psychotic disorder, which was not a result of merely acute cannabis intoxication, would be associated with higher hospital readmission rates over a longer-term follow-up. As gender and ethnicity have been shown to be the most consistent unique predictors of lifetime substance use disorders in patients in the early stage of their psychosis (Brunette et al., 2018), exploratory analyses assessed the potential role of these variables in the association between cannabis use and hospital readmission rates.

2. Methods

2.1. Study design and sample

This chart review study was conducted at the Early Intervention inpatient Unit of the South London and Maudsley NHS Foundation Trust (SLaM), an inpatient facility specifically devoted to the care of young people aged between 18 and 35 experiencing psychosis for the first time, as part of a clinical audit. All consecutive admissions to the inpatient service over the 2010 calendar year were included into the study. Patients with a known or suspected acute substance intoxication as well as organic cause for psychosis were excluded. This study incorporates a longitudinal design. In fact, although data was collected retrospectively, this information was extracted from prospectively recorded routine clinical information over the follow-up period following the index admission in 2010. For all patients, we were able to extract data over the 6-year follow-up period after their admission to the inpatient unit, obtaining satisfactory data in terms of number of readmissions and days spent in hospital. The design of the electronic system didn't allow a systematic assessment of patients' cognitive function or symptom severity.

The authors assert that the work described here has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans as well as the Uniform Requirements for manuscripts submitted to biomedical journals.

2.2. Case-tracing procedure

All relevant information about the study participants was extracted from the clinical records held on the South London and Maudsley Mental Health NHS Foundation Trust (SLaM) electronic Patient Journey System (ePJS). The SLaM ePJS comprises fields for demographic information as well as fields from case notes and correspondence where history, mental state examination, diagnostic formulation and management plan are primarily recorded. All of the following measures were extracted by a qualified psychiatrist and/ or clinical researcher retrospectively from the electronic mental health records system.

2.3. Data extracted at admission

Socio-demographic information including gender, self-reported ethnicity, and age at the time of the admission was extracted from the clinical records. Duration of current admission and information on potential previous contacts with psychiatric services were also recorded. Finally, information on lifetime use of cannabis and other common substances, including tobacco, alcohol, and stimulants (such

as amphetamine, cocaine, etc.) was extracted from fields in the ePJS including clinical assessments, reviews and correspondence between healthcare professionals.

2.4. Data extracted at follow-up

The six-year follow-up period was considered from the date of in-patient admission in 2010 to the SLaM Early Intervention inpatient Unit for psychosis until the 31st of December 2016. Outcome variables of interest were the number of readmissions and total number of days spent in hospital within the follow-up period.

2.5. Data analysis

Negative binomial regressions were used to test for an effect of baseline cannabis use (yes/ no) as recorded at the index hospitalization on number of hospital readmissions and length of stay (LOS, number of inpatient days) in the following 6 years, controlling for the confounding effects of socio-demographic characteristics (age, gender, ethnicity), clinical characteristics at baseline (duration of current admission, number of previous admissions to inpatient mental health services) and other substance use (tobacco, alcohol, stimulants). Negative binomial regressions were also used to explore the interaction between cannabis use and gender as well as cannabis use and ethnicity on number of hospital readmissions and days spent in hospital in the following 6 years, controlling for the same confounders.

3. Results

3.1. Sociodemographic characteristics

There were 161 new admissions to the Early Intervention Unit in 2010. Out of this cohort, 13 patients (8.1%) had a second admission and 1 (0.6%) patient had a third admission within the same calendar year. Also, 61% of the patients were male and their average age at the time of admission was 29.8 years (± SD, ± 9.5 years). 28% of the patients were White, 50.7% Black African/ Caribbean, 13.3% Asian, and 8% had a mixed self-reported ethnicity.

3.2. Clinical measures

The current admission lasted on average 54.3 ± 75 days. Patients had 1.7 ± 2.7 (Mean ± SD) previous inpatient admissions(s). Over the following 6 years patients had 2.2 ± 2.8 hospital readmissions, for a total of 197.4 ± 331.5 days (length of stay, LOS).

3.3. Cannabis and other substance use

Information on cannabis use was available for 141 early psychosis patients. At admission, 62.4% had a lifetime history of cannabis use as recorded in the case notes, which was considered clinically significant. Lifetime use of other substances as recorded in case notes was also frequent, with 61.2% tobacco users, 64.5% alcohol users, and 38.5% stimulant users. Sociodemographic characteristics, clinical measures, and other substance use in early psychosis patients with and without a history of cannabis use are reported in Table 1.

3.4. Effect of cannabis use on hospital readmission rates

A negative binomial regression to test for an effect of cannabis use on the number of hospital readmissions over the following 6 years, adjusting for sociodemographic (age, gender, and ethnicity) and other clinical characteristics at baseline (duration of current admission, number of previous contact(s) with inpatient psychiatric services), suggested that cannabis use significantly predicted the number of hospital readmissions over the following 6 years (B = 0.56, SE = 0.26,

Table 1
Sociodemographic characteristics, clinical measures, and other substance use in psychosis patients with and without a lifetime history of cannabis use.

	Total group	Cannabis users	Cannabis-naïve
	N (%)	N (%)	N (%)
	141 (100)	88 (62.4)	53 (37.6)
Gender			
Male	87 (62.1)	63 (71.6)	24 (46.2)
Female	53 (37.9)	25 (28.4)	28 (53.8)
Missing	1		
Ethnicity			
Asian	15 (11.3)	8 (9.4)	7 (14.6)
Black African/ Caribbean	68 (51.1)	43 (50.6)	25 (52.1)
Mixed	12 (9)	8 (9.4)	4 (8.3)
White	38 (28.6)	26 (30.6)	12 (25)
Missing	8		
Alcohol use			
Yes	74 (63.2)	58 (84.1)	16 (33.3)
No	43 (36.8)	11 (15.9)	32 (66.7)
Missing	24		
Tobacco use			
Yes	60 (60)	53 (96.4)	7 (15.6)
No	40 (40)	2 (3.6)	38 (84.4)
Missing	41		
Stimulant use			
Yes	41 (36.3)	40 (65.6)	1 (1.9)
No	72 (63.7)	21 (34.4)	51 (98.1)
Missing	28		
Substance use			
At least one other substance[a]	93 (77)	74 (97)	19 (42)
No other substance	28 (23)	2 (3)	26 (58)
Missing	20		
	M (SD)	M (SD)	M (SD)
Age (years)	29.21 (9.29)	28.52 (9.25)	30.36 (9.34)
[range]	[18–69]	[18–69]	[18–59]
Current admission (days)	57.61 (78.25)	64.57 (93.88)	46.06 (39)
[range]	[1–554]	[1–554]	[1–146]
Previous admissions	1.59 (2.69)	1.64 (2.65)	1.51 (2.78)
[range]	[0–15]	[0–12]	[0–15]
Subsequent admissions	2.21 (2.84)	2.59 (3.05)	1.58 (2.34)
[range]	[0–14]	[0–14]	[0–9]
Subsequent LOS (days)	218.48 (348.55)	269.98 (393.44)	132.98 (236.99)
[range]	[0–1572]	[0–1572]	[0–1130]

LOS, length of stay (number of subsequent inpatient days).
[a] Using one or more substances other than cannabis.

Chi square = 4.74, p = 0.029; Table 2A).

A further negative binomial regression, adjusting also for use of psychoactive substances other than cannabis (tobacco, alcohol, and stimulants) in addition to sociodemographic and other clinical characteristics at baseline, failed to reach significance for an effect of cannabis use on the number of hospital readmissions over the following 6 years (B = 1.18, SE = 0.66, Chi square = 3.23, p = 0.072; Table 2B). This was carried in a smaller subset (N = 71) of the larger cohort for whom data on use of psychoactive substances other than cannabis (tobacco, alcohol, and stimulants) was recorded in clinical notes.

A second negative binomial regression to test for an effect of cannabis use on length of stay (LOS, number of days spent in hospital) over the following 6 years, adjusting for sociodemographic and other clinical characteristics at baseline, suggested that cannabis use significantly predicted LOS over the following 6 years (B = 0.77, SE = 0.23, Chi square = 10.97, p = 0.001; Table 3A).

A further negative binomial regression, adjusting also for use of psychoactive substances other than cannabis in addition to socio-demographic and other clinical characteristics at baseline, demonstrated an effect of cannabis use on LOS over the following 6 years (B = 1.41, SE = 0.70, Chi square = 4.04, p = 0.044; Table 3B). This was carried in the smaller subset (N = 71) of the larger cohort for whom data on use of psychoactive substances other than cannabis was

Table 2
Effect of cannabis use on inpatient hospital readmissions over the following 6 years.

	B	SE	Wald Chi-Square	p value
		A		
Cannabis use	0.558	0.256	4.744	0.029
Age	0.002	0.012	0.037	0.848
Gender (Male)	−0.012	0.263	0.002	0.963
Ethnicity (Asian)	−0.028	0.428	0.004	0.948
Ethnicity (Black)	0.845	0.275	9.434	0.002
Ethnicity (Mixed)	0.577	0.446	1.671	0.196
Current admission	0.001	0.002	0.001	0.982
Previous admissions	0.150	0.044	11.622	< 0.001
N = 133; Likelihood Ratio Chi square = 34.03, *p* < 0.001, df = 8				

	B	SE	Wald Chi-Square	p value
		B		
Cannabis use	1.177	0.655	3.227	0.072
Age	0.010	0.016	0.378	0.539
Gender (male)	−0.181	0.359	0.253	0.615
Ethnicity (Asian)	−0.492	0.566	0.754	0.385
Ethnicity (Black)	0.766	0.415	3.408	0.065
Ethnicity (Mixed)	0.991	0.599	2.733	0.098
Alcohol use	−0.391	0.451	0.754	0.385
Tobacco use	−0.626	0.719	0.757	0.384
Stimulant use	0.366	0.484	0.572	0.450
Current admission	−0.001	0.003	0.076	0.783
Previous admissions	0.166	0.084	3.942	0.047
N = 71; Likelihood Ratio Chi square = 25.29, *p* = 0.008, df = 11				

A refers to the effect of cannabis use on hospital readmissions over the following 6 years, controlling for baseline clinical characteristics; B refers to the effect of cannabis use on hospital readmissions over the following 6 years, controlling for baseline clinical characteristics as well as other substances use such as tobacco, alcohol and stimulants.

Table 3
Effect of cannabis use on inpatient length of stay (LOS) over the following 6 years.

	B	SE	Wald Chi-Square	p value
		A		
Cannabis use	0.767	0.231	10.967	0.001
Age	−0.019	0.009	4.182	0.041
Gender (male)	0.049	0.250	0.038	0.844
Ethnicity (Asian)	0.034	0.322	0.011	0.917
Ethnicity (Black)	0.718	0.207	12.010	0.001
Ethnicity (Mixed)	0.549	0.346	2.521	0.112
Current admission	0.002	0.001	1.382	0.240
Previous admissions	0.177	0.050	12.378	< 0.001
N = 133; Likelihood Ratio Chi square = 46.53, *p* < 0.001, df = 8				

	B	SE	Wald Chi-Square	p value
		B		
Cannabis use	1.412	0.702	4.045	0.044
Age	−0.013	0.014	0.867	0.352
Gender (male)	−0.163	0.382	0.183	0.668
Ethnicity (Asian)	0.448	0.459	0.951	0.330
Ethnicity (Black)	1.745	0.349	25.031	< 0.001
Ethnicity (Mixed)	2.030	0.547	13.762	< 0.001
Alcohol use	−1.415	0.392	13.006	< 0.001
Tobacco use	−0.684	0.658	1.081	0.299
Stimulant use	1.050	0.445	5.578	0.018
Current admission	0.005	0.003	2.976	0.084
Previous admissions	0.331	0.089	13.712	< 0.001
N = 71; Likelihood Ratio Chi square = 73.68, *p* < 0.001, df = 11				

A refers to the effect of cannabis use on inpatient length of stay (LOS) over the following 6 years, controlling for baseline clinical characteristics; B refers to the effect of cannabis use on inpatient length of stay (LOS) over the following 6 years, controlling for baseline clinical characteristics as well as other substances use such as tobacco, alcohol and stimulants.

Table 4
Interaction between cannabis use and gender on inpatient length of stay (LOS) over the following 6 years.

	B	SE	Wald Chi-Square	p value
Male Cannabis users	1.494	0.722	4.284	0.038
Male Cannabis-naïve	−0.640	0.426	2.257	0.133
Female Cannabis users	0.734	0.776	0.894	0.344
Age	−0.014	0.014	1.038	0.308
Ethnicity (Asian)	0.662	0.501	1.750	0.186
Ethnicity (Black)	1.989	0.368	29.237	< 0.001
Ethnicity (Mixed)	2.149	0.539	15.889	< 0.001
Alcohol use	−1.487	0.374	15.847	< 0.001
Tobacco use	−0.640	0.667	0.921	0.337
Stimulant use	0.601	0.517	1.352	0.245
Current admission	0.006	0.003	3.649	0.056
Previous admissions	0.341	0.096	12.653	< 0.001

N = 71; Likelihood Ratio Chi square = 78.59, *p* < 0.001, df = 12.

recorded in clinical notes.

3.5. Exploratory analyses

A negative binomial regression adjusting for all the modeled potential confounders (sociodemographic and other clinical characteristics, and substance use) failed to show a significant interaction between cannabis use and gender on the number of hospital readmissions over the following 6 years. However, a further negative binomial regression adjusting for all the modeled potential confounders (sociodemographic and other clinical characteristics, and substance use) showed a significant interaction between cannabis use and gender on LOS over the following 6 years. Compared to female cannabis-naïve patients, cannabis use predicted LOS over the following 6 years among male (B = 1.49, SE = 0.72, Chi square = 4.28, *p* = 0.038; Table 4) but not female patients (*p* = 0.34; Table 4).

A second negative binomial regression adjusting for all the modeled potential confounders (sociodemographic and other clinical characteristics, and substance use) showed a significant interaction between lifetime cannabis use and ethnicity on the number of hospital readmissions over the following 6 years. Compared to White cannabis-naïve patients, cannabis use was significantly associated with the number of hospital readmissions over the following 6 years among patients of Black African/ Caribbean (B = 1.54, SE = 0.79, Chi square = 3.86, *p* = 0.049; Table 5A), but not White (*p* = 0.90; Table 5A) or Asian ethnicity (*p* = 0.82; Table 5A).

A further negative binomial regression adjusting for all the modeled potential confounders (sociodemographic and other clinical characteristics, and substance use) showed a significant interaction between cannabis use and ethnicity on LOS over the following 6 years. Compared to White cannabis-naïve patients, cannabis use predicted LOS over the following 6 years among patients of Black African/ Caribbean (B = 2.39, SE = 0.90, Chi square = 7.10, *p* = 0.008; Table 5B), but not White (*p* = 0.53; Table 5B) or Asian ethnicity (*p* = 0.29; Table 5B).

4. Discussion

To our knowledge, this is the first study to systematically examine the association of cannabis use and hospital outcomes over a longer-term in an inpatient cohort of early psychosis patients. The results indicated that having a history of cannabis use when admitted to hospital in the early stage of psychosis predict a higher number of hospital readmissions as well as a longer length of stay (LOS, number of days spent in hospital) in the subsequent 6 years. The association between cannabis use and LOS remained significant when controlling for the confounding effects of use of other common substances, such as alcohol, tobacco, and stimulants. Finally, the negative effect of cannabis use in

Table 5
Interaction between cannabis use and ethnicity on inpatient hospital readmissions and length of stay (LOS) over the following 6 years.

	B	SE	Wald Chi-Square	*p* value
			A. Inpatient hospital readmissions	
Asian Cannabis users	0.225	0.969	0.054	0.817
Asian Cannabis-naïve	−1.321	0.961	1.889	0.169
Black Cannabis users	1.545	0.787	3.859	0.049
Black Cannabis -naïve	0.046	0.597	0.006	0.939
Mixed Cannabis users	1.632	1.099	2.205	0.138
Mixed Cannabis-naïve	0.407	0.861	0.224	0.636
White Cannabis users	0.118	0.920	0.017	0.898
Age	0.018	0.018	0.999	0.318
Gender (Male)	−0.170	0.363	0.220	0.639
Alcohol use	−0.372	0.448	0.689	0.407
Tobacco use	−0.654	0.739	0.783	0.376
Stimulant use	0.409	0.520	0.617	0.432
Current admission	−0.001	0.003	0.040	0.842
Previous admissions	0.174	0.086	4.130	0.042

$N = 71$; Likelihood Ratio Chi square = 28.27, $p = 0.013$, df = 14

			B. Length of stay (LOS)	
Asian Cannabis users	1.084	1.029	1.111	0.292
Asian Cannabis-naïve	−0.680	0.584	1.355	0.244
Black Cannabis users	2.392	0.898	7.103	0.008
Black Cannabis -naïve	0.735	0.500	2.162	0.141
Mixed Cannabis users	2.630	1.076	5.976	0.015
Mixed Cannabis-naïve	0.922	0.866	1.132	0.287
White Cannabis users	−0.633	1.004	0.397	0.529
Age	0.004	0.016	0.068	0.794
Gender (Male)	0.172	0.393	0.191	0.662
Alcohol use	−1.456	0.381	14.603	< 0.001
Tobacco use	−0.318	0.825	0.149	0.700
Stimulant use	0.775	0.515	2.264	0.132
Current admission	0.007	0.003	3.845	0.050
Previous admissions	0.308	0.093	10.830	0.001

$N = 71$; Likelihood Ratio Chi square = 86.76, $p < 0.001$, df = 14.

terms of longer hospital readmissions was greater in cannabis-using patients of male gender and Black ethnicity compared to the female gender and other ethnic groups, respectively.

The mean age of the cannabis-using group was consistent with previous studies investigating the effect of cannabis use on psychosis onset in patients presenting with their first episode of psychosis to the adult in-patient units of the South London and Maudsley NHS Foundation Mental Health Trust (Di Forti et al., 2014). Our inpatient cohort was characterized by high rates of cannabis and other substance use, in line with previous surveys of drug use in psychosis (Moore et al., 2012). However, the prevalence of substance use we found was higher compared to that of other studies investigating substance use in early psychosis because we included any kind of use and not only categorically defined substance use disorders (Addington and Addington, 2007; Myles et al., 2012; Van Mastrigt et al., 2004). Substance use and other mental disorders frequently co-occur, complicating diagnosis because many symptoms, such as insomnia, can fulfill criteria for intoxication, withdrawal syndrome, or other mental disorders (Hasin et al., 2013). Studies indicated that substance use disorders represent a dimensional condition with no natural threshold, with a binary diagnostic decision potentially resulting in a marked perturbation in prevalence (Russo et al., 2014). Also, defining patients on the basis of a comorbid substance use disorder would have affected the generalizability of the results, limiting their application only to early psychosis patients at the extreme hand side of substance use comorbidity.

Our study evaluated the impact of cannabis use on hospital readmission rates controlling for a number of clinical and sociodemographic variables. In the 1990s, methodologically robust studies started to suggest that several features may influence readmissions rates among psychiatric patients. The number of previous admissions appeared to be the best explanatory clinical factor for subsequent admissions (Colenda

and Hamer, 1989; Wan and Ozcan, 1991). Also, among sociodemographic exploratory variables, patients of male gender were reported at higher future risk of single and multiple readmissions and of subsequently remaining longer in hospital (Kastrup, 1987). Other studies have consistently shown that younger age (Lewis and Joyce, 1990; Zilber et al., 1990) and ethnicity (Bhugra et al., 1997) are associated with poor outcome in those with psychosis. Clinical and sociodemographic exploratory variables for higher risk of readmission found in the present study (Tables 2 and 3) are entirely consistent with previous work. Our findings indicated that cannabis use affect hospital readmissions rates and LOS even beyond the early years of illness even after controlling for these potential confounders, and has demonstrated this association in an inpatient cohort. Our results also extended previous evidence (Bhugra et al., 1997; Kastrup, 1987), indicating that the risk of hospital readmission due to cannabis use is significantly higher in male and Black patients compared to female patients and patients of other ethnicity.

Stimulant and alcohol use appeared to have an effect on the LOS but not on the number of hospital admissions in the subsequent 6 years. In particular, stimulant use was associated with longer LOS, complementing previous evidence that stimulant use, especially cocaine, may increase the risk of psychosis relapse independent of cannabis use (San et al., 2013). Conversely, alcohol use was associated with a shorter LOS. Research evidence has suggested a negative association between frequency of cannabis use and hazardous alcohol use (Berge et al., 2014). However, while the current study controlled for the confounding effect of other substance use in the association between cannabis use and hospital readmission rates, it was not designed to investigate the effect of hazardous alcohol use on risk of being readmitted to hospital. Thus, these findings will not be further discussed.

Several explanations may account for the higher risk of being readmitted to hospital in cannabis-using early psychosis patients. A review of clinical studies suggested that cannabis use may impact negatively on a number of psychosocial factors, including employment rates and quality of life (Zammit et al., 2008). Moreover, substance use has been shown to affect physical health (Colton and Manderscheid, 2006; Crump et al., 2013), with approximately 60% of premature deaths in schizophrenia patients being due to medical conditions caused by modifiable risk factors such as smoking, alcohol consumption, and drug use (Hartz et al., 2014). Also, neurobiological mechanisms may be involved in light of evidence that cannabis-using and nonusing patients with psychosis may differ on a number of biological characteristics (reviewed here (Sami and Bhattacharyya, 2018)). Chronic cannabis use has also been suggested to lead to low striatal dopamine synthesis and release, which in turn may drive craving for further drug use (Bloomfield et al., 2014; Murray et al., 2014). Antipsychotic medications block dopamine and therefore may compound this low striatal dopamine leading to greater craving and dropout from treatment (Miller et al., 2009). Cannabis use is also a well-known risk factor for poor medication adherence (Colizzi et al., 2016; Foglia et al., 2017; Schoeler et al., 2017a). Furthermore, experimental studies have shown that the main psychoactive ingredient in cannabis can induce psychotic symptoms in healthy individuals (Bhattacharyya et al., 2015; Bhattacharyya et al., 2012; Bhattacharyya et al., 2009; D'Souza et al., 2004) and exacerbate their severity in those with pre-existing psychosis (D'Souza et al., 2005), suggesting that comorbid cannabis use may increase the risk of readmission simply by making patients with psychosis more unwell. All these factors may globally affect the mental health of patients with psychosis, increasing their risk of being readmitted to hospital.

In summary, this study adds to the larger body of evidence indicating a detrimental effect of cannabis use on psychosis outcome. In particular, cannabis use increased the risk of being readmitted to hospital in the 6 years after discharge from an inpatient early psychosis unit, especially in patients of male gender and Black ethnicity. On the available epidemiological evidence (Schoeler et al., 2016a), despite

being one of the most potentially preventable risk factors of psychosis, cannabis use represents a great obstacle to the effective treatment of the disorder. The establishment of training and education programs in psychosis with comorbid cannabis use for health professionals, care providers, as well as for the general population may increase knowledge of cannabis use as a risk factor for relapse and hospital readmission in psychosis and help to improve patients' outcome in the long-term. Encouraging future research oriented to early intervention in psychosis with comorbid cannabis use can speed the process of identifying evidence-based best practices, support the creation of public policies, and reduce subsequent burden on services, being eventually beneficial to society.

The main strengths of the present study were its in-patient cohort design, the prospective long-term follow-up, and the fact that it controlled for potential confounding effects of the most common sociodemographic and clinical characteristics, and other substance use. Also, having patient clinical information stored electronically increased availability of data and helped reducing loss to follow-up. However, the possibility of disengagement from the clinical team after the hospitalization, transfer to other mental health services within the UK, or moving abroad cannot be completely ruled out. Moreover, all information was recorded by trained assessors over multiple assessments during the 6-year follow-up, ensuring the reliability of data collected. However, as the electronic system is not primarily designed for research purposes, clinical notes may lack of standardization and information that is not important to clinical care may be missing. For instance, information on frequency and type of cannabis use was not systematically reported, precluding the evaluation of the effect of different patterns of cannabis use on hospital readmission. Also, the lack of systematic assessment of alcohol, tobacco, and stimulant use across patients limited the statistical power of analyses conducted adjusting for the potential confounding effect of other commonly used substances. Nevertheless, the substantial overlap in terms of results between analyses conducted with and without other substances use as a confounder, excludes that the present findings may be systematically affected by a potential selection bias in data availability. Furthermore, not having information whether cannabis use continued over the follow-up period represented another limitation of this study.

Conflict of interest

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