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Demographic and socioenvironmental predictors of premorbid marijuana use among patients with first-episode psychosis

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ABSTRACT

Objective: We identified, in subjects with first-episode psychosis, demographic and socioenvironmental predictors of three variables pertaining to premorbid marijuana use: age at initiation of marijuana use, trajectories of marijuana use in the five years prior to onset of psychosis, and the cumulative “dose” of marijuana intake in that same premorbid period.

Methods: We enrolled 247 first-episode psychosis patients and collected data on lifetime marijuana/alcohol/tobacco use, age at onset of psychosis, diverse socioenvironmental variables, premorbid adjustment, past traumatic experiences, perceived neighborhood-level social disorder, and cannabis use experiences. Bivariate tests were used to examine associations between the three premorbid marijuana use variables and hypothesized predictors. Regression models determined which variables remained independently significantly associated.

Results: Age at initiation of cigarette smoking was linked to earlier initiation, faster escalation, and higher cumulative dose of premorbid marijuana use. During childhood, poorer academic performance was predictive of an earlier age at initiation of marijuana use, while poorer sociability was related to more rapid escalation to daily use and a higher cumulative dose. As expected, experiencing euphoric effects was positively correlated with trajectories and cumulative dose, but having negative experiences was unrelated. Traumatic childhood/adolescent experiences were correlated with rapid escalation and amount of marijuana used, but not with age at initiation of marijuana use.

Conclusion: These data expand the very limited literature on predictors of premorbid marijuana use in first-episode psychosis. Given its association with earlier age at onset of psychosis, and poorer outcomes among first-episode patients, prevention and treatment efforts should be further developed.

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1. Introduction

Marijuana is the most consumed illicit drug worldwide (UNODC, 2016). A recent survey on the prevalence of marijuana use in the United States (Hasin et al., 2015) found that past-year prevalence of marijuana use has doubled during the last decade, reaching 9.5% of the nationally representative sample. As widely demonstrated, the risk of psychotic disorders is nearly doubled by marijuana use, especially use in adolescence (Smit et al., 2004), with marijuana use also showing

an association with increased symptom severity (Zammit et al., 2008) and earlier onset of psychosis (Compton et al., 2009; Kelley et al., 2016). Saddichha et al. (2010) found a greater association between marijuana use and the development of psychosis than any other substance. Even though extensively discussed in the literature, the exact role of marijuana use in the genesis of psychotic disorders remains unclear. For example, a recent study found that marijuana use moderates the association between genetic risk for schizophrenia and cortical maturation (French et al., 2015). Nevertheless, despite a potential etiological role of marijuana use in the development of psychosis (Burns, 2013; Smit et al., 2004), no solid conclusions have been made about a causal relationship (Minozzi et al., 2010). Furthermore, a better understanding of how patterns of marijuana use are affected by individual-

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and social-level determinants is of importance, especially for the planning and development of effective clinical and public policy interventions.

The amount and duration of marijuana consumption can influence the onset of psychosis (Arseneault et al., 2002; Henquet et al., 2005). The clearest demonstration of this dose effect comes from Di Forti et al. (2009), who found that when examining use for the 5 years prior to assessment, marijuana users with first-episode psychosis were more likely to have taken marijuana for a longer duration and daily, compared with unaffected controls from the general population. Insufficiently detailed methods used to assess patterns of use are a common limitation of studies examining premorbid use of marijuana. Age at first consumption and trajectories of use are often not specifically addressed. Some studies have considered large-timeframe categories for age at initiation or have not measured specific frequency of use. Others simply compared groups based on presence or absence of use, or a diagnosis of abuse/dependence. In a previous paper (Kelley et al., 2016), we approached premorbid substance use focusing on three variables: (1) age at initiation of marijuana use, (2) trajectories of marijuana use in the five years prior to onset of psychosis, and (3) the cumulative 'dose' of marijuana intake in that premorbid period. We found that escalation of premorbid use in the five years prior to onset was highly predictive of an increased risk for onset; daily use approximately doubled the rate of onset, even after controlling for simultaneous alcohol/tobacco use. We were able to show that cumulative marijuana exposure was associated with an increased rate of onset of psychosis, independent of sex and family history, which is possibly the reason for age at initiation of marijuana use also being associated with age at onset of psychosis.

Marijuana use in early-course psychosis has been found to be strongly and independently associated with being younger, male, unemployed, and single (Barnes et al., 2008; Mueser et al., 1992; Patel et al., 2015; Tosato et al., 2013). Aspects of one's childhood environment are also associated with marijuana use; for example, greater and more persistent use has been found in subjects who grew up in an urban environment compared with those from rural surroundings (Cougnard et al., 2007; Kuepper et al., 2011). Furthermore, childhood trauma and intolerance to normal stress increase the risk of substance misuse (De Bellis, 2002). Both environmental and trauma-related factors influencing marijuana use have also been found to be independently associated with psychosis (Janssen et al., 2004; Krabbendam and van Os, 2005; Pelayo-Terán et al., 2012), with some authors suggesting a synergistic interaction in determining psychotic symptoms (Harley et al., 2010).

As an extension of our prior study (Kelley et al., 2016), the current analysis sought to identify demographic and socioenvironmental predictors of three variables pertaining to premorbid marijuana use. The variables we previously found to be linked to an earlier onset of psychosis are: (1) age at initiation of marijuana use, (2) trajectories of marijuana use in the five years prior to onset of psychosis, and (3) the cumulative 'dose' of marijuana intake in that same premorbid period. We hypothesized that *earlier initiation of marijuana use* would be predicted by male sex, poorer social and academic functioning in the 6–11-year age period, earlier initiation of cigarette smoking, greater childhood trauma exposure, and greater perceived neighborhood-level social disorder. We also hypothesized that both a *more rapid escalation pattern of marijuana use* and *cumulative dose of premorbid marijuana intake* would be predicted by these same variables, as well as a greater Cannabis Experiences Questionnaire (CEQ) pleasurable experiences subscale score and lower CEQ negative experiences subscale scores.

2. Methods

2.1. Setting and subjects

The sample was recruited from consecutively admitted patients with first-episode psychosis, which was operationalized as having

received <3 months of prior antipsychotic treatment and having never been hospitalized for psychosis earlier than three months prior to index admission, though the vast majority were completely naïve to any psychiatric treatment prior to hospital admission. Patients were drawn from three inpatient psychiatric units in Atlanta, Georgia and three in Washington, D.C. Among 713 subjects referred as potentially eligible or approached due to likely being eligible, a total of 247 (34.6%) were enrolled from August 2008 to June 2013. Inclusion and exclusion criteria are described in the earlier report (Kelley et al., 2016). The subjects referred but not enrolled did not differ from the study sample in terms of age, race, and ethnicity, but there was a higher percentage of females in the excluded group (37.6%, compared to 25.5% of those enrolled).

Diagnoses (based on the *Structured Clinical Interview for DSM-IV Axis I Disorders*; (SCID); First et al., 1996) included: schizophrenia, paranoid type (97, 39%); psychotic disorder, not otherwise specified (38, 15%); schizophrenia, undifferentiated type (33, 13%); schizophreniform disorder (29, 12%); schizoaffective disorder, depressive type (26, 11%); schizophrenia, disorganized type (11, 5%); schizoaffective disorder, bipolar type (5, 2%); delusional disorder (4, 2%); brief psychotic disorder (2, 1%); and schizophrenia, catatonic type (2, 1%). The mean age of the sample was 23.9±4.8 years, 184 patients were male (74.5%), and 213 (86.2%) were African American. Other sociodemographic characteristics of the sample are given in Table 1. We found a mean age at onset of psychotic symptoms of 21.7±5.0 years. In order to perform the bivariate analyses and build subsequent models, we selected only participants who had used cannabis at least once (214, 86.6%). The most common mode of consumption was smoking joints, not mixed with tobacco.

2.2. Measures and rating scales

2.2.1. Lifetime Substance Use Recall (LSUR)

Information on substance use was obtained using the Lifetime Substance Use Recall (LSUR; Ramsay et al., 2011), an instrument designed specifically for the parent study (Kelley et al., 2016). It has a timeline that is completed collaboratively with the patient, to inform and guide data collection. It indicates the beginning and end of life milestones and activities, and trends in tobacco, alcohol, and drug use. The LSUR interview guide was developed to facilitate collection of calendar-year-specific estimates of tobacco, alcohol, and drug use, beginning with the year of first use and repeating for each year until the present. During Step 1, information is collected on first use, first weekly use, and first daily use of tobacco, alcohol, marijuana, and any other drug that had ever been used. In Step 2, the average number of days of use per month is collected and recorded on the LSUR Scoring Sheet, for each year from the year of first use to present. The validity of the LSUR has been demonstrated, finding medium-to-large effect size (r , ρ , or $d > |0.50|$) associations between key cannabis-related variables from the

Table 1
Sociodemographic characteristics of the sample (N=247).

	Mean	SD
Age (years)	23.9	4.8
Years of education	11.9	2.2
Age at onset of psychosis (n=224)	21.7	5.0
N		%
Sex		
Male	184	74.5
Female	63	25.5
Race		
African American	213	86.2
Caucasian	19	7.7
Other	15	6.1
Single and never married	213	86.2
Living with parents/relatives	162	65.6
Unemployed in the month prior to hospitalization	169	68.4
Ever incarcerated (n=236)	138	55.9

LSUR (e.g., age at onset of daily cannabis use, lifetime cumulative cannabis “dose,” cannabis-related problem behaviors, past 12-week cannabis dose) and variables derived from the *Retrospective Use of Alcohol and Other Substances* (RETROSUB; Windle, 2005), the *Brief Drug Abuse Screening Test* (Brief DAST, Skinner, 1982), and the *SCID* (First et al., 1996).

2.2.2. Premorbid Adjustment Scale (PAS)

The Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) evaluates functioning prior to the initial onset of prodromal or psychotic symptoms. The instrument has been used widely in schizophrenia research (Cahn et al., 2015; Monte et al., 2008). Using Cronbach’s alpha, the estimated reliability for the scale and subscales is between 0.81 and 0.93. It assesses four age periods: childhood (6–11years), early adolescence (12–15years), late adolescence (16–18years), and adulthood (≥ 19 years). Functioning in each of these age periods is rated from 0 (normal adjustment) to 6 (severe impairment) and is evaluated in five major psychosocial domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual functioning. Social-sexual functioning is not included as a psychosocial domain during the childhood period, while scholastic performance and adaptation to school are not measured for the adulthood period. Information on premorbid adjustment was gathered by a semi-structured interview with the patient after a thorough chart review. In this analysis, we focused on social adjustment and academic adjustment before adolescence; i.e., during the childhood period (ages 6–11).

2.2.3. Trauma Experiences Checklist (TEC)

The Trauma Experiences Checklist (TEC; Cristofaro et al., 2013) is a 41-item questionnaire in which participants are asked to report the frequency (0, 1, 2, 3, or >3) of a broad range of traumatic and stressful events experienced across different contexts (e.g., family, neighborhood, school) before the age of 18years. Item 41 (“Have you ever had a parent who did drugs?”) is the only “yes/no” item. Examples of trauma and stressful events include personal injury (e.g., item 31: “Have you ever had a knife pulled on you and you were physically wounded?”); extreme environmental stress (e.g., item 1: “Have you ever experienced a tornado, earthquake, flood, or hurricane?”); interpersonal violence (e.g., item 28: “Have you ever been hurt by a family member?”); and other forms of relational trauma (e.g., item 7: “Have you ever had a parent in jail?” and item 13: “Have you ever had a close friend commit suicide?”). The scale has demonstrated acceptable internal consistency reliability and concurrent validity (Cristofaro et al., 2013). We considered the total TEC score in this analysis.

2.2.4. Neighborhood Disorder Scale (NDS)

The Neighborhood Disorder Scale (NDS) is a 15-item measure of perceived neighborhood disorder constructed by Ross and Mirowsky (2001). According to the scale’s developers, perceived neighborhood disorder refers to conditions and activities—both major or minor, and criminal and non-criminal—that residents perceive to be signs of breakdown of social order. Items such as “Vandalism is common in my neighborhood” and “My neighborhood is safe” cover both physical and social disorder, respectively. Items are rated on a 4-point Likert scale (1 = strongly disagree to 4 = strongly agree) with higher scores (after reverse scoring where needed) indicating a higher level of neighborhood disorder. The Cronbach’s alpha internal consistency reliability coefficient was 0.92 in the current sample. We computed a total NDS score as the mean of the item scores.

2.2.5. Cannabis Experiences Questionnaire (CEQ)

The Cannabis Experiences Questionnaire (CEQ; Barkus et al., 2006) is a 56-item self-report scale measuring subjective experiences related to marijuana use. Participants indicate how frequently they have had various experiences on a 5-point scale (rarely or never to almost always or always). The CEQ was originally divided into three subscales. The

Pleasurable Experiences and Psychosis-Like Experiences subscales examine immediate reactions to marijuana, while the After-Effects subscale pertains to responses once the initial marijuana intoxication has lessened. We used factors derived from a previously conducted exploratory factor analysis (Birnbaum et al., 2017) of all 56 items of the CEQ in the current sample of patients with first-episode psychosis because confirmatory factor analysis did not support the use of the originally suggested subscales (Birnbaum et al., 2017). Our four factors were: *Distortions of Reality and Self-Perception*, 18 items ($\alpha=0.89$); *Euphoria Effects*, 16 items ($\alpha=0.89$); *Slowing and Amotivational Effects*, 7 items ($\alpha=0.81$); and *Anxiety and Paranoia Effects*, 6 items ($\alpha=0.79$) (Birnbaum et al., 2017).

2.3. Statistical analyses

Basic descriptive statistics were examined. Bivariate tests (Student’s *t*-test and Pearson correlations) were used to test associations between age at initiation of marijuana use, trajectories of marijuana use in the five years prior to onset of psychosis, the cumulative dose of marijuana intake in the premorbid period, and the hypothesized predictors. Those variables significantly associated with the premorbid cannabis use variables in bivariate tests were used to build regression models (multiple linear regression models for age at initiation of marijuana use and cumulative dose of marijuana intake; an ordinal regression model for trajectories of marijuana use) to determine which variables remained independently significantly associated.

3. Results

3.1. Age at initiation of marijuana use

Male sex (mean difference, 0.42 ± 0.59 , $t=0.71$, $p=0.478$), PAS childhood social subscale ($r=-0.13$, $p=0.102$), and NDS ($r=-0.13$, $p=0.106$) were not associated with an earlier age at initiation of marijuana use. A poorer (higher) PAS childhood academic subscale score was significantly correlated ($r=-0.20$, $p=0.008$) with an earlier initiation of marijuana use. Age at first cigarette use was highly correlated ($r=0.52$, $p<0.001$) with age at initiation of marijuana use. The TEC total score was also modestly ($r=-0.15$, $p=0.054$) associated with age at first marijuana use.

Using the statistically significant variables from the bivariate tests (childhood PAS academic score, age at fist cigarette use, and TEC total score), a multiple linear regression model was built. When age at first cigarette use was entered into the model, the other variables became non-significant. However, because age at first cigarette use could be deemed too collinear with the dependent variable, we repeated the analysis without that variable. In that model, only childhood PAS academic score remained a significant predictor of age at initiation of marijuana use (standardized $\beta=-0.22$, $p=0.006$), indicating that poorer childhood academic functioning was associated with an earlier initiation of marijuana use.

3.2. Marijuana use trajectories

We took into consideration four different marijuana use trajectories in the five years before the onset of psychosis (see Kelley et al., 2016): (a) increase from none to occasionally, (b) increase from weekly to daily, (c) increase from none to daily, and (d) constant, daily use. No significant associations were found between trajectories and sex ($\chi^2=1.43$, $df=3$, $p=0.698$), childhood PAS academic functioning ($r=0.14$, $p=0.079$), NDS total score ($r=0.06$, $p=0.505$), the CEQ slowing and amotivational effects subscale ($r=0.12$, $p=0.165$), or the CEQ anxiety and paranoia effects subscale ($r=0.08$, $p=0.361$). Statistically significant associations were found with: childhood PAS social functioning ($r=-0.18$, $p=0.028$, indicating that better social functioning was associated with more rapid escalation in use), age at first cigarette use ($r=-0.20$,

$p=0.024$); TEC total score ($r=0.248, p=0.003$), the CEQ euphoria effects subscale ($r=0.19, p=0.022$), and the CEQ distortions of reality and self-perception subscale ($r=0.20, p=0.017$).

An ordinal regression model was built including all significant variables (as well as sex) from the bivariate tests; however, when including all variables, none were independently significant (data not shown). We then examined the set of predictors aside from the effects of marijuana (CEQ euphoria effects and CEQ distortions of reality and self-perception effects). When these variables were removed, childhood PAS social score, age at first cigarette use, and TEC total score were independently significant predictors of escalating marijuana use trajectories (Table 2).

3.3. Cumulative dose of premorbid marijuana intake in the five years before onset of psychosis

Cumulative dose was log-transformed to reduce the effect of outliers. No associations were observed between cumulative dose and PAS childhood academic functioning ($r=0.12, p=0.105$), NDS total score ($r=0.09, p=0.209$), the CEQ distortions of reality and self-perception effects subscale ($r=0.12, p=0.117$), the CEQ slowing and amotivational effects subscale ($r=0.09, p=0.227$), and the CEQ anxiety and paranoia effects subscale ($r=0.06, p=0.442$). Statistically significant associations were found for male sex (males had a higher ln (dose), difference= $1.96\pm 0.39, t=-4.99, p<0.0005$), PAS childhood social functioning ($r=-0.16, p=0.026$, meaning that better social functioning was associated with greater cumulative dose), age at first cigarette use ($r=-0.28, p<0.001$), TEC total score ($r=0.33, p<0.001$), and the CEQ euphoria effects subscale ($r=0.39, p<0.001$).

A multiple linear regression model was built entering all variables that were statistically significant in bivariate tests. In this model, TEC became nonsignificant ($p=0.215$), but all other predictors remained associated at $p<0.10$ (Table 3). Then, we examined the same set of variables but removed the variable pertaining to effects of marijuana (CEQ euphoria effects subscale). This model revealed that all four predictors (sex, childhood PAS social score, age at first cigarette use, and TEC total score) were significant predictors of cumulative dose at $p<0.05$ (Table 4).

4. Discussion

Several interesting findings emerged from this analysis of the effects of premorbid social and academic functioning, subjective marijuana experiences, adverse life events, and other variables on patterns of marijuana use (age at first use, trajectories of use, and cumulative premorbid dose) in a sample of patients with first-episode psychosis. First, age at initiation of cigarette smoking affects all three aspects of marijuana use, leading to an earlier initiation, faster escalation, and higher cumulative dose. Second, during childhood (ages 6–11), poorer academic functioning was predictive of an earlier age at initial marijuana use, while better social functioning was related to more rapid escalation to daily use and a higher cumulative dose. Third, while we expected that experiencing euphoric effects would be positively correlated with trajectories and dose, we believed that negative experiences would have affected the pattern of use as well, when in fact they did not. Fourth, traumatic experiences in childhood and adolescence are correlated

Table 3
Multiple linear regression of cumulative dose (ln), including subjective effects of marijuana use.

	β	SE(β)	t	p
Sex	0.78	0.41	1.92	0.058
Childhood PAS social score	-0.26	0.13	-1.95	0.053
Age at first cigarette use	-0.16	0.04	-3.68	<0.0005
TEC total score	0.47	0.38	0.10	0.215
CEQ euphoria effects subscale score	0.51	0.02	2.83	0.005

with a more rapid escalation and a greater cumulative amount of marijuana used, but not with age at initiation of marijuana use.

Several studies have reported the association between tobacco use and marijuana use, not only in the general population, but also in subjects with schizophrenia (De Leon and Diaz, 2005). Gage et al. (2014) found that, in subjects with psychotic experiences at the age of 18, marijuana use was associated with age at initiation of tobacco use younger than 16 years, as well as daily tobacco consumption. In first-episode psychosis, eight out of 10 patients using tobacco met criteria for cannabis use disorder (Wade et al., 2005). These findings, aligned with ours, highlight the importance of prevention of early tobacco use, not as a primary risk factor for psychosis, but as a possible gateway to marijuana and other drug use. Further studies are necessary to better understand the relationship between tobacco use and marijuana use, in light of the gateway drug hypothesis, the common route of administration (smoking behavior) model, and the shared liability model, in order to decipher the influence that one drug has on the other in terms of initiation and continuation of use in this very vulnerable population (Agrawal and Lynskey, 2009; Mayet et al., 2016).

While below-average school performance has previously been shown to be associated with the development of a cannabis use disorder (Hayatbakhsh et al., 2008), our data suggest that poor academic performance during childhood is predictive of an earlier age at marijuana use initiation. On the other hand, higher sociability during childhood is associated with faster escalation to daily use and a higher total cumulative dose, which is in line with the hypothesis suggested by Yücel and colleagues (2010)—patients who use cannabis must have comparatively good social skills in order to be able to acquire drugs and sustain a drug habit. Academic struggles combined with social competence during childhood may represent additive risk factors associated with an earlier and more severe trajectory of use.

While euphoric effects were, not surprisingly, positively correlated with marijuana trajectories and cumulative dose, predominantly negative experiences had no clear impact on patterns of use. This supports the hypothesis of an intrinsic sensitivity to marijuana that could find an explanation in an underlying genetic vulnerability (Meyers and Dick, 2010) that may or may not be influenced by unpleasant subjective responses during and after marijuana intoxication. Bianconi et al. (2016) found that both “bad” and “enjoyable” experiences were more commonly reported by first-episode psychosis patients than controls, suggesting a higher sensitivity to cannabis effects. Our findings could represent important information when considering motivational interviewing techniques designed to increase one's motivation for change. Simply identifying the unpleasant experiences associated with marijuana use may not be sufficient to help facilitate harm reduction or abstinence.

Table 2
Ordinal logistic regression of marijuana use trajectories.

	β	SE(β)	χ^2	p
Sex	-0.64	0.38	2.89	0.089
Childhood PAS social score	-0.28	0.12	5.29	0.021
Age at first cigarette use	-0.09	0.04	4.64	0.031
TEC total score	0.91	0.35	6.62	0.010

Table 4
Multiple linear regression of cumulative dose (ln), excluding subjective effects of marijuana use.

	β	SE(β)	t	p
Sex	1.09	0.41	2.69	0.008
Childhood PAS social score	-0.29	0.13	-2.23	0.027
Age at first cigarette use	-0.18	0.04	-4.01	<0.0005
TEC total score	1.11	0.38	2.95	0.004

In our sample, individuals who reported a greater number of traumatic experiences used greater amounts of marijuana and had more concerning trajectories of escalating use. It is conceivable that use of marijuana is meant as self-medication (Khantzian, 2003) to alleviate post-traumatic negative affects and cognitions. Previous studies have demonstrated that adolescents exposed to traumatic events are more likely to use substances than those who have not been (Giaconia et al., 2000) and that marijuana use may be aimed at reducing post-traumatic symptoms (Bonn-Miller et al., 2007; Bujarski et al., 2012).

Several methodological limitations of this analysis should be noted. First, our instruments were self-report questionnaires that can be affected by the patients' ability to recall past life events and experiences. Second, in focusing our analysis on premorbid social and academic functioning, traumatic life events, and marijuana-related experiences, we did not take into consideration biological and genetic factors that may be relevant to marijuana use patterns among patients with first-episode psychosis. Third, our sample was predominantly African American; as such, we could not examine the potential effects of race and ethnicity, and our results may not be generalizable to the broader population of first-episode psychosis patients in terms of racial and ethnic composition. Nonetheless, our results are likely to have very good internal validity within this population and are of value given the lack of research on this topic among socially disadvantaged African American patients. Similarly, given that nearly all patients were low-income and socially disadvantaged (e.g., from fragmented homes, with low occupational attainment, and often lacking health insurance), we could not consider socioeconomic status as a variable and thus could not adjust for socioeconomic status in analyses that included such variables as premorbid social and academic performance. Fourth, although smoking joints (not mixed with tobacco) was the most common mode of marijuana use, the finding of a strong association with age at initiating tobacco use remains difficult to interpret. Had most participants who used cannabis done it in the same joint with tobacco (or even at the same time as smoking cigarettes), the association of tobacco use with the escalation in frequency and dose of cannabis use over time could be confounded by the development of nicotine dependence or the evolution of smoking-related behavior and lifestyle.

An earlier onset of psychosis significantly impacts patients' prognosis and outcomes. Evidence for the effects of premorbid marijuana use on age at onset of psychosis are widely proven (Compton et al., 2009; Di Forti et al., 2013; Large et al., 2011; Kelley et al., 2016). Furthermore, Di Forti and colleagues (2014) found that daily cannabis use, and the use of high-potency cannabis, are independently associated with a significantly higher hazard of contact with services for psychosis, and that younger age at first cannabis use is associated with younger age at onset of psychosis only in those who had used cannabis daily. This is in line with the findings from our prior study in this same sample, which showed an important effect of premorbid escalation and daily use of cannabis on the onset of psychosis (Kelley et al., 2016). Preventing or limiting exposure to marijuana in predisposed individuals would be a key step toward prevention. This work, expanding the extant literature, highlights how cigarette smoking represents a potential opening to marijuana consumption and also how life events and social/academic functioning affect this behavior. Such research could move the field toward prevention or reduction of premorbid marijuana use, thereby delaying onset of psychosis and improving long-term course.

Conflicts of interest

The authors know of no conflicts of interest pertaining to this research.

Contributors

All authors contributed to the conceptualization and writing of this article, and all approved the final version for publication.

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References

- Agrawal, A., Lynskey, M.T., 2009. Tobacco and cannabis co-occurrence: does route of administration matter? *Drug Alcohol Depend.* 99 (1):240–247. <https://doi.org/10.1016/j.drugalcdep.2008.08.007>.
- Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *Br. Med. J.* 325 (7374):1212–1213. <https://doi.org/10.1136/bmj.325.7374.1212>.
- Barkus, E.J., Stirling, J., Hopkins, R.S., Lewis, S., 2006. Cannabis-induced psychosis-like experiences are associated with high schizotypy. *Psychopathology* 39 (4):175–178. <https://doi.org/10.1159/000092678>.
- Barnes, T.R.E., Leeson, V.C., Mutsatsa, S.H., Watt, H.C., Hutton, S.B., Joyce, E.M., 2008. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br. J. Psychiatry* 193 (3):203–209. <https://doi.org/10.1192/bjp.bp.108.049718>.
- Bianconi, F., Bonomo, M., Marconi, A., Koliakou, A., Stilo, S.A., Iyegbe, C., Gurillo Muñoz, P., Homayoun, S., Mondelli, V., Luzzi, S., Dazzan, P., Prata, D., La Cascia, C., O'Connor, J., David, A., Morgan, C., Murray, R.M., Lynskey, M., Di Forti, M., 2016. Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychol. Med.* 46 (5):995–1003. <https://doi.org/10.1017/S0033291715002494>.
- Birnbaum, M.L., Cleary, S.D., Ramsay Wan, C., Pauselli, L., Compton, M.T., 2017. Factor structure of the Cannabis Experiences Questionnaire in a first-episode psychosis sample. *Early Interv. Psychiatry* <https://doi.org/10.1111/eip.12509>.
- Bonn-Miller, M.O., Vujanovic, A.A., Feldner, M.T., Bernstein, A., Zvolensky, M.J., 2007. Post-traumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *J. Trauma. Stress.* 20 (4):577–586. <https://doi.org/10.1002/jts.20243>.
- Bujarski, S.J., Feldner, M.T., Lewis, S.F., Babson, K.A., Trainor, C.D., Leen-Feldner, E., Badour, C.L., Bonn-Miller, M.O., 2012. Marijuana use among traumatic event-exposed adolescents: posttraumatic stress symptom frequency predicts coping motivations for use. *Addict. Behav.* 37 (1):53–59. <https://doi.org/10.1016/j.addbeh.2011.08.009>.
- Burns, J.K., 2013. Pathways from cannabis to psychosis: a review of the evidence. *Front. Psychiatry* 4:128. <https://doi.org/10.3389/fpsy.2013.00128>.
- Cahn, W., Bruggeman, R., De Haan, L., Kahn, R., Myin-Germeys, I., Van Os, J., 2015. Long-term outcome in schizophrenia: a six-year follow-up in over 1000 patients. *Eur. Psychiatry* 30, 238.
- Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr. Bull.* 8 (3), 470.
- Compton, M.T., Kelley, M.E., Ramsay, C.E., Pringle, M., Goulding, S.M., Esterberg, M.L., Stewart, T., Walker, E.F., 2009. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *Am. J. Psychiatry* 166 (11):1251–1257. <https://doi.org/10.1176/appi.ajp.2009.09030311>.
- Cougnard, A., Marcellis, M., Myin-Germeys, I., De Graaf, R., Vollebregt, W., Krabbendam, L., Lieb, R., Wittchen, H.U., Henquet, C., Spauwen, J., van Os, J., 2007. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness–persistence model. *Psychol. Med.* 37 (04): 513–527. <https://doi.org/10.1017/S0033291706009731>.
- Cristofaro, S.L., Cleary, S.D., Ramsay Wan, C., Broussard, B., Chapman, C., Haggard, P.J., Jananeh, S., Myers, N.L., Compton, M.T., 2013. Measuring trauma and stressful events in childhood and adolescence among patients with first-episode psychosis: initial factor structure, reliability, and validity of the Trauma Experiences Checklist. *Psychiatry Res.* 210 (2):618–625. <https://doi.org/10.1016/j.psychres.2013.06.015>.
- De Bellis, M.D., 2002. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* 27 (1):155–170. [https://doi.org/10.1016/S0306-4530\(01\)00042-7](https://doi.org/10.1016/S0306-4530(01)00042-7).
- De Leon, J., Diaz, F.J., 2005. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr. Res.* 76 (2): 135–157. <https://doi.org/10.1016/j.schres.2005.02.010>.
- Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T.R., Handley, R., Luzzi, S., Russo, M., Paparelli, A., Butt, A., 2009. High potency cannabis and the risk of psychosis. *Br. J. Psychiatry* 195 (6), 488–491.
- Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., Dazzan, P., 2013. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr. Bull.* 40 (6), 1509–1517.
- First, M.B., Spitzer, R.L., Robert, L., Gibbon, M., Gibbon, W., Janet, B.W., 1996. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. American Psychiatric Press, Inc., Washington, D.C.

- French, L., Gray, C., Leonard, G., Perron, M., Pike, G.B., Richer, L., Séguin, J.R., Veillette, S., Evans, C.J., Artiges, E., Banaschewski, T., Bokde, A.W.L., Bromberg, U., Bruhl, R., Buchel, C., Cattrell, A., Conrod, P.J., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Lemaitre, H., Martinot, J.-L., Nees, F., Orfanos, D.P., Pangelinan, M.M., Poustka, L., Rietschel, M., Smolka, M.N., Walter, H., Whelan, R., Timpson, N.J., Schumann, G., Smith, G.D., Pausova, Z., Paus, T., 2015. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. *JAMA Psychiatry* 72 (10):1002–1011. <https://doi.org/10.1001/jamapsychiatry.2015.1131>.
- Gage, S.H., Hickman, M., Heron, J., Munafò, M.R., Lewis, G., Macleod, J., Zammit, S., 2014. Associations of cannabis and cigarette use with psychotic experiences at age 18: findings from the Avon longitudinal study of parents and children. *Psychol. Med.* 44 (16): 3435–3444. <https://doi.org/10.1017/S0033291714000531>.
- Giaconia, R.M., Reinherz, H.Z., Hauf, A.C., Paradis, A.D., Wasserman, M.S., Langhammer, D.M., 2000. Comorbidity of substance use and post-traumatic stress disorders in a community sample of adolescents. *Am. J. Orthopsychiatry* 70 (2), 253–262.
- Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., Fitzpatrick, C., Cannon, M., 2010. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychol. Med.* 40 (10):1627–1634. <https://doi.org/10.1017/S0033291709991966>.
- Hasin, D.S., Saha, T.D., Kerridge, B.T., Goldstein, R.B., Chou, S.P., Zhang, H., Jung, J., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Grant, B.F., 2015. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry* 72 (12):1235–1242. <https://doi.org/10.1001/jamapsychiatry.2015.1858>.
- Hayatbakhsh, M.R., O'Callaghan, M.J., Jamrozik, K., Najman, J.M., Mamun, A.A., Alati, R., Bor, W., 2008. The association between school performance at 14 years and young adults' use of cannabis: an Australian birth cohort study. *J. Drug Issues* 38 (2): 401–418. <https://doi.org/10.1177/002204260803800202>.
- Henquet, C., Murray, R., Linszen, D., van Os, J., 2005. The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* 31 (3):608–612. <https://doi.org/10.1093/schbul/sbi027>.
- Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebbergh, W., De Graaf, R., Van Os, J., 2004. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr. Scand.* 109 (1):38–45. <https://doi.org/10.1046/j.0001-690X.2003.00217.x>.
- Kelley, M.E., Wan, C.R., Broussard, B., Crisafio, A., Cristofaro, S., Johnson, S., Reed, T.A., Amar, P., Kaslow, N.J., Walker, E.F., Compton, M.T., 2016. Marijuana use in the immediate 5-year premorbid period is associated with increased risk of onset of schizophrenia and related psychotic disorders. *Schizophr. Res.* 171 (1):62–67. <https://doi.org/10.1016/j.schres.2016.01.015>.
- Khantzian, E.J., 2003. The self-medication hypothesis revisited: the dually diagnosed patient. *Primary Psychiatry* 10 (9), 47–54.
- Krabbendam, L., van Os, J., 2005. Schizophrenia and urbanicity: a major environmental influence - conditional on genetic risk. *Schizophr. Bull.* 31 (4):795–799. <https://doi.org/10.1093/schbul/sbi060>.
- Kuepper, R., van Os, J., Lieb, R., Wittchen, H.-U., Höfler, M., Henquet, C., 2011. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ* 342:d738. <https://doi.org/10.1136/bmj.d738>.
- Large, M., Sharma, S., Compton, M.T., Slade, T., Nielsen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis cannabis use and earlier onset of psychosis. *Arch. Gen. Psychiatry* 68 (6):555–561. <https://doi.org/10.1001/archgenpsychiatry.2011.5>.
- Mayet, A., Legleye, S., Beck, F., Falissard, B., Chau, N., 2016. The gateway hypothesis, common liability to addictions or the route of administration model? A modelling process linking the three theories. *Eur. Addict. Res.* 22 (2):107–117. <https://doi.org/10.1159/000439564>.
- Minozzi, S., Davoli, M., Bargagli, A.M., Amato, L., Vecchi, S., Perucci, C.A., 2010. An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. *Drug Alcohol Rev.* 29 (3):304–317. <https://doi.org/10.1111/j.1465-3362.2009.00132.x>.
- Monte, R.C., Goulding, S.M., Compton, M.T., 2008. Premorbid functioning of patients with first-episode nonaffective psychosis: a comparison of deterioration in academic and social performance, and clinical correlates of Premorbid Adjustment Scale scores. *Schizophr. Res.* 104 (1), 206–213.
- Mueser, K.T., Bellack, A.S., Blanchard, J.J., 1992. Comorbidity of schizophrenia and substance abuse: implications for treatment. *J. Consult. Clin. Psychol.* 60 (6):845–856. <https://doi.org/10.1037/0022-006X.60.6.845>.
- Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., Bhattacharyya, S., 2015. Cannabis use and treatment resistance in first episode psychosis: a natural language processing study. *Lancet* 385:579. [https://doi.org/10.1016/S0140-6736\(15\)00394-4](https://doi.org/10.1016/S0140-6736(15)00394-4).
- Pelayo-Terán, J., Suárez-Pinilla, P., Chadi, N., Crespo-Facorro, B., 2012. Gene-environment interactions underlying the effect of cannabis in first episode psychosis. *Curr. Pharm. Des.* 18 (32):5024–5035. <https://doi.org/10.2174/138161212802884609>.
- Ramsay, C.E., Abedi, G.R., Marson, J.D., Compton, M.T., 2011. Overview and initial validation of two detailed, multidimensional, retrospective measures of substance use: the Lifetime Substance Use Recall (LSUR) and longitudinal substance use recall for 12 weeks (LSUR-12) instruments. *J. Psychiatr. Res.* 45 (1):83–91. <https://doi.org/10.1016/j.jpsychires.2010.04.018>.
- Ross, C.E., Mirowsky, J., 2001. Neighborhood disadvantage, disorder, and health. *J. Health Soc. Behav.*:258–276 <https://doi.org/10.2307/3090214>.
- Saddichha, S., Sur, S., Sinha, B.N., Khess, C.R., 2010. How is substance use linked to psychosis? A study of the course and patterns of substance dependence in psychosis. *Subst. Abuse.* 31 (1):58–67. <https://doi.org/10.1080/08897070903442699>.
- Skinner, H.A., 1982. The drug abuse screening test. *Addict. Behav.* 7 (4):363–371. [https://doi.org/10.1016/0306-4603\(82\)90005-3](https://doi.org/10.1016/0306-4603(82)90005-3).
- Smit, F., Bolier, L., Cuijpers, P., 2004. Cannabis use and the risk of later schizophrenia: a review. *Addiction* 99 (4):425–430. <https://doi.org/10.1111/j.1360-0443.2004.00683.x>.
- Tosato, S., Lasalvia, A., Bonetto, C., Mazzoncini, R., Cristofalo, D., De Santi, K., Bertani, M., Bissoli, S., Lazzarotto, L., Marrella, G., Lamonaca, D., Riolo, R., Gardellini, F., Urbani, A., Tansella, M., Ruggeri, M., 2013. The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients. Data from the Psychosis Incident Cohort Outcome Study (PICOS). *J. Psychiatr. Res.* 47 (4):438–444. <https://doi.org/10.1016/j.jpsychires.2012.11.009>.
- United Nations Office on Drugs and Crime (UNODC), 2016. World Drug Report 2016. <http://www.unodc.org/wdr2016/>, Accessed date: April 2017.
- Wade, D., Harrigan, S., Edwards, J., Burgess, P.M., Whelan, G., McGorry, P.D., 2005. Patterns and predictors of substance use disorders and daily tobacco use in first-episode psychosis. *Aust. N. Z. J. Psychiatry* 39 (10):892–898. <https://doi.org/10.1080/j.1440-1614.2005.01699.x>.
- Windle, M., 2005. Retrospective use of alcohol and other substances by college students: psychometric properties of a new measure. *Addict. Behav.* 30 (2):337–342. <https://doi.org/10.1016/j.addbeh.2004.04.023>.
- Yücel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M., Fornito, A., Wood, S.J., McGorry, P.D., 2010. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. *Schizophr. Bull.* 38 (2), 316–330.
- Zammit, S., Moore, T.H.M., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., Lewis, G., 2008. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br. J. Psychiatry* 193 (5):357–363. <https://doi.org/10.1192/bjp.bp.107.046375>.