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Self-Medicated but Stressed-Out: Relations between Stress and Cannabis Use in Youth at Risk for Psychosis

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Abstract

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By Roberto A. España

Cannabis and stress have been established as risk factors in the development of psychotic disorders. Research suggests a dose-dependent relation between cannabis use and risk of psychotic outcomes. There is also an established link between stress exposure and cannabis use in healthy and clinical samples. Recent research on psychosis etiology has focused on individuals at clinical high risk of psychosis (CHR), a stage often referred to as the prodromal period and characterized by the manifestation of attenuated psychotic symptoms. Although both cannabis and stress have been linked to poorer outcomes among CHR individuals, to date, there have been no prospective studies examining the stress antecedents, cross-sectional correlates, and subsequent stress outcomes of cannabis use in CHR youth. Thus, we do not know whether CHR cannabis users have been exposed to higher levels of previous life-event stress or experience more sensitivity to current or future stressors. Hence, the aims of the present study were to examine whether: 1) CHR cannabis users (CU) reported more exposure to life-event stress (LEtot) than CHR non-users (NU); 2) the CU group reported greater sensitivity to daily stress (DSS) at baseline than the NU group; 3) the CU group experienced greater DSS at 12-month follow-up than the NU group; and 4) LEtot predicted transitioning to cannabis use among the NU group. The present study (N=732) utilized data from the second phase of the North American Prodrome Longitudinal Study. Results indicated that the CU group had experienced more LEtot exposure at baseline and higher levels of DSS at 12-month follow-up. A significant interaction between time and cannabis group was also present, such that the CU group demonstrated less decline in DSS from baseline to follow-up than the NU group. The implications of these findings as well as study limitations are discussed.

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I. Introduction

Presently, cannabis is the most commonly consumed illicit drug in the United States (Johnston et al., 2012). A burgeoning interest in medicinal use and economic opportunities related to cannabis have sparked efforts to legalize this substance. As this trend continues, however, it is imperative that cannabis consumers become educated on the differential behavioral effects produced by cannabis. For instance, delta-9-tetrahydroncannbinol (THC), the main psychoactive component found in cannabis, has been found to elevate levels of anxiety and psychotic-like symptoms in healthy individuals (D'Souza et al., 2004). Cannabis also contains cannabidiol (CBD), which in contrast to THC, has been found to produce anxiolytic and antipsychotic effects in healthy individuals (Zuardi, Crippa, Hallak, Moreira, & Guimarães, 2006; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982).

Due to the wider availability of cannabis, and evidence that use may be associated with risk for psychotic disorders, research on the precursors and consequences of cannabis use is increasingly important. This is especially the case for youth who are entering the major developmental risk period for the onset of serious mental disorders. The present study focuses on stress exposure and stress-sensitivity as correlates, antecedents, and potential consequences of cannabis use in youth at clinical high-risk for psychotic disorders.

Cannabis and Psychosis

In the last few decades, there has been increasing evidence to suggest that cannabis may play a role in the development of psychotic disorders (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; D'Souza, Sewell, & Ranganathan, 2009; van Os et al., 2002; Wilkinson, Radhakrishnan, & D'Souza, 2014).

While there is limited evidence that cannabis use *causes* psychosis, there does appear to be dose-dependent risk of psychotic outcomes among cannabis users (Andreasson et al., 1987; Arseneault et al., 2002). One of the earliest findings regarding cannabis use outcomes came from a cohort study of Swedish soldiers, which found that heavier cannabis use at age 18 increased the risk of developing a psychotic disorder later in life (Andreasson et al., 1987). Furthermore, it has also been reported that an earlier onset of psychotic symptoms in patients with schizophrenia is associated with a history of cannabis use (Addington & Addington, 1998; Compton et al., 2009; Green, Young, & Kavanagh, 2005). Similarly, psychotic individuals who concurrently consume cannabis present poorer life outcomes, worse symptoms, and increased likelihood of relapse (Wilkinson et al., 2014).

Given the developmental nature of psychotic disorders, the need for earlier intervention has influenced clinical researchers to shift their focus to individuals at risk for developing psychosis, often referred to as prodromal or clinical high risk (CHR) for psychosis. It has been demonstrated that the onset of schizophrenia and other psychotic disorders is typically preceded by a period of functional decline and gradual onset of positive symptoms that can last from months to years prior to crossing the threshold into clinical psychosis (Addington & Heinssen, 2012). The positive symptoms of psychosis are the defining features of the disorder, and include delusions, hallucinations, and though/communication disorder (American Psychiatric Association, 2013). Attenuated positive symptoms are subclinical manifestations of these symptoms, such as unusual ideations and sensory experiences, and disturbances in communication (Yung & McGorry, 1996). Structured diagnostic interviews have been developed to assess these symptoms in youth (McGlashan, Walsh, & Woods, 2010; Miller et al., 2004), and research has shown that those who meet research-based criteria for CHR show heightened rates

of psychosis in the subsequent two to four years (Fusar-Poli et al., 2012). In addition to attenuated positive symptoms, youth who meet CHR criteria manifest a range of other psychiatric symptoms, including anxiety and depression, as well as conduct and personality disorders (Addington et al., 2017). This is consistent with evidence from retrospective studies of patients with schizophrenia, and other psychotic disorders, which show that the prodrome to psychosis is characterized by a broad range of emotional and behavioral impairments and higher rates of substance use (Buchy, Cadenhead, et al., 2015).

A recent meta-analysis of cannabis use and psychotic symptoms in CHR individuals reported high rates of cannabis-use disorders and increased severity of symptoms, like unusual thought content and suspiciousness of others, when compared to controls (Carney, Cotter, Firth, Bradshaw, & Yung, 2017). Moreover, CHR youth who use cannabis are more likely to transition to clinical psychosis, when compared to CHR patients who are non-users (Kraan et al., 2016). Despite these outcomes, cannabis use is prevalent among CHR individuals, as evidenced by their high rate of cannabis consumption compared to the general population (Buchy, Cadenhead, et al., 2015).

Interestingly, a review found that the most commonly cited reason for cannabis use among chronic consumers is to cope with stress (Hyman & Sinha, 2009). In fact, stress-reduction motives appear to be unique to cannabis compared to other substances and is largely applicable to chronic users (Copeland, Swift, & Rees, 2001; Cuttler et al., 2017). Thus, some healthy users, and presumably some who are at risk for mental illness, are using cannabis to ‘self-medicate’ distress. Given the stigma of psychosis and potential roadblocks to accessing mental health resources, vulnerable individuals may view cannabis as an attractive option to cope with life stressors.

As described above, the present study is concerned with the relation of stress with current and later cannabis use in individuals at CHR for psychotic disorders. As described below, there is evidence that life event and daily stress is linked with cannabis use in healthy and clinical populations. Using retrospective and prospective longitudinal methods, this research is aimed at shedding greater light on causal relations between stress and cannabis use.

Relation of Trauma and Life Event Stress with Cannabis Use in Healthy and Clinical Samples

There is considerable evidence linking negative life events and cannabis use in both healthy and clinical samples. For instance, Butters (2002) found that greater family stressors increased the probability of cannabis use among a sample of healthy adolescent students. Drawing on the unique hardships faced by undocumented immigrants and their families, Zapata-Roblyer et al. (2016) examined the relationship between stress and substance use among adolescents growing up in families with one or more undocumented members. In their cross-sectional study, adolescent stress was operationalized as low parental involvement due to contextual constrains (i.e., difficult working conditions due to undocumented legal status) and family economic insecurity, in relation to alcohol, cigarette, and cannabis use. Their results showed that greater adolescent stress increased the likelihood of lifetime cigarette and marijuana use, suggesting that stress arising from familial dynamics may be a risk factor for cannabis use among young people living with undocumented family members. Similarly, low parental support and negative life events have been associated with and cannabis use among adolescents (Siqueira, Diab, Bodian, & Rolnitzky, 2001).

Longitudinal studies have also found similar results. Fergusson & Horwood (1997) followed participants from birth to age 18 and examined early onset cannabis use (<16 years)

and psychosocial adjustment later in life. After classifying the participants into three groups based on cannabis use in the last year: never used, used between 1-9 times, and used more than 10 times, their results indicated that early-onset users (prior to age 16), especially more frequent users, were more likely to have experienced negative life events, such as coming from a socially disadvantaged background, early experiences of familial adversity, and poorer relationships with parents. Furthermore, their results indicated that early-onset users demonstrated significantly higher rates of later cannabis use, in addition to higher rates of juvenile offending, poor academic and occupational functioning, and mental health problems (Fergusson & Horwood, 1997). In a prospective analysis of tobacco, alcohol, and cannabis use among a large sample of adolescents, life event stress was positively correlated with initial substance use as well greater use over time (Wills, Sandy, Yaeger, Cleary, & Shinar, 2001).

Similar relations between cannabis use and life stress have also been observed in individuals diagnosed with PTSD. Building on Khantzian's self-medication hypothesis (1985), Bremner, Southwick, Darnell, & Charney were among the earliest researchers to measure PTSD symptoms and substance use in a longitudinal sample of combat veterans (1996). In their study, the onset and severity of PTSD symptoms (i.e., hyperarousal, avoidance, intrusions) as well as patterns of substance use, were assessed in 61 Vietnam veterans diagnosed with PTSD. Their results indicated that onset of substance use, in this case alcohol, cannabis, heroin, and benzodiazepines, was associated with the onset of numerous PTSD related symptoms. Furthermore, symptom severity and frequency of substance use were also positively correlated, such that greater intensity of symptoms paralleled greater substance use levels, particularly in relation to alcohol and cannabis (Bremner et al., 1996). Since then, several studies have corroborated the link between cannabis use and PTSD symptomatology. Focusing on current

cannabis users with exposure to at least one traumatic life event, Bonn-Miller, Vujanovic, Feldner, Bernstein, & Zvolensky examined the relation between posttraumatic stress severity and motives for cannabis use among a sample of 103 adults (2007). Respondents were asked to report if they had experienced any of 12 traumatic events as outlined in the Posttraumatic Diagnostic Scale (Foa, 1996), and to share their motives for consuming cannabis, per The Marijuana Smoking History Questionnaire (Bonn-Miller, Zvolensky, Leen-Feldner, Feldner, & Yartz, 2005)**.** Their responses demonstrated a significantly positive relationship between posttraumatic symptom severity and coping motives for cannabis use (Bonn-Miller et al., 2007). Large scale investigations have also demonstrated similar relationships between PTSD and cannabis use. Utilizing a nationally representative survey of adults in the United States, Cougle and colleagues observed that lifetime and past PTSD diagnoses were associated with greater odds of lifetime cannabis use as well as daily use in the past year (Cougle, Bonn-Miller, Vujanovic, Zvolensky, & Hawkins, 2011). Collectively, the literature on cannabis and life stress provides evidence to suggest that there is a greater risk for early onset cannabis use and subsequent progression to heavier use in response to more negative life events among healthy and clinical samples. In this manner, stressful life events may trigger later cannabis use based on the assumption that it may help relieve distress (Hyman & Sinha, 2009). As described below, however, the notion that cannabis reduces stress does not receive support from empirical research.

Relation between Cannabis Use and Subjective Stress (Self-Reported, Daily)

Given that the most commonly reported motive for cannabis use among chronic users is to cope with perceived stress (i.e., self-medication) (Hyman & Sinha, 2009; Lloyd & Patrick, 1986), it is perhaps unsurprising to see the high comorbidity of cannabis use with anxiety-related

and symptoms. In a review of the relevant literature, Crippa et al. (2009) found that chronic cannabis users consistently had a higher prevalence rate of anxiety disorders compared to the general population and that those with anxiety disorders also had high rates of cannabis use (Crippa et al., 2009). Corroborating this, Kedzior and Laeber found a positive association between anxiety disorders and past 12-month cannabis use among the general population in a meta-analysis of 31 cannabis and anxiety related studies (2014). In at least five of these investigations, baseline cannabis use was associated with greater anxiety at follow-up points (Kedzior & Laeber, 2014), suggesting that cannabis use may be prospectively contributing to subjective distress. Relatedly, investigations have found that cannabis use is associated with an increase in current and future panic attacks and panic disorder (Zvolensky et al., 2006), with those experiencing panic symptoms showing higher levels of anxiety during acute cannabis intoxication compared to symptomatic individuals who are not under the influence of cannabis (Szuster, Pontius, & Campos, 1988).

As summarized above, research indicates that cannabis use is linked with greater symptoms of anxiety at follow-up evaluations. In addition to longitudinal, naturalistic studies, several experimental studies have documented a dose-dependent association between cannabis use and anxiety/distress. Recently, Hunault et al. (2014) reported a dose-dependent relationship between cannabis cigarettes (ranging from 29-69 mg THC) and increased levels of anxiety, suggesting that higher concentrations of THC are associated with greater experiences of subjective anxiety. However, even smaller doses have been shown to produce similar effects. For instance, D'Souza et al. (2004) found that 2.5mg and 5mg of intravenous THC were associated with increased anxiety among healthy individuals. Similarly, Crippa et al. (2009) noted that

perceived anxiogenic effects were more prominent among higher doses of cannabis than lower doses.

Despite the above findings, other studies have found evidence of relaxation after cannabis consumption. One study indicated that 20mg of oral THC increased feelings of relaxation among daily users (Hart et al., 2002), contrasting findings where higher doses of THC have been associated with greater levels of anxiety. But this study also showed that in the days following administration, some negative subjective effects were increased (e g., ratings of "irritable" and "miserable"). Childs et al. (2017) found that 7.5 mg THC significantly reduced self-reported subjective distress after the Trier Social Stress Test (TSST) and reduced appraisals of the test as threatening and challenging. But at higher doses (12.5mg), THC was associated with increased "negative mood" before and during the tasks as well as more frequent, subjective appraisal of TSST tasks as "threatening" and "challenging", as reported by subjects.

In summary, it appears that, contrary to the perceptions of some users, THC does not have a generalized dampening effect on subjective stress or anxiety. Instead, it appears that the effect varies as a function of dose, as well as previous cannabis use. Higher doses are associated with a significant increase in negative subjective responses, such as stress/anxiety, but for regular cannabis users, smaller doses may enhance relaxation, at least acutely. Moreover, the data from the experimental studies described above indicate that there are individual differences in the response to THC, and these are likely due to age and preexisting neurobiological factors, as well as previous exposure.

Effects of THC on Biological Stress Response in CHR, Psychotic Patients, and Healthy Subjects

In addition to examining the relationship between THC and subjective stress, investigators have also looked at the effects of THC on biological indices of stress, mainly cortisol. Among healthy, recreational users, acute administration of THC has been shown to raise cortisol in a dose-dependent manner (D'Souza et al., 2004). Interestingly, the relative increase in cortisol in response to THC administration has been observed to be smaller in habitual users versus healthy controls (Ranganathan et al., 2009). Given that cannabis use is an associated outcome of greater life stress, it is possible that the disproportionate increase in cortisol among habitual users and healthy controls is a function of habitual users presenting higher baseline stress because of greater exposure to life stress, thus potentially accounting for the smaller change in cortisol levels. Elevated presentations of cortisol in response to the administration of THC have also been observed in patients with schizophrenia, who present higher levels of cortisol relative to controls post-intravenous administration of THC (D'Souza et al., 2004). Although the developmental nature of psychotic disorders has helped shift the focus of research onto youth at risk of developing psychosis, only one study has investigated the relationship between cortisol and cannabis use among CHR youth. In that study, CHR cannabis users were shown to have higher baseline salivary cortisol levels compared to CHR non-users and healthy controls (Carol, Spencer, & Mittal, 2017).

Potential Mechanisms Involved in the Relation between Cannabis Use and Stress-Sensitivity

To better understand the robust effects of cannabis on stress-sensitivity, it essential to look at the endocannabinoid system, the main biological target for THC in the human body (Hill

& Tasker, 2012; Pertwee, 2008). An in-depth explanation of the endocannabinoid system is beyond the scope of this paper, so readers are encouraged to consult a recent comprehensive review by Hill & Tasker for additional information (2012). Briefly, however, the endocannabinoid system has been found to regulate inhibitory and excitatory signaling within the HPA axis, with a primary focus on limiting activation of the HPA axis (Gorzalka, Hill, & Hillard, 2008; Hill & McEwen, 2010; Hill et al., 2010). The endocannabinoid system is governed by two receptors, CB_1 and CB_2, which are uniquely distributed across the body (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Munro, Thomas, & Abu-Shaar, 1993). In the brain, CB_1 receptors are densely populated on the axonal terminals of glutamatergic and GABAergic neurons, which are in turn heavily expressed across the regions that regulate the negative feedback loop of the HPA axis (Carol et al., 2017; Freund, Katona, & Piomelli, 2003; Pertwee, 2008; Sapolsky, Armanini, Packan, Sutton, & Plotsky, 1990). Under basal conditions, endogenous cannabinoids (i.e., anandamide and 2-arachidonoylglycerol) help regulate presynaptic release of glutamate through activation of CB_1 receptors on glutamatergic terminals within the basolateral amygdala (BLA), a region that indirectly projects onto the paraventricular nucleus (PVN). Normally, activation of these CB_1 receptors initiates a cascade of events that reduces the outflow of BLA projection neurons onto the PVN, thus inhibiting PVN activity. It is likely that acute ingestion of THC mimics endogenous cannabinoid activity and subsequent inhibition of the PVN, thus decreasing cortisol release and contributing to a perceived reduction in tension. Over time, however, chronic cannabis use may lead to a down-regulation of CB_1 receptors resulting in a disinhibition of glutamatergic inputs to projection neurons within the BLA. The resulting increase in BLA activity may contribute to an over-activation of the PVN and subsequent release of cortisol.

Given the role cannabinoid receptors play in the regulation of HPA activity, chronic cannabis use may alter the stress response by dysregulating cortisol release and making individuals more sensitive to stressors (i.e., experience greater subjective stress in response to adverse events). In line with the idea that a dysregulated HPA system may confer greater sensitivity to stress, CHR subjects, who have been found to have elevated cortisol levels (Karanikas & Garyfallos, 2015), also tend to self-report more stressful experiences than controls, with those progressing to psychosis reporting even greater stress from events than CHR, non-converters (Trotman et al., 2014). To date, there has only been one study examining the relationship between cannabis use and baseline cortisol levels in a CHR sample, and the results indicated a positive relation (Carol et al., 2017). There are no published reports on the potential association between cannabis use and stress-sensitivity in CHR individuals.

The Present Study

Given the heightened rate of cannabis use by people at risk for psychosis, coupled with the evidence that cannabis use has the potential to exacerbate or trigger psychotic symptoms, research on the precipitants and consequences of cannabis use in CHR individuals is a high priority. While studies of both healthy and clinical samples of cannabis users have shown that they often attribute their use to stress/anxiety reduction, cumulative research findings suggest that cannabis use is associated with elevations in past stress exposure, current stress/anxiety, and adverse subsequent clinical outcomes in CHR and psychotic samples. The association of cannabis with both self-report and biological (e g., cortisol) indices of stress has been shown in controlled experimental studies, as well as naturalistic, correlational studies. To date, however, there have been no prospective studies that examine the stress antecedents, cross-sectional correlates, and subsequent stress outcomes of cannabis use in CHR youth. Thus, we do not know

whether CHR cannabis users have previously been exposed to higher levels of life-event stress, or experience more sensitivity to current (i.e., daily) or future stress exposure. As described above, one study of CHR subjects revealed increased cortisol levels in cannabis users, consistent with the notion that CHR cannabis users may currently show greater sensitivity to stress exposure. Our understanding of the longitudinal relations of cannabis use with stress is also limited. There is no research on the relation of cannabis use with current or subsequent stress-sensitivity in CHR subjects, although the association of cannabis use with symptom severity and transition to psychosis suggests that cannabis use may increase stress-sensitivity in CHR patients.

The present study will test the following hypotheses about the relation of self-report measures of stress with cannabis use in CHR individuals:

1) CHR cannabis users will report a higher level of exposure to life-event stress than nonusers. This prediction is based on past research findings, including the evidence suggesting that individuals often use cannabis to self-medicate or cope with stress.
2) Compared to CHR non-users, cannabis users will report greater sensitivity to daily stressors. In other words, when controlling for the number of exposures, CHR users will report higher stress levels.
3) Based on the assumption that cannabis use can exacerbate stress-sensitivity, it is predicted that, when compared to non-users, CHR patients who are using cannabis at baseline will show a greater increase in stress-sensitivity at one-year follow-up.
4) Given evidence that life-event stress appears to confer a risk for later cannabis use, it is predicted that higher levels of life-event stress exposure at baseline will predict a higher likelihood of transition from cannabis nonuse to use at one-year follow-up.

II. Method

Study Design and Procedure

The current study utilizes data from the North American Prodrome Longitudinal Study, Phase 2 (NAPLS-2) to examine history of substance use, frequency of stressful events, and subjective responses to these stressful events in subjects at clinical high risk of psychosis. NAPLS-2 was a multi-site, prospective longitudinal study of prodromal symptoms focused on improving prediction of psychosis and understanding the neural mechanisms behind conversion to psychosis (Addington et al., 2012).

Participants

At conclusion, the final sample consisted of 770 clinical high risk (CHR) participants and 279 healthy controls (HC) (50.5% male). The age of participants at baseline ranged from 12 to 35 years, with a mean age of 18.54 years (SD 4.24) for the CHR group and 19.75 years (SD 4.66) for the HC group. The protocol was approved by Institutional Review Boards at all NAPLS sites (Addington et al., 2012). All participants provided informed consent or assent. For the purposes of the present study, the focus was on the CHR sample, which was dichotomized into two groups at baseline and follow-up: cannabis users (CU) and non-users (NU). All measures described below were administered at baseline and 12-month follow-up visits.

Measures

Structured Interview for Prodromal Syndromes. To assess the presence of psychotic symptoms, participants were interviewed using the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2004). The SIPS is a standardized, structured diagnostic interview that is intended to rate the major symptom dimensions associated with the prodrome to psychosis, such odd or unusual thought content, suspiciousness/paranoia, feelings of grandiosity,

perceptual abnormalities, and disorganized communication. Responses to SIPS items, which are categorized under the P1-P5 scales of the Scale of Prodromal Symptoms (SOPS), are quantified in severity ranging from 0 (absent) to 6 (severe, psychotic) (Miller et al., 2004). Subjects who present symptoms severe enough to warrant an index score of 3 or higher on any P1-P5 dimension, have experienced a brief intermittent psychotic syndrome, or meet criteria for a combined genetic risk of a schizophreniform spectrum disorder coupled with a history of functional deterioration, are then classified as clinically high-risk individuals (CHR) (McGlashan et al., 2010). Individuals who meet criteria for CHR status on the SIPS have been shown to have a subsequent rate of psychotic disorders that is significantly higher that the population base rate of 1-2%: estimates of conversion to clinical psychosis in youth who meet SIPS CHR criteria range from 10-30% (Fusar-Poli et al., 2012).

Participants were excluded from the present study if they had ever met criteria for an axis I psychotic disorder, presented an IQ<70, or had a history of central nervous system disorder. Healthy control participants were also excluded if they had a first-degree relative with a current or past psychotic disorder. A more detailed description of recruitment, inclusion/exclusion criteria, and participant details is provided elsewhere (Addington et al., 2012)

Life-Event Stress. Study participants completed a revised version of the Psychiatric Epidemiology Research Interview Life Events Scale (LES) (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978). The LES was modified from its original version to exclude items that were not relevant to the adolescent/young adult age range, such as “getting a divorce” or “encountering serious financial loss”. The modified version of the LES then, included 59 items describing significant events or life changes that could theoretically be experienced at any age in the adolescent/young adult period. During the administration of the LES, participants were asked

to indicate A) whether an event ever occurred in their lives and, B) the associated, subjective stress rating of the experienced event. Ratings were based on a 7-point Likert scale ranging from "did not occur" to "caused me to panic". The sum value of the total number of events reported on the LES was used to represent total life events (LEtot).

Daily Stress and Stress-Sensitivity. In addition to the LES, participants completed the Daily Stress Inventory (DSI) (Brantley, Waggoner, Jones, & Rappaport, 1987) which is a measure consisting of 58-items reflecting minor, common hassles potentially experienced within the last 24 hours. Some examples are "interrupted during a task/activity" or "had [my] sleep disturbed". Participants were first asked to indicate whether they had experienced any of the events listed on the DSI before reporting the level of subjective stress experienced for each endorsed "hassle" with the same 0-7 Likert scale described above. Based on the total number of events and the total subjective stress reported on the DSI, a daily stress-sensitivity (DSS) ratio was derived for each subject by dividing the total subjective stress rating by the total number of events reported on the DSI. The resulting ratio thus provides a unique, numeric representation of the magnitude of perceived stress *per stressor* after controlling for the number of events.

Cannabis Use. To assess characteristics of cannabis use, participants were administered the Cannabis Scale to collect self-reported lifetime history of cannabis use that including age of onset, frequency of use, and total instances of use in their lifetime on a scale from 0-300. Subjects' patterns of cannabis, alcohol, tobacco, and other substance use in the previous month were rated using the Alcohol and Drug Use Scale (AUS/DUS) which records severity (1=abstinent, 2=use without impairment, 3=abuse, 4=dependence) and frequency of use (0=no use, 1=once or twice per month, 2=3–4 times per month, 3=1–2 times per week, 4=3–4 times per week, 5=almost daily) in the last 30 days (Drake, Mueser, & McHugo, 1996). These measures

have often been used to assess substance use in clinical high-risk samples (Buchy, Cadenhead, et al., 2015; Buchy, Perkins, Woods, Liu, & Addington, 2014; Buchy, Seidman, et al., 2015). CHR subjects were then classified into two groups (CU and NU) based on whether they had used cannabis in the month prior to the baseline assessment.

Analytic Approach

Statistical analyses were conducted with SPSS 25 software. Independent sample t-tests were used to compare the CU and NU groups on demographic characteristics. Hierarchical regression analyses were conducted to test the relation of cannabis use in the last month with Daily and Life Event stress measures. An additional logistical regression analysis tested the predictive power of the number of reported LE at baseline on the likelihood of transitioning to cannabis use at 12-month follow-up. All regression analyses included age, sex, and alcohol use in the last month as covariates entered in the first block. A repeated-measures ANCOVA was conducted to test the prediction of changes in DSS from baseline to 12-month follow-up with age, sex, and alcohol use in the last month as covariates.

III. Results

Demographic Characteristics of the Groups

As described in the previously published overview of NAPLS (Addington et al., 2012), the CHR group included a greater proportion of males than the HC group, but did not differ in mean age. As would be expected, the CU and NU CHR subgroups were statistically different in mean age (19.42, 18.22, $p < .001$) and sex ($p < .005$), such that the CU group included an older subset of individuals and a greater proportion of males than the NU group. This is consistent with studies of the demographics of cannabis use in healthy and clinical samples. These results, along with additional demographic characteristics, are summarized in Table 1.

Substance Use Characteristics of the Groups

A substantial overview of substance use characteristics across the CHR sample, including mean age of onset, frequency of use, level of impairment, and comorbid use, can be found in a published report (Buchy, Cadenhead, et al., 2015). For the current study, tobacco and alcohol use in the last month were assessed for each group. At baseline, 77% and 55% of CU endorsed using alcohol and tobacco, respectively, in the month prior to baseline assessment (Table 2). These proportions were much smaller, 29% and 14%, in the NU group. Group comparisons of other recreational substances were not conducted because approximately 98% of the sample denied consuming other recreational substances at baseline (Buchy, Cadenhead, et al., 2015).

Cross-Sectional Analyses

Hierarchical regression analyses were first conducted on the total number of life events (LEtot) reported at baseline, with age, sex, and alcohol use in the last month as covariates entered in the first block, then baseline cannabis use in the last month as a predictor in the second block. The results demonstrated that baseline cannabis in the last month was a significant predictor of LEtot (R^2=.21, $F\ (4,665)$ = 44.01 p <.001), such that the CU group reported significantly more LEtot that the NU after controlling for covariates (b = .08, p < .001) (Figure 1). As expected, age, sex, and baseline alcohol use in the last month were also significant predictors of baseline LEtot (R^2 = .21, $F\ (3,666)$ = 57.10 p < .001). Alcohol use in the last month was associated with higher LEtot (b = .08, p < .001), and older subjects (b = .03, p < .001) and females (b = -.06, p < .005) reported more life events

Results of the analysis of DSS indicated that neither baseline cannabis use, nor alcohol use, in the last month were significantly associated with baseline DSS (p = .362; p = .775). Again, the analyses indicated that sex and age were significant predictors of baseline DSS (R^2 =

.08, *F (3,624)* = 17.08, $p < .001$). Specifically, female subjects ($b = -.07$, $p < .001$) and older subjects ($b = .01$, $p < .001$) reported greater DSS.

Longitudinal Analyses

To determine whether the baseline CU group experienced greater DSS at 12-month follow-up than the NU group, 12-month DSS was analyzed with covariates and baseline cannabis use in the last month as predictors. The results indicated that baseline cannabis use was a significant predictor of DSS at 12-month follow-up, and it explained a significant increase in the proportion of variance in DSS accounted for (R^2=.04, *F (4,335)* = 3.52, $p < .01$). The CU group showed significantly higher DSS at 12 months than the NU group ($b = .06$, $p < .05$), as did female subjects overall, compared to males ($b = -.05$, $p < .05$). There was no relation of age (p = .136) or alcohol use in the last month ($p = .341$) with 12-month DSS.

To assess the relation of CU with changes in DSS from baseline to 12-month follow-up, a repeated-measures ANCOVA was conducted with DSS at baseline and 12 months (Time) as the repeated measure, baseline CU/NU groups as a factor, and sex, age, and baseline alcohol use in the last month as covariates. The results indicated a significant interaction effect of Time with cannabis use group (*F (1,303) = 5.22*, $p < .05$), such that the relation of baseline cannabis with DSS varied as a function of time. As shown in Figure 2, both groups showed a decline in DSS over time, but while the baseline CU and NU groups demonstrated similar levels of DSS at baseline, they differed significantly at 12-month follow-up. The NU group manifested greater *decrease* in DSS from baseline to 12-month follow-up when compared to the baseline CU group.

Lastly, to determine whether LEtot at baseline was associated with a higher likelihood of transitioning from cannabis nonuse to use at 12-month follow-up, a logistical regression procedure was conducted with covariates in the first block, LEtot at baseline as a predictor, and

12-month follow-up cannabis use in the last month as the dependent measure. Results indicated no relation between LEtot and follow-up CU/NU status, as non-users with a history of life events were not significantly more likely to transition to cannabis use at 12-month follow-up (p = .126).

IV. Discussion

Examination of the determinants and consequences of cannabis use in CHR individuals is an important, contemporary research priority, given the coupling of high rates of cannabis use by people at risk for psychosis with evidence that cannabis use has the potential to exacerbate or trigger psychotic symptoms. Previous investigations of both healthy and clinical samples of cannabis users have shown that subjects often attribute their cannabis use to reductions in stress/anxiety (Bonn-Miller et al., 2007; Copeland et al., 2001; Hyman & Sinha, 2009). Further, cumulative research findings from CHR samples indicate associations between cannabis use and elevations in symptom severity and conversion to psychosis (Carney et al., 2017; Kraan et al., 2016). There are, however, no published reports on the relation of stress with cannabis use in CHR youth. No study has examined whether CHR cannabis users have experienced higher levels of previous life-event stress or experience more sensitivity to current or future stressors compared to CHR non-users. The goal of the present study was to investigate the stress-related antecedents, cross-sectional correlates, and ensuing stress-related outcomes among CHR cannabis users.

In the case of determining whether CHR cannabis users had experienced more stressful life-events than CHR non-users, the findings suggest that cannabis use in the last month is associated with higher levels of exposure to stressful life events. Such results are not surprising considering previously established associations between negative life events and cannabis use (Fergusson & Horwood, 1997; Zapata-Roblyer et al., 2016) and the tendency for individuals to

report self-medicating with cannabis to reduce stress (Hyman & Sinha, 2009). Thus, it appears that the elevated cumulative LE stress that characterizes CHR youth, which has also been hypothesized to contribute to vulnerability to psychosis, can also increase the likelihood of their exposure to another risk factor – the use of cannabis. Further, given evidence that psychotic patients who use cannabis have poorer prognoses and worse symptoms (Wilkinson et al., 2014), CHR youth who use cannabis and subsequently convert to psychosis are likely to have a poorer prognosis along with cannabis-related impairments in occupational and interpersonal functioning.

As illustrated in Figure 2, both CHR groups showed decreases in stress-sensitivity from baseline to 12-month follow-up. This is to be expected, in that individuals are typically referred for baseline CHR assessment when they are experiencing noticeable increases in attenuated positive symptoms which are often associated with acute, subjective distress. For most CHR youth, however, there is a subsequent decline in symptom severity and distress, and they do not convert to psychosis (Devylder et al., 2013). The present findings indicate that this is also the case for stress-sensitivity; most CHR youth show a decline over time. It should also be noted that an age-related decrease in stress-sensitivity has also been reported in healthy adolescents and young adults, therefore the decrease observed between baseline and follow-up in the present study is, in part, normative.

CHR cannabis users, however, showed a *smaller decrease* in stress-sensitivity, such that at follow-up, they reported experiencing more stress to daily hassles than non-users. In other words, compared to baseline non-users, CHR users are experiencing more subjective stress to everyday stressors 12 months later, even after accounting for sex, age, alcohol use, and number of stressors. This observation is consistent with some previous reports, including some

experimental studies, that cannabis contributes to subjective distress as well as stress hormone release. Thus, contrary to subjective reports of some users that cannabis helps "cope with stress", the present results suggest that it may be exacerbating an individual's reaction to stress. In line with "stress-reduction" motives for cannabis use, experiencing more stressful life events may precipitate cannabis consumption as a means of alleviating stress. Paradoxically, however, cannabis use may confer greater vulnerability to stressors. In turn, greater *perceived* levels of stress may promote cannabis consumption and extend a cycle of: subjective experience of stress → consume cannabis to reduce stress → greater sensitivity to future stress → more cannabis use, and so on.

Given that CHR subjects tend to experience greater sensitivity to daily stressors than healthy controls (Trotman et al., 2014) and consume cannabis at a higher rate than the general population (Buchy, Cadenhead, et al., 2015), it is important to explore the neurobiological mechanisms mediating the relation between cannabis and stress, and also conduct research on interventions aimed at reducing both stress-sensitivity and cannabis use in CHR youth.

Lastly, although it was expected that a greater frequency of life events would increase the odds of transitioning from nonuse to cannabis use at follow-up, per stress-reduction coping methods of substance use (Khantzian, 1997; Wills & Hirky, 1996), the results did not support this. There are several potential explanations for this. First, the more intense monitoring associated with enrollment in CHR research may play a role. Specifically, as symptoms worsen around the time of baseline assessment, treatment providers, parents, and other family members more actively discourage cannabis use. During this same period, CHR youth often withdraw from peers and have less opportunity to access drugs. Social withdrawal from peers may also reduce the likelihood of experiencing life event stress. Thus, factors associated with baseline

CHR status may mitigate both the likelihood of transitioning to cannabis use and exposure to life stressors.

The current study contributes novel findings to the literature on antecedents, correlates, and outcomes of cannabis use among CHR youth. By using a large sample of CHR youth from the NAPLS project, statistical power for detecting cross-sectional and longitudinal relations was enhanced. As with many investigations, however, the current study relied on self-reported information pertaining to life events, daily hassles, and features of substance use. Self-report is susceptible to recall errors and selective endorsement. Thus, subjects could underreport frequency of life stressors, minimize personal substance use characteristics, and broadly engage in an impression management response style. Furthermore, we were unable to account for the potency (THC concentration) of the cannabis subjects endorsed consuming, which could be important given that different concentrations of THC have been observed to have disparate psychological effects (Childs et al., 2017; D'Souza et al., 2004; Hart et al., 2002; Hunault et al., 2014). Similarly, while the increasing legalization of medical cannabis has allowed researchers to begin investigating the differential effects of various cannabis strains on the human organism (Pearce, Mitsouras, & Irizarry, 2014), the scientific evidence linking cannabis with stress and risk for psychosis would raise ethical concerns about conducting such research on CHR youth. Nonetheless, future investigations of healthy adult subjects will likely shed light on the effects of various cannabis strains and accompanying THC concentrations. Finally, the current study only focused on baseline and 12-month time points. To better discern potential changes in stress-sensitivity, researchers may wish to include additional time points in a longitudinal examination of cannabis and stress-related correlates and outcomes.

Despite these limitations, the present findings expand the literature on cannabis use and CHR youth while highlighting important interactions between cannabis and the longitudinal course of stress-sensitivity in this vulnerable population. The findings can be used to guide the development of meaningful psychoeducational interventions for individuals at risk of psychosis with comorbid cannabis use while simultaneously contributing to the larger debate on cannabis legalization that is sweeping the nation.

Table 1. Demographic and Clinical Characteristics of the Groups

	CU (*n* = 172)	NU (*n* = 560)	*p*
Sex			
Male	115 (66.9)	(306) 54.6	<.001
Female	57 (33.1)	254 (45.2)	
Mean Age (S.D.)	19.42 (3.26)	18.22 (4.45)	<.005
Mean Years of Education (S.D.)	12.18 (2.44)	11.03 (2.86)	
Race			
First Nations	(3) 1.7	(11) 2.0	
East Asian	(5) 2.9	(14) 2.5	
Southeast Asian	0	(15) 2.7	
South Asian	(2) 1.2	(18) 3.2	
Black	(25) 14.5	(84) 15	
Central/South American	(3) 1.7	(29) 5.2	
West/Central Asian & Middle Eastern	0	(6) 1.1	
White	(119) 69.2	(304) 54.3	
Native Hawaiian or Pacific Islander	0	(2) .4	
Interracial	(15) 8.7	(77) 13.8	

Data are given as number of participants (percentage) unless otherwise indicated. CU = cannabis user, NU = non-user. S.D. = standard deviation.

Table 2. Alcohol and Tobacco Use at Baseline

	CU (*n* = 172)	NU (*n* = 560)
Alcohol Use	132 (76.7)	164 (29.2)
Tobacco Use	95 (55.2)	79 (14.1)

Data are given as number of participants (percentage) unless otherwise indicated. CU = cannabis user, NU = non-user.

Figure 1. Total Number of Life Events by Baseline Cannabis Use

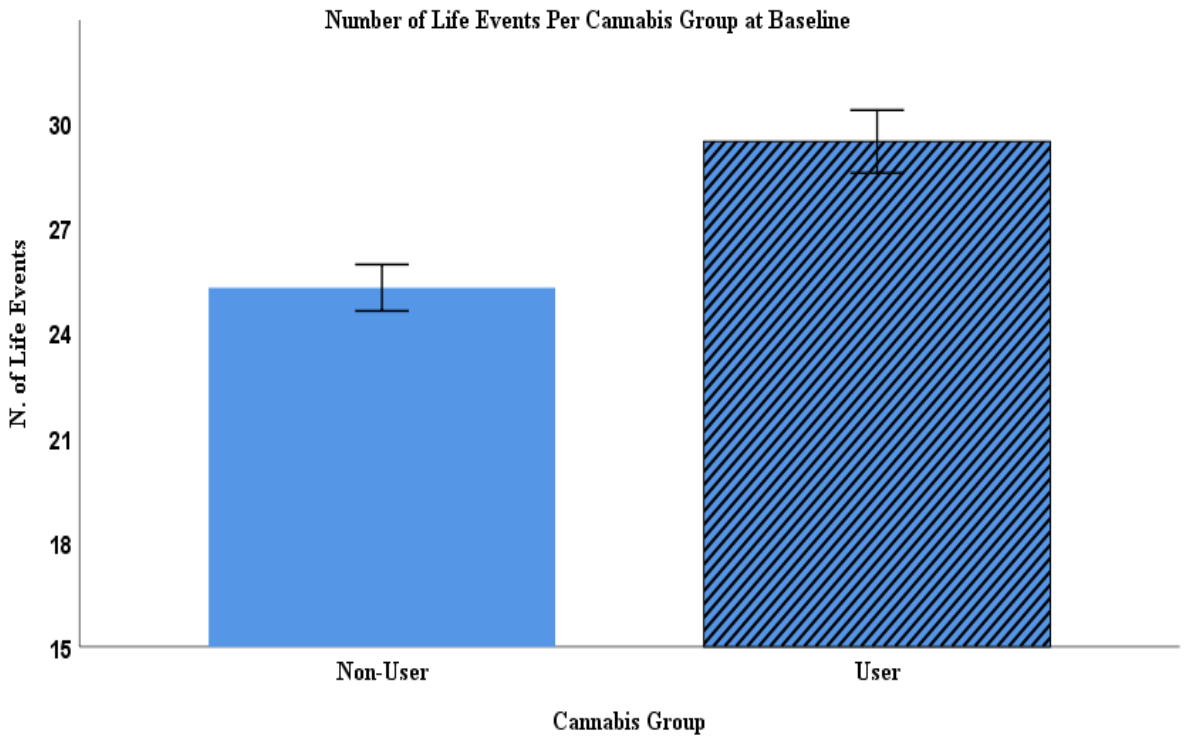
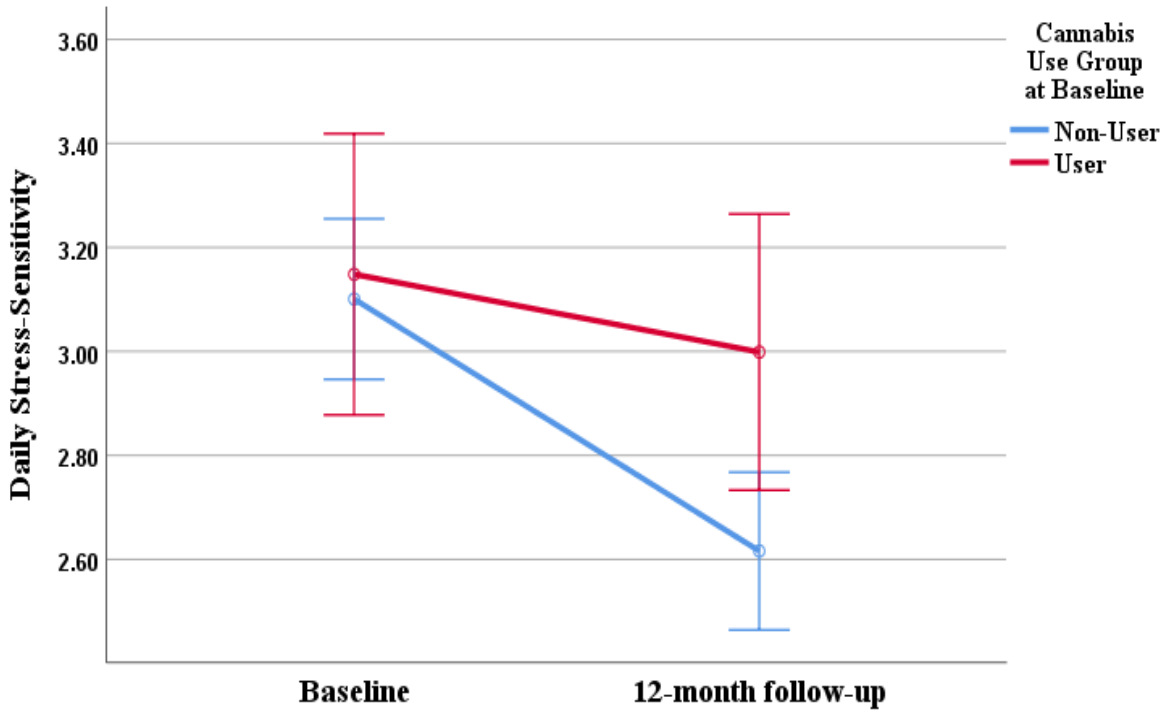


Figure 2. Daily Stress-Sensitivity Scores at Baseline and Follow-up by Baseline Cannabis Use



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