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Psychosis Spectrum Symptoms Before and After Adolescent Cannabis Use Initiation

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IMPORTANCE Adolescent cannabis use has been consistently posited to contribute to the onset and progression of psychosis. However, alternative causal models may account for observed associations between cannabis use and psychosis risk, including shared vulnerability for both cannabis use and psychosis or efforts to self-medicate distress from psychosis spectrum symptomology.

OBJECTIVE To test 3 hypotheses that may explain cannabis–psychosis risk associations by modeling psychosis spectrum symptom trajectories prior to and after cannabis initiation across adolescent development (approximately 10-15 years of age).

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from 5 waves across 4 years of follow-up from the Adolescent Brain Cognitive Development (ABCD) Study. The ABCD study is an ongoing large-scale, longitudinal study of brain development and mental and physical health of children in the US launched in June 2016. Data are collected from 21 research sites. The study included data from 11 868 adolescents aged 9 to 10 years at baseline. Three participants were excluded from the present analysis owing to missing data. Data analysis was performed from September 2023 to July 2024.

MAIN OUTCOMES AND MEASURES Discontinuous growth curve modeling was used to assess trajectories of psychosis spectrum symptoms before and after cannabis initiation. Control variables considered for this investigation were age, sex, internalizing and externalizing symptoms, socioeconomic status, parental mental health, and other substance use.

RESULTS Among the 11 858 participants at wave 1, the mean (SD) age was 9.5 (0.5) years; 6182 (52%) participants were male. Consistent with a shared vulnerability hypothesis, adolescents who used cannabis at any point during the study period reported a greater number of psychosis spectrum symptoms (B, 0.86; 95% CI, 0.68-1.04) and more distress (B, 1.17; 95% CI, 0.96-1.39) from psychosis spectrum symptoms relative to those who never used cannabis. Additionally, consistent with a self-medication hypothesis, the number of psychosis spectrum symptoms (B, 0.16; 95% CI, 0.12-0.20) and distress (B, 0.23; 95% CI, 0.21-0.26) from psychosis spectrum symptoms increased in the time leading up to cannabis initiation. We observed mixed evidence for an increase in psychosis symptoms after cannabis initiation (ie, contributing risk hypothesis).

CONCLUSION AND RELEVANCE The findings underscore the importance of accounting for shared vulnerability and self-medication effects when modeling cannabis–psychosis risk associations.

Supplemental content

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Individuals who use cannabis are at a 2- to 4-fold increased risk of psychosis relative to those who never use cannabis.[1-3] This risk is further increased for individuals who initiate cannabis use in childhood and early adolescence.[4-6] Cannabis initiation in early adolescence has been associated with earlier onset of psychotic disorders, more severe symptoms, and greater likelihood of symptom relapse among those who develop psychosis.[4,5,7-10] Cannabis is the most frequently used illicit substance among adolescents, and this trend is increasing (from 11% to 22% over the past 2 decades) alongside a decrease in its perceived risk of harm among adolescents (from 36.3% to 25% for weekly use).[11,12] Thus, it is becoming increasingly important to understand the association between adolescent cannabis initiation and psychosis spectrum symptomology to inform cannabis-psychosis risk models and early intervention efforts.

Debate continues regarding the nature of the association between adolescent cannabis use and psychosis risk.[13,14] For example, it has been theorized that adolescent cannabis use may causally contribute to the emergence of psychosis via the disruption of normative neurodevelopmental processes[15,16] (ie, the contributing risk hypothesis). According to this hypothesis, adolescent cannabis use may increase psychosis risk by disrupting or altering endocannabinoid system involvement in fundamental neuromaturation processes across key brain regions implicated in psychosis pathophysiology (eg, the prefrontal cortex and striatum).[4,17,18] These cannabis-induced changes may directly increase risk through subtle but enduring neurobiological changes during critical neuromaturation periods that are unmasked in early adulthood[17] or may reflect the neurobiological effects of cumulative exposure across longer time periods.[10,19]

Alternative models suggest that the association between cannabis use and psychosis may reflect a shared vulnerability for both cannabis use and psychosis or individuals' attempts to self-medicate in response to distress from psychosis spectrum symptomology. A shared vulnerability hypothesis[20] postulates that genetic, gestational, or environmental factors may confer vulnerability for both cannabis use and psychosis.[20,21] For example, research in twin samples has provided evidence that psychosis spectrum symptoms and adolescent cannabis use covary, in part, due to environmental factors,[22] with evidence for genetic contributions being mixed.[22,23] A self-medication hypothesis suggests that individuals may initiate cannabis use in an attempt to alleviate psychosis spectrum and secondary symptoms, such as anxiety and dysphoria, reflecting an effort to self-medicate by affected individuals (ie, the self-medication hypothesis).[24,25] Indeed, individuals across the schizophrenia spectrum have self-reported symptom management as one reason for using cannabis,[26,27] along with other factors, such as social influence (ie, friends using cannabis).[28]

Broadly, there is evidence supporting each of the contributing risk, shared vulnerability, and self-medication hypotheses.[4,20,29,30] However, there is a dearth of prospective longitudinal research in adolescence.[4] The handful of longitudinal studies that have examined associations between cannabis use and psychosis spectrum symptoms in adolescence[31-36] have largely focused on mid- to late adolescence, combined adolescent and adult samples, or used retrospective reports of adolescent cannabis use in adult samples. Further, most did not test whether cannabis use preceded symptom changes or vice versa. Of the studies that tested leading and lagging associations, evidence was generally consistent with the contributing risk hypothesis, such that cannabis use predicted subsequent symptoms.[33,36] Evidence was generally more mixed for the self-medication hypothesis, such that symptoms predicted subsequent cannabis use in some studies[36] but not in others.[16,33] Considering cannabis initiation in early adolescence has been consistently associated with greater psychosis risk relative to initiation in later developmental periods,[4,5,7-10] it is important to clarify the nature of the association between cannabis initiation and psychosis spectrum pathology in adolescence to substantively inform current cannabis-psychosis risk models. Further, given evidence that using cannabis even once in adolescence is associated with increases in psychosis spectrum symptoms across time,[33] clarifying the association between psychosis spectrum symptom trajectories and adolescent cannabis initiation would inform intervention and educational efforts aimed at reducing cannabis use during critical developmental periods in childhood and adolescence.

To this end, the present study used a 5-wave longitudinal research design to examine changes in psychosis spectrum symptoms before and after the initiation of cannabis use in childhood and early adolescence. Relative to previous research, this focus on childhood and early adolescence enabled us to model psychosis spectrum symptom trajectories before and after cannabis initiation and to capture initiation during a period that has been posited to confer the greatest risk.[4,33] We applied a novel life events analytic approach[37,38] to these data, which enabled a test of the contributing risk, shared vulnerability, and self-medication hypotheses. To evaluate the contributing risk hypothesis, we tested whether psychosis spectrum symptoms increased after cannabis initiation. To test the shared vulnerability hypothesis, we tested

Key Points

Question Does adolescent cannabis initiation contribute to changes in psychosis spectrum symptoms, reflect a shared vulnerability for both cannabis use and psychosis risk, or suggest efforts to self-medicate symptoms?

Findings This cohort study of 11 868 adolescents found that adolescents who used cannabis at any point during the study period reported a greater number of psychosis spectrum symptoms and more distress from symptoms relative to those who never used cannabis, providing evidence for shared vulnerability. Additionally, consistent with a self-medication hypothesis, the number of psychosis spectrum symptoms and distress from symptoms increased in the time leading up to cannabis initiation, whereas mixed evidence was observed for an increase in psychosis symptoms after cannabis initiation (ie, contributing risk).

Meaning These findings underscore the importance of accounting for shared vulnerability and self-medication effects when modeling cannabis–psychosis risk associations, particularly in adolescence.

Table 1. Descriptive Statistics of Substance Use and Clinical Measures[a]

	Wave, mean (SD) [range]				
	1 (n = 11 858)	2 (n = 11 213)	3 (n = 10 941)	4 (n = 10 308)	5 (n = 4737)
Age, y	9.48 (0.50) [8-11]	10.4 (0.64) [9-13]	11.57 (0.70) [10-14]	12.46 (0.68) [11-15]	13.64 (0.73) [11-16]
Sex assigned at birth, No. (% of wave)[b]					
Male	6182 (52)	5862 (52)	5735 (52)	5409 (52)	2478 (52)
Female	5673 (48)	5348 (48)	5203 (48)	4896 (48)	2258 (48)
Race and ethnicity, No. (% of wave)[c,d]					
Asian[e]	251 (2)	240 (2)	231 (2)	220 (2)	110 (2)
Black	1782 (15)	1594 (14)	1553 (14)	1354 (13)	505 (11)
Hispanic	2407 (20)	2221 (20)	2157 (20)	2067 (20)	972 (21)
White	6170 (52)	5982 (53)	5846 (53)	5582 (54)	2678 (57)
Multiple or other[f]	1246 (11)	1174 (10)	1153 (11)	1084 (11)	472 (10)
Substance use, No. (% of full sample)					
Cannabis[g]	9 (0.08)	17 (0.15)	30 (0.27)	86 (0.84)	155 (3.28)
Nicotine[h]	53 (0.45)	26 (0.23)	61 (0.56)	144 (1.40)	201 (4.25)
Alcohol[i]	21 (0.18)	8 (0.07)	27 (0.25)	78 (0.76)	137 (2.90)
Cannabis + nicotine, No. (% of cannabis users)	3 (33)	5 (29)	15 (50)	48 (56)	102 (66)
Cannabis + alcohol, No. (% of cannabis users)	0	0	4 (13)	24 (28)	61 (39)
PQB-C score					
No. of symptoms	2.63 (3.56) [0-21]	1.93 (3.19) [0-21]	1.59 (2.83) [0-21]	1.29 (2.48) [0-21]	1.15 (2.33) [0-19]
Distress	6.32 (10.61) [0-104]	4.62 (9.38) [0-117]	3.64 (7.89) [0-89]	2.90 (6.63) [0-70]	2.64 (6.60) [0-84]
CBCL score					
Internalizing	5.05 (5.53) [0-51]	5.12 (5.56) [0-48]	4.94 (5.62) [0-50]	5.15 (5.84) [0-49]	5.14 (6.11) [0-50]
Externalizing	4.46 (5.87) [0-49]	4.18 (5.66) [0-47]	3.93 (5.52) [0-50]	3.91 (5.45) [0-48]	3.49 (5.21) [0-42]

Abbreviations: CBCL, Child Behavior Checklist; PQ-BC, Prodromal Questionnaire–Brief Child Version.

[a] Values and percentages are derived from nonmissing complete cases.

[b] Three participants who identified as intersex were coded as missing for this variable.

[c] Race and ethnicity data were collected via caregiver report and included to characterize the representativeness of the sample.

[d] Two values were missing at wave 1, 2 at wave 2, 1 at wave 3, and 1 at wave 4.

[e] Includes Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, and other Asian (unspecified).

[f] Multiple or other included Native American/Alaska Native, Native Hawaiian or Other Pacific Islander, multiple and other (unspecified) consolidated owing to small numbers.

[g] A total of 263 participants (2.2%) ever used cannabis.

[h] A total of 413 participants (3.5%) ever used nicotine.

[i] A total of 239 participants (2.0%) ever used alcohol.

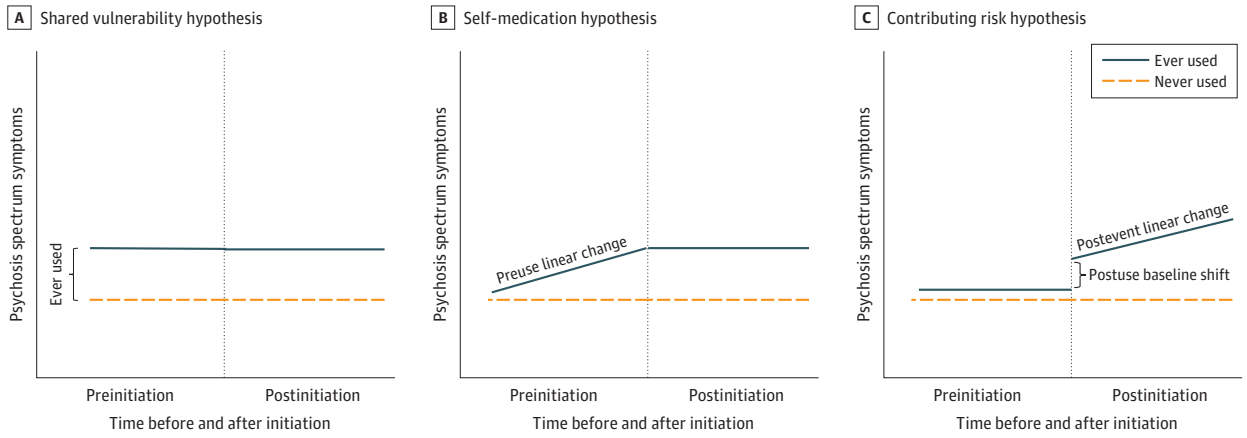
whether psychosis spectrum symptoms differed between adolescents who used cannabis and those who did not. To evaluate the self-medication hypothesis, we tested whether psychosis spectrum symptoms increased leading up to the initiation of cannabis use. We also tested if associations were unique to cannabis and psychosis spectrum symptoms or if they were shared with other substances (ie, nicotine and alcohol) or if they could be explained by broader psychopathology dimensions (ie, internalizing and externalizing symptoms). In this way, the study builds on the current literature, as no previous work has examined trajectories of psychosis spectrum symptoms in the period immediately before and after cannabis initiation to test the 3 most prominent competing hypotheses for cannabis-psychosis risk associations. A key novel aspect of this study is its ability to disentangle drivers of cannabis initiation from the outcomes of cannabis initiation, increasing the internal validity of tests of the contributing risk hypothesis. Our focus on the earliest developmental period in which cannabis initiation typically occurs enabled us to use this unique design by capturing the period before and after initiation without reliance on retrospective reporting.

Methods

Participants

The Adolescent Brain Cognitive Development (ABCD) study is an ongoing large-scale, longitudinal study of brain development and mental and physical health of children in the US (N = 11 868) launched in June 2016.[39-41] Data are collected from 21 research sites, which are geographically distributed across the nation's 4 major regions. For each site, the catchment area was defined as all schools within 50 miles of the research institution.[42] Centralized institutional review board approval was obtained from the University of California, San Diego, institutional review board. Verbal assent was obtained for individuals younger than 18 years with written informed consent obtained from their legal guardians. Analyses used data from all participants at all waves (ie, 1-5) of the ABCD Study 5.0 Data Release. Participants' demographic characteristics are shown in **Table 1**. Race and ethnicity data were collected via caregiver report and included to characterize the representativeness of the sample. See the eMethods in Supplement 1 for inclusion and exclusion criteria and study site locations. Three

Figure 1. Illustrations of Potential Conceptual Patterns of Alternative Models



The figure depicts expected patterns of psychosis spectrum symptom trajectories if a shared vulnerability hypothesis, self-medication hypothesis, or contributing risk hypothesis is supported. These patterns and hypotheses are not mutually exclusive and are meant to illustrate the primary effect consistent with each hypothesis. As such, observed findings may consist of combinations of these patterns.

participants were excluded from the analytic sample because they did not have outcome data at any measurement wave or because they were missing data on 1 or more covariates. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Measures

Descriptive statistics of study measures are shown in Table 1. Detailed descriptions of measures are reported in the eMethods in Supplement 1. Substance use was assessed using the ABCD study's semistructured Substance Use Interview.[43] Substance use initiation was defined as the date of first use as self-reported by the participant (see the eMethods in Supplement 1 for details). Some participants reported substance use but had missing dates for their first use. We imputed their first use date by subtracting 6 months from the interview date at which they first reported using the substance (ie, the midpoint between measurement waves). Psychosis spectrum symptoms and distress from symptoms were assessed with the Prodromal Questionnaire-Brief Child Version.[44] Consistent with previous research,[45-47] total psychosis spectrum symptoms and distress from symptoms were calculated (ie, total score and distress score). The parent-reported Child Behavior Checklist[48] was used to assess internalizing and externalizing symptoms.

Statistical Analysis

Data were analyzed using the lme4 package[49] in R version 4.3.1 (R Foundation). R code is available on OSF.[50] We used 3-level discontinuous growth curve models,[37,51] which use both time-invariant and time-varying predictors to model associations between the onset of life events (ie, initiation of cannabis use) and outcomes (eg, psychosis spectrum symptoms). Because psychosis spectrum symptoms were assessed with count variables, we used generalized linear mixed models with the Poisson likelihood and log link function. Individual data points were nested within participants, which were nested within families and sites. In the statistical models, we did not include within-site nesting as it only accounted for approximately 3% of the variance in psychosis spectrum symptoms. It was computationally impossible to estimate random effects for all time-varying predictors because the total number of estimated random effects would exceed the number of available data points. Thus, consistent with prior research using this modeling approach,[37] we modeled fixed and random intercepts and only fixed effects for all time-varying predictors. See the eMethods in Supplement 1 for the model equation for the primary model, details on how missing data were handled, attrition analyses, and sensitivity analyses including random slopes. **Figure 1** provides an illustration of conceptual patterns consistent with the contributing risk, shared vulnerability, and self-medication hypotheses. Two-tailed *P* values less than .05 were considered statistically significant.

Time-Invariant Effects Indicating Group Differences

More psychosis spectrum symptoms among participants who used cannabis at any point during the study period (compared to participants who never used cannabis) would be consistent with the shared vulnerability hypothesis. To model these differences, we created a dummy variable called ever used, which was coded 1 for participants who used cannabis at any point during the study period and 0 for those who never used cannabis. We applied this same approach to nicotine and alcohol use.

Time-Varying Effects Indicating Within-Person Change

We predicted within-person changes in psychosis spectrum symptoms from age and 3 additional time-varying predictors related to cannabis initiation. First, the preuse linear change predictor reflects the rate of linear change in the outcome (ie, psychosis spectrum symptoms) leading up to the life event (ie, initiation of cannabis use). To compute the preuse linear change predictor, we subtracted the date of first use from each inter-

view date. This resulted in a linear variable with negative values on all occasions preceding cannabis use (eg, −2 indicates an interview date 2 years prior to cannabis initiation). At all time points after cannabis initiation, the preuse linear change was coded as 0. Increases in psychosis spectrum symptoms leading up to cannabis initiation would be consistent with the self-medication hypothesis.

Second, the postuse shift predictor indicates a change in an outcome variable (ie, psychosis spectrum symptoms) after a life event (ie, initiation of cannabis use). This is a dummy variable with a value of 0 for the measurement occasions preceding cannabis initiation and a value of 1 for measurement occasions after cannabis initiation. Third, the postuse linear change predictor reflects linear change in the outcome (ie, psychosis spectrum symptoms) after the event (ie, initiation of cannabis use). To compute the postuse linear change predictor, we subtracted each interview date from the date of first use. This resulted in a linear variable with positive values on all occasions after cannabis initiation (eg, 2 indicates an interview date 2 years after cannabis initiation). At all points prior to cannabis initiation, the postuse linear change was coded as 0. Increases in psychosis spectrum symptoms after cannabis initiation, including a positive postuse shift or postuse linear change effect, would be consistent with a contributing effect of cannabis to psychosis.

Age (in years) was included as a time-varying covariate in all models. Sex assigned at birth (male = 0; female = 1) was included as a time-invariant covariate in all models. In sensitivity analyses, we additionally controlled for time-varying internalizing and externalizing symptoms, their random effects, and time-invariant nicotine and alcohol use. Age and internalizing and externalizing psychopathology were grand-mean centered. Additional sensitivity analyses controlling for more covariates and including survey weights to account for sample representativeness are reported in the eMethods in Supplement 1. Exploratory analyses examining the interactive effects of cannabis use with alcohol and nicotine use are reported in the eMethods in Supplement 1. Data analysis was performed from September 2023 to July 2024.

Results

Among the 11 858 participants at wave 1, the mean (SD) age was 9.5 (0.5) years; 6182 participants (52%) were male and 5673 (48%) were female; 3 individuals have sex coded as missing for this analysis (eMethods in Supplement 1). According to caregiver report, at wave 1, 251 participants (2%) were Asian, 1782 (15%) were Black, 2407 (20%) were Hispanic, 6170 (52%) were White, and 1246 (11%) were of another race or ethnicity, including Native American/Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races or ethnicities, and other (unspecified), consolidated owing to small numbers.

Trajectories of Psychosis Spectrum Symptoms

On average, the number of psychosis spectrum symptoms and distress from symptoms decreased across adolescence. Thus, when results reference increases in symptoms before or after cannabis initiation, this refers to relative increases after controlling for average age-related pattern.

Transactions Between Cannabis Initiation and Psychosis Spectrum Symptoms

See **Table 2** and **Figure 2** for statistics and visualization of modeled effects, respectively. Consistent with the shared vulnerability hypothesis, the significant positive effect of the ever used predictor indicates that participants who used cannabis at some point during the study period had more psychosis spectrum symptoms (B, 0.86; 95% CI, 0.68-1.04), as well as greater distress from symptoms (B, 1.17; 95% CI, 0.96-1.39), compared to those who never used cannabis (Table 2). Further, consistent with the self-medication hypothesis, the significant positive effect of the preuse linear change predictor indicates that both the number of (B, 0.16; 95% CI, 0.12-0.20) and distress from (B, 0.23; 95% CI, 0.21-0.26) psychosis spectrum symptoms increased leading up to cannabis initiation. There was not a significant effect of the postuse shift predictor on the number of psychosis spectrum symptoms. By contrast, there was a significant negative effect of the postuse shift predictor on distress from psychosis spectrum symptoms, indicating that distress went down in the time period of initiation. We did not observe support for the contributing risk hypothesis in primary analyses. Specifically, there were no significant positive effects of either the postuse shift or the postuse linear change predictor.

When controlling for time-varying internalizing and externalizing symptoms, their random effects, and time-invariant nicotine and alcohol use, the direction of effects remained the same, except that 2 additional effects now reached statistical significance. Specifically, a significant negative effect of the postuse shift predictor on the number of psychosis spectrum symptoms emerged. Further, a significant positive effect of the postuse linear change predictor on distress from psychosis spectrum symptoms emerged. These effects indicate that after cannabis initiation, there was an overall decrease in the number of and distress from psychosis spectrum symptoms. However, over time, distress from symptoms increased despite this initial short-term decrease. Results of all other sensitivity and exploratory analyses are reported in eTables 1-5 in Supplement 1.

Transactions Between Other Substances and Psychosis Spectrum Symptoms

See **Table 3** and Figure 2 for statistics and visualization of modelled effects, respectively. Consistent with the patterns observed for cannabis initiation, participants who used nicotine or alcohol at some point during the study period had more psychosis spectrum symptoms (nicotine: B, 0.66; 95% CI, 0.51-0.81; alcohol: B, 0.48; 95% CI, 0.28-0.68) and greater distress from symptoms (nicotine: B, 0.88; 95% CI, 0.71-1.06; alcohol: B, 0.53; 95% CI, 0.29-0.76) compared to those who never used nicotine or alcohol. Further, distress from symptoms increased leading up to both nicotine and alcohol initiation (nicotine: B, 0.03; 95% CI, 0.01-0.05; alcohol: B, 0.03; 95% CI, 0.00-0.06). In contrast to the cannabis findings, the number of psychosis spectrum symptoms did not significantly change

Table 2. Associations Between Cannabis Initiation and Psychosis Spectrum Symptoms

	No. of symptoms				Distress from symptoms			
	Base model		Sensitivity analyses		Base model		Sensitivity analyses	
Fixed effects	B (95% CI)	*P* value	B (95% CI)	*P* value	B (95% CI)	*P* value	B (95% CI)	*P* value
Intercept	−0.16 (−0.20 to −0.12)	<.001	−0.28 (−0.32 to −0.24)	<.001	0.26 (0.21 to 0.31)	<.001	−0.25 (−0.32 to −0.18)	<.001
Sex assigned at birth	−0.01 (−0.07 to 0.04)	.63	−0.05 (−0.11 to 0.00)	.07	0.08 (0.01 to 0.14)	.03	0.02 (−0.07 to 0.11)	.68
Age	−0.21 (−0.21 to −0.20)	<.001	−0.25 (−0.26 to −0.24)	<.001	−0.22 (−0.23 to −0.22)	<.001	−0.28 (−0.29 to −0.27)	<.001
CBCL internalizing score	NA	NA	0.01 (0.01 to 0.02)	<.001	NA	NA	−0.01 (−0.02 to 0.00)	.15
CBCL externalizing score	NA	NA	0.01 (0.01 to 0.02)	<.001	NA	NA	−0.02 (−0.03 to −0.01)	.003
Nicotine (ever used)[a]	NA	NA	0.56 (0.40 to 0.73)	<.001	NA	NA	1.02 (0.76 to 1.28)	<.001
Alcohol (ever used)[a]	NA	NA	0.21 (0.00 to 0.41)	.046	NA	NA	0.15 (−0.17 to 0.47)	.35
Cannabis (ever used)[a]	0.86 (0.68 to 1.04)	<.001	0.53 (0.31 to 0.76)	<.001	1.17 (0.96 to 1.39)	<.001	0.68 (0.35 to 1.02)	<.001
Preuse linear change[b]	0.16 (0.12 to 0.20)	<.001	0.17 (0.12 to 0.22)	<.001	0.23 (0.21 to 0.26)	<.001	0.25 (0.21 to 0.29)	<.001
Postuse baseline shift[c]	−0.08 (−0.20 to 0.05)	.24	−0.31 (−0.50 to −0.12)	.001	−0.17 (−0.25 to −0.09)	<.001	−0.78 (−0.93 to −0.62)	<.001
Postuse linear change[d]	0.04 (−0.04 to 0.12)	.32	0.04 (−0.08 to 0.16)	.52	0.01 (−0.04 to 0.06)	.77	0.13 (0.03 to 0.23)	.01
Random effects	**SD**	***P* value**	**SD**	***P* value**	**SD**	***P* value**	**SD**	***P* value**
Intercept for participants	0.90	NA	0.83	NA	1.25	NA	1.71	NA
Intercept for families	0.96	NA	0.95	NA	1.19	NA	1.30	NA
Internalizing symptoms	NA	NA	0.15	NA	NA	NA	0.41	NA
Externalizing symptoms	NA	NA	0.14	NA	NA	NA	0.45	NA

Abbreviations: CBCL, Child Behavior Checklist; NA, not applicable.

[a] The ever used predictor variable was coded 1 for participants who used cannabis at any point during the study period and 0 for participants who never used cannabis.

[b] The preuse linear change predictor variable reflects the rate of linear change in the outcome (ie, psychosis spectrum symptoms) leading up to the life event (ie, initiation of substance use).

[c] The postuse baseline shift dummy predictor variable was coded with a value of 0 for the measurement occasions preceding cannabis initiation and a value of 1 for measurement occasions after cannabis initiation that indicates a change in an outcome variable (ie, psychosis spectrum symptoms) after a life event (ie, initiation of substance use).

[d] The postuse linear change predictor variable reflects linear change in the outcome (ie, psychosis spectrum symptoms) after the event (ie, initiation of substance use).

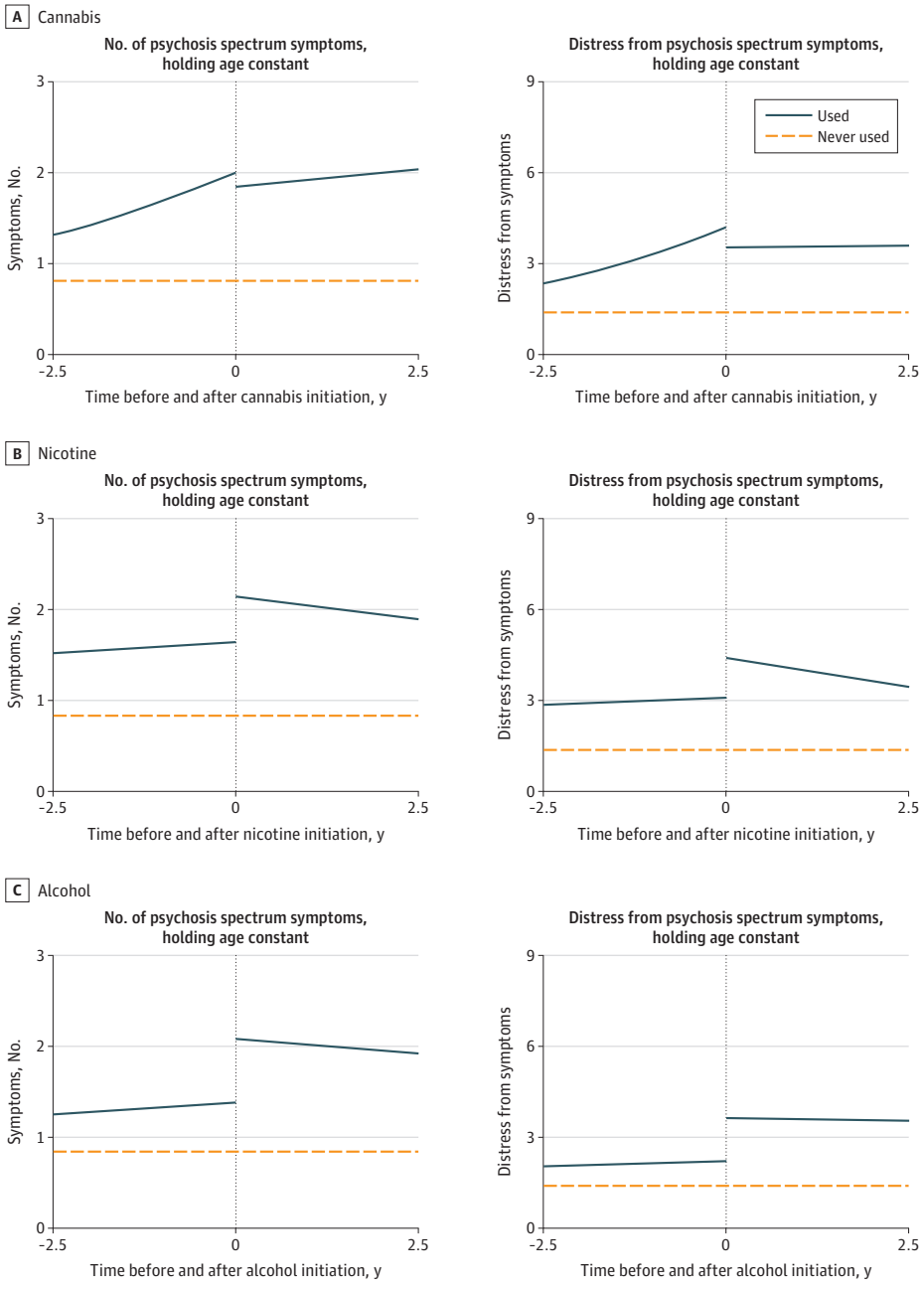
leading up to either nicotine or alcohol initiation (nicotine: B, 0.03; 95% CI, -0.00-0.07); alcohol: B, 0.04; 95% CI, -0.01-0.09). Also, in contrast to the cannabis findings, both the number of symptoms and distress from symptoms initially increased after the initiation of both nicotine and alcohol use. For nicotine only, after the initial post-initiation increase, distress from symptoms declined. See eTable 2 in Supplement 1 for sensitivity analyses controlling for externalizing and internalizing disorders.

Discussion

In this cohort study, several important findings emerged that substantively inform current models of cannabis-psychosis risk associations. First, consistent with a shared vulnerability hypothesis, adolescents who used cannabis at any point in the study period experienced more psychosis spectrum symptoms and greater distress from these symptoms relative to those who never used cannabis. Second, consistent with a self-medication hypothesis, both the number of psychosis spectrum symptoms and distress from symptoms increased leading up to cannabis initiation. We did not observe evidence for the contributing risk hypothesis in the primary analyses, as psychosis spectrum symptoms generally did not increase after cannabis initiation. However, mixed evidence for the contributing risk hypothesis was observed in sensitivity analyses. These findings underscore the importance of accounting for shared vulnerability and self-medication effects in theoretical models and empirical tests of cannabis-psychosis risk associations.

Within a shared vulnerability framework, adolescents who use cannabis may share certain time-invariant characteristics before, during, and after cannabis initiation that are also related to psychosis risk (eg, genetic, gestational, and environmental factors). In the present study, we modeled the effects of these characteristics by including a time-invariant predictor of psychosis spectrum symptomology that distinguished between adolescents who used cannabis at any point during the study period and those who never used cannabis. Thus, the present finding of greater psychosis spectrum symptoms among those who used cannabis suggests that there may be a

Figure 2. Observed Patterns of Substance Use Initiation and Psychosis Spectrum Symptom Associations



On average, the number of and distress from psychosis spectrum symptoms decreased across adolescence. Thus, we controlled for this average age-related pattern to better depict increases and decreases in psychosis spectrum symptoms before and after substance use initiation. The figure depicts the observed trajectories between the number of (left) and distress from (right) psychosis spectrum symptoms before and after cannabis, nicotine, and alcohol initiation. Each y-axis scale is 1 standard deviation.

shared vulnerability among adolescents for using cannabis and experiencing psychosis spectrum symptoms. Further, consistent with the self-medication hypothesis, the number of psychosis spectrum symptoms and distress from symptoms increased leading up to cannabis initiation. This provides longitudinal evidence that is consistent with cross-sectional retrospective research[52] and with individuals' self-reports of using cannabis to cope with symptoms across the psychosis spectrum.[24,26,27] We also observed a reduction in distress from symptoms after initiation. However, this finding does not indicate that adolescent cannabis use is an effective means for reducing psychosis spectrum symptoms. This point is particularly important given adolescents' already low perceptions of the risks of cannabis use.[11,12] Such conclusions would require study designs capable of examining the shorter-term (eg, in the moment) and longer-term (eg, across several years) effects of cannabis use on symptoms, and findings would need to be carefully weighed against dose-response evidence for cannabis contributing to psychosis pathogenesis.

We did not find evidence for the contributing risk hypothesis in primary analyses, and we found mixed evidence for the contributing risk hypothesis in sensitivity analyses. Importantly, this should not be construed as evidence against a causal or contributing role of adolescent cannabis use on psychosis

Table 3. Associations Between Nicotine and Alcohol Initiation and Psychosis Spectrum Symptoms

	Nicotine				Alcohol			
	No. of symptoms		Distress from symptoms		No. of symptoms		Distress from symptoms	
Fixed effects	B (95% CI)	*P* value	B (95% CI)	*P* value	B (95% CI)	*P* value	B (95% CI)	*P* value
Intercept	−0.17 (−0.20 to −0.13)	<.001	0.25 (0.20 to 0.30)	<.001	−0.16 (−0.19 to −0.12)	<.001	0.27 (0.22 to 0.32)	<.001
Sex assigned at birth	−0.02 (−0.07 to 0.03)	.50	0.07 (0.00 to 0.14)	.04	−0.02 (−0.07 to 0.04)	.54	0.07 (0.01 to 0.14)	.03
Age	−0.21 (−0.21 to −0.20)	<.001	−0.22 (−0.22 to −0.22)	<.001	−0.21 (−0.21 to −0.20)	<.001	−0.22 (−0.22 to −0.22)	<.001
Ever used[a]	0.66 (0.51 to 0.81)	<.001	0.88 (0.71 to 1.06)	<.001	0.48 (0.28 to 0.68)	<.001	0.53 (0.29 to 0.76)	<.001
Preuse linear change[b]	0.03 (−0.00 to 0.07)	.09	0.03 (0.01 to 0.05)	.008	0.04 (−0.01 to 0.09)	.09	0.03 (0.00 to 0.06)	.04
Postuse baseline shift[c]	0.27 (0.17 to 0.37)	<.001	0.35 (0.29 to 0.42)	<.001	0.41 (0.27 to 0.54)	<.001	0.50 (0.41 to 0.59)	<.001
Postuse linear change[d]	−0.05 (−0.10 to 0.00)	.06	−0.10 (−0.13 to −0.06)	<.001	−0.03 (−0.09 to 0.03)	.31	−0.01 (−0.05 to 0.04)	.70
Random effects	**SD**	***P* value**	**SD**	***P* value**	**SD**	***P* value**	**SD**	***P* value**
Intercept for participants	0.89	NA	1.25	NA	0.89	NA	1.25	NA
Intercept for families	0.96	NA	1.19	NA	0.96	NA	1.20	NA

Abbreviation: NA, not applicable.

[a] The used predictor variable was coded 1 for participants who used nicotine or alcohol at any point during the study period and 0 for participants who never used nicotine or alcohol.

[b] The preuse linear change predictor variable reflects the rate of linear change in the outcome (ie, psychosis spectrum symptoms) leading up to the life event (ie, nicotine and alcohol use initiation).

[c] The postuse baseline shift dummy predictor variable was coded with a value of 0 for the measurement occasions preceding cannabis initiation and a value of 1 for measurement occasions after cannabis initiation that indicate a change in an outcome variable (ie, psychosis spectrum symptoms) after a life event (ie, nicotine and alcohol use initiation).

[d] The postuse linear change predictor variable reflects linear change in the outcome (ie, psychosis spectrum symptoms) after the event (ie, nicotine and alcohol use initiation).

risk. Several lines of evidence implicate a dose-dependent association between cannabis use and psychosis risk, with risk increasing with greater frequency and quantity of use and higher cannabis potency.[3,4,6,9,53] Thus, limited findings for the contributing risk hypothesis in the present study relative to past research may be due to our focus on childhood and early adolescence when frequent and high-volume cannabis use is less common. Our focus on this early developmental period enabled us to model psychosis spectrum symptom trajectories before cannabis initiation and to capture cannabis initiation during a period that has been posited to be especially risky,[4,33] but it may have also limited our ability to observe contributing effects of cannabis use on psychosis spectrum symptomology. Evidence for the contributing risk hypothesis may emerge in later stages of development as cannabis use continues to increase throughout adolescence.[17]

Taking the above discussion together, an integrated theory of these 3 hypotheses may best capture the dynamic associations between cannabis use and psychosis risk throughout development. Specifically, shared risk vulnerabilities and attempts to self-medicate symptom-related distress may lead to initial cannabis initiation in adolescence, whereas subsequent increases in the frequency and quantity of cannabis use throughout adolescent development may then contribute to psychosis onset in young adulthood. This cannabis-psychosis risk association could be particularly insidious in the instance that cannabis use serves as a primary means for symptom management while also driving illness progression. Future releases of the ABCD Study will be well positioned to examine such cannabis-psychosis risk developmental models and questions.

Notably, the observed findings generally held when controlling for internalizing and externalizing symptoms, providing further support for unique associations between adolescent cannabis use and psychosis risk above and beyond broader adolescent psychopathology. We also observed a unique association between cannabis initiation and psychosis spectrum symptoms relative to other substance initiation. Specifically, the number of psychosis symptoms and distress from symptoms increased leading up to the initiation of cannabis use. By contrast, only distress from symptoms (but not the number of symptoms) increased leading up to nicotine and alcohol initiation. Together, this may suggest that whereas individuals may use substances more broadly to self-medicate from distress, there may be a unique association between the progression of psychosis spectrum symptomology in adolescence and cannabis initiation.

Limitations

The following limitations and constraints on generalizability should be considered. First, consistent with what would be expected in an early adolescent sample, rates of cannabis use were generally low. This prevented the current study from examining the potential effects of frequency, quantity, use type, or potency of cannabis, which may have revealed interesting findings particularly relevant for informing the contributing risk hypothesis. As cannabis use has been found to increase throughout adolescence,[54] future ABCD Study

releases should be well positioned to investigate such questions. Second, the current study focused on subclinical psychosis spectrum symptoms, which occur at a greater frequency in the general population than do psychotic disorders. Although evidence suggests that individuals who experience distress from psychosis spectrum symptoms are at greater risk of future psychotic disorders,[55,56] results may differ when examining formal psychosis symptoms or the onset of a psychotic disorder.

Conclusions

In sum, the current research provides support for the shared vulnerability and self-medication explanations for associations between cannabis use and psychosis risk. More research following up with individuals for a longer period after cannabis initiation is needed to provide a diagnostic test of the contributing risk hypothesis.

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Acquisition, analysis, or interpretation of data: All authors.
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