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Cannabis Use, Polysubstance Use, and Psychosis Spectrum Symptoms in a Community-Based Sample of US Youth

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Abstract

Purpose—To examine how cannabis use and polysubstance use among cannabis users relate to psychosis spectrum (PS) symptoms in a large community-based sample of US youth.

Methods—4,171 youth (age 14–21; mean=16.90, *SD*=1.85; 55% female) from the Philadelphia Neurodevelopmental Cohort (PNC) completed assessments of substance use, PS symptoms, and confounding variables (e.g., demographics, comorbid psychopathology, trauma exposure).

Results—After adjusting for confounds, cannabis use by itself was not associated with increased odds of being classified as “psychosis spectrum.” However, cannabis use in combination with tobacco or other substance use was associated with increased odds of PS classification (adjusted odds ratios [ORs] = 1.37 to 1.76). Follow-up symptom-level analyses revealed that cannabis use in combination with other substances was associated with subclinical positive symptoms (ORs=1.95 and 2.24) and frequent cannabis use was associated with subclinical negative/disorganized symptoms (OR=2.14). However, these symptom-level findings were reduced to trends after correction for multiple comparisons. Neither cannabis use nor polysubstance use was associated with threshold delusions or hallucinations.

Conclusions—After adjusting for important confounds, there was minimal evidence for associations between cannabis use by itself and PS symptoms. More compelling evidence emerged

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Conflict of Interest

The authors have declared that they have no competing or potential conflicts of interest. The study sponsors did not have a role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

Implications and Contribution: This study found minimal evidence for associations between cannabis use alone and psychosis spectrum (PS) symptoms in US youth. However, cannabis use in combination with other substance use was associated with PS symptoms, highlighting the importance of considering polysubstance use and potential confounds in understanding associations between cannabis and PS symptoms.

for associations between polysubstance use among cannabis users and PS symptoms. This study highlights the importance of considering polysubstance use and confounds when examining associations between cannabis use and PS symptoms. Further longitudinal research is necessary to determine whether these findings represent causal associations or shared genetic and/or environmental vulnerability for substance use and PS symptoms.

Keywords

cannabis; marijuana; polysubstance; psychosis; schizophrenia; Philadelphia Neurodevelopmental Cohort

Cannabis is the most commonly used illicit substance among young people in the United States (US) [1]. An estimated 1.8 million adolescents and 6.8 million young adults in the US are current cannabis users, and the prevalence of cannabis use in the US is increasing [1,2]. In addition, relative to prior years, US adolescents now report more permissive attitudes toward cannabis use and perceive regular cannabis use as less of a health risk [3,4]. Given the ongoing societal-level changes in the use and legalization of cannabis in the US, a critical task for researchers is to advance knowledge about potential associations between cannabis use and adolescent health and adjustment.

Cannabis Use and Psychosis

Researchers and clinicians have long been interested in associations between cannabis use and mental health. Much of the research in this area has focused on possible links between cannabis use and the psychosis spectrum (PS) — a continuum ranging from subclinical psychotic-like experiences which may or may not persist, to threshold delusions and hallucinations that cause significant distress and impairment [5,6]. Examples of subclinical psychotic-like experiences include attenuated positive symptoms, such as odd or unusual thoughts and perceptual illusions, and attenuated negative or disorganized symptoms, such as blunted affect and diminished volition or social interest. Such symptoms are relatively common in the general population [6], particularly among young people. An estimated 17% of children and 7.5% of adolescents report subclinical psychotic-like experiences [7]. Young people who experience these subclinical psychotic symptoms are at increased risk of developing a psychotic disorder [8], and these symptoms are associated with poorer global functioning, comorbid psychological difficulties, and increased suicidality [5,9].

Mounting empirical evidence supports an association between cannabis use and the psychosis spectrum [10,11]. Studies have shown that cannabis use during adolescence is associated with subclinical positive and negative symptoms [12] and predicts the onset of psychotic disorders in adulthood [13]. In general, studies have shown a dose-response relation between cannabis and psychosis outcomes, with frequent use more strongly associated with psychotic experiences and disorders than less frequent use [11]. Some studies have found that early onset cannabis use (e.g., before age 16) is more strongly associated with subclinical positive and negative symptoms and subsequent psychotic disorders than later onset use [12,14].

It is noteworthy that nearly all of the community research on adolescent cannabis use and PS symptoms has been conducted outside of the US. In other parts of the world the type of cannabis used (e.g., hash, skunk) and its cannabinoid concentrations may vary from the types used in the US [15], making generalizations to US samples challenging. To the best of our knowledge, associations between cannabis use and PS symptoms have only been examined in one other large cohort of non-help-seeking US adolescents [16,17]. In this sample of male adolescents, cannabis use did not predict the subsequent development of a psychotic disorder [17]; however, sustained cannabis use across adolescence predicted an increased risk of subclinical positive psychotic symptoms [16]. Additional research with non-clinical samples of US youth is warranted to address the limitations of prior work and expand upon these initial findings.

Polysubstance Use and Psychosis

Many cannabis users also use other substances [18]. A recent review reported that up to 29% of adolescents who use cannabis also use other drugs [19]. This raises the possibility that associations between cannabis and PS symptoms could be due to the confounding effects of other substances or the combined effects of polysubstance use. Controlling for other substance use has been found to attenuate the associations between cannabis use and psychotic-like experiences and, in some cases, reduce the associations to non-significance [20,21]. Moreover, the few studies examining polysubstance use have reported that cannabis use combined with other substance use is more strongly associated with psychotic-like experiences than cannabis use alone [20,21]. Thus, it is important to account for polysubstance use when examining the associations between cannabis use and PS symptoms.

The Present Study

We utilized data from the Philadelphia Neurodevelopmental Cohort (PNC) to examine how cannabis use and polysubstance use relate to PS symptoms in a large, non-help-seeking sample of US youth. Our previous broad analysis of predictors of PS classification in the PNC suggested that lifetime “ever use” of cannabis was not predictive of psychosis risk [5]. Here, we more comprehensively evaluate the associations between cannabis use and PS symptoms. Based on previous work [11,12,20,21] we hypothesized that frequent cannabis use, early cannabis use, and polysubstance use would be associated with increased odds of being classified as PS and with greater subclinical positive and negative/disorganized symptoms. Given the previously reported null findings from another US cohort [17], we did not make specific predictions about the links between cannabis use and threshold delusions/hallucinations.

This study adds to the literature in a number of ways. As noted above, there has been minimal investigation into the links between cannabis use and PS symptoms in non-help-seeking US youth. The previous smaller scale US cohort study [16,17] only included male adolescents, did not examine the effects of polysubstance use on PS symptoms, did not examine subclinical negative/disorganized symptoms, and did not control for trauma exposure. We address these limitations in the present study. Recent research has underscored

the importance of investigating risk indicators associated with a wide range of symptoms in the psychosis continuum as young people develop [6]. Thus, our inclusion of a broad spectrum of psychosis-relevant symptoms-from subclinical symptoms to threshold delusions/hallucinations — is a notable strength. In addition, extensive, structured, in-person assessments in the PNC enabled us to model many variables that could confound the relation between cannabis use and PS symptoms, including: demographics, intellectual function, comorbid psychopathology, use of other substances, trauma exposure, and family history of substance abuse [5,10,20].

Methods

Participants

The PNC includes 9,498 youths between the ages of 8 and 21 from the Philadelphia area. Importantly, the PNC is a community-based sample that was not selected or oversampled for psychiatric or substance-related problems. The study design and procedures have been described in detail elsewhere [22]. The present study included 4,208 youths aged 14–21 (mean age=16.90, *SD*=1.85; 55% female). Participants younger than 14 were not included here due to low endorsement of cannabis use. The sample was racially diverse: 57% White, 33% African American, 9% mixed race, and 1% Asian/Alaska Native/Pacific Islander.

Procedures

Participants over 18 provided written consent. Parental permission and written assent were obtained for participants under 18. Participants were assessed in private spaces separate from their parents/guardians and informed that their responses would be kept confidential with the exception of legal reporting requirements related to child abuse or self/other harm. The Institutional Review Boards at the University of Pennsylvania and Children's Hospital of Philadelphia approved study procedures.

Measures

Cannabis use—Cannabis use was assessed with an abbreviated and locally computerized version of the Minnesota Center for Twin and Family Research self-report substance use measure [23]. Participants reported on lifetime use, age at first use, and frequency of current use of cannabis, alcohol, and tobacco, as well as lifetime and past year use of various other substances (e.g., inhalants, cocaine). Five participants were missing cannabis use data and 32 participants were excluded for endorsing use of fake drugs [24], resulting in a final analytic sample of 4,171 youths.

We categorized participants as frequent cannabis users, occasional cannabis users, or nonusers. Frequent users reported using cannabis "3–4 times/week" or "every day or nearly every day" over the past year. Occasional users reported either a) using cannabis "1–2 times/week" or less over the past year or b) lifetime cannabis use. To examine associations between early cannabis use and PS symptoms, we categorized participants 16 years and older (n=2,699) as early users (before age 16), later users (16 years or later), or nonusers [12,14]. These criteria were also applied to create variables reflecting frequency of use and age at first use of alcohol and tobacco.

We grouped cannabis users by patterns of polysubstance use. We created variables reflecting: a) cannabis and alcohol use (Cannabis+Alcohol), b) cannabis and tobacco use (Cannabis+Tobacco), c) cannabis and other substance use (Cannabis+Other), and d) frequent cannabis and frequent tobacco use (Frequent Cannabis+Tobacco). There were too few frequent alcohol users to create a frequent cannabis and frequent alcohol use group.

Psychopathology—Major psychopathology domains were screened using GOASSESS, a computerized, structured interview adapted from the K-SADS [see 22]. This interview assesses lifetime prevalence, symptom frequency/duration, and distress/impairment across multiple domains of psychopathology, and treatment history. As in prior reports, we created summary variables reflecting endorsement of significant symptoms of any mood, anxiety, or behavioral disorder. Symptoms were considered "significant" if they approximated DSM-IV criteria for frequency/duration and were accompanied by significant distress/impairment (i.e., a rating of ≥ 5 on separate 11-point scales from 0="no bother/problems" to 10="extremely serious bother/problems").

Psychosis spectrum—Three screening tools, embedded within the GOASSESS interview, were used to determine PS classification [see 5, for details]. Past year subclinical positive symptoms were assessed with the assessor-administered 12-item Prime Screen-Revised [25,26], which asks participants to rate agreement (from 0=definitely disagree to 6=definitely agree) with statements describing psychotic-like thoughts and experiences. Clinical threshold levels of positive symptoms (i.e., lifetime delusions or hallucinations) were assessed with the K-SADS psychosis screen questions. Subclinical negative/disorganized symptoms were assessed with six items from the Scale of Prodromal Symptoms [27], as previously detailed [5]. Given age effects on ratings of subclinical positive and negative/disorganized symptoms, two age-deviant indices were created to identify youth with extreme ratings on positive and/or negative/disorganized symptoms compared to age-mates [5].

Participants were categorized as PS if they met any of the following criteria: a) age-deviant scores of $z \geq 2$ on subclinical positive or negative/disorganized symptoms, b) extreme agreement on subclinical positive symptoms using traditional criteria (at least one PRIME Screen-Revised item rated 6 "definitely agree" or at least three items rated 5 "somewhat agree" [26], or c) threshold delusions or hallucinations occurring outside the context of physical illness or substance use that persisted for at least one day and were accompanied by significant impairment or distress (a rating of at least 5 on 0–10 scales). PS classification in the PNC has been shown to be a valid and clinically significant indicator of psychosis risk that is associated with comorbid psychopathology, reduced global functioning, neurocognitive deficits, and structural brain abnormalities consistent with those seen in adults with psychosis [5,28,29].

Trauma exposure—Eight items from the PTSD section of the GOASSESS interview were used to create an indicator of trauma exposure. Given evidence that adverse experiences characterized by hostility, threat, and intent to harm may be particularly strong risk factors for psychosis [30], we created a three-level variable reflecting assaultive trauma exposure, non-assaultive trauma exposure, and no trauma exposure.

Intellectual function—The Reading subtest of the Wide Range Achievement Test-4 (WRAT-4) [31] was used as an IQ estimate.

Family history of substance abuse—Family history of substance abuse was coded from adult proband or collateral informant responses to an abbreviated version of the Family Interview for Genetic Studies [32], which screened for lifetime history of substance use problems and treatment in first-degree relatives of the proband.

Results

Analysis Overview

We performed preliminary analyses to calculate descriptive statistics and compare the PS and non-PS youth on the predictors and potential confounds. For the principal analyses, we used logistic regression to examine how cannabis use and polysubstance use related to PS classification. For follow-up symptom-level analyses, we used logistic regression to examine how cannabis use and polysubstance use related to each of the symptom criteria for determining PS classification described in the Methods section.

Preliminary Analyses

Descriptive statistics are presented in Tables 1 and 2. Notably, PS youth differed from non-PS youth on many of the covariates included in the analyses.

Principal Analyses

Cannabis Use, Polysubstance Use, and PS Classification—Although several significant associations emerged in the unadjusted analyses, cannabis use by itself was not associated with increased odds of PS classification after adjusting for confounds. However, Cannabis+Tobacco, Frequent Cannabis+Tobacco, and Cannabis+Other were each associated with increased odds of PS classification (Table 3).

Follow-up Symptom-Level Analyses

Subclinical symptoms—Cannabis use alone was not associated with subclinical positive symptoms (Table 4). However, Cannabis+Other was associated with age-deviant scores and extreme agreement on the positive symptom scale. In addition, frequent cannabis users were more likely to have high age-deviant scores on the subclinical negative/disorganized symptom scale relative to nonusers. Correcting for multiple comparisons reduced all significant symptom-level findings to trends.

Threshold delusions/hallucinations—Neither cannabis use nor polysubstance use was associated with threshold delusions/hallucinations.

Discussion

Despite increasing rates of cannabis use among US youth [1,2] and widespread interest among researchers and clinicians in the potential connections between cannabis use and psychotic symptoms and disorders [10], almost no research has examined how cannabis use

relates to PS symptoms in non-help-seeking US youth. We utilized data from a large sample of adolescents and young adults in the PNC to address this gap in the literature.

Cannabis Use, Polysubstance Use, and the Psychosis Spectrum

In contrast to recent findings in another US cohort [16], we found little evidence for associations between cannabis use by itself and PS symptoms. In adjusted analyses, neither frequent nor early cannabis use predicted increased odds of PS classification. It is possible that these null findings are due to our inclusion of various important confounds (e.g., concurrent use of other substances, comorbid psychopathology, trauma exposure, IQ) that could account for the previously reported associations between cannabis use and PS symptoms. Alternatively, it is possible that persistent cannabis use across adolescence, rather than frequency of use at any single point in time, is more predictive of PS symptoms. This possibility is supported by the findings of Bechtold and colleagues [16].

Given the relatively young age of our sample, the null findings related to early cannabis use may suggest that the effects of early use on PS symptoms emerge later in development. PNC participants are still in the developmental period during which early signs of psychosis risk typically emerge. As such, participants who did not currently endorse PS symptoms may subsequently develop these symptoms, and links with cannabis use may then emerge. Alternatively, it may be that cumulative use over time, rather than early use, is associated with PS symptoms [10,16], and that cumulative use effects may not appear until after adolescence. We also note that we limited our examination of the effects of early cannabis use to participants aged 16 and older, which reduced our sample size and potentially decreased our statistical power to detect small effects.

In follow-up analyses, we found that frequent cannabis use was associated with greater subclinical negative/disorganized symptoms. Although this result was reduced to a trend after correcting for multiple comparisons, it is noteworthy given the limited examination of negative/disorganized symptoms in this literature and consistency with previous findings. In a prior study of non-US community youth, frequent cannabis use was associated with more severe subclinical negative symptoms [12]. In addition, THC administration has been found to induce transient, schizophrenia-like negative (as well as positive) symptoms in healthy individuals [33]. Despite these previous findings, reverse causation is a possibility. Perhaps young people experiencing negative symptoms such as social anhedonia or diminished experience and expression of emotion use cannabis to alleviate these symptoms. Although previous studies have cast doubt on the reverse causality hypothesis [16,34], these studies focused only on subclinical positive symptoms. Future examination of the reverse causality hypothesis with subclinical negative/disorganized symptoms is warranted.

More compelling evidence emerged for associations between polysubstance use among cannabis users and PS symptoms. Yet, it is important to note that these effects were modest in size. Cannabis use combined with tobacco or other substance use was associated with increased odds of PS classification. In addition, the follow-up symptom-level analyses indicated that polysubstance use was associated with subclinical positive symptoms (although these symptom-level findings were reduced to trends after correcting for multiple comparisons). These findings are consistent with evidence indicating that use of tobacco and

other illicit substances (e.g., amphetamines) is associated with psychosis risk [35,36]. It is possible that using other substances in conjunction with cannabis heightens the psychoactive effects of cannabis, resulting in greater endorsement of odd/unusual thinking or perceptual abnormalities. For example, the common practice of including tobacco in cannabis preparations substantially increases the amount of THC inhaled per gram of cannabis [37], which may increase its potency and resultant psychosis risk [38]. Further, previous work [21] found that users of both cannabis and other illicit drugs reported more positive symptoms than non-cannabis users and than users of both cannabis and legal drugs.

Threshold Delusions and Hallucinations

Neither cannabis use nor polysubstance use was associated with threshold delusions/hallucinations. Prior cohort studies [10] reporting links between cannabis use and threshold psychosis symptoms included adult participants rather than adolescents and young adults, making our findings difficult to compare. We also adjusted for potential confounds that have not always been considered. Associations between cannabis use and threshold symptoms may not emerge in predominantly adolescent samples in which symptoms may still be developing.

Although speculative, another possibility is that individuals who show early development of threshold delusions and hallucinations represent a sub-group that is distinct from those who develop these symptoms later, and such symptoms may be driven by biological or environmental factors independent of cannabis or other substance use. Finally, although we supplemented the K-SADS psychosis section with structured questions, it is possible that this highly structured screen yielded more false positives, or conversely more false negatives, than would a comprehensive clinical interview. This, in turn, may have weakened the relationship between cannabis use and threshold symptoms. Ongoing longitudinal follow-up of youths with PS symptoms from the PNC will assist in differentiating among these possibilities.

Interpretation Considerations

The nature of the association between cannabis use and PS symptoms is likely complex and is still a source of considerable debate [39]. Although our findings suggest an association between polysubstance use among cannabis users and psychosis risk in US youth, the cross-sectional design of this study precludes a causal interpretation. Even if polysubstance use among cannabis users has a causal effect on psychosis risk, it is likely one of many contributing causes that interacts with other biological and environmental risk factors. Alternatively, the relation between substance use and PS symptoms may reflect shared genetic and/or environmental vulnerabilities rather than a causal effect [39]. Ongoing follow-up of the PNC sample will enable us to examine longitudinal associations among cannabis use, polysubstance use, and PS symptoms in US youth and draw firmer conclusions about causation.

Limitations and Future Directions

First, given the scale and timeframe of the PNC study, measures had to be designed to allow assessment of as many as 165 participants per week over a two-year period. Thus, the

substance use and PS assessments were, by necessity, relatively brief. Nonetheless, the PNC PS assessment has proven to be a clinically significant indicator of psychosis risk and has yielded findings consistent with those observed in the broader schizophrenia/psychosis literature [5,28,29]. In addition, the substance use measure used in the PNC has been shown to be a reliable and valid measure of substance use in previous large-scale adolescent studies [23,24]. Furthermore, like many studies in this area, cannabis use was measured via self-report, which can be susceptible to reporting biases. Future studies could utilize objective measures of cannabis use (e.g., hair samples) to confirm use and examine more specific questions about the effects of THC and other cannabinoid levels on PS symptoms.

Second, some PS symptoms show similarities to symptoms of acute intoxication (e.g., perceptual changes), and we did not directly account for potential intoxication effects in this study. However, we assessed a broad range of PS symptoms, many of which are unlikely to be due to intoxication. In addition, a meta-analysis of this literature concluded that the link between cannabis use and PS symptoms is unlikely to be due to transient intoxication effects [11]. Nonetheless, future work should include follow-up probes to confirm that endorsed PS symptoms were experienced outside of an intoxicated state, and we have included this in our ongoing prospective investigations of the cohort.

Third, although we accounted for many confounds in our analyses, some potentially important confounds were not measured in this study (e.g., urbanicity; 40), but should be considered in future work.

Fourth, the PNC is a young cohort still in the developmental period during which early signs of psychosis risk typically emerge and cannabis use begins, so ongoing follow-up will be critical for understanding the neurodevelopmental evolution of relations between cannabis use and psychosis risk.

Conclusions

Overall, we found minimal evidence for associations between cannabis use by itself and PS symptoms after adjusting for important confounds. More compelling evidence emerged for associations between polysubstance use among cannabis users and PS symptoms. This study highlights the importance of considering polysubstance use and confounding when examining associations between cannabis use and PS symptoms. Ongoing prospective evaluations will seek to enhance our understanding of the role that cannabis use and polysubstance use may play in the development of psychosis risk.

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Abbreviations

PS	psychosis spectrum
PNC	Philadelphia Neurodevelopmental Cohort

References

1. Center for Behavioral Health Statistics and Quality. Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015. HHS Publication No. SMA 15-4927, NSDUH Series H-50
2. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. JAMA Psychiatry. 2015; 72:1235.doi: 10.1001/jamapsychiatry.2015.1858 [PubMed: 26502112]
3. Lipari, R., Kroutil, LA., Pemberton, MR. NSDUH Data Review: Risk and protective factors and initiation of substance use: Results from the 2014 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality; p. 2015
4. Miech RA, Johnston LD, O'Malley PM, et al. Trends in use of marijuana and attitudes toward marijuana among youth before and after decriminalization: The case of California 2007–2013. Int J Drug Policy. 2015; 26:336–344. DOI: 10.1016/j.drugpo.2015.01.009 [PubMed: 25662893]
5. Calkins ME, Moore TM, Merikangas KR, et al. The psychosis spectrum in a young US community sample: findings from the Philadelphia Neurodevelopmental Cohort. World Psychiatry. 2014; 13:296–305. DOI: 10.1002/wps.20152 [PubMed: 25273303]
6. van Os J, Linscott RJ, Myin-Germeys I, et al. A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med. 2009; 39:179–195. DOI: 10.1017/S0033291708003814 [PubMed: 18606047]
7. Kelleher I, Connor D, Clarke MC, et al. Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. Psychol Med. 2012; 42:1857–1863. DOI: 10.1017/S0033291711002960 [PubMed: 22225730]
8. Kaymaz N, Drukker M, Lieb R, et al. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. Psychol Med. 2012; 42:2239–2253. DOI: 10.1017/S0033291711002911 [PubMed: 22260930]
9. Kelleher I, Corcoran P, Keeley H, et al. Psychotic symptoms and population risk for suicide attempt: a prospective cohort study. JAMA Psychiatry. 2013; 70:940–948. DOI: 10.1001/jamapsychiatry.2013.140 [PubMed: 23863946]
10. Gage S, Hickman M, Zammit S. Association between cannabis and psychosis: Epidemiologic evidence. Biol Psychiat. 2016; 79:549–556. DOI: 10.1016/j.biopsych.2015.08.001 [PubMed: 26386480]
11. Moore T, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. Lancet. 2007; 370:319–328. DOI: 10.1016/s0140-6736(07)61162-3 [PubMed: 17662880]
12. Stefanis N, Delespaul P, Henquet C, et al. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. Addiction. 2004; 99:1333–1341. DOI: 10.1111/j.1360-0443.2004.00806.x [PubMed: 15369572]
13. Zammit S, Allebeck P, Andreasson S, et al. Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. Brit Med J. 2002; 325:1199–1201. DOI: 10.1136/bmj.325.7374.1199 [PubMed: 12446534]
14. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. Br J Med. 2002; 325:1195–1199.

15. Niesink R, Rigter S, Koeter M, et al. Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–15. Addiction. 2015; 110:1941–1950. DOI: 10.1111/add.13082 [PubMed: 26234170]
16. Bechtold J, Hipwell A, Lewis DA, et al. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. Am J Psychiatry. 2016; 173:781–789. DOI: 10.1176/appi.ajp.2016.15070878 [PubMed: 27138587]
17. Bechtold J, Simpson T, White HR, et al. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. Psychol Addict Behav. 2015; 29:552–563. DOI: 10.1037/adb0000103 [PubMed: 26237286]
18. Moss H, Chen C, Yi H. Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. Drug Alcohol Depend. 2014; 136:51–62. DOI: 10.1016/j.drugalcdep.2013.12.011 [PubMed: 24434016]
19. Tomczyk S, Isensee B, Hanewinkel R. Latent classes of polysubstance use among adolescents-a systematic review. Drug Alcohol Depend. 2016; 160:12–29. DOI: 10.1016/j.drugalcdep.2015.11.035 [PubMed: 26794683]
20. Gage S, Hickman M, Heron J, et al. Associations of cannabis and cigarette use with psychotic experiences at age 18: Findings from the Avon Longitudinal Study of Parents and Children. Psychol Med. 2014; 44:3435–3444. DOI: 10.1017/s0033291714000531 [PubMed: 25066001]
21. Van Dam NT, Earleywine M, DiGiacomo G. Polydrug use, cannabis, and psychosis-like symptoms. Hum Psychopharm Clin. 2008; 23:475–485. DOI: 10.1002/hup.950
22. Calkins ME, Merikangas KR, Moore TM, et al. The Philadelphia neurodevelopmental cohort: Constructing a deep phenotyping collaborative. J Child Psychol Psychiatry. 2015; 56:1356–1369. DOI: 10.1111/jcpp.12416 [PubMed: 25858255]
23. Han C, Mcgue M, Iacono W. Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses. Addiction. 1999; 94:981–993. DOI: 10.1046/j.1360-0443.1999.9479814.x [PubMed: 10707437]
24. Derringer J, Krueger RF, McGue M, et al. Genetic and environmental contributions to the diversity of substances used in adolescent twins: a longitudinal study of age and sex effects. Addiction. 2008; 103:1744–1751. DOI: 10.1111/j.1360-0443.2008.02305.x [PubMed: 18821880]
25. Kobayashi H, Nemoto T, Koshikawa H, et al. A self-reported instrument for prodromal symptoms of psychosis: Testing the clinical validity of the PRIME Screen—Revised (PS-R) in a Japanese population. Schizophr Res. 2008; 106:356–362. DOI: 10.1016/j.schres.2008.08.018 [PubMed: 18809299]
26. Miller TJ, Cicchetti D, Markovich PJ, et al. The SIPS Screen: A brief self-report screen to detect the schizophrenia prodrome. Schizophr Res. 2004; 70(suppl1):78.
27. McGlashan, TH., Miller, TJ., Woods, SW., et al. Structured Interview for Prodromal Syndromes (version 4.0). Prime Clinic Yale School of Medicine; New Haven, CT: 2003.
28. Shanmugan S, Wolf DH, Calkins ME, et al. Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. Am J Psychiatry. 2016; 173:517–526. DOI: 10.1176/appi.ajp.2015.15060725 [PubMed: 26806874]
29. Satterthwaite TD, Wolf DH, Calkins ME, et al. Structural brain abnormalities in youth with psychosis spectrum symptoms. JAMA Psychiatry. 2016; 73:515–524. DOI: 10.1001/jamapsychiatry.2015.3463 [PubMed: 26982085]
30. Morgan C, Gayer-Anderson C. Childhood adversities and psychosis: Evidence, challenges, implications. World Psychiatry. 2016; 15:93–102. DOI: 10.1002/wps.20330 [PubMed: 27265690]
31. Wilkinson, GS., Robertson, GJ. Wide Range Achievement Test. 4th. Lutz: Psychological Assessment Resources; 2006.
32. Maxwell, ME. Family Interview for Genetic Studies. Clinical Neurogenetics Branch, Intramural Research Program. National Institute of Mental Health; 1996.
33. D'Souza D, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. Neuropsychopharmacol. 2004; 29:1558–1572. DOI: 10.1038/sj.npp.1300496

34. Fergusson DM, Horwood LJ, Ritter EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction. 2005; 100:354–366. DOI: 10.1111/j.1360-0443.2005.001001.x [PubMed: 15733249]

35. Gurillo P, Jauhar S, Murray RM. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry. 2015; 2:718–725. DOI: 10.1016/S2215-0366(15)00152-2 [PubMed: 26249303]

36. Barkus E, Murray RM. Substance use in adolescence and psychosis: Clarifying the relationship. Annu Rev Clin Psychol. 2010; 6:365–389. DOI: 10.1146/annurev.clinpsy.121208.131220 [PubMed: 20192802]

37. Van der Kooy F, Pomahacova B, Verpoorte R. Cannabis smoke condensate II: Influence of tobacco on tetrahydrocannabinol levels. Inhal Toxicol. 2009; 21:87–90. DOI: 10.1080/08958370802187296 [PubMed: 18855154]

38. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry. 2015; 2:233–238. DOI: 10.1016/s2215-0366(14)00117-5 [PubMed: 26359901]

39. Ksir C, Hart C. Cannabis and psychosis: A critical overview of the relationship. Curr Psychiatry Rep. 2016; 18doi: 10.1007/s11920-015-0657-y

40. Kuepper R, van OSJ, Lieb R, et al. Do cannabis and urbanicity co-participate in causing psychosis? Evidence from a 10-year follow-up cohort study. Psychol Med. 2011; 41:2121–2129. DOI: 10.1017/S0033291711000511 [PubMed: 21466750]

Table 1

Descriptive Statistics of Psychosis Spectrum and Predictor Variables in the Total Sample, PS Youth, and Non-PS Youth

Variable	(%) Total Sample	(%) PS Youth	(%) Non-PS Youth
Psychosis Spectrum			
Psychosis Spectrum Classification	19%	100%	0%
Positive: Age Deviant $z \geq 2$	6%	34%	0%
Positive: Extreme Agreement[a]	12%	64%	0%
Negative/Disorganized: Age Deviant $z \geq 2$	5%	26%	0%
Threshold Delusions/Hallucinations	5%	25%	0%
Cannabis User			
Occasional	23%	24%	22%
Frequent	5%	**11%**	**4%**
Early User[b]	17%	**26%**	**15%**
Later User	20%	20%	20%
Polysubstance User[c]			
Cannabis+Alcohol	16%	**19%**	**15%**
Cannabis+Tobacco	12%	**17%**	**11%**
Cannabis+Other	5%	**9%**	**4%**
Frequent Cannabis+ Tobacco	3%	**6%**	**2%**

Notes.

[a] Rated one 6 or three 5s on the PRIME Screen-Revised.

[b] Use before age 16 among participants ≥ 16 years old.

[c] Use of both substances in the past year. Bold indicates significant difference between PS and non-PS youth ($p < .05$).

Table 2

Descriptive Statistics of Potential Confounds in the Total Sample, PS Youth, and Non-PS Youth

Variable	(%) Total Sample	(%) PS Youth	(%) Non-PS Youth
Alcohol User			
Occasional	41%	42%	41%
Frequent	1%	2%	1%
Early User	25%	**30%**	**24%**
Later User	28%	**23%**	**29%**
Tobacco User			
Occasional	20%	21%	20%
Frequent	7%	**12%**	**6%**
Early User	17%	**24%**	**15%**
Later User	18%	18%	18%
Other Substance User			
Lifetime Other Substance	17%	**23%**	**16%**
Past Year Other Substance	14%	**19%**	**13%**
Significant Other Psychopathology			
Mood Disorder	20%	**41%**	**15%**
Anxiety Disorder	52%	**70%**	**48%**
Behavior Disorder	40%	**68%**	**33%**
Other Potential Confounds			
Trauma Exposure			
Assaultive Trauma	15%	**28%**	**12%**
Non-Assaultive Trauma	38%	**44%**	**36%**
Family History of Substance Abuse	21%	**30%**	**20%**
Racial Minority Status	43%	**61%**	**39%**
Female Sex	55%	53%	56%
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age	16.90 (1.85)	16.82 (1.87)	16.92 (1.84)
Maternal Education	14.39 (2.40)	**13.79 (2.28)**	**14.52 (2.40)**
WRAT-4 Reading Score (standardized)	101.83 (17.08)	**97.05 (17.16)**	**103.00 (16.84)**

Bold indicates significant difference between PS and non-PS youth ($p < .05$).

Table 3

Logistic Regression Analyses of Cannabis Use, Polysubstance Use, and Psychosis Spectrum Classification

	Psychosis Spectrum Classification	
	Odds Ratio (95% CI)	
Predictor	**Unadjusted**	**Adjusted**
Frequency Group[a] (nonuser = ref)		
Occasional	1.23* (1.02, 1.49)	1.01 (.75, 1.34)
Frequent	2.78* (2.09, 3.72)	1.51 (.97, 2.36)
Early Cannabis[b] (nonuser = ref)		
Early User	2.07* (1.62, 2.64)	1.28 (.78, 2.11)
Later User	1.19 (.92, 1.54)	1.14 (.73, 1.79)
Cannabis+Alcohol[c]	1.36* (1.11, 1.66)	.95 (.71, 1.27)
Cannabis+Tobacco[d]	1.67* (1.35, 2.07)	1.37* (1.02, 1.83)
Cannabis+Other[e]	2.25* (1.66, 3.06)	1.76* (1.18, 2.64)
Frequent Cannabis+Tobacco[f]	2.99* (2.06, 4.32)	1.73* (1.10, 2.70)

Notes.

*$p < .05$. All models adjusted for age, sex, racial minority status, maternal education, WRAT-4 reading subtest score, family history of substance use problems, significant symptoms of mood, anxiety, and behavioral disorders, and trauma exposure.

[a]Additional adjustment for: alcohol frequency group, tobacco frequency group, and past year other substance use.

[b]Additional adjustment for: early alcohol use, early tobacco use, past year cannabis use, and lifetime other substance use.

[c]Additional adjustment for: past year tobacco and other substance use.

[d]Additional adjustment for: past year alcohol and other substance use.

[e]Additional adjustment for: past year alcohol and tobacco use.

[f]Additional adjustment for: frequent alcohol use and past year other substance use.

Table 4

Logistic Regression Analyses of Cannabis Use, Polysubstance Use, and Psychosis Spectrum Classification Symptom Criteria

	Subclinical Positive ($z \geq 2$)		Subclinical Positive (extreme agreement)		Subclinical Negative ($z \geq 2$)		Threshold Delusions/Hallucinations	
	Odds Ratio (95% CI)		Odds Ratio (95% CI)		Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Predictor	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Frequency Group[a] (nonuser = ref)								
Occasional	1.10 (.81, 1.50)	.80 (.52, 1.23)	1.24 (.99, 1.55)	1.09 (.78, 1.52)	1.54* (1.11, 2.15)	1.20 (.74, 1.96)	1.13 (.80, 1.58)	.75 (.46, 1.21)
Frequent	2.85* (1.91, 4.26)	1.16 (.63, 2.16)	2.37* (1.70, 3.31)	1.25 (.75, 2.09)	4.01* (2.63, 6.12)	2.14* (1.11, 4.14)	1.52 (.87, 2.63)	.77 (.36, 1.68)
Early Cannabis Use[b] (nonuser = ref)								
Early User	1.84* (1.27, 2.67)	.77 (.35, 1.67)	1.98* (1.48, 2.65)	1.07 (.59, 1.93)	2.91* (1.94, 4.36)	1.63 (.75, 3.54)	1.24 (.78, 1.97)	.54 (.22, 1.33)
Later User	.97 (.63, 1.49)	.67 (.33, 1.38)	1.20 (.88, 1.64)	1.01 (.59, 1.71)	1.45 (.91, 2.31)	1.57 (.76, 3.22)	1.00 (.63, 1.60)	.69 (.31, 1.55)
Cannabis+Alcohol[c]	1.42* (1.04, 1.94)	.95 (.63, 1.45)	1.32* (1.04, 1.68)	1.00 (.71, 1.39)	1.74* (1.24, 2.43)	1.05 (.67, 1.65)	1.25 (.87, 1.81)	1.03 (.63, 1.69)
Cannabis+Tobacco[d]	1.66* (1.20, 2.31)	1.16 (.76, 1.78)	1.52* (1.18, 1.97)	1.27 (.91, 1.79)	2.10* (1.48, 2.98)	1.30 (.83, 2.05)	1.30 (.87, 1.93)	1.09 (.66, 1.81)
Cannabis+Other[e]	2.58* (1.69, 3.93)	2.24* (1.30, 3.88)	2.27* (1.60, 3.20)	1.95* (1.24, 3.08)	2.18* (1.33, 3.57)	1.09 (.58, 2.06)	2.08* (1.26, 3.46)	1.39 (.70, 2.76)
Frequent Cannabis+Tobacco[f]	2.27* (1.32, 3.91)	1.03 (.55, 1.90)	2.44* (1.60, 3.72)	1.26 (.76, 2.09)	3.58* (2.12, 6.03)	1.53 (.83, 2.82)	1.39 (.67, 2.89)	.78 (.32, 1.89)

Notes.

*$p < .05$. $z \geq 2$ = Age deviant Z-scores. extreme agreement = rated one 6 or three 5s on the PRIME-Screen Revised.

All models adjusted for sex, racial minority status, maternal education, WRAT-4 reading subtest score, family history of substance use problems, significant symptoms of mood, anxiety, and behavioral disorders, and trauma exposure. Subclinical positive symptoms (extreme ratings) and threshold delusions/hallucinations were adjusted for age.

[a]Additional adjustment for: alcohol frequency group, tobacco frequency group, and past year other substance use.

[b]Additional adjustment for: early alcohol use, early tobacco use, past year cannabis use, and lifetime other substance use.

[c] Additional adjustment for: past year tobacco and other substance use.

[d] Additional adjustment for: past year alcohol and other substance use.

[e] Additional adjustment for: past year alcohol and tobacco use.

[f] Additional adjustment for: frequent alcohol use and past year other substance use.