

Adolescent Cannabis Use and Adult Psychoticism: A Longitudinal Co-Twin Control Analysis Using Data From Two Cohorts

Jonathan D. Schaefer¹, Seon-Kyeong Jang², Scott Vrieze², William G. Iacono², Matt McGue²,
and Syla Wilson¹

¹ Institute of Child Development, University of Minnesota

² Department of Psychology, University of Minnesota

Observational studies have repeatedly linked cannabis use and increased risk of psychosis. We sought to clarify whether this association reflects a causal effect of cannabis exposure or residual confounding. We analyzed data from two cohorts of twins who completed repeated, prospective measures of cannabis use ($N = 1544$) and cannabis use disorder symptoms ($N = 1458$) in adolescence and a dimensional measure of psychosis-proneness (the Personality Inventory for *DSM-5* Psychoticism scale) in adulthood. Twins also provided molecular genetic data, which were used to estimate polygenic risk of schizophrenia. Both cumulative adolescent cannabis use and use disorder were associated with higher Psychoticism scores in adulthood. However, we found no evidence of an effect of cannabis on Psychoticism or any of its facets in co-twin control models that compared the greater-cannabis-using twin to the lesser-using co-twin. We also observed no evidence of a differential effect of cannabis on Psychoticism by polygenic risk of schizophrenia. Although cannabis use and disorder are consistently associated with increased risk of psychosis, the present results suggest this association is likely attributable to familial confounds rather than a causal effect of cannabis exposure. Efforts to reduce the prevalence and burden of psychotic illnesses thus may benefit from greater focus on other therapeutic targets.

General Scientific Summary

Epidemiological studies have repeatedly shown that individuals who use cannabis are more likely to develop psychotic disorders than individuals who do not. It has been suggested that these associations represent a causal effect of cannabis use on psychosis, and that psychosis risk may be particularly elevated when use occurs in adolescence or in the context of genetic vulnerability. This study, however, does not support these hypotheses, suggesting instead that observed associations are more likely due to confounding by common vulnerability factors.

Keywords: cannabis, marijuana, psychosis, adolescence, twin

Supplemental materials: <https://doi.org/10.1037/abn0000701.supp>

Jonathan D. Schaefer  <https://orcid.org/0000-0003-4112-9268>

Scott Vrieze  <https://orcid.org/0000-0003-3861-7930>

William G. Iacono  <https://orcid.org/0000-0002-3194-3090>

Matt McGue  <https://orcid.org/0000-0002-5580-1433>

Syla Wilson  <https://orcid.org/0000-0003-0144-524X>

The Institutional Review Board of the University of Minnesota approved these studies (“A Twin/Family Study of Vulnerability to Substance Abuse,” IRB protocol 8704M00020; “Adult Consequences of Youth Substance Use: Twin Study Enriched for SUD Risk, IRB protocol 1305M32821) at each wave.

Research reported in this article was supported by the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Human Genome Research

Institute of the National Institutes of Health under Awards T32MH015755 (Jonathan D. Schaefer), R01DA037904 (Scott Vrieze), R01DA044283 (Scott Vrieze), R01HG008983 (Scott Vrieze), R37DA005147 (William G. Iacono), R01DA036216 (William G. Iacono), R01DA042755 (Scott Vrieze and Matt McGue), R21AA026632 (Syla Wilson), and K01DA037280 (Syla Wilson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Partial results from this article have previously been presented as a poster and five-minute talk as part of the University of Minnesota College of Education and Human Development’s “Research Day” (March 16, 2021).

Correspondence concerning this article should be addressed to Jonathan D. Schaefer, Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN 55455, United States. Email: schae567@umn.edu

Acute cannabis intoxication can produce mild, transient psychotic experiences in healthy users and often worsens symptoms in individuals already diagnosed with a psychotic disorder (Alvarez-Jimenez et al., 2012; D'Souza et al., 2004). Cannabis use has also been repeatedly and consistently linked to increased odds of developing schizophrenia-spectrum disorders in longitudinal studies (Marconi et al., 2016), with larger increases in risk observed among individuals reporting higher frequencies of use as well as earlier age of use onset (van der Steur et al., 2020). Together, these streams of research have fostered a concern that cannabis use may contribute to the development of long-term psychotic illnesses, particularly when use occurs in adolescence.

Nevertheless, many researchers have warned against interpreting the results of these studies as establishing a causal link between cannabis use and psychotic symptoms that persists beyond the acute effects of cannabis intoxication (Ksir & Hart, 2016), noting that although the prevalence of cannabis use (and particularly heavy use) has increased, the incidence of psychotic disorder has remained largely stable over time (Frisher et al., 2009). These findings raise the possibility that the links between cannabis use and psychosis seen in observational studies reflect residual confounding, rather than a true causal effect of cannabis on psychosis. This possibility deserves serious consideration given converging streams of evidence showing (a) psychotic illness and substance use share many of the same environmental and contextual risk factors (Radua et al., 2018; Stone et al., 2012), (b) observational studies that adjust for larger numbers of confounders tend to report smaller effects (Moore et al., 2007), and (c) cannabis use and schizophrenia are characterized by considerable genetic overlap (Karcher et al., 2019; Pasman et al., 2018), with Mendelian randomization studies suggesting that polygenic risk of lifetime cannabis use or cannabis use disorder may be causally associated with schizophrenia risk (Johnson et al., 2021; Vaucher et al., 2018). It is also possible that cannabis exposure increases risk of psychosis only in a subset of particularly vulnerable individuals, which might explain why observed effects in the general population are often relatively small.

One powerful approach that can be helpful in testing for residual confounding involves comparing both monozygotic (MZ) and dizygotic (DZ) twins who differ in their cannabis exposure. Termed “discordant twin” or “co-twin control” analyses, this approach allows for examination of the effects of cannabis use while simultaneously controlling for all measured and unmeasured genetic and environmental factors shared between twins (McGue et al., 2010). If cannabis is a causal contributor to long-term psychotic illness, both MZ and DZ twins who use more cannabis in adolescence than their co-twins should be more likely to experience psychosis. If this “twin difference” is not observed, it suggests the association between cannabis and psychosis is likely driven by confounding familial factors.

To date, only two studies have tested links between cannabis and psychotic symptoms using co-twin comparisons. Both reported that these associations were largely attributable to shared familial factors, but also that they observed evidence consistent with a small, independent, and potentially causal effect (Karcher et al., 2019; Nesvåg et al., 2017). However, these studies are also characterized by a shared set of limitations, which constrains the implications of their findings. One limitation is that both studies used data from cross-sectional surveys of adult twins, which precluded tests focusing specifically on cannabis use occurring during the sensitive period of adolescence. A

second limitation is that both studies used single, lifetime assessments of cannabis use and use disorder, which are subject to the many well-documented sources of bias that reduce the accuracy of retrospective measures (e.g., normal forgetting, revisionist recall). Methodological research suggests that this reduction in accuracy may be particularly problematic in a twin study context, as exposure measurement error tends to bias within-twin-pair estimates more dramatically than corresponding unpaired associations (Frisell et al., 2012). Finally, the relatively coarse, binary measures of cannabis exposure used by these studies (including current use [yes/no], frequent use [$>100\times$ /not], and lifetime use disorder) are characterized by reduced variability relative to more continuous measures of cannabis use, and thus a reduced power to detect effects. Co-twin control studies of cannabis and psychosis that employ repeated, dimensional measures of cannabis use over time are thus needed to address these concerns and establish more accurate estimates of cannabis's true causal effects.

The present study aimed to address these needs by examining associations between adolescent cannabis exposure and psychosis in a twin sample that combines data from two longitudinal cohort studies at the Minnesota Center for Twin and Family Research (MCTFR). In contrast to the few previous co-twin control studies, twins in these cohorts were assessed repeatedly using gold-standard, self-report and interview measures of cannabis use administered prospectively throughout adolescence. Using these measures, we created a continuous index measuring cumulative cannabis use prior to and during adolescence (“adolescent cannabis use index”) and a binary variable indicating presence or absence of a diagnosable cannabis use disorder (i.e., abuse or dependence) prior to and during adolescence. Consistent with accumulating evidence indicating that psychosis is a dimensional phenomenon with similar etiological influences across clinical and subthreshold manifestations (Guloksuz & van Os, 2018), we assessed psychosis-proneness using the Psychoticism scale of the Personality Inventory for *DSM-5*, administered in adulthood. In addition to leveraging our twin design to test for evidence of a potential causal relationship between cannabis and psychoticism, we also examined whether associations might be stronger in subsets of genetically vulnerable twins by testing for interactions between cannabis exposure and polygenic risk of schizophrenia (Pardiñas et al., 2018), given reports documenting altered patterns of brain maturation in cannabis users at high polygenic risk of schizophrenia relative to users at lower risk (e.g., French et al., 2015).

Method

Participants and Procedures

Participants were drawn from two longitudinal studies of same-sex twin pairs at the MCTFR (Cohort 1: $N = 998$ [606 MZ/392 DZ], 47.9% male, 91% White; Cohort 2: $N = 1512$ [972 MZ/540 DZ], 49.7% male, 98% White), prospectively assessed every 3 to 7 years. The design of each study is summarized in Table 1. Briefly, participants in both cohorts were identified using publicly available birth certificates. To be eligible for study participation, twins had to reside within a day's drive of Minneapolis, live with at least one biological parent, and have no physical or mental conditions that would interfere with completion of a day-long, in-person assessment. Detailed

Table 1
Design of the Two Twin Studies Constituting the Combined Sample

Target age	Cohort 1			Cohort 2			Combined sample		
	Age mean (SD)	Years	N (%)	Age mean (SD)	Years	N (%)	Age mean (SD)	Years	N (%)
Adolescence									
11 years	11.9 (0.4)	1999–2006	998 (100%)	11.7 (0.4)	1990–1996	1,512 (100%)	11.8 (0.4)	1990–2006	2,510 (100%)
14 years	15.1 (0.6)	2003–2010	930 (93.2%)	14.8 (0.5)	1993–2000	1,404 (92.9%)	14.9 (0.6)	1993–2010	2,334 (93.0%)
17 years	17.9 (0.5)	2006–2012	913 (91.5%)	18.2 (0.7)	1996–2004	1,320 (87.3%)	18.1 (0.6)	1996–2004	2,233 (89.0%)
Adulthood									
24 years	24.4 (0.9)	2013–2017	809 (81.1%)	—	—	—	—	—	—
34 years	—	—	—	34.6 (1.3)	2014–2018	868 (57.4%)*	29.7 (5.2)	2013–2018	1,677 (66.8%)

Note. All information in Table 1 refers to the full twin cohorts rather than the analytic sample. Target age = targeted age of assessment wave. Years = calendar years during which each assessment wave took place.

* Only a subset of participants were invited to take part in the assessment targeting age 34 in Cohort 2; the N for this assessment wave is thus lower by design.

overviews of the MCTFR, twin cohorts, inclusion/exclusion criteria, and procedures and assessments are provided in previous articles (Iacono et al., 2006; Keyes et al., 2009; Wilson et al., 2019). Cohort 1 was enriched for childhood externalizing disorders via inclusion of a “high-risk” screened subsample in which at least one twin in each family exceeded a predefined threshold on a phone screen for childhood disruptive disorders (i.e., attention-deficit/hyperactivity, oppositional defiant, and conduct disorder). No participants in Cohort 2 were screened in this way. Participants in both cohorts completed an informed consent/assent process (parental consent for their own participation and that of their children under 18 years, twin assent before 18 years and consent after age 18 years).

Measures

Cannabis Use Index

Cannabis use and abuse was assessed at ages 11, 14, and 17 using either a Computerized Substance Use Inventory, the Diagnostic Interview for Children and Adolescents—Revised edition (DICA-R; Reich & Welner, 1988), the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (Robins et al., 1987), or a combination of these measures. All interview-based measures were administered by interviewers with at least a bachelor-level degree in psychology or related discipline who had completed intensive training in psychiatric assessment. We computed cannabis use indices at ages 11, 14, and 17 as twins’ mean scores on items from each measure assessing frequency of use (in the preceding year) and number of uses (generally assessed lifetime¹). Because responses to these items were skewed and sparse, they were transformed into ordinal measures (six categories per item) prior to averaging. For frequency of use, twins scored either 0 (no use), 1 (<1×/month), 2 (1–3×/month), 3 (1–4×/week), 4 (every day or nearly every day) or 5 (>1×/day). For number of uses, twins scored either 0 (no uses), 1 (1–4 uses), 2 (5–30 uses), 3 (31–100 uses), 4 (101–400 uses), or 5 (>400 uses or “too many to count”). Because twins’ scores on the cumulative versions of these items were highly correlated ($r = .86, p < .001$), we derived an index of cumulative cannabis use for each twin by averaging together all cannabis use index scores available across adolescence.

Cannabis Use Disorder

Both the DICA-R and SAM assess *Diagnostic and Statistical Manual of Mental Disorders (DSM)* diagnostic criteria for cannabis abuse and dependence. Diagnoses were based on twins’ self-report and parent-report using a best-estimate approach and were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*). Kappa reliabilities exceeded .90 (Iacono et al., 1999). Because *DSM-5* no longer distinguishes between cannabis abuse and dependence, we aggregated across diagnoses, assigning twins a “1” if they met criteria for either disorder in adolescence or a “0” if they did not.

Personality Inventory for DSM-5 (PID-5) Psychoticism

In young adulthood, a subset of twins ($n = 1613$) completed the Psychoticism scale from the Personality Inventory for *DSM-5* (PID-5). We excluded data from 69 participants (4.2%) with invalid responses to embedded validity questions (e.g., “two plus two equals four”), leaving 1,544 with valid data. Psychoticism is composed of three facet scales: Unusual Beliefs & Experiences (e.g., “I have seen things that weren’t really there,” “Sometimes I can influence other people just by sending my thoughts to them”; Cronbach’s alpha = .78), Eccentricity (e.g., “My thoughts often do not make sense to others,” “I’ve been told more than once that I have a number of odd quirks or beliefs”; Cronbach’s alpha = .95), and Perceptual Dysregulation (e.g., “Sometimes I feel ‘controlled’ by thoughts that belong to someone else,” “It’s weird, but sometimes ordinary objects seem to be a different shape than usual”; Cronbach’s alpha = .82). Pearson correlations among the Psychoticism facet scales range from $r = .63$ to $.70$ (all $ps < .001$). Previous research has established that Psychoticism scale scores can be used to differentiate between individuals with and without psychosis as well as patients with a psychotic disorder versus those with other psychiatric conditions (Bastiaens et al., 2019; Longenecker et al., 2020).

¹ Cohort 1 and female Cohort 2 participants assessed at the first follow-up wave targeting age 14 were asked to estimate their number of cannabis uses in the last 3 years, rather than lifetime. All other assessment waves in both cohorts assessed lifetime number of uses.

This document is copyrighted by the American Psychological Association or one of its allied publishers. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.

Polygenic Risk of Schizophrenia

Genotyping procedures used in MCTFR have been described previously (Miller et al., 2012). Briefly, participants were genotyped on Illumina 660W-Quad (Illumina, Inc., San Diego, California). Imputation was conducted using the Haplotype Reference Consortium panel and the Michigan imputation server (Das et al., 2016; McCarthy et al., 2016). We selected only twins of primarily European ancestry for polygenic scoring. To identify these individuals, we calculated four principal components (PCs) for the European sample in the 1000 Genomes Project Consortium (1000G; The 1000 Genomes Project Consortium, 2015), scored MCTFR genotypes with these 1000G PC weights using PLINK1.9 (Chang et al., 2015), and selected twins falling within the boundaries of the four 1000G European PCs.

Polygenic risk of schizophrenia was estimated using summary statistics from a recently published genome-wide association study (GWAS) of schizophrenia (Pardiñas et al., 2018). Prior to score estimation, we conducted the following quality-control procedures: (1) extracted variants from the European-ancestry subset of HapMap3, as these variants are well-characterized; (2) removed indels, multiallelic sites, variants falling within the MHC region (chr6:28477797–33448354), and those having a minor allele frequency less than .01; and (3) pruned MCTFR genotypes to the variants with imputation quality (R^2) greater than .7. Polygenic scoring was conducted using LDpred v.1.11, a Bayesian method that estimates posterior mean effect sizes from GWAS summary statistics conditioning on a genetic architecture prior and linkage disequilibrium (LD) of the reference sample (Vilhjálmsdóttir et al., 2015). Based on an infinitesimal model of complex traits (Boyle et al., 2017), we assumed the proportion of causal variants in the LDpred model to be 1.

Statistical Analyses

Statistical analyses were run using all twins with valid PID-5 Psychoticism data ($n = 1544$). There was no significant association between PID-5 completion and either measure of adolescent cannabis exposure (mean [SD] raw cannabis use index score for those included versus excluded = .26 [.52] versus .27 [.51], OR [95% CI] = .87 [.50, 1.52], $p = .629$; % with cannabis use disorder, included versus excluded = 13.0% versus 14.6%, OR [95% CI] = .82 [.36, 1.87], $p = .642$). Twins providing PID-5 Psychoticism data were also statistically comparable to twins missing this data in terms of zygosity (% MZ, included vs. excluded = 61.5% vs. 65.1%, OR [95% CI] = .56 [.22, 1.30], $p = .186$), but included slightly fewer males (% male, included vs. excluded = 43.4% vs. 58.0%, OR [95% CI] = .08 [.02, .26], $p < .001$) and tended to come from families with slightly higher maternal education (mean [SD] years of education, included vs. excluded = 14.3 [2.00] vs. 13.8 [1.88], OR [95% CI] = 1.62 [1.29, 2.14], $p < .001$). All twins who provided valid psychoticism data also provided sufficient data to allow computation of an adolescent cannabis use index score. Data on adolescent cannabis use disorder were missing for 86 twins who provided valid psychoticism data; however, these twins with missing data were statistically comparable to the rest of the sample ($n = 1458$) in terms of their adult psychoticism scores (mean [SD] raw psychoticism score, included vs. excluded = .40 [.40] vs. .44 [.42], $OR = .25$ [.03, 1.92], $p = .170$).

We examined associations between adolescent cannabis exposure and adult Psychoticism using (1) individual-level models, comparable to linear regression models in a sample of singletons, and (2) co-twin control models, which control for shared familial confounds. Our primary exposure variables were twins' cumulative adolescent cannabis use index scores and presence or absence of an adolescent cannabis use disorder; however, as a sensitivity analysis we also ran models using twins' scores on items assessing frequency of cannabis use or number of uses, averaged across assessment waves. These models generated the same substantive results as those ran using our primary exposure variables and are thus presented in the online supplemental materials (see Supplemental Tables 1–2).

Co-twin control analyses decompose each individual twin's cannabis exposure into between-pair and within-pair effects (Begg & Parides, 2003; McGue et al., 2014). The between-pair effect is represented by the twin pair's mean on either our cumulative cannabis use index or cannabis use disorder variable, and the within-pair effect is represented by the difference between the twin pair's mean and an individual twin's score. Ignoring covariates and the constant (intercept), the model can be written as

$$Y_{ij} = b_B * \bar{X}_j + b_W(X_{ij} - \bar{X}_j),$$

where Y_{ij} is the expected value of the outcome for the i_{th} twin in the j_{th} pair, X_{ij} is the use index score or use disorder status of the i_{th} twin in the j_{th} pair, and \bar{X}_j is the mean use index score or use disorder status for the j_{th} pair. This equation can be re-expressed using simple algebra as

$$Y_{ij} = b_{B*} * \bar{X}_j + b_W X_{ij},$$

with the between-pair effect now represented by b_{B*} to distinguish it from b_B in the original equation. Doing so yields the identical estimate of the within-pair, or exposure effect, while providing a more appropriate estimate of the between-pair effect (McGue et al., 2014). The between-pair effect in this parameterization largely captures genetic and shared environmental propensity toward cannabis use severity or disorder status among reared-together twins, independent of individual twins' cannabis use or use disorder status, and a significant between-pair effect suggests that differences in Psychoticism are consistent with a preexisting liability toward cannabis use or use disorder status.

In addition to these main analyses, we also conducted planned follow-up analyses testing for (1) associations between polygenic risk of schizophrenia and adult Psychoticism, (2) incremental contributions to Psychoticism from adolescent cannabis exposure and polygenic risk of schizophrenia, and (3) interactions between adolescent cannabis exposure and polygenic risk of schizophrenia. All analyses were conducted in R Studio Version 1.2.5019 using the "lmer" and "glmer" functions from the "lme4" package, which implement linear mixed effects models for continuous and binary outcomes, respectively, that account for the nested family structure. In all models, we included sex, zygosity, cohort membership, and age at time of outcome assessment as covariates. Models involving the schizophrenia polygenic score included additional covariates capturing the first 10 genetic principal components, with models testing for interactions between cannabis exposure and polygenic risk also including terms adjusting for possible

interactions between the schizophrenia Polygenic score (PGS) or cannabis exposure measures with covariates (Keller, 2014). Prior to analyses, twins' cannabis use index scores, scores on PID-5 Psychoticism and its respective facet scales, polygenic risk of schizophrenia, and all continuous covariates were standardized to a mean of 0 and standard deviation of 1 within the analytic sample ($n = 1,544$). Estimates are thus reported as standardized betas, with those for our measures of adolescent cannabis exposure reflecting the standard deviation increase in PID-5 Psychoticism scores associated either (a) with each standard deviation increase in cumulative adolescent cannabis use or (b) with an adolescent cannabis use disorder diagnosis (vs. not receiving this diagnosis).

Results

Descriptive data for our measures of cannabis use and disorder as well as PID-5 Psychoticism are presented in Table 2. Cannabis use was relatively common in our analytic sample, with approximately one third of participants (31.2%) reporting at least some cannabis use in adolescence, one in seven (13.0%) meeting criteria for an adolescent cannabis use disorder, and close to one in ten (8.9%) reporting at least one past-year period of at least weekly cannabis use. Among those who reported at least some cannabis use in our most recent adolescent assessment wave (targeting age 17 years), the mean score on our "frequency of use" item was 1.63 ($SD = 1.43$), suggesting cannabis use occurring between $<1\times$ /month and $1-3\times$ /month over the past year. Similarly, the mean number of uses reported at this wave by twins who endorsed at least some adolescent use was 2.33 ($SD = 1.46$), suggesting between 5 and 30 and 31-100 lifetime uses. Regarding twin discordance, 522 twin pairs (67.6%) had no difference in their cumulative adolescent cannabis use index scores, 214 pairs (27.7%) had a difference that was > 0 but ≤ 1 SD s, and 36 pairs (4.7%) had a difference > 1 SD s. For cannabis use disorder, 653 twin pairs (89.6%) were concordant in their adolescent cannabis use disorder status, whereas 76 pairs (10.4%) were discordant. Finally, regarding our primary outcome, 112 twin pairs had no difference in their PID-5 Psychoticism scores (14.5%), 602 pairs (78.0%) had a difference > 0 but ≤ 1 SD s, and 58 pairs (7.5%) had a difference > 1 SD .²

Twin-trait correlations for our exposure and outcome measures are presented in Table 3. The observation that all within-trait MZ twin correlations were < 1 suggests that unique environmental influences explain individual variability in each measure (although this can also be attributable to measurement error or epigenetic differences). The higher within-trait twin correlations in MZ twins relative to DZ twins indicate that phenotypic variation was also influenced by additive genetic factors. Finally, the generally higher cross-twin, cross-trait (i.e., cannabis-psychoticism) correlations in MZ versus DZ twin pairs suggest that genetic factors likely at least partially account for phenotypic cannabis-psychoticism associations.

Is Greater Cannabis Exposure in Adolescence Associated With Greater Psychoticism in Adulthood?

Results from individual-level models are presented in Table 4. Consistent with previous reports, these analyses indicated that each measure of adolescent cannabis exposure (i.e., use index and

use disorder) were associated with higher scores on the Psychoticism scale as well as its respective facets (for full model results, see Supplemental Table 3).

Previous studies have indicated that men and women use cannabis at different rates and amounts (see Calakos et al., 2017, for a review). This pattern also held true in our analytic samples, with males scoring significantly higher on the cumulative cannabis use index than females (mean raw score [SD] for males vs. females = .32 [.57] vs. .21 [.46]; b_{sex} [95% CI] = .10 [.04, .16], $p < .002$). However, interaction terms added to our individual-level models to capture sex differences in the association between each measure of cannabis exposure and psychoticism were all nonsignificant (all $ps > .07$), indicating that both types of cannabis exposure were associated with comparable increases in psychoticism in men and women.

Because our two cohorts differed in age at the time of PID-5 assessment by about 10 years, we tested for statistically significant differences between cohorts in the association between both measures of adolescent cannabis exposure and PID-5 Psychoticism scores. Although the interaction terms involving cannabis use disorder were statistically significant ($p < .05$), effects in all models were in the same direction across cohorts, and we thus present results from pooled analyses in the main text. Results from cohort-specific analyses can be found in Supplemental Tables 4-5.

Does Adolescent Cannabis Exposure Predict Greater Adult Psychoticism Independent of Shared Environmental and Genetic Factors, Consistent With a Causal Effect?

Results from co-twin control analyses are also presented in Table 4. Co-twin control models capitalize on twin differences to examine effects of cannabis exposure accounting for familial liability. In contrast to our individual-level analyses, these models indicated predominantly significant between-pair effects (estimates ranging from .14 to .20 for cannabis use index and from .43 to .59 for cannabis use disorder), suggesting an effect of preexisting, shared familial liability. They also indicated consistently small, nonsignificant within-pair effects (estimates ranging from $-.01$ to .01 for cannabis use index and from $-.04$ to .06 for cannabis use disorder), suggesting no effect of cannabis exposure (for full model results, see Supplemental Table 6). Interactions between twin differences in both measures of cannabis exposure and (1) sex and (2) zygosity tested in separate models were also consistently nonsignificant (all $ps > .133$ and .257, respectively).

Although our co-twin control models indicated virtually no effect of adolescent cannabis exposure on psychoticism once shared environmental and genetic factors are controlled for, it is reasonable to wonder whether this null result arises because differences in cannabis exposure among twins are generally small. Even in twin pairs discordant for adolescent cannabis use disorder, it is theoretically possible for one twin to just meet the cut-off for the diagnosis, and the other twin to fall just below the diagnostic

² Because standardization was conducted at the phenotypic level, twin differences for continuous variables (i.e., cannabis use index and adult psychoticism), as well as betas for corresponding the within-pair effects in co-twin control models, should be interpreted in terms of the SD for the analytic sample rather than the SD of twin differences.

Table 2
Descriptive Statistics for Adolescent Cannabis Exposure and Adult Psychoticism

Adolescent cannabis exposure	Cohort 1		Cohort 2		Combined sample	
	<i>M (SD)</i> /no. (%)	Range	<i>M (SD)</i> /no. (%)	Range	<i>M (SD)</i> /no. (%)	Range
11 Years						
Cannabis use index	0.00 (0.03)	0.00–0.50	0.00 (0.04)	0.00–1.00	0.00 (0.04)	0.00–1.00
Frequency of use*	0.33 (0.58)	0.00–1.00	0.00 (0.00)	0.00–0.00	0.17 (0.41)	0.00–1.00
Number of uses*	0.67 (0.58)	0.00–1.00	1.33 (0.58)	1.00–2.00	1.00 (0.63)	0.00–2.00
% with CUD	0 (0%)	—	0 (0%)	—	0 (0%)	—
14 Years						
Cannabis use index	0.12 (0.51)	0.00–4.50	0.19 (0.64)	0.00–4.50	0.16 (0.58)	0.00–4.50
Frequency of use*	1.33 (1.34)	0.00–4.00	1.65 (1.19)	0.00–4.00	1.53 (1.25)	0.00–4.00
Number of uses*	1.75 (1.23)	0.00–5.00	1.91 (1.10)	0.00–5.00	1.85 (1.15)	0.00–5.00
% with CUD	12 (2%)	—	16 (2%)	—	28 (2%)	—
17 Years						
Cannabis use index	0.58 (1.17)	0.00–5.00	0.69 (1.24)	0.00–5.00	0.64 (1.21)	0.00–5.00
Frequency of use*	1.61 (1.43)	0.00–5.00	1.65 (1.43)	0.00–5.00	1.63 (1.43)	0.00–5.00
Number of uses*	2.38 (1.46)	1.00–5.00	2.30 (1.45)	0.00–5.00	2.33 (1.46)	0.00–5.00
% with CUD	82 (12%)	—	94 (12%)	—	176 (12%)	—
Cumulative through 17 years						
Cannabis use index	0.23 (0.49)	0.00–3.17	0.28 (0.53)	0.00–3.00	0.25 (0.51)	0.00–3.17
% with CUD	86 (13%)	—	103 (13%)	—	189 (13%)	—
Adult psychoticism						
	<i>M (SD)</i>	Range	<i>M (SD)</i>	Range	<i>M (SD)</i>	Range
24 Years (Cohort 1)/34 Years (Cohort 2)						
PID-5 Psychoticism	0.48 (0.43)	0.00–2.21	0.32 (0.36)	0.00–2.13	0.40 (0.40)	0.00–2.21
Unusual beliefs & experiences	0.40 (0.44)	0.00–2.50	0.31 (0.39)	0.00–2.25	0.35 (0.42)	0.00–2.50
Eccentricity	0.67 (0.64)	0.00–2.85	0.43 (0.54)	0.00–2.69	0.54 (0.60)	0.00–2.85
Perceptual dysregulation	0.37 (0.37)	0.00–1.75	0.24 (0.30)	0.00–1.92	0.30 (0.34)	0.00–1.92

Note. All values are calculated based on the analytic sample (twins with PID-5 Psychoticism data and each measure of adolescent cannabis exposure; cannabis use index: $n = 1,544$, cannabis use disorder: $n = 1,458$). No. (%) = number of participants and percent of those with data. CUD = cannabis use disorder. Cannabis use index scores were calculated by averaging twins' scores on frequency of use and number of uses items at each wave (or just using twins' score on one item if data for the other was missing). Cumulative cannabis index scores were calculated by averaging available cannabis use index scores across each assessment wave.

* Summary statistics for frequency of use and number of uses items refer only to the subset of participants who endorsed using cannabis during this

threshold. To address this possibility, we identified twin pairs in which one twin scored ≥ 2 on our raw cannabis use index for at least one wave and the other twin reported complete cannabis abstinence (i.e., scored "0" on our measure of cumulative adolescent use). This created a subset of 41 twin pairs, roughly evenly matched on sex (24 male/17 female) and zygosity (18 MZ/23 DZ). Results from discordant twin models predicting Psychoticism and its constituent facets in this subsample as a function of cannabis use status (exposed vs. unexposed) and controlling for sex, zygosity, age, and cohort membership again indicated no significant association between twin differences in cannabis exposure and any outcome (Supplemental Table 7).

Do We Find Evidence Suggesting a Potential Causal Effect of Cannabis on Psychoticism in Genetically Vulnerable Individuals?

Although we observed no significant within-pair associations suggesting a causal effect of cannabis exposure on psychoticism in the full analytic sample, this does not rule out the possibility that cannabis may increase psychoticism in subsets of particularly vulnerable individuals. Consequently, we next conducted analyses examining this possibility using one of the most obvious indicators of potential vulnerability: polygenic risk of schizophrenia.

Results from these analyses are presented in Table 5. Our first set of models showed that, consistent with our expectations, twins with higher schizophrenia polygenic risk scores tended to score higher on our measure of adult psychoticism as well as its facet scales. Higher polygenic risk of schizophrenia was also associated with higher scores on our adolescent cannabis use index (b [95% CI] = .08 [.02, .14], $p = .014$), and higher likelihood of meeting criteria for an adolescent cannabis use disorder (OR [95% CI] = 1.53 [1.11, 2.20], $p = .010$). Our second set of models indicated that schizophrenia polygenic risk and each measure of cannabis exposure both generally made incremental contributions to the prediction of scores on the adult psychoticism scale and its facets. Our third set of models tested the hypothesis that cannabis and polygenic risk interact such that individuals with higher levels of genetic risk are more affected by adolescent cannabis exposure. Interactions between the cannabis use index and polygenic risk in these models were all nonsignificant (β s [95% CIs] ranging from $-.04$ [$-.10, .02$] to $.04$ [$-.02, .10$], all $ps \geq .213$). Similarly, all interactions between cannabis use disorder and polygenic risk in corresponding models were also nonsignificant (β s [95% CIs] ranging from $-.04$ [$-.20, .12$] to $.12$ [$-.04, .28$], all $ps \geq .141$), except in the model predicting Perceptual Dysregulation (β [95% CI] = $.17$ [.01, .34], $p = .038$). Nevertheless, because this single significant result would not survive correction for multiple testing, we conclude that results suggest little to no moderation of the

This document is copyrighted by the American Psychological Association or one of its allied publishers. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.

Table 3
Twin-Trait Correlations for Monozygotic (Above the Diagonal) and Dizygotic (Below the Diagonal) Twins

Variables	Cannabis use index		Cannabis use disorder		Psychoticism		Unusual beliefs & experiences		Eccentricity		Perceptual dysregulation	
	Twin A	Twin B	Twin A	Twin B	Twin A	Twin B	Twin A	Twin B	Twin A	Twin B	Twin A	Twin B
Cannabis use index: Twin A	—	.69 (.64, .74)	.75 (.71, .79)	.58 (.52, .65)	.22 (.12, .31)	.13 (.03, .22)	.23 (.14, .32)	.10 (.00, .19)	.16 (.07, .26)	.08 (-.02, .17)	.20 (.10, .29)	.18 (.09, .27)
Cannabis use index: Twin B	.57 (.48, .64)	—	.57 (.50, .63)	.76 (.71, .80)	.21 (.12, .30)	.11 (.02, .21)	.23 (.13, .31)	.09 (-.01, .18)	.16 (.07, .25)	.08 (-.02, .17)	.19 (.10, .28)	.15 (.06, .24)
Cannabis use disorder: Twin A	.81 (.77, .85)	.54 (.45, .63)	—	.80 (.67, .89)	.20 (.10, .29)	.17 (.07, .27)	.23 (.13, .32)	.15 (.05, .24)	.15 (.05, .24)	.13 (.03, .22)	.16 (.06, .25)	.20 (.11, .29)
Cannabis use disorder: Twin B	.39 (.28, .50)	.69 (.62, .75)	.68 (.47, .81)	—	.22 (.12, .31)	.17 (.07, .26)	.22 (.12, .31)	.11 (.02, .21)	.18 (.08, .27)	.15 (.06, .25)	.20 (.10, .29)	.19 (.09, .28)
PID-5 Psychoticism: Twin A	.05 (-.07, .18)	.10 (-.02, .22)	.08 (-.04, .21)	.08 (-.05, .20)	—	.46 (.38, .54)	.88 (.86, .90)	.37 (.29, .45)	.92 (.90, .93)	.44 (.36, .51)	.88 (.85, .90)	.39 (.31, .47)
PID-5 Psychoticism: Twin B	.14 (.02, .26)	.20 (.08, .31)	.04 (-.09, .16)	.09 (-.03, .22)	.30 (.19, .41)	—	.39 (.30, .46)	.84 (.81, .87)	.45 (.37, .52)	.92 (.91, .94)	.40 (.32, .48)	.86 (.83, .88)
Unusual beliefs & experiences: Twin A	.03 (-.09, .15)	.11 (-.01, .23)	.06 (-.07, .18)	.09 (-.04, .21)	.87 (.83, .90)	.28 (.16, .39)	—	.37 (.28, .45)	.68 (.62, .72)	.34 (.25, .42)	.72 (.67, .76)	.31 (.22, .40)
Unusual beliefs & experiences: Twin B	.13 (.01, .25)	.19 (.07, .30)	.05 (-.08, .17)	.10 (-.03, .22)	.23 (.11, .34)	.85 (.82, .88)	.23 (.12, .35)	—	.31 (.22, .40)	.63 (.57, .68)	.33 (.24, .41)	.64 (.57, .69)
Eccentricity: Twin A	.06 (-.07, .18)	.09 (-.03, .21)	.09 (-.04, .21)	.07 (-.05, .20)	.92 (.90, .93)	.26 (.15, .37)	.65 (.58, .72)	.19 (.07, .31)	—	.46 (.39, .54)	.72 (.67, .76)	.36 (.28, .44)
Eccentricity: Twin B	.13 (.01, .25)	.17 (.04, .28)	.01 (-.11, .14)	.07 (-.05, .20)	.28 (.16, .39)	.92 (.90, .94)	.25 (.14, .37)	.65 (.57, .71)	.25 (.14, .37)	—	.35 (.26, .43)	.71 (.65, .75)
Perceptual dysregulation: Twin A	.05 (-.07, .17)	.06 (-.06, .19)	.06 (-.06, .19)	.04 (-.09, .16)	.83 (.79, .86)	.25 (.13, .36)	.65 (.57, .71)	.18 (.06, .30)	.65 (.58, .70)	.23 (.11, .34)	—	.39 (.31, .47)
Perceptual dysregulation: Twin B	.11 (-.01, .23)	.18 (.06, .29)	.06 (-.07, .18)	.08 (-.05, .20)	.29 (.18, .40)	.89 (.87, .92)	.26 (.15, .37)	.70 (.63, .76)	.25 (.13, .36)	.75 (.69, .80)	.27 (.15, .38)	—

Note. Within-twin phenotypic, twin, and cross-twin cross-trait correlations and 95% confidence intervals for monozygotic (MZ) twin pairs are above the diagonal; corresponding correlations and 95% confidence intervals for dizygotic (DZ) twins are below the diagonal. All estimates represent Pearson correlations, except for those involving cannabis use disorder (CUD), which are either tetrachoric correlations (for the cross-twin correlation between Twin A CUD and Twin B CUD) or point-biserial correlations (all others). All significant correlations ($p < .05$) are in bold. $N = 400$ – 422 MZ twin pairs; 244–257 DZ twin pairs.

effects of cannabis on Psychoticism by polygenic risk of schizophrenia overall. Similar to previous models, interactions between both measures of cannabis exposure and (1) sex and (2) zygosity were consistently nonsignificant (for full model results, see Supplemental Table 8).

Finally, we tested whether twins with a history of heavy adolescent cannabis exposure who scored highly on our measure of adult psychoticism had lower levels of polygenic risk, on average, than twins with high psychoticism scores who were not heavy cannabis users. This possibility is indirectly supported by evidence indicating that people with psychotic disorders who used cannabis heavily prior to their psychosis have fewer premorbid neurodevelopmental abnormalities (Ruiz-Veguilla et al., 2012) and is potentially consistent with an additive model of risk. A linear mixed-effects model comparing mean schizophrenia polygenic risk scores for twins scoring at least one standard deviation above the mean on our measure of psychoticism both with ($n = 44$) and without ($n = 142$) an adolescent cannabis use disorder indicated a significant difference in polygenic risk between the two groups (β [95% CI] = .44 [.08, .80], $p = .02$), but one where genetic risk was higher in the group with an adolescent cannabis use disorder diagnosis (mean [SD] = .49 [1.02] vs. .06 [1.04]) (for distributions of schizophrenia polygenic risk as a function of cannabis use disorder diagnosis across the full analytic sample, see Supplemental Figure 1). We thus found no evidence to suggest that individuals with a history of heavy adolescent cannabis exposure tended to develop high psychoticism scores at a lower threshold of genetic risk than individuals without such a history.

Discussion

Our findings suggest the widely-reported associations between adolescent cannabis use and increased risk of psychotic illness may reflect familial confounding rather than a causal effect of cannabis exposure. Because the Minnesota Twin Family study was designed specifically to examine the effects of adolescent substance use on later mental health, our analyses are characterized by several strengths. One is that we used gold-standard, interview-based measures of cannabis exposure administered repeatedly over time, minimizing many of the well-known limitations of retrospective data as well as measurement error that could bias our within-pair effects. A second advantage is that we used a continuous measure of psychosis-proneness, PID-5 Psychoticism, which, along with our continuous measure of cannabis use, should have maximized our power to detect true effects. Third, our analytic sample combines data from two cohorts, which together cover adolescent cannabis use occurring over two decades. This design feature allowed us to examine the consistency of results across cohorts and over time.

These findings extend results from previous co-twin control studies of cannabis in several ways. First, they buttress existing findings indicating that the lion’s share of the association between cannabis and long-term psychotic outcomes reflects familial confounding, rather than a causal effect of cannabis (Karcher et al., 2019; Nesvåg et al., 2017). Indeed, the only point at which our results diverge from those of previous work is in suggesting that these associations may be entirely accounted for by these unmeasured confounds—a finding in line with those of several other previous co-twin control studies examining associations between cannabis and other brain-related outcomes, such as depression and

Table 4
Individual-Level and Co-Twin Control Models of Adolescent Cannabis Exposure and Adult Psychoticism

Exposure	Psychoticism Scale	N	Individual-level models			Co-twin control models		
			Estimate [95% CI]	p value	Between-pair effect		Within-pair effect	
					Estimate [95% CI]	p value	Estimate [95% CI]	p value
Cumulative adolescent cannabis use index	PID-5 Psychoticism	1544	0.14 [0.09, 0.19]	<0.001	0.18 [0.12, 0.24]	<0.001	0.00 [-0.10, 0.10]	0.965
	Unusual Thoughts & Experiences		0.12 (0.07, 0.17)	<0.001	0.16 (0.11, 0.22)	<0.001	-0.01 (-0.12, 0.09)	0.840
	Eccentricity		0.10 (0.05, 0.15)	<0.001	0.14 (0.08, 0.20)	<0.001	0.00 (-0.09, 0.10)	0.930
	Perceptual Dysregulation		0.16 (0.11, 0.21)	<0.001	0.20 (0.14, 0.26)	<0.001	0.01 (-0.09, 0.12)	0.805
Adolescent cannabis use disorder	PID-5 Psychoticism	1458	0.35 (0.20, 0.50)	<0.001	0.55 (0.36, 0.74)	<0.001	0.02 (-0.22, 0.26)	0.865
	Unusual Thoughts & Experiences		0.31 (0.16, 0.47)	<0.001	0.48 (0.29, 0.67)	<0.001	0.00 (-0.27, 0.26)	0.980
	Eccentricity		0.29 (0.14, 0.44)	<0.001	0.43 (0.24, 0.62)	<0.001	0.06 (-0.18, 0.31)	0.607
	Perceptual Dysregulation		0.36 (0.21, 0.52)	<0.001	0.59 (0.40, 0.78)	<0.001	-0.04 (-0.29, 0.22)	0.784

Notes. Individual-level analyses examined associations between cumulative adolescent cannabis use index or adolescent cannabis use disorder diagnosis and young adult scores on the PID-5 Psychoticism factor and its facets. Co-twin control analyses decompose effects from individual-level models into between-pair (reflecting pre-existing, shared familial liability) and within-pair (cannabis exposure) effects. Estimates are reported as standardized betas, reflecting the standard deviation increase in Psychoticism associated either (a) with each standard deviation increase in cumulative adolescent cannabis use or (b) with an adolescent cannabis use disorder diagnosis (vs. not receiving this diagnosis). Because standardization was conducted at the phenotypic level, betas for the within-pair effects of the adolescent cannabis use index should be interpreted in terms of the SD for the entire sample rather than the SD of twin differences. The number of complete pairs contributing data to each set of analyses is 679 for the cannabis use index and 644 for cannabis use disorder. The number of families contributing data to each set of analyses is 865 for the cannabis use index and 814 for cannabis use disorder. All models included participant age, sex, zygosity, and cohort as covariates. CI = confidence interval.

cognitive ability (Jackson et al., 2016; Lynskey et al., 2004; Meier et al., 2018; Ross et al., 2020). Our study also failed to find support for the hypothesis that cannabis use may increase risk of psychotic symptoms only in individuals at higher genetic risk of schizophrenia. Although these results do not rule out the possibility that the association between cannabis use and psychosis may vary depending on other vulnerability factors we did not consider, the null results from our co-twin control models suggest that, if these especially vulnerable individuals exist, they likely make up a very small part of the overall population.

Nevertheless, we acknowledge limitations. First, because the cohorts used in our analyses both consisted of predominantly white participants born and raised in Minnesota between the late 1970s and early 2000s, results from this study may not generalize to communities with different demographic characteristics. Moreover, frequency of cannabis use in our sample is low relative to present-day patterns of use, which also tend to involve cannabis products of higher potency (Elsohly et al., 2016). Second, our study lacked biological measures of cannabis exposure, which means our results are dependent on the accuracy of our self-report measures. Future studies could combine self-report measures of cannabis use (which are needed to assess patterns of use) with these objective measures to strengthen their conclusions. Third, although twins in our sample were assessed repeatedly for cannabis exposure in adolescence, psychoticism was assessed at only one time point in early adulthood. In some ways, the timing of this psychoticism measure in early adulthood is a strength, in that the temporal distance from adolescence helps to ensure that we are capturing associations between cannabis use and long-term elevations in psychotic symptoms (rather than the acute effects of adolescent use). However, it remains possible that different patterns of association might emerge between adolescent cannabis exposure and psychoticism measured at other points in development. Indeed, future work should test whether different cannabis-psychosis associations emerge for different developmental trajectories of cannabis exposure (e.g., variations in age of initiation, slope, or age of peak use). Baseline measures of psychoticism in childhood or early adolescence (which were not available in our cohorts) would also aid causal inference by ruling out the possibility that differences in psychoticism predate cannabis exposure. Fourth, we acknowledge limitations to the co-twin control approach, including heightened vulnerability to measurement error relative to individual-level analyses (Frisell et al., 2012), an inability to conclusively rule out confounding due to nonshared environmental influences, and the possibility that lesser-using twins in discordant pairs could have been exposed to cannabis second-hand. Nevertheless, except for second-hand exposure, these confounds would mostly likely serve to inflate the within-pair effect of cannabis use on psychoticism, making the consistent null results we observe even more remarkable.

Results from our polygenic risk score analyses should also be interpreted with certain caveats in mind. First, polygenic risk scores may not be ideal measures for tests of gene-environment interaction, as GWAS analyses weight polygenic score “risk” alleles according to the size of their “main effect” (i.e., one averaged over multiple different environments) and therefore may be unlikely to capture genes that interact strongly with specific environmental exposures. It is even possible that a certain subset of schizophrenia risk genes interacts with cannabis to produce

Table 5
Tests for Incremental and Interaction Effects Between Adolescent Cannabis Exposure and Polygenic Risk of Schizophrenia in Predicting Adult Psychoticism

Predictors	N	PID-5 Psychoticism		
		1	2	3
Polygenic risk of schizophrenia		0.08** (0.03, 0.14)	0.07* (0.02, 0.13)	0.17 (-0.09, 0.43)
Cumulative adolescent cannabis use index	1,345	—	0.12*** (0.07, 0.18)	0.10 (-0.17, 0.36)
Interaction		—	—	0.01 (-0.05, 0.07)
Polygenic risk of schizophrenia		0.08** (0.03, 0.14)	0.08* (0.02, 0.13)	0.17 (-0.10, 0.44)
Cannabis use disorder	1,291	—	0.28*** (0.12, 0.43)	0.01 (-0.78, 0.79)
Interaction		—	—	0.10 (-0.06, 0.26)

Predictors	N	Unusual beliefs & experiences			Eccentricity			Perceptual dysregulation		
		1	2	3	1	2	3	1	2	3
Polygenic risk of schizophrenia		0.08** (0.02, 0.14)	0.07* (0.01, 0.13)	0.13 (-0.13, 0.39)	0.06* (0.01, 0.12)	0.06 (0.00, 0.11)	0.10 (-0.17, 0.37)	0.09** (0.03, 0.15)	0.08** (0.02, 0.14)	0.27 (0.00, 0.54)
Cumulative adolescent cannabis use index	1,345	—	0.11*** (0.06, 0.17)	0.05 (-0.21, 0.31)	—	0.09*** (0.04, 0.14)	0.13 (-0.14, 0.39)	—	0.14*** (0.09, 0.20)	0.08 (-0.18, 0.35)
Interaction		—	—	-0.04 (-0.10, 0.02)	—	—	0.04 (-0.02, 0.10)	—	—	0.02 (-0.04, 0.08)
Polygenic risk of schizophrenia		0.08** (0.02, 0.14)	0.06* (0.01, 0.12)	0.15 (-0.12, 0.41)	0.06* (0.01, 0.12)	0.06* (0.00, 0.12)	0.07 (-0.20, 0.35)	0.09** (0.03, 0.15)	0.08** (0.02, 0.14)	0.28* (0.00, 0.55)
Cannabis use disorder	1,291	—	0.26** (0.10, 0.41)	-0.23 (-1.02, 0.57)	—	0.23** (0.08, 0.39)	0.39 (-0.41, 1.18)	—	0.29*** (0.13, 0.45)	-0.30 (-1.11, 0.51)
Interaction		—	—	-0.04 (-0.20, 0.12)	—	—	0.12 (-0.04, 0.28)	—	—	0.17* (0.01, 0.34)

Note. Results from individual-level models testing for (1) associations between polygenic risk of schizophrenia and adult Psychoticism, (2) incremental contributions to Psychoticism from adolescent cannabis exposure and polygenic risk of schizophrenia, and (3) interactions between adolescent cannabis exposure and polygenic risk of schizophrenia. Estimates are reported as standardized betas with 95% confidence intervals, reflecting the standard deviation increase in Psychoticism associated either (a) with each standard deviation increase in cumulative adolescent cannabis use/polygenic risk of schizophrenia or (b) with an adolescent cannabis use disorder diagnosis (vs. not receiving this diagnosis). All models included participant age, sex, zygosity, cohort, and the first 10 genetic principal components as covariates. Models testing for interaction between polygenic risk of schizophrenia and cannabis exposure additionally included terms adjusting for possible interactions between the schizophrenia PGS or cannabis exposure measures with covariates.

* $p < .05$. ** $p < .01$. *** $p < .001$.

increased risk of psychosis, while other variants (perhaps in different genes) reduce the effect of cannabis on psychosis risk. Second, it is possible that rare genetic variants (excluded from our polygenic risk measure) would be more likely to show gene–environment interactions with cannabis use than common polymorphisms; thus, individuals whose genetic susceptibility to schizophrenia is driven primarily by rare variants may still be particularly affected by cannabis.

Despite these limitations, our findings have several implications for public health and clinical practice. First, although there are many reasonable arguments that can be made against cannabis legalization, our results suggest that the threat of potential harm to adolescents via meaningful increases in risk of long-term psychotic illness may be overstated. This threat of potential harm is also undermined by emerging research studying the effects of cannabis legalization on adolescent cannabis use, which generally suggests increases in use among adults following legalization but stable or decreasing use among teens (Cerdá et al., 2017; Wen et al., 2015; although see also Cerda et al., 2020, which found increases in adolescent cannabis use disorder following recreational cannabis legalization). Second, our results reinforce the notion that although adolescent cannabis use is a reliable indicator of many negative later-life outcomes, there is relatively little convincing evidence that it is a significant root cause. Thus, clinical and public health interventions aimed at decreasing the prevalence and burden of psychotic illnesses may benefit from focusing their attention elsewhere.

References

- Alvarez-Jimenez, M., Priede, A., Hetrick, S. E., Bendall, S., Killackey, E., Parker, A. G., McGorry, P. D., & Gleeson, J. F. (2012). Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Schizophrenia Research, 139*(1-3), 116–128. <https://doi.org/10.1016/j.schres.2012.05.007>
- Bastiaens, T., Smits, D., De Hert, M., Thys, E., Bryon, H., Sweers, K., Teugels, T., Van Looy, J., Verwerft, T., Vanwalleghem, D., Van Bouwel, L., & Claes, L. (2019). The relationship between The Personality Inventory for the DSM-5 (PID-5) and the psychotic disorder in a clinical sample. *Assessment, 26*(2), 315–323. <https://doi.org/10.1177/1073191117693922>
- Begg, M. D., & Parides, M. K. (2003). Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Statistics in Medicine, 22*(16), 2591–2602. <https://doi.org/10.1002/sim.1524>
- Boyle, E. A., Li, Y. I., & Pritchard, J. K. (2017). An expanded view of complex traits: From polygenic to omnigenic. *Cell, 169*(7), 1177–1186. <https://doi.org/10.1016/j.cell.2017.05.038>
- Calakos, K. C., Bhatt, S., Foster, D. W., & Cosgrove, K. P. (2017). Mechanisms underlying sex differences in cannabis use. *Current Addiction Reports, 4*(4), 439–453. <https://doi.org/10.1007/s40429-017-0174-7>
- Cerda, M., Mauro, C., Hamilton, A., Levy, N. S., Santaella-Tenorio, J., Hasin, D., Wall, M. M., Keyes, K. M., & Martins, S. S. (2020). Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry, 77*(2), 165–171.
- Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *GigaScience, 4*(1), s13742-015-0047-8. <https://doi.org/10.1186/s13742-015-0047-8>
- Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A. E., Kwong, A., Vrieze, S. I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.-R., Iacono, W. G., Swaroop, A., Scott, L. J., Cucca, F., Kronenberg, F., Boehnke, M., . . . Fuchsberger, C. (2016). Next-generation genotype imputation service and methods. *Nature Genetics, 48*(10), 1284–1287. <https://doi.org/10.1038/ng.3656>
- D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y., Braley, G., Gueorguieva, R., & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology, 29*(8), 1558–1572. <https://doi.org/10.1038/sj.npp.1300496>
- EiSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., & Church, J. C. (2016). Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry, 79*(7), 613–619. <https://doi.org/10.1016/j.biopsych.2016.01.004>
- French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., Séguin, J. R., Veillette, S., Evans, C. J., Artiges, E., Banaschewski, T., Bokde, A. W. L., Bromberg, U., Bruehl, R., Buchel, C., Cattrell, A., Conrod, P. J., Flor, H., Frouin, V., . . . Paus, T. (2015). Early cannabis use, polygenic risk score for schizophrenia, and brain maturation in adolescence. *JAMA Psychiatry, 72*(10), 1002–1011. <https://doi.org/10.1001/jamapsychiatry.2015.1131>
- Frisell, T., Öberg, S., Kuja-Halkola, R., & Sjölander, A. (2012). Sibling comparison designs: Bias from non-shared confounders and measurement error. *Epidemiology, 23*(5), 713–720. <https://doi.org/10.1097/EDE.0b013e31825fa230>
- Frisher, M., Crome, I., Martino, O., & Croft, P. (2009). Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005. *Schizophrenia Research, 113*(2-3), 123–128. <https://doi.org/10.1016/j.schres.2009.05.031>
- Guloksuz, S., & van Os, J. (2018). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine, 48*(2), 229–244. <https://doi.org/10.1017/S0033291717001775>
- Iacono, W. G., Carlson, S. R., Taylor, J., Elkins, I. J., & McGue, M. (1999). Behavioral disinhibition and the development of substance-use disorders: Findings from the Minnesota Twin Family Study. *Development and Psychopathology, 11*(4), 869–900. <https://doi.org/10.1017/S0954579499002369>
- Iacono, W. G., McGue, M. K., & Krueger, R. F. (2006). Minnesota Center for Twin and Family Research. *Twin Research and Human Genetics, 9*(6), 978–984. <https://doi.org/10.1375/183242706779462642>
- Jackson, N. J., Isen, J. D., Khoddam, R., Irons, D., Tuvblad, C., Iacono, W. G., McGue, M., Raine, A., & Baker, L. A. (2016). Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies. *Proceedings of the National Academy of Sciences of the United States of America, 113*(5), E500–E508. <https://doi.org/10.1073/pnas.1516648113>
- Johnson, E. C., Hatoum, A. S., Deak, J. D., Polimanti, R., Murray, R. M., Edenberg, H. J., Gelemtier, J., Forti, M. D., & Agrawal, A. (2021). The relationship between cannabis and schizophrenia: A genetically informed perspective. *Addiction*. Advance online publication. <https://doi.org/10.1111/add.15534>
- Karcher, N. R., Barch, D. M., Demers, C. H., Baranger, D. A. A., Heath, A. C., Lynskey, M. T., & Agrawal, A. (2019). Genetic predisposition vs individual-specific processes in the association between psychotic-like experiences and cannabis use. *JAMA Psychiatry, 76*(1), 87–94. <https://doi.org/10.1001/jamapsychiatry.2018.2546>
- Keller, M. C. (2014). Gene × environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. *Biological Psychiatry, 75*(1), 18–24. <https://doi.org/10.1016/j.biopsych.2013.09.006>
- Keyes, M. A., Malone, S. M., Elkins, I. J., Legrand, L. N., McGue, M., & Iacono, W. G. (2009). The enrichment study of the Minnesota twin family study: Increasing the yield of twin families at high risk for externalizing psychopathology. *Twin Research and Human Genetics, 12*(5), 489–501. <https://doi.org/10.1375/twin.12.5.489>

- Ksir, C., & Hart, C. L. (2016). Cannabis and psychosis: A critical overview of the relationship. *Current Psychiatry Reports*, 18(2), Article 12. <https://doi.org/10.1007/s11920-015-0657-y>
- Longenecker, J. M., Krueger, R. F., & Sponheim, S. R. (2020). Personality traits across the psychosis spectrum: A Hierarchical Taxonomy of Psychopathology conceptualization of clinical symptomatology. *Personality and Mental Health*, 14(1), 88–105. <https://doi.org/10.1002/pmh.1448>
- Lynskey, M. T., Glowinski, A. L., Todorov, A. A., Bucholz, K. K., Madden, P. A. F., Nelson, E. C., Statham, D. J., Martin, N. G., & Heath, A. C. (2004). Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Archives of General Psychiatry*, 61(10), 1026–1032. <https://doi.org/10.1001/archpsyc.61.10.1026>
- Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, 42(5), 1262–1269. <https://doi.org/10.1093/schbul/sbw003>
- McCarthy, S., Das, S., Kretschmar, W., Delaneau, O., Wood, A. R., Teumer, A., Kang, H. M., Fuchsberger, C., Danecek, P., Sharp, K., Luo, Y., Sidore, C., Kwong, A., Timpson, N., Koskinen, S., Vrieze, S., Scott, L. J., Zhang, H., Mahajan, A., . . . and for the Haplotype Reference Consortium. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nature Genetics*, 48(10), 1279–1283. <https://doi.org/10.1038/ng.3643>
- McGue, M., Malone, S., Keyes, M., & Iacono, W. G. (2014). Parent–offspring similarity for drinking: A longitudinal adoption study. *Behavior Genetics*, 44(6), 620–628. <https://doi.org/10.1007/s10519-014-9672-8>
- McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, 5(5), 546–556. <https://doi.org/10.1177/1745691610383511>
- Meier, M. H., Caspi, A., Danese, A., Fisher, H. L., Houts, R., Arseneault, L., & Moffitt, T. E. (2018). Associations between adolescent cannabis use and neuropsychological decline: A longitudinal co-twin control study. *Addiction*, 113(2), 257–265. <https://doi.org/10.1111/add.13946>
- Miller, M. B., Basu, S., Cunningham, J., Eskin, E., Malone, S. M., Oetting, W. S., Schork, N., Sul, J. H., Iacono, W. G., & McGue, M. (2012). The Minnesota center for twin and family research genome-wide association study. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, 15(6), 767–774. <https://doi.org/10.1017/thg.2012.62>
- Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *The Lancet*, 370(9584), 319–328. [https://doi.org/10.1016/S0140-6736\(07\)61162-3](https://doi.org/10.1016/S0140-6736(07)61162-3)
- Nesvåg, R., Reichborn-Kjennerud, T., Gillespie, N. A., Knudsen, G. P., Bramness, J. G., Kendler, K. S., & Ystrom, E. (2017). Genetic and environmental contributions to the association between cannabis use and psychotic-like experiences in young adult twins. *Schizophrenia Bulletin*, 43(3), 644–653. <https://doi.org/10.1093/schbul/sbw101>
- Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S. E., Bishop, S., Cameron, D., Hamshere, M. L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J. H., McCarrroll, S. A., Baune, B. T., Breen, G., . . . Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics*, 50(3), 381–389. <https://doi.org/10.1038/s41588-018-0059-2>
- Pasman, J. A., Verweij, K. J. H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., Abdellaoui, A., Nivard, M. G., Baselmans, B. M. L., Ong, J.-S., Ip, H. F., van der Zee, M. D., Bartels, M., Day, F. R., Fontanillas, P., Elson, S. L., de Wit, H., Davis, L. K., MacKillop, J., . . . Vink, J. M. (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal effect of schizophrenia liability. *Nature Neuroscience*, 21(9), 1161–1170. <https://doi.org/10.1038/s41593-018-0206-1>
- Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phipphothatsanee, N., Amir, T., Yenn Thoo, H., Oliver, D., Davies, C., Morgan, C., McGuire, P., Murray, R. M., & Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*, 17(1), 49–66. <https://doi.org/10.1002/wps.20490>
- Reich, W., & Welner, Z. (1988). *Diagnostic Interview for Children and Adolescents-Revised: DSM-III-R Version (DICA-R)*. Washington University.
- Robins, L. N., Baber, T., & Cottler, L. B. (1987). *Composite International Diagnostic Interview: Expanded Substance Abuse Module*. Department of Psychiatry, Washington University.
- Ross, J. M., Ellingson, J. M., Rhee, S. H., Hewitt, J. K., Corley, R. P., Lessem, J. M., & Friedman, N. P. (2020). Investigating the causal effect of cannabis use on cognitive function with a quasi-experimental co-twin design. *Drug and Alcohol Dependence*, 206, 107712. <https://doi.org/10.1016/j.drugalcdep.2019.107712>
- Ruiz-Veguilla, M., Callado, L. F., & Ferrin, M. (2012). Neurological soft signs in patients with psychosis and cannabis abuse: A systematic review and meta-analysis of paradox. *Current Pharmaceutical Design*, 18(32), 5156–5164. <https://doi.org/10.2174/138161212802884753>
- Stone, A. L., Becker, L. G., Huber, A. M., & Catalano, R. F. (2012). Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addictive Behaviors*, 37(7), 747–775. <https://doi.org/10.1016/j.addbeh.2012.02.014>
- The 1000 Genomes Project Consortium. (2015). A global reference for human genetic variation. *Nature*, 526(7571), 68–74. <https://doi.org/10.1038/nature15393>
- van der Steur, S. J., Batalla, A., & Bossong, M. G. (2020). Factors moderating the association between cannabis use and psychosis risk: A systematic review. *Brain Sciences*, 10(2), 97. <https://doi.org/10.3390/brainsci10020097>
- Vaucher, J., Keating, B. J., Lasserre, A. M., Gan, W., Lyall, D. M., Ward, J., . . . Holmes, M. V. (2018). Cannabis use and risk of schizophrenia: A Mendelian randomization study. *Molecular Psychiatry*, 23(5), 1287–1292. <https://doi.org/10.1038/mp.2016.252>
- Vilhjálmsdóttir, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P.-R., Bhatia, G., Do, R., Hayeck, T., Won, H.-H., Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., Holmans, P. A., Lee, P., . . . Price, A. L. (2015). Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *The American Journal of Human Genetics*, 97(4), 576–592. <https://doi.org/10.1016/j.ajhg.2015.09.001>
- Wen, H., Hockenberry, J. M., & Cummings, J. R. (2015). The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. *Journal of Health Economics*, 42, 64–80. <https://doi.org/10.1016/j.jhealeco.2015.03.007>
- Wilson, S., Haroian, K., Iacono, W. G., Krueger, R. F., Lee, J. J., Luciana, M., Malone, S. M., McGue, M., Roisman, G. I., & Vrieze, S. (2019). Minnesota Center for Twin and Family Research. *Twin Research and Human Genetics*, 22(6), 746–752. <https://doi.org/10.1017/thg.2019.107>

Received June 25, 2020

Revision received March 23, 2021

Accepted May 24, 2021 ■