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The Effect of Cannabis Use and Cognitive Reserve on Age at Onset and Psychosis Outcomes in First-Episode Schizophrenia

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Objective: **Cannabis use is associated with a younger age at onset of psychosis, an indicator of poor prognosis, but better cognitive function, a positive prognostic indicator. We aimed to clarify the role of age at onset and cognition on outcomes in cannabis users with first-episode schizophrenia as well as the effect of cannabis dose and cessation of use.** ***Methods*****: Ninety-nine patients without alcohol or substance abuse other than cannabis were divided into lifetime users and never-users of cannabis and compared on measures of premorbid function, cognition, and clinical outcome.** ***Results:*** **Cannabis users demonstrated better cognition at psychosis onset, which was explained by higher premorbid IQ. They also showed better social function and neither measure changed over the subsequent 15 months. Cannabis users had an earlier age at onset of psychosis, and there was a strong linear relationship between age at first cannabis use and age at onset of both prodromal and psychotic symptoms. Cannabis use spontaneously declined over time with 3-quarters of users giving up altogether. Later age at first cannabis use predicted earlier cessation of use and this in turn was linked to fewer positive psychotic symptoms and days in hospital during the first 2 years.** ***Conclusions:*** **Cannabis use brings forward the onset of psychosis in people who otherwise have good prognostic features indicating that an early age at onset can be due to a toxic action of cannabis rather than an intrinsically more severe illness. Many patients abstain over time, but in those who persist, psychosis is more difficult to treat.**

Key words: cognition/prognosis/longitudinal

Introduction

Recent evidence suggests that cannabis use during adolescence increases the risk of developing psychosis.[1] The evidence as to whether psychosis outcomes are worse in schizophrenia patients who use cannabis is more inconsistent, with the strongest being for poor treatment adherence and increased frequency of relapse and rehospitalisation.[2,3]

Evaluating psychosis outcomes in cannabis users is complex because some of the reported characteristics of this group may in themselves influence prognosis over and above the continuing influence of cannabis use. For example, several studies show that cannabis users have an earlier age at onset of psychosis than never-users.[4] Earlier age at onset is associated with poorer outcomes in schizophrenia and is considered to reflect the severity of the underlying neuropathological process.[5] On the other hand, different studies find that people with schizophrenia and cannabis use tend to have better cognitive function than nonsubstance users.[6] This seems incompatible with the age at onset effect as better cognitive function is thought to reflect greater cognitive reserve and less illness severity.[7] This is supported by findings in schizophrenia that higher premorbid IQ and IQ at psychosis onset predict better functional outcomes in the early years of illness.[8]

Taken together, these 2 observations suggest that cannabis can trigger psychosis earlier in individuals who otherwise have good prognostic features and that the age at onset effect may be due to an action of cannabis rather than a reflection of an intrinsically more severe illness. We tested this hypothesis by examining age at onset of psychosis and cognition in schizophrenia patients with no substance abuse other than cannabis and tobacco and compared these with patients who had never used cannabis. We predicted that cannabis users would demonstrate evidence of higher cognitive reserve and have an earlier age at onset. We also predicted that if cannabis use brings forward the onset of psychosis, then there would be a temporal relationship between age at first use of cannabis and age of onset of not only frank psychosis but also prodromal symptoms. Finally, in order to understand how cannabis use influences clinical outcomes

other than age of onset, we examined the effect of frequency of use and cessation of use on symptoms, social function, and time spent in hospital over the 2 years following psychosis onset. If cannabis users have an intrinsically less severe form of the illness as hypothesized, abstinence should result in better outcomes than persistent use.

Methods

Subjects

Inpatients and outpatients with a first-psychotic episode were recruited as part of the West London study and were eligible if aged between 16 and 60 years and had received <12 weeks of antipsychotic medication. Diagnoses according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria were ascertained using the diagnostic module of the Diagnostic Interview for Psychosis-Diagnostic Module (DIP-DM).[9]

One hundred and twenty-one patients were eligible for inclusion in the current study on the basis that they had received a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder and had completed all neuropsychological and clinical assessments at presentation. We excluded 22 patients who reported abuse or dependency on alcohol according to the Alcohol Use Scale[10] or use of other substances on more than a monthly basis at any point in their life, which left a final sample of 99 patients. Tobacco use was not an exclusion criterion because of its high association with cannabis use.

We obtained Research Ethics Committee approval to conduct the study. Participants gave written informed consent and received an honorarium for their time. This is a different patient cohort to that previously reported.[11]

Substance Use Assessment

Information on substance use was obtained using the semistructured interview within the DIP-DM.

For each drug used, age at first use, amount and maximum frequency of use over the lifetime, the previous 12 months and previous 3 months were documented. The DIP-DM records frequency of use on a 5-point scale as "not used," "daily or almost daily," "1–2 days a week," "2–4 times a month," and "less than monthly." Cannabis users were defined as those reporting having used the drug at all during their lifetime. For the purpose of this study, we collapsed cannabis use into 3 categories: nonuser, high-frequency user (comprised of those patients who reported "daily or almost daily use"), and low-frequency user (comprised of patients reporting a pattern of cannabis use fitting 1 of the remaining 3 categories of use). This cutoff was chosen because daily or almost daily use suggests habitual use, whereas use at a frequency of twice a week or less suggests recreational use.

The Alcohol Use Scale[10] was used to elicit details of alcohol use during the past 6 months, classified as abstinent, use without impairment, abuse, dependence, or dependence with institutionalization.

Neuropsychological Assessments

"Premorbid IQ" was estimated using the Wechsler Test of Adult Reading (WTAR).[12] "Current IQ" was measured using a 4 subtest form of the Wechsler Adult Intelligence Scale III validated for use in schizophrenia.[13]

"Verbal learning" was measured using the Rey Auditory Verbal Learning Task[14] in which subjects are read a list of 15 nouns and asked to recall as many as possible. The total sum of words recalled over 5 trials was used. Other tests were from the Cambridge Automated Neuropsychological Test Battery[15] as follows: "Working memory manipulation": This self-ordered search task necessitates remembering the location of previously found "tokens" while searching for new tokens. Total errors, when a participant returns to the location where a token has already been found, were measured. "Working memory span": This test of forward spatial span is akin to the Corsi block test. The maximum number of consecutively presented spatial locations that were successfully recalled is measured. "Planning": This is analogous to the Tower of London task. Subjects plan and execute a sequence of moves of stimuli in a visual array to match a goal array, with 12 trials in total. The total number of perfect solutions was measured.

Clinical Assessments

Mental state was assessed with the Scales for the Assessment of Positive and Negative Symptoms.[16] Scores for the 3 symptom-derived syndromes of schizophrenia, negative, positive, and disorganization were then calculated. Affective symptoms were assessed with the Young Mania Rating Scale[17] and the Hamilton Rating Scale for Depression.[18] Social function was assessed using the Social Function Scale[19] which collects information from individuals on their abilities in various areas of daily living and occupational and social activity.

The Nottingham Onset Scale[20] was used to establish the timing of onset of prodrome and psychosis. Duration of prodrome was taken as the time between the 2 and the duration of untreated psychosis as the time between psychosis onset and treatment initiation. Ages at onset of prodromal and psychotic symptoms were also calculated using these data. The Premorbid Social Adjustment Scale assessed schizoid and schizotypal traits between ages 5–11 and 12–16 years via patients and career interview.[21]

We also used the Schedule for the Assessment of Insight[22] to establish patients' capacity to relabel psychotic experiences, awareness of need for treatment and illness; the

Table 1. Demographics, Social, and Clinic Functioning in Patients With First-Episode Psychosis Reporting Lifetime Cannabis Compared With Never-Users

Variable	Never-Users (NU) (n = 34)		Cannabis Users (HF) (n = 65)		Comparison		
	%		%		X^2		P
Sex (% male)	53		71		3.10		.078
Tobacco user (%)	18		72		27.83		<.001
Diagnosis (schizophrenia/schizophreniform/schizoaffective[a])	79/3/18		92/0/8		2.42		.120
Medication type (second generation/first generation/both[a]/naïve[a])	94/0/6/0		86/9/5/0		3.31		.069
	Mean	SD	Mean	SD	F	df	P
Age at testing (y)	28.29	10.87	23.42	6.06	8.26	1,98	.005
Age at prodrome onset (y)	26.35	10.62	21.22	6.04	9.43	1,98	.003
Age at psychosis onset (y)	27.12	10.68	21.97	5.80	9.71	1,98	.002
Years of education (SD)	12.79	2.01	12.46	1.91	0.66	1,98	.420
Mode of onset	3.42	1.30	3.31	1.18	0.20	1,97	.657
Premorbid social adjustment (5–11 y)	2.22	1.02	2.28	0.98	0.08	1,80	.789
Premorbid social adjustment (12–16 y)	2.49	1.04	2.26	0.89	0.96	1,80	.331
Social function	108.24	9.81	113.10	9.13	5.90	1,97	.017
Insight	9.00	4.38	7.70	4.61	1.54	1,83	.218
Compliance	5.53	1.38	4.78	1.66	5.02	1,98	.027
Negative syndrome	0.40	0.28	0.30	0.26	2.86	1,98	.094
Positive syndrome	0.72	0.22	0.72	0.22	0.01	1,98	.990
Disorganization syndrome	0.43	0.33	0.40	0.29	0.26	1,98	.613
Depression	14.32	8.81	13.02	8.87	0.49	1,98	.487
Mania	8.65	10.21	8.70	10.09	0.01	1,97	.979
	Mean	SD	Mean	SD	U		P
Duration of untreated psychosis (wk)	49.29	79.00	38.82	75.19	899		.125
Duration of prodrome (wk)	76.42	142.80	86.34	128.72	931		.284

Note: *df*, degrees of freedom.
[a]Group not included in analysis.

Compliance Rating Scale[23] to assess adherence to medication; and DIP-DM ratings of mode of illness onset in which patients rate their illness development on a scale 1–5 ranging from abrupt onset within hours or days to insidious onset over a period greater than 6 months. Information on a family history of schizophrenia was also elicited. Two years after initial assessment, a casenote review was performed to determine the number of days spent in hospital.

Analyses

Analyses were performed using SPSS 15. When comparing groups, ANOVA were used or ANCOVA when controlling for another variable. When measures were compared at different time points, repeated measure ANOVAs were used. Correlations were tested using Pearson's r. To determine predictors of continuous dependent variables, stepwise linear regressions were used, with goodness of fit evaluated using r^2adj, which is a modification of r^2 that adjusts for the number of explanatory terms in a model. For binary dependent variables, conditional logistic regression was used to determine predictors of dependent variables. Categorical data were compared using chi-squared and nonnormally distributed continuous data using Mann–Whitney.

Results

Cannabis Use, Demographics and Clinical Characteristics, and Social Function

Cannabis users had a younger age at prodrome and psychosis onset and were younger at the time of testing. Cannabis users had better social function at onset than never-users. There were no differences in symptoms, duration of untreated psychosis, mode of onset, and social adjustment up to the age of 16 years. Antipsychotic medication type did not differ but cannabis users were less adherent to medication at the time of the assessment (table 1).

Cannabis Use and Cognition

Cannabis users showed better cognitive task performance than never-users on all measures except working memory manipulation. When premorbid IQ was entered as

Table 2. Comparison of Cognitive Function at First-Episode in Lifetime Cannabis Users and Never-Users

	Never-Users		Cannabis Users		Comparison			Premorbid IQ as Covariate		
Cognitive Test Variable	Mean	SD	Mean	SD	*F*	*df*	*P*	*F*	*df*	*P*
WTAR premorbid IQ	88.91	11.73	95.54	12.79	6.33	1,98	.013	–		
WAIS-III current IQ	81.15	17.67	89.20	17.51	5.69	1,98	.033	0.29	1,96	.591
Verbal learning	33.12	12.82	38.40	10.81	4.69	1,98	.033	1.10	1,96	.298
Working memory span	4.94	1.37	5.53	1.43	3.91	1,96	.050	1.19	1,94	.278
Working memory manipulation[a]	40.19	14.14	34.07	18.79	2.15	1,86	.147	—		
Planning	5.52	3.39	7.21	2.29	8.66	1,95	.004	5.36	1,93	.023

Note: Comparisons are also shown after controlling for WTAR premorbid IQ. df, degrees of freedom; WAIS, Wechsler Adult Intelligence Scale; WTAR, Wechsler Test of Adult Reading.
[a]Lower scores are better.

a covariate, all between group differences in cognition became nonsignificant except planning. Premorbid IQ did not explain differences in social function (WTAR covariate effect: $F_{1,95} = 0.11$, $P = .745$, Social Function Scale corrected model: $F_{1,95} = 5.88$, $P = .017$) (table 2).

Age at First Cannabis Use and Age at Illness Onset

Age at psychosis onset did not significantly correlate with premorbid social adjustment (12–16 years: $r = -.06$, $P = .590$) or premorbid IQ ($r = .13$, $P = .250$) and was not different between those with and without a family history of psychosis ($F_{1,97} = 1.53$, $P = .880$). Males had an earlier onset (mean = 21.71, SD = 7.52) than females (mean = 27.34, SD = 8.11; $F_{1,97} = 11.77$, $P = .001$). Age at psychosis onset was not significantly correlated with severity of symptoms at onset (positive: $r = -.06$, $P = .581$; negative: $r = .01$, $P = .908$; disorganization: $r = .08$, $P = .452$).

Fifty-three patients were able to state with confidence their age when they first used cannabis. The average was 15 years, 281 days, and time between first cannabis use and psychosis onset was 6 years, 33 days. Age at first cannabis use correlated significantly with age at prodrome onset ($r = .47$, $P < .001$) and psychosis onset ($r = .56$, $P < .001$). Figure 1 shows the correlation between age at first cannabis use and age at onset of prodrome and psychosis.

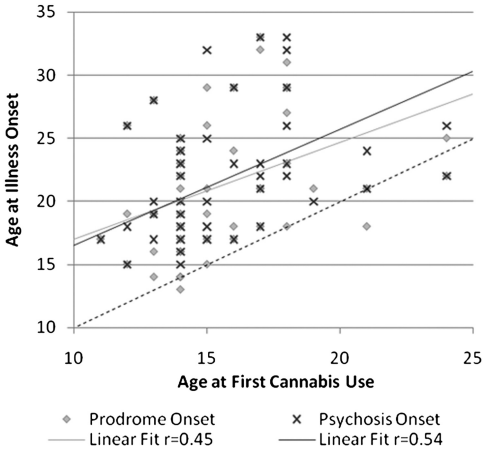

Fig. 1. Scatterplot of the relationship between self-reported age at first cannabis use and age at onset of prodrome and psychosis ($n = 53$). The dashed line represents the equivalent age on both axes. Cases below the dashed line are those with onset of cannabis use after onset of prodromal ($n = 3$) and psychotic symptoms ($n = 1$).

Age at first cannabis use was entered into a stepwise regression model along with sex as potential predictors of age at psychosis onset; both younger age at first cannabis use ($\beta = 0.92$, $P < .001$) and being male ($\beta = 4.40$, $P = .002$) entered as independent predictors of earlier psychosis onset (model $r^2 = .43$, $F_{2,50} = 18.85$, $P < .001$).

Effects of Frequency of Cannabis Use

Thirty-five patients admitted to low-frequency (twice a week or less) and 30 to high-frequency (daily or almost daily) cannabis use during their lifetime. These 2 groups did not differ on sex ($X^2 = 1.84$, $P = .174$), age at testing ($F_{1,63} = 0.02$, $P = .903$), age at onset of prodrome ($F_{1,64} = 0.22$, $P = .638$), or psychosis ($F_{1,64} = 0.01$, $P = 0.997$), years between first cannabis use and psychosis onset ($F_{1,51} = 0.15$, $P = .699$), premorbid social adjustment (age 5–11: $F_{1,57} = 0.59$, 0.447; age 12–16: $F_{1,57} = 0.28$. $P = .600$), mode of onset ($F_{1,64} = 0.34$, $P = .565$), or premorbid IQ ($F_{1,64} = 2.00$, $P = .162$). The low-frequency users had significantly higher current IQ ($F_{1,63} = 4.02$, $P = .049$) and showed trend level superiority on verbal learning ($F_{1,63} = 3.90$, $P = .053$) and working memory span ($F_{1,62} = 3.03$, $P = .087$). The groups did not differ on working memory manipulation ($F_{1,58} = 0.49$, $P = .486$) or planning ($F_{1,61} = 0.25$, $P = .619$). The relationship between age at first cannabis use and age at onset of psychosis was significant for both groups (low frequency: $r = .38$, $P = .045$; high frequency: $r = .65$, $P < .001$).

Fifteen-Month Outcome

Seventy-one patients (72%) were reassessed an average of 15 months and 10 days after their initial assessment. There was no significant difference in the follow-up rate of the groups (never-users 62%, cannabis users 77%, $X^2 = 2.53$, $P = .112$).

Symptoms and insight improved over time, with no group differences in the rate of improvement. Social

Table 3. Change Over Time in Cannabis Users and Never-Users, With Positive Scores Reflecting Improvement, and Repeated Measures ANOVA Comparing Presentation and Follow-up Measures in These Groups

	Cannabis Users		Never-Users		Effect of Time			Time by Group Interaction		
Measure	Mean Change	SD Change	Mean Change	SD Change	*F*	*df*	*P*	*F*	*df*	*P*
Negative syndrome	0.15	0.23	0.06	0.27	11.00	1,68	.001	1.65	1,68	.204
Positive syndrome	0.46	0.44	0.33	0.29	62.53	1,68	<.001	1.72	1,68	.194
Disorganization syndrome	0.33	0.29	0.23	0.34	50.07	1,68	<.001	1.78	1,68	.187
Depression	8.59	9.54	7.48	9.45	41.92	1,68	.001	0.20	1,68	.654
Mania	6.75	11.24	5.24	10.99	16.84	1,68	<.001	0.27	1,68	.606
Insight	2.73	6.06	1.06	4.93	5.43	1,57	.023	1.06	1,57	.307
Compliance	0.13	2.77	0.71	1.74	1.64	1,67	.205	0.81	1,67	.372
Social function	2.26	9.30	−0.22	9.51	0.70	1,68	.405	1.03	1,68	.314
Current IQ (WAIS-III)	1.73	10.05	−0.30	5.96	0.35	1,66	.555	0.71	1,66	.403
Verbal learning	−4.07	10.15	−1.22	10.85	3.29	1,58	.075	0.95	1,58	.333
Working memory span	−0.02	1.32	0.29	0.99	0.59	1,60	.445	0.80	1,60	.374
Working memory manipulation	3.95	18.09	5.63	16.85	3.74	1,56	.058	0.11	1,56	.735
Planning	3.09	0.47	2.87	0.64	1.01	1,62	.317	0.12	1,62	.735

Note: Abbreviations are explained in the first footnote to table 1.

function, compliance, and cognitive measures remained stable across time and group. The groups did not differ on the number of days spent in hospital during the index admission (never-users mean = 66, SD = 75; cannabis users mean = 55, SD = 73, $F_{1,65} = 0.26$, $P = .611$) or in total during the first 2 years of illness (never users mean = 94, SD = 99, cannabis users mean = 118, SD = 148, $F_{1,65} = 0.39$, $P = .534$) (table 3).

Predictors and Effects of Cannabis Use Cessation

There was attrition in the number reporting cannabis use during the year leading up to presentation: high frequency = 87%; low frequency = 71%; this had declined further by the 3 months prior to presentation: high frequency = 60%; low frequency = 51%. To identify factors contributing to discontinuing cannabis use early in the course of the illness, we performed a logistic regression on all lifetime cannabis users with current use at presentation as the binary dependent variable and potential predictors—sex, age at psychosis onset, age at first cannabis use, frequency of lifetime cannabis use, premorbid IQ, premorbid social adjustment age 11–16, in a forward conditional analysis. Age at first cannabis use was the only significant predictor of persistent use at presentation (Wald = 6.22, $P = .012$, OR = 1.43). The mean age at first cannabis use was 14.53 years (SD = 1.94) for persistent users and 17.39 years (SD = 4.19) for abstinent users. Premorbid IQ did not differ between persistent and abstinent cannabis users ($F_{1,64} = 0.04$, $P = .841$).

Of the subgroup assessed at follow-up, none of the never-user group had taken up cannabis use during this period. Of the low-frequency users, 23% reported persistent use (20% at low frequency, 3% at high frequency). Of the high-frequency users, 31% reported persistent use (5% at high frequency, 26% at low frequency). When only the past 3 months' use before follow-up was examined, the rate of continued use had dropped further to 19% of low-frequency users and 26% of high-frequency users.

We next examined whether lifetime frequency of use (low, reference category 0 or high) or abstinence during the 3 months prior to presentation (persistent, reference category 0 or abstinent) predicted clinical variables at presentation in the cannabis users using stepwise regression. The level of negative symptoms was increased by high-frequency use (r^2adj = .05, $\beta = .25$, $P = .045$) but not influenced by abstinence. By contrast, positive symptoms were fewer in abstinent users (r^2adj = .11, $\beta = -.35$, $P = .004$), as were disorganization symptoms (r^2adj = .05, $\beta = -.25$, $P = .043$). Affective symptoms, social function, insight, and compliance were not predicted by frequency of use or abstinence (all predictors $P > .05$).

In those cannabis users that were followed-up, we examined the same binary predictors for relationship with measures of symptoms and functioning at follow-up. None of the symptoms or clinical measures at 15-month follow-up were predicted by lifetime frequency of use or abstinence prior to presentation (all predictors $P > .05$). However, when we examined hospitalizations, the length of the index admission was shorter in those abstinent at presentation (r^2adj = .14, $\beta = -.40$, $P = .005$), as was the total number of days spend in hospital during the first 2 years (r^2adj = .20, $\beta = -.46$, $P = .001$). Figure 2 shows the difference between persistent and abstinent cannabis users on days in hospital during the first 2 years following presentation.

Discussion

Some studies have shown that cannabis use is associated with a younger age at onset of psychosis, which is an indicator of a more severe illness linked to poor prognosis.[5]

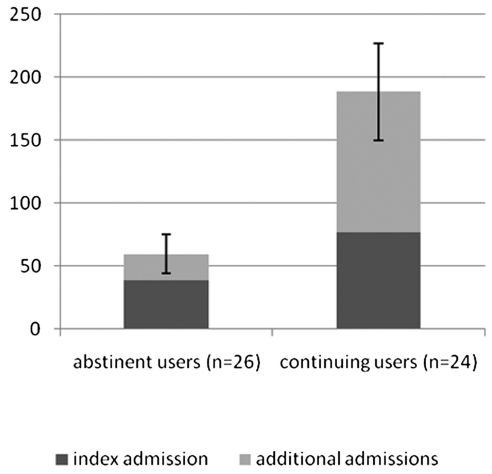

Fig. 2. Number of days spent in hospital during the first 2 years in cannabis using patients who were either continuing users at presentation or abstinent users at presentation and during the previous 3 months. SE bars are shown for the total number of days.

Others find that cannabis users tend to have better cognitive function than nonusers, which is a good prognostic indicator.[8] These findings suggest that in cannabis users the earlier age of onset may be related to a toxic effect of cannabis rather than an intrinsically more severe illness. The main aim of this study was to examine the relationship between age of onset, cognition, and clinical outcome in patients with schizophrenia with and without a history of cannabis use.

To clarify the role of cannabis use in psychosis, we excluded patients with other substance or alcohol misuse; 69% of the remaining patients reported cannabis use at some point in their life, and this was daily or almost daily in over one third.

At psychosis onset, cannabis users exhibited better cognitive function than never-users and there were no differential group changes in cognition over the following 15 months. Cannabis users had higher current IQ and better verbal learning, working memory span, and planning ability. The current ability of the cannabis users was moderated by superior premorbid IQ which, when covaried, reduced all group differences and rendered them nonsignificant for current IQ, verbal learning, and working memory span. This suggests that the group differences in cognition reflect higher intellectual functioning in the cannabis users prior to psychosis onset.

Some researchers suggest that better cognition in cannabis users is due to the drug having a neuroprotective effect on the developing brain prior to psychosis onset and base this on evidence from animal models that cannabis upregulates neurotrophins and enhances prefrontal neurotransmitter release.[24,25] Others argue that people who develop schizophrenia in the absence of cannabis use have different premorbid vulnerabilities, which are neurodevelopmental and reflected in poor cognition.[26,27] If the former hypothesis is true, high-frequency users should have better cognitive function than low-frequency users, whereas we found the reverse effect. Thus, our findings support the view that those who develop psychosis in the context of cannabis use have better cognitive function because they have fewer neurodevelopmental risk factors rather than there being an advantageous pharmacological action of the drug prior to psychosis onset. This conclusion is supported by the observation that the cannabis users had better social function at onset than never-users, independently of premorbid IQ and in the context of no differences in symptom profile or duration of untreated psychosis.[28]

Higher cognitive reserve is normally associated with a later onset of psychosis and is a positive moderator of the impact of psychosis on clinical outcomes.[7,8,29] The cannabis-users in our study had higher cognitive reserve than the never-users as evidenced by better premorbid IQ and better outcome with respect to social function over the first 15 months of illness. Yet, we also found that they had an earlier onset of psychotic symptoms, replicating findings of other studies[4] and an earlier onset of prodromal symptoms. These findings were similar in low- and high-frequency users suggesting that cannabis use, even at ''recreational'' levels, can counteract the normally protective effect of cognitive reserve on age at psychosis onset and precipitate an earlier onset than might be expected. Male sex was an additional independent risk factor for an earlier onset of psychosis, in keeping with other studies.[11,30,31] Given the high proportion of males reporting cannabis use in this study, men may be particularly at risk of an early onset even with relatively low levels of cannabis intake.

The link between cannabis use and an early onset of psychosis is strengthened by our finding of a linear relationship between the age at first cannabis use and age at onset of psychotic symptoms. Only one other study that we know of has reported such a relationship, and this was in mixed substance users.[31] Cannabis use that predates the onset of psychosis has been hypothesized to reflect either a response to emergent prodromal symptoms (ie, ''self medication'') or a factor which predisposes to psychosis development.[32] Importantly, in the current study, age at first cannabis use also predicted age at onset of prodromal symptoms and in only 3 of the 53 patients who could confidently date first cannabis use did this postdate the development of prodromal symptoms. Our findings therefore support the temporal priority of cannabis use in the development of psychotic symptoms. They also complement a study showing that the escalation of frequency of cannabis use up to daily intake shortens the time to onset of prodromal and psychotic symptoms.[4] Although we did not find a significant difference in the time to psychosis onset between low- and high-frequency users, the effect size for the relationship between age at first cannabis use, and onset of psychosis was larger for those with high frequency ($r = .65$) than low

frequency ($r = .38$) use suggesting that the role of cannabis in time to onset of symptoms may be more prominent in those patients with daily use.

Earlier first use of cannabis predicted continuing cannabis use at the time of psychosis onset, with persistent users having an average age of first use of 15 years. This mirrors general population studies, which show that early cannabis use increases the risk of later dependence.[33] In contrast, population studies report fairly high rates of persistent cannabis use,[34] whereas we found a substantial attrition of use in our patients. We questioned them about cannabis use in different phases: lifetime; 12 and 3 months prior to presentation and 12 and 15 months following presentation. The cumulative rates of attrition were respectively: 29%, 49%, 77%, and 81% for low-frequency and 13%, 40%, 69%, and 74% for high-frequency users. In addition, most of the high-frequency persistent users had reduced the amount they were consuming. Similar rates of attrition by the time of presentation have been seen in 2 other first-episode schizophrenia cohorts,[35,36] and longitudinal first-episode studies found subsequent attrition of cannabis use of 52%,[37] 42%,[35] and 24%.[38] Thus, cannabis use in psychosis patients appears to decline spontaneously during the year leading up to presentation and continues to decline following treatment initiation. In our study, the mean duration of untreated symptoms, including the prodrome, exceeded 1 year in cannabis users. Thus, early abstinence could have been related to the emergence of psychotic symptoms by either hindering access or because the drug had become aversive. In support of the latter, a qualitative study found that, compared with controls, patients were more sensitive to the negative effects of cannabis during the prodromal phase that included depression, less control over thoughts, and social problems.[39] Regarding later abstinence and frequency reduction, it is possible that this was related to antipsychotic medication causing a reduction of the reinforcing effects of cannabis, especially as our patients did not receive interventions specifically aimed at substance abuse.

Early abstinence was clearly beneficial for early outcome. The cannabis users who had given up by the time of first contact with services did not differ from the persistent cannabis users in premorbid IQ or social function but had fewer positive and disorganization symptoms, shorter index admissions, and spent fewer days in hospital during the first 2 years of illness. We did not observe similar differences in symptoms at the follow-up assessment, and it is possible that the benefits of abstinence from cannabis use are most evident in the early period following giving up, with long-term damage from cannabis use becoming evident later. Alternatively, this may have been because a number of those classified as persistent users at onset had become abstinent in the follow-up period. Other studies have either reported continuing psychotic symptoms[35,38] or higher rates of psychotic relapse in persistent cannabis users at follow-up.[2] Our findings are also in accordance with a recent meta-analysis which concluded that the strongest evidence regarding cannabis and outcome is with regard to poor treatment adherence and increased frequency of relapse and rehospitalisation[3] as our cannabis users were less medication adherent than never-users at first assessment.

In summary, our data suggest that cannabis use may bring forward the onset of psychosis in people who otherwise have good prognostic features, as indicated by premorbid cognition and social function. Thus, the earlier age at onset in cannabis users could be due to the toxic action of cannabis rather than an intrinsically more severe illness. Public health policies aimed at preventing cannabis use, if successful, might therefore delay the onset of psychosis in vulnerable young people and improve outcomes further. Although many patients abstain over time, cannabis use has an additional harmful effect in those who persist because it makes psychosis more difficult to treat. Persistent cannabis use after psychosis onset has been related to a reduction in dysphoria and enhancement of sociability despite patients being aware that it worsens their psychotic symptoms.[40] Thus, focusing on the treatment of mood disturbance in persistent cannabis users with prominent affective symptoms may be a strategy to improve already high rates of spontaneous cannabis cessation early in the illness.

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