Psychological Medicine

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Original Article

Cite this article: Hjorthøj C, Stürup A, Karlsen M, Speyer H, Osler M, Ongur D, Nordentoft M (2024). Use of antipsychotic medication, benzodiazepines, and psychiatric hospitalization in cannabis-related versus cannabis-unrelated schizophrenia – a nationwide, register-based cohort study. *Psychological Medicine* **54**, 2634–2643. https://doi.org/10.1017/S0033291724000758

Received: 14 July 2023
Revised: 11 January 2024
Accepted: 29 February 2024
First published online: 4 April 2024

Keywords:
antipsychotics; benzodiazepines; cannabis; psychiatric service use; schizophrenia

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Use of antipsychotic medication, benzodiazepines, and psychiatric hospitalization in cannabis-related versus cannabis-unrelated schizophrenia – a nationwide, register-based cohort study

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Abstract

Background. Evidence suggests that cannabis may be a causal factor for development of schizophrenia. We aimed to investigate whether use of antipsychotic medication, benzodiazepines, and psychiatric service use differs among patients with schizophrenia depending on whether psychosis was precipitated by a diagnosis of cannabis use disorder (CUD).

Methods. We utilized the nationwide Danish registries to identify all individuals with an incident diagnosis of schizophrenia from 1995 to 2016. We also collected information on whether first CUD diagnosis preceded schizophrenia and thus defined a group of potentially cannabis-related schizophrenia. We compared the cannabis-related schizophrenia group both with all non-cannabis-related patients with schizophrenia and with non-cannabis-related patients with schizophrenia that were propensity-score matched to cases using a range of potentially confounding variables.

Results. We included 35 714 people with incident schizophrenia, including 4116 (11.5%) that were cannabis-related. In the unmatched-comparison analyses, there were no clear differences over time in use of antipsychotics and benzodiazepines related to whether the diagnosis of schizophrenia was cannabis-related. After propensity-score matching, use of antipsychotics and benzodiazepines was significantly lower among cannabis-related cases of schizophrenia. In the unmatched comparison, the cannabis-related group had significantly more days admitted than the non-cannabis-related group. This was markedly attenuated after propensity-score matching.

Conclusions. Our findings indicate the importance of considering cannabis-related cases of schizophrenia as a potentially distinct disorder in terms of prognosis. It is unclear, however, if these differences are due to different biological types of schizophrenia being compared or if they rather indicate behavioral differences such as reduced adherence and treatment-seeking.

Introduction

Use and misuse of cannabis have repeatedly been shown to be more prevalent in people with schizophrenia compared with the general population (Green, Young, & Kavanagh, 2012; Myles, Myles, & Large, 2016). Studies suggest that comorbid cannabis use disorder in patients with schizophrenia is associated with poorer prognosis on a range of outcomes, including symptom severity, rehospitalization, suicide, and all-cause mortality (Hjorthøj et al., 2015; Schoeler et al., 2016). Some of this association may be due to reverse causation, with patients more heavily affected by psychotic symptoms using cannabis as a form of self-medication (Ferdinand et al., 2005; Macleod et al., 2004; Petersen, Toftdahl, Nordentoft, & Hjorthøj, 2019). However, many of the associations have remained intact even in studies adjusting for a range of potential confounding factors, including illness severity. A meta-analysis from 2017 concluded that cannabis use was associated with antipsychotic non-adherence in patients with schizophrenia; however, the included studies were very small and of variable methodological quality, and furthermore, the influence of confounding factors on the association could not be readily established (Foglia, Schoeler, Klamerus, Morgan, & Bhattacharyya, 2017). Furthermore, one study found that cannabis use was associated with readmission in schizophrenia, whereas benzodiazepine use was not (Rømer Thomsen et al., 2018).

Several studies implicate cannabis as a possible causal factor for schizophrenia, and it is thus possible that a cannabis-related type of schizophrenia exists, which may in turn be quite different from other types of schizophrenia (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Moore et al., 2007; Nielsen, Toftdahl, Nordentoft, & Hjorthøj, 2017). This remains, however, a hypothesis, and few studies have tested this hypothesis directly. In terms of prognosis, for instance, it is unclear whether the apparently poorer prognosis observed in patients with schizophrenia with comorbid cannabis use may just reflect that many of these cases of schizophrenia may, in fact, have been caused by cannabis use.

The overarching hypothesis in this study is that cannabis-induced schizophrenia has a different course than cannabis unrelated schizophrenia. It may be associated with a more severe course (measured with proxy outcomes; medication, hospitalizations, and number of outpatients contact) or it may be less severe if substance abuse is resolved. To test this hypothesis, we have articulated to following three questions:

1. What are the patterns of use of antipsychotic medication, benzodiazepines, and psychiatric hospitalizations and outpatient contacts, in the years following incident schizophrenia, and does this differ depending on whether the schizophrenia was cannabis-related or not?
2. Are any differences between the cannabis-related and cannabis-unrelated cases of schizophrenia observed in question 1 attributable to confounding factors?
3. In the two groups of patients with schizophrenia, which proportion is neither hospitalized nor using antipsychotic medication in the years following incident schizophrenia?

Methods

We defined the population as all individuals with an incident diagnosis of schizophrenia (ICD-10 F20.X) from 1995 to 2016. Incident schizophrenia was defined as not having a previous diagnosis of schizophrenia (ICD-10 F20.X or ICD-8 295.X except 295.7) during a person's lifetime.

Cannabis use disorder, use of antipsychotic medication, and other variables

Information regarding cannabis use disorder was obtained from the Psychiatric Central Research Register and National Patient Registry as ICD-8 codes 304.5 and ICD-10 codes F12.X (Lynge, Sandegaard, & Rebolj, 2011; Mors, Perto, & Mortensen, 2011). Furthermore, cannabis use disorder was registered in the registers for municipal alcohol and substance use disorder treatment (Sundhedsdatastyrelsen, 2021a, 2021b). Redemption of prescriptions for antipsychotic medication was identified in the National Prescription Registry as ATC-codes N05A, and benzodiazepines were identified in the same register using ATC-codes N05BA (Kildemoes, Sørensen, & Hallas, 2011). The following covariates were used for propensity score matching using logistic regression: alcohol use disorder was identified in the same registers as ICD-8 codes 291.X, 303.X, 571.0; ICD-10 codes F10.X, E24.4, E52, G31.2, G62.1, G72.1, K29.2, K70, K86.0, O35.4, Y57.3, Z50.2, Z71.4, and Z72.1; and ATC-codes N07BB*. Substance use disorder was identified in the same registers using ICD-8 codes 304.X except 304.5; ICD-10 codes F1X.X except F10.X and F12.X, Z50.3, Z71.5, and Z72.2; and ATC-codes N07BC*. Other variables were sex, age at incident schizophrenia, and whether a person was Danish-born or a first or second generation immigrant (all from the Civil Registration System (Pedersen, 2011); the latter two categories had to be combined due to small numbers); social and occupational functioning was described using tables from Statistics Denmark regarding employment status, marital status, number of people living in the household, number of children living in the household, and type of household, all defined at the time of incident schizophrenia; other psychiatric disorders prior to schizophrenia; parental history of the same psychiatric disorders as described above, defined using the same ICD-codes; parental education, classified according to ISCED, was obtained from Statistics Denmark.

Outcome variables included psychiatric inpatient days and admissions and psychiatric outpatient visits (defined in the National Patient Registry by coding of contact type and duration) and defined daily doses of redeemed prescriptions for antipsychotics or benzodiazepines.

Statistics

First, the population was characterized using descriptive statistics (means and proportions). The primary exposure-variable of interest was whether or not the incident schizophrenia was potentially cannabis-related (the person had a diagnosis of cannabis use disorder at any time prior to the onset of schizophrenia) or seemingly cannabis-unrelated (no diagnosis of cannabis use disorder prior to the onset of schizophrenia). In a sensitivity analysis, we only considered case of schizophrenia to be cannabis-related if it had been diagnosed at least 365 days after an incident diagnosis of cannabis use disorder, in order to minimize the risk of the association being due to a detection bias. Characteristics of the study population was compared using *t* test and chi-square tests, as appropriate.

Next, we estimated the patterns of medication use (antipsychotics and benzodiazepines, operationalized as defined daily doses as defined by the register) and psychiatric hospitalization and outpatient visits for each quarter following incident schizophrenia, for up to ten years. This was done using negative binomial regression with the logarithm of a person's observation time as the offset. Once a person died or emigrated, or after final follow-up of the cohort (on 31 December 2018), they were no longer considered under observation. These negative binomial regressions were used to estimate incidence rates of the outcome in the cannabis-related and the cannabis-unrelated groups, respectively, as well as to estimate incidence rate ratios (IRR) with the cannabis-unrelated group as the reference group.

We then used propensity score matching to identify one control (cannabis-unrelated schizophrenia) for each case (cannabis-related schizophrenia) to investigate whether any associations observed in the previously mentioned negative binomial regression models might be due to confounding factors. For each cannabis-related case of schizophrenia, one propensity-score-matched cannabis-unrelated control was selected. Exact matching was performed on sex, and all covariates previously described were used to estimate propensity scores. The best matching potential control (nearest neighbor) was selected for each case, and in cases where two or more potential controls were equally suited, one was selected at random. We estimated the standardized mean difference (SMD) before and after the matching procedure to indicate the appropriateness of the balancing (Austin, 2009). The SMD for categorical variables was estimated using Austin's formula (Austin, 2009). An SMD between −0.1 and 0.1 was interpreted as a well-balanced propensity score-matched sample (Stuart, Lee, & Leacy, 2013). The same analytical setup as before was then applied to the matched

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sample. Due to problems with the originally planned fixed effects conditional Poisson or negative binomial regression models, we instead used normal negative binomial regression models adjusting for the propensity score and used the matching information to obtain a clustered sandwich estimator of the variance.

Finally, we estimated the proportion of each of the three groups (cannabis-related, cannabis-unrelated before matching, and cannabis-unrelated after matching) of patients with schizophrenia who, in the past 91 days (three months) had:

- Neither been admitted to a psychiatric hospital nor used antipsychotic medication.
- Not been admitted but used antipsychotic medication.
- Been admitted and not used antipsychotic medication (except, perhaps, while admitted, information regarding which was not available in the registers).
- Been admitted and used antipsychotic medication.

In all cases, this was estimated and plotted for each day from 91 days after incident schizophrenia until 10 years after incident schizophrenia. For each day, only individuals who had not yet been censored were included, with censoring occurring at death, emigration, or end-of-follow-up on 31 December 2018. Results were plotted both as proportions and as odds ratios from binary logistic regression models with the cannabis-unrelated group as reference.

$p < 0.05$ (two-sided) was considered statistically significant.

Purely register-based studies do not require ethical approval according to Danish law. Analyses were performed using the Stata/MP 17.0 software.

Results

We included 35 714 individuals with incident schizophrenia, of whom 4116 (11.5%) were classified as being potentially cannabis-related. Demographics of the population are presented in Table 1, with evidence of statistically significant differences between cannabis-related and cannabis-unrelated cases of schizophrenia on all investigated variables.

Unadjusted analyses regarding use of psychiatric medication and treatment services

The top half of Fig. 1 shows the unadjusted incidence rates of psychiatric inpatient days and outpatient visits and DDD's of antipsychotic medication and benzodiazepines in people with cannabis-related and cannabis-unrelated schizophrenia, respectively, for each quarter for the first ten years after incident schizophrenia. Use of antipsychotics gradually increased over time in both groups, whereas use of benzodiazepines was relatively stable. Psychiatric inpatient days were much more frequent shortly after incident diagnosis of schizophrenia in both groups, and then decreased markedly over time. The same was true for outpatient visits, except that the decline was less pronounced.

Figure 2 shows the same information summarized as incidence rate ratios of the cannabis-related group against the cannabis-unrelated group as reference. For antipsychotics and benzodiazepines, it varied without clear trends over time whether the cannabis-related schizophrenia group used more or less of the medication than the cannabis-unrelated schizophrenia, but with confidence intervals generally crossing the IRR = 1 line, indicating no statistically significant difference between the two groups. For psychiatric inpatient days, however, the cannabis-related schizophrenia group was consistently admitted more days than the cannabis-unrelated schizophrenia group. The association increased over time until it stabilized around IRR = 2 after approximately three years. Outpatient visits were also slightly more prevalent in the cannabis-related group.

Propensity-score matched analyses regarding use of psychiatric medication and treatment services

To test whether these differences might be due to confounding factors, we performed propensity score matching as previously described. Table 1 displays balancing diagnostics as SMD's before and after the matching procedure, indicating that after matching, all observed potential confounders were balanced between the two groups of schizophrenia patients. We then used this new sample to construct the lower halves of Figs 1 and 2, showing incidence rates and incidence rate ratios, respectively, in the matched sample. The patterns observed for incidence rates in the propensity score matched sample were very similar to those observed in the unmatched sample. The propensity score-adjusted incidence rate ratios, however, revealed a different picture in the matched sample. Use of antipsychotics was generally lower in the cannabis-related schizophrenia group compared to the cannabis-unrelated group, a difference which was statistically significant in approximately the first half of the follow-up period. Use of benzodiazepines was statistically significantly lower in the cannabis-related group than the cannabis-unrelated group for almost the entire follow-up period. The cannabis-related group still had more inpatient psychiatric days, but the magnitude was much smaller than in the unmatched analysis and not always statistically significant. The increased frequency of outpatient visits was also reduced in the matched analyses, but still statistically significant for the majority of the time. The precise incidence rates and incidence rate ratios depicted in Figs 1 and 2 are listed in online Supplementary Tables S1 through S8.

Not using antipsychotic medication not being admitted to a psychiatric hospital

Figure 3 displays the proportion of patients, on a daily basis, who had neither used antipsychotic medication, nor been admitted as an inpatient to a psychiatric hospital, in the preceding three months (91 days). This is displayed for three groups: The cannabis-related group, the unadjusted cannabis-unrelated group, and the propensity-score-matched cannabis-unrelated group. For all three groups, the proportion started at about 20%, increasing to about 40% a little after a year, and then stabilized a little below 40% after a few years. In unadjusted analyses, i.e. comparing against the unmatched sample, the cannabis-related group initially had slightly lower odds of not being neither hospitalized nor using antipsychotic medication, but this difference quickly became statistically not-significant. In adjusted analyses, i.e. comparing against the propensity-score matched sample, however, the cannabis-related schizophrenia group was statistically significantly more likely to be neither hospitalized nor using antipsychotic medication for most of the first five years after incident schizophrenia, after which point the association was no longer statistically significant.

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Table 1. Baseline characteristics and balancing diagnostics before and after propensity score matching

	Cannabis-related schizophrenia ($n = 4116$)		Cannabis-unrelated schizophrenia Before matching ($n = 31\,598$)			Cannabis-unrelated schizophrenia After matching ($n = 4116$)		
	Mean	S.D.	Mean	S.D.	*d*	Mean	S.D.	*d*
Age at incident schizophrenia (years)	29.1	9.2	34.7	15.4	−0.38	29.7	10.2	−0.06
	N	%	N	%	d	N	%	d
Male (exact match)	3330	80.9	17 242	54.6	0.59	3330	80.9	0.00
Previous alcohol use disorder	1551	37.7	5355	16.9	0.48	1500	36.4	0.03
Previous substance use disorder	2008	48.8	3203	10.1	0.94	2006	48.7%	0.00
Previous other psychiatric disorders	3728	90.6%	23 283	73.7%	0.45	3726	90.5%	0.00
Paternal schizophrenia	78	1.9	408	1.3	0.05	70	1.7	0.01
Paternal cannabis use disorder	77	1.9	237	0.8	0.10	78	1.9	0.00
Paternal alcohol use disorder	638	15.5	2837	9.0	0.20	620	15.1	0.01
Paternal substance use disorder	208	5.1	853	2.7	0.12	182	4.4	0.03
Paternal other psychiatric disorders	766	18.6	4349	13.8	0.13	740	18.0	0.02
Maternal schizophrenia	113	2.7	634	2.0	0.05	102	2.5	0.02
Maternal cannabis use disorder	57	1.4	134	0.4	0.10	56	1.4	0.00
Maternal alcohol use disorder	419	10.2	1669	5.3	0.18	389	9.5	0.02
Maternal substance use disorder	234	5.7	934	3.0	0.13	237	5.8	0.00
Maternal other psychiatric disorders	1150	27.9	6210	19.7	0.20	1102	26.8	0.03
First / second generation immigrant	653	15.9	5674	18.0	−0.06	671	16.3	−0.01
Employed	303	7.4	3982	12.6	−0.18	356	8.6	−0.05
Maternal education: none	1815	44.1	11 297	35.8	0.17	1859	45.2	−0.02
Maternal education: highschool	626	15.2	4437	14.0	0.03	619	15.0	0.00
Maternal education: vocational	28	0.7	315	1.0	−0.03	31	0.8	−0.01
Maternal education: university	256	6.2	1942	6.1	0.00	252	6.1	0.00
Maternal education: unknown	1391	33.8	13 607	43.1	−0.19	1355	32.9	0.02
Paternal education: none	1361	33.1	8506	26.9	0.13	1372	33.3	−0.01
Paternal education: highschool	1076	26.1	6729	21.3	0.11	1051	25.5	0.01
Paternal education: vocational	54	1.3	357	1.1	0.02	56	1.4	0.00
Paternal education: university	209	5.1	2224	7.0	−0.08	232	5.6	−0.02
Paternal education: unknown	1416	34.4	13 782	43.6	−0.19	1405	34.1	0.01
N children at home: 0	3554	86.3	23 916	75.7	0.27	3542	86.1	0.01
N children at home: 1	277	6.7	3245	10.3	−0.13	275	6.7	0.00
N children at home: 2	167	4.1	2557	8.1	−0.17	170	4.1	0.00
N children at home: 3	54	1.3	925	2.9	−0.11	59	1.4	−0.01
N children at home: 4+	15	0.4	418	1.3	−0.10	14	0.3	0.00
N children at home: unknown	49	1.2	537	1.7	−0.04	56	1.4	−0.02
Number people at home: 1	3266	79.3	20 903	66.2	0.30	3242	78.8	0.01
Number people at home: 2	430	10.4	4388	13.9	−0.11	438	10.6	−0.01
Number people at home: 3	195	4.7	2570	8.1	−0.14	202	4.9	−0.01
Number people at home: 4+	176	4.3	3200	10.1	−0.23	178	4.3	0.00
Number people at home: unknown	49	1.2	537	1.7	−0.04	56	1.4	−0.02

(*Continued*)

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Table 1. (*Continued.*)

	Cannabis-related schizophrenia (*n* = 4116)		Cannabis-unrelated schizophrenia Before matching (*n* = 31 598)			Cannabis-unrelated schizophrenia After matching (*n* = 4116)		
	Mean	S.D.	Mean	S.D.	*d*	Mean	S.D.	*d*
Widow	15	0.4	664	2.1	−0.16	17	0.4	−0.01
Divorced	318	7.7	3895	12.3	−0.15	365	8.9	−0.04
Married	183	4.4	3846	12.2	−0.28	205	5.0	−0.03
Unmarried	3551	86.3	22 656	71.7	0.36	3473	84.4	0.05
Unknown	49	1.2	537	1.7	−0.04	56	1.4	−0.02

Not being admitted to a psychiatric hospital but continuously using antipsychotics

Figure 4 displays the proportion of patients, on a daily basis, who had not been admitted to a psychiatric hospital but had continuously used antipsychotic medication for the preceding 91 days, for the same three groups as described before. This proportion started at around 10% for all three groups, and then increased gradually to around 35% for all groups, but somewhat slower in the cannabis-related schizophrenia group. The odds ratios for the cannabis-related group were very similar regardless of whether unadjusted or adjusted (propensity-score matched) analyses were performed, and for much of the time were statistically significantly lower than 1.

Being admitted to a psychiatric hospital but not using antipsychotics (online Supplementary Figure S9) shows the proportion of patients in the three groups who had been hospitalized at some

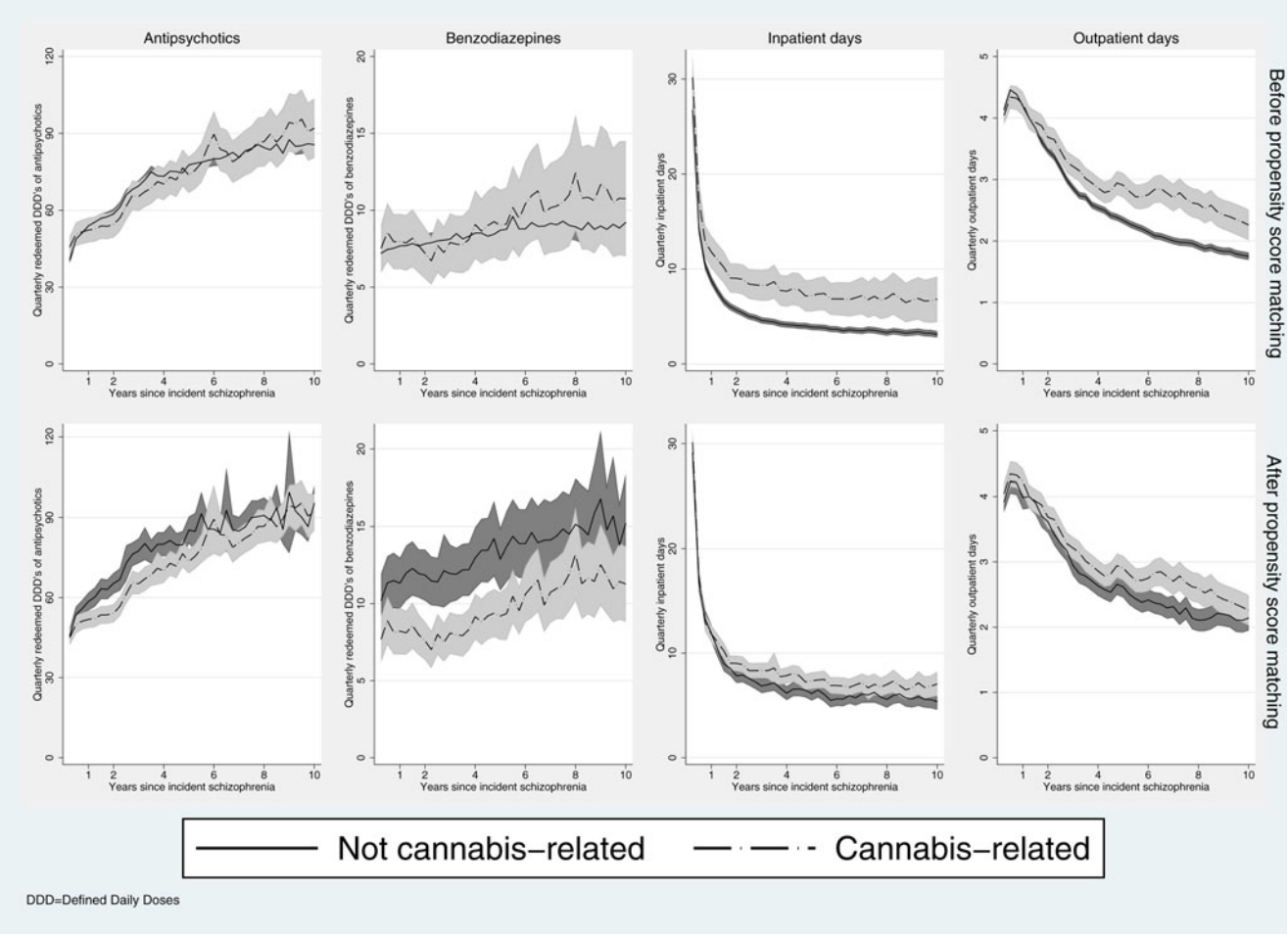

Figure 1. Incidence rates for medicine and service use for cannabis-related and cannabis-unrelated cases of schizophrenia.

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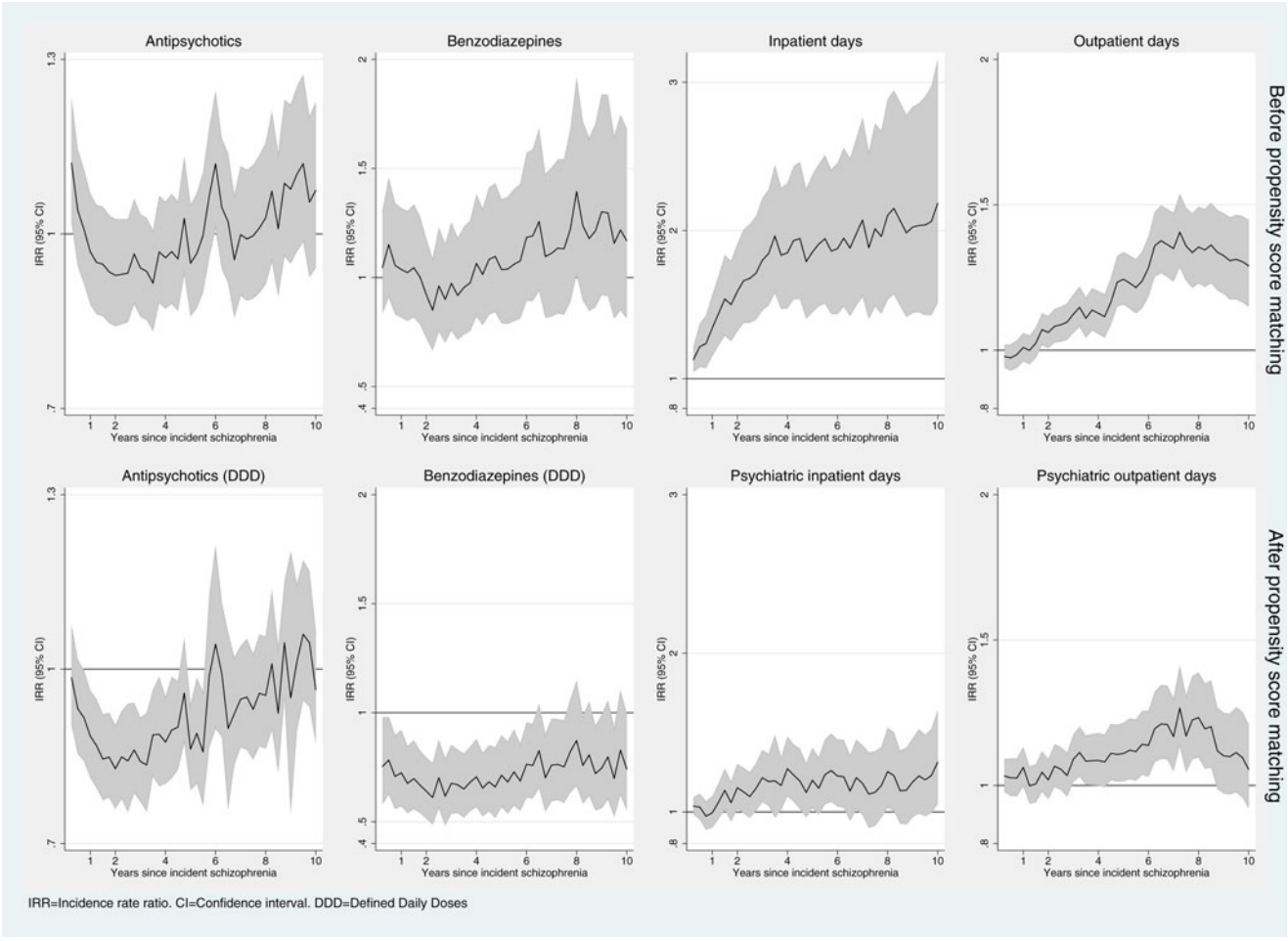

Figure 2. Incidence rate ratios for medicine and service use in cannabis-related schizophrenia cases compared with cannabis-unrelated cases of schizophrenia (reference group).

point in the preceding 91 days, and not used antipsychotics (by prescription) in the same period (except, perhaps, for medication provided at the hospital). This was consistently more common in the cannabis-related schizophrenia group than in the cannabis-unrelated schizophrenia group, although the differences were much reduced when adjusting using propensity-score matching.

Being admitted to a psychiatric hospital and continuously using antipsychotics

Online Supplementary Figure S10 shows the proportion of patients in the three groups who had been hospitalized at some point in the preceding 91 days and had continuously used antipsychotic medication in the same period. This was much more pronounced in the cannabis-related schizophrenia group than the cannabis-unrelated schizophrenia group, but this difference largely disappeared after propensity score matching.

Supplementary Figure S11 shows the proportion of patients who had been hospitalized in the past 91 days, but only among those patients who had been continuously using antipsychotics in the same period. While this was more common in the cannabis-related group of patients with schizophrenia, this difference was strongly attenuated in the propensity-score matched comparison handling confounding factors.

Sensitivity analyses

Results from sensitivity analyses in which schizophrenia was only considered potentially cannabis-related if at least 365 days had passed between the diagnoses of cannabis use disorder and schizophrenia are presented in online Supplementary Figures S12 (for incidence rates) and S13 (for incidence rate ratios), showing very similar results to the main analyses.

Discussion

In this nationwide, register-based study, we found that people with cannabis-related schizophrenia redeemed fewer prescriptions of both antipsychotic medication and benzodiazepines when relevant confounders were accounted for, compared with people with schizophrenia not preceded by cannabis use disorder. The cannabis-related group also had more psychiatric inpatient days, but a large proportion of this was explained by confounders. Indeed, for the first approximately five years after incident schizophrenia, there was a larger proportion of patients who had neither redeemed prescriptions for antipsychotic medication nor been admitted to a psychiatric hospital in the preceding three months, in the group of patients for whom the schizophrenia diagnosis appeared related to cannabis. The cannabis-related schizophrenia group consistently had more outpatient visits, although not by a large margin.

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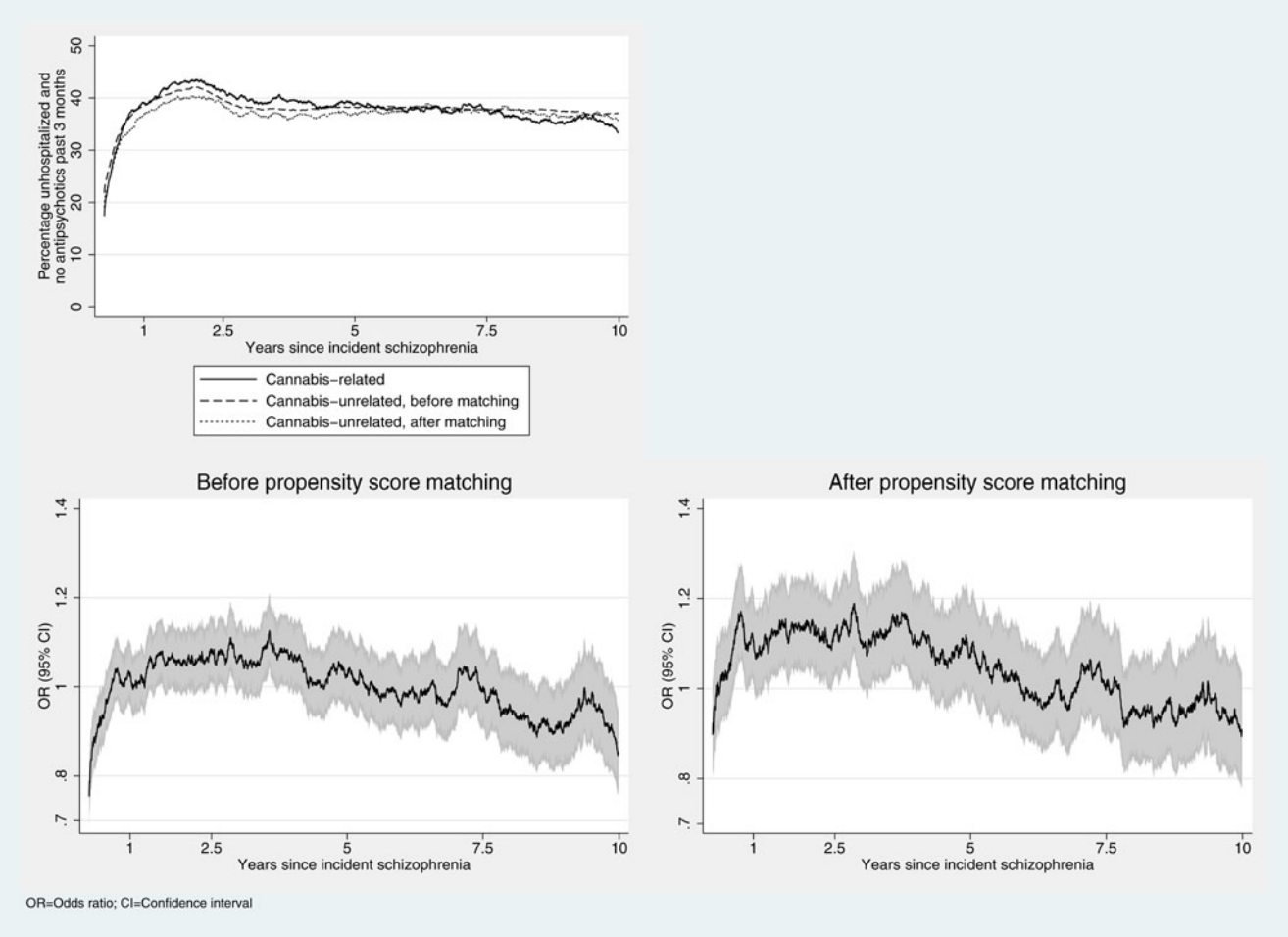

Figure 3. Proportion of patients who have neither used antipsychotic medication nor been admitted to a psychiatric hospital in the preceding three months.

The fact that many associations were altered when handling confounding through propensity score matching is not surprising when considering the often extreme differences in sociodemographic and other factors between the cannabis-related and cannabis-unrelated schizophrenia groups. In particular, we can conclude that cannabis-related schizophrenia occurs at a younger age, something which others have found to be an indicator of a potential causal relationship between cannabis and schizophrenia (Myles, Newall, Nielssen, & Large, 2012). Further, differences were observed related to alcohol and other substance use disorders, other psychiatric disorders, household size and number of children living at home, and marital status differed wildly between the two groups.

The initial lower use of antipsychotic medication in the cannabis-related group of patients with schizophrenia, compared with the propensity-score-matched controls, could be in line with the literature indicating reduced antipsychotic adherence among patients with comorbid schizophrenia and cannabis use (Foglia et al., 2017). We did not investigate concurrent use, for two reasons. First, this would lead to potential problems with directionality (does concurrent cannabis use decrease adherence or does decreased adherence increase the risk of cannabis use); and second, it is difficult to use treatment registers as indicators of ongoing use. Consequently, we cannot determine if the reduced use of antipsychotics in the cannabis-related schizophrenia group may just be caused by continued, concurrent use of cannabis. It does, however, highlight that it is possible early on to identify a large group of patients with schizophrenia who are at increased risk of not using antipsychotic medication. Furthermore, it appears that confounding factors could actually mask this decreased use of antipsychotic medication in the cannabis-related group of patients with schizophrenia. In light of the increasing perception of cannabis as being relatively harmless (Carliner, Brown, Sarvet, & Hasin, 2017), it is thus important to acknowledge that even apparent lack of harmful effects could be due to confounders masking the true association. One possibility is that patients with schizophrenia who have at least a history of cannabis use disorder are more likely to self-medicate with cannabis rather than to use antipsychotics (Gregg, Barrowclough, & Haddock, 2007; Mané et al., 2015). Conversely, such patients may lose contact with treatment facilities, whether by choice or by being rejected by treatment facilities until such time as their substance use disorder has been treated. Moreover, while the cannabis-related schizophrenia group appeared to use less benzodiazepines than the cannabis-unrelated schizophrenia group, this finding is only applicable to prescribed use of benzodiazepines. It is possible that this group instead uses benzodiazepines obtained illegally.

The cannabis-related group of patients with schizophrenia had much higher incidence rates of psychiatric inpatient days, but this

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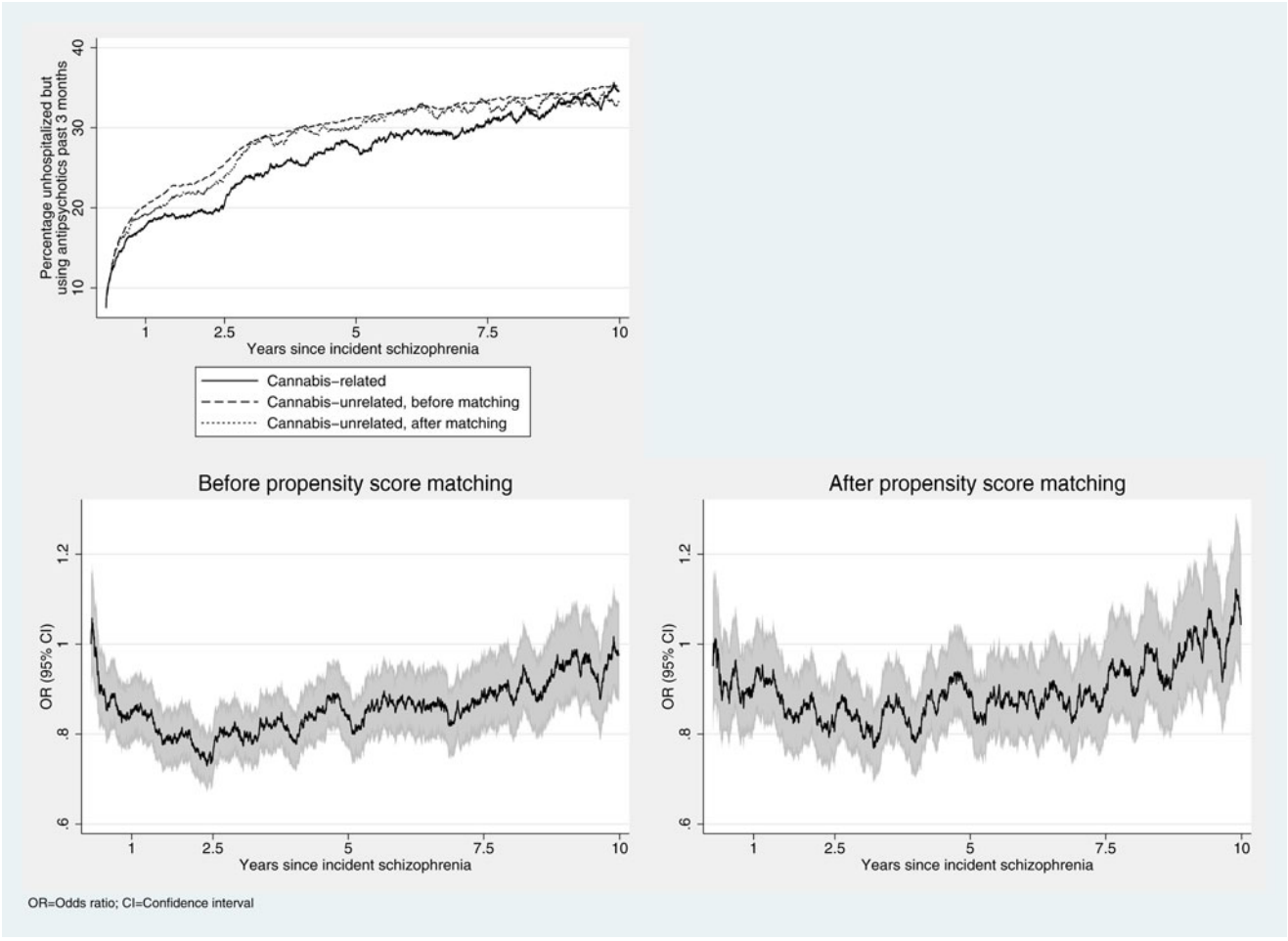

Figure 4. Proportion of patients who have not been admitted to a psychiatric hospital but had continuously used antipsychotic medication for the preceding three months.

was heavily attenuated when adjusting for relevant confounders. Indeed, there was a larger proportion of patients in the cannabis-related group than in the propensity-score-matched cannabis-unrelated group who had neither used antipsychotic medication nor been psychiatrically hospitalized, for most of the first approximately five years after the incident diagnosis of schizophrenia. The associations were rather weak but are nonetheless interesting. If the reduced use of antipsychotic medication was truly harmful, then one would expect a larger proportion to also be hospitalized in the cannabis-related group. Similarly, while unadjusted analyses revealed a much higher proportion of patients in the cannabis-related schizophrenia group being hospitalized in the absence of antipsychotic medication, most (albeit not all) of this excess risk disappeared when adjusting for relevant confounders in the propensity-score-matched analyses. However, the proportion of patients who did not become hospitalized and continuously used antipsychotic medication was lower in the cannabis-related schizophrenia groups and was not particularly influenced by confounding. Finally, while the proportion of patients being hospitalized in spite of continuous use of antipsychotics originally appeared much higher in the cannabis-related schizophrenia group, this difference largely disappeared when controlling for relevant confounders. Concurrently, we saw a moderate increase in the frequency of psychiatric outpatient visits in the cannabis-related schizophrenia group, possibly indicating a group with slightly more severe psychopathology, or a group receiving more outpatient attention either because treatment staff are aware of their cannabis use or possibly because of their reduced use of antipsychotics incurring more attention.

All things considered, our results indicate that the group of patients with schizophrenia which may be cannabis-related initially uses less antipsychotic medication and is hospitalized somewhat more than the group of patients with schizophrenia which does not appear to be cannabis-related. Further, the reduced use of benzodiazepines in the cannabis-related group could have several explanations. One possibility is that some patients with schizophrenia use cannabis for self-medication. We did not control for continued use of cannabis, but being originally diagnosed with cannabis use disorder, it is certainly plausible that this group of patients prefer cannabis to benzodiazepines for management of certain symptoms. Another possibility is that psychiatrists are reluctant to prescribe benzodiazepines to a group of patients with schizophrenia who are known to have a history of abuse or dependence on a different type of substance, namely cannabis.

Strengths and limitations

The register-based nature of this study is a strength in as much as it means that we could include the entire Danish population with

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schizophrenia, without the need for consent to participate, which is not required under Danish data privacy laws. Consequently, the risk of selection bias is very low, as is the risk of attrition bias due to the absence of attrition. We were able to perform propensity score matching on a range of potentially important confounders, which is a further strength. However, using registers also comes with a range of limitations. We do not have information on untreated illness, so while psychiatric admissions and outpatient visits are used as proxies for illness severity, there is a risk that some very ill individuals will not receive treatment. Similarly, we only have information on redeemed prescriptions, not on whether the study population actually took the medication they bought, or whether prescriptions were made but not redeemed. Many patients will also receive medication while admitted, but this information was not available in the registers, which caused us to count all people as using antipsychotics while they were admitted, in most analyses. There may be other cases in which patients receive antipsychotic medication from their outpatient clinics or in forensic psychiatry. These data were also not available to us, indicating that we likely underestimate the use of antipsychotic medication at least to a small degree. Finally, we are limited by the information available in the registers, meaning that potential confounders such as tobacco smoking and perceived stress were not available to us and could thus not be handled by the propensity score matching. This also means that only treated CUD was available as a proxy for severe cannabis use. Some individuals with CUD will thus not be registered as such, which would draw our results toward the null hypothesis. Conversely, the definition would not catch individuals with frequent use not meeting criteria for CUD, which in turn would also draw our results toward the null hypothesis. Finally, it is possible that those individuals with CUD who end up receiving treatment for such are more likely help seeking, which would lead to overestimates of the true associations investigated in this study.

Our findings indicate the importance of considering cannabis-related cases of schizophrenia as a potentially distinct disorder. It is unclear, however, if these differences are due to different biological types of schizophrenia being compared or if they rather indicate behavioral differences such as reduced adherence and treatment-seeking. Clinicians should be particularly aware that patients with schizophrenia preceded by cannabis use may have very different treatment needs than other patients with schizophrenia, and that these needs may be masked by a range of confounders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000758.

Data availability statement. We may not share data, but Danish register data may be made available to other researchers by the Danish authorities, provided they adhere to Danish data regulations.

Funding statement. No specific funding.

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