Associations between adolescent cannabis use and young-adult functioning in three longitudinal twin studies

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Observational studies have linked cannabis use to an array of negative outcomes, including psychiatric symptoms, cognitive impairment, and educational and occupational underachievement. These associations are particularly strong when cannabis use occurs in adolescence. Nevertheless, causality remains unclear. The purpose of the present study was thus to examine associations between prospectively assessed adolescent cannabis use and young-adult outcomes (psychiatric, cognitive, and socioeconomic) in three longitudinal studies of twins (n = 3,762). Twins reporting greater cumulative cannabis use in adolescence reported higher levels of psychopathology as well as poorer socioeconomic outcomes in young adulthood. However, cannabis use remained associated only with socioeconomic outcomes (i.e., educational attainment, occupational status, and income) in monozygotic-cotwin control analyses, which account fully for shared genetic and environmental confounding. Follow-up analyses examining associations between twin differences in adolescent cannabis use and longitudinal change in academic functioning during the middle- and high-school years provided a possible mechanism for these associations, indicating that greater cannabis use during this period was associated with decreases in grade point average and academic motivation as well as increases in academic problem behavior and school disciplinary problems. Our findings thus suggest that cannabis use in adolescence has potentially causal, deleterious effects on adolescent academic functioning and young-adult socioeconomic outcomes despite little evidence suggesting a strong, causal influence on adult mental health or cognitive ability.

cannabis | marijuana | adolescence | education | twin

The legality of cannabis in the United States is changing rapidly. A total of 16 states and the District of Columbia have legalized recreational cannabis use, and the majority now allow medical marijuana. Although research is still in its infancy, studies have generally concluded that legalization is associated with increased rates of use, frequent use, and cannabis-use disorders among adults (1–4) but with stable or even decreasing use among adolescents (3–5). Despite these findings, many individuals and institutions have cited concerns regarding the effects of cannabis on minors whose access may increase with the legalization of adult use, with medical authorities such as the American Academy of Pediatrics and US Surgeon General putting out statements warning against potential dangers (6, 7).

Concerns regarding adolescent cannabis use are supported by three streams of research. First, large-scale observational studies have shown that adolescent use is associated with many negative outcomes, including mental health problems (8–11), misuse of alcohol and other drugs (8, 11, 12), cognitive impairment (13–16), reduced socioeconomic attainment (11, 17), and unemployment (18, 19). Most studies find these associations become increasingly likely the earlier cannabis use is initiated. Second, neuroimaging studies have reported associations between chronic cannabis use and long-term changes in brain activity in areas responsible for reward and emotion processing (e.g., ventral striatum and amygdala), which some have hypothesized may contribute to compulsive behavior and greater negative emotionality among users (20). Third, studies from the animal literature routinely report cannabis-induced alterations in molecular, neural, and behavioral assays, with one recent review summarizing these findings as "clearly indicat[ing] that adolescent-onset exposure to cannabinoids can catalyze molecular processes that lead to persistent functional deficits in adulthood, deficits that are not found to follow adult-onset exposure" (21).

The Causal Status of Cannabis–Outcome Associations

Despite the seemingly unambiguous findings from animal studies, the extent to which associations between cannabis and negative outcomes in humans reflect the causal effects of cannabis use remains unclear. These associations could reflect one of at least three possibilities: 1) cannabis use causes subsequent problems for users (simple causation), 2) these problems predispose individuals to cannabis use (reverse causation), or 3) associations between cannabis and negative outcomes are driven by other, unmeasured factors (the "third variable" or "statistical confounding" explanation).

There are many reasons to take options 2 and 3 seriously. First, genetic influences account for roughly 50% of the variance in cannabis abuse, and many forms of familial and environmental

Significance

A widely voiced concern regarding cannabis legalization in the United States is that cannabis is harmful to minors, affecting the developing brain to increase emotional and cognitive problems while impairing functioning. However, these associations may be due to confounding by common vulnerability factors that make some individuals more prone to both cannabis use and negative outcomes. We evaluate this possibility by conducting a series of cotwin control analyses in a sample that combines data from three longitudinal studies. Our findings provide little support for a strong, causal relationship between adolescent cannabis use and adult mental health or cognitive ability but do suggest that cannabis use may impair academic functioning during the secondary school years, with downstream effects on socioeconomic status.

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adversity (e.g., maltreatment or socioeconomic disadvantage) occur disproportionately among individuals who use cannabis (22–25). Twin studies examining associations between cannabis use and psychosocial outcomes have similarly found that a significant proportion of the covariance between these measures is attributable to the same underlying genetic and environmental risk factors, with genetic correlations ranging from relatively modest (e.g., 0.23 for major depressive disorder) to large (e.g., >0.90 for other illicit drug use see ref. 26, but see also ref. 27), shared environmental correlations ranging from moderate (e.g., 0.50 for early school leaving) to large (1.00 for other illicit drug use) (26, 27), and unique environmental correlations ranging from negligible (0.00 for early school leaving) to moderate (e.g., 0.34 for other illicit drug use) (26, 27). Similarly, results from Mendelian randomization studies that use polygenic risk of lifetime cannabis use to test for potentially causal relationships between cannabis use and different outcomes have been mixed, reporting positive associations with risk of suicide attempts and schizophrenia (28, 29) and null findings for self-harm, major depression, and other substance use (30–33).

Second, although neuroimaging studies have reported associations between cannabis use and differences in brain structure and/or functioning, the overwhelming majority of these studies have been cross-sectional in nature, meaning that they cannot account for brain differences that existed prior to cannabis use onset and that may predict cannabis use initiation and severity. While it is plausible that prolonged cannabis exposure could lead to neurodevelopmental changes, other studies have shown that brain and neurocognitive differences may also precede the onset of, and correlate with, cannabis use (34, 35). Findings from these and other small-scale neuroimaging studies must also be interpreted cautiously, as the small sample sizes and weak links between brain and behavior have led to a relatively high prevalence of false-positive findings (36).

Investigations that differentiate between various etiological possibilities are thus needed to guide policy decisions that affect cannabis legalization and use, because if the relationship between cannabis and negative outcomes is largely noncausal, we would expect policies affecting adolescent use to have little to no positive impact. One such approach involves comparing twins that differ in their levels of cannabis exposure. Termed "discordant twin" or "cotwin control" analyses, this approach allows for examination of the effects of cannabis use while simultaneously controlling for all measured and unmeasured familial confounds shared between monozygotic (MZ) and dizygotic (DZ) twins. Cotwin control models conducted in samples of MZ twins only, who share 100% of their genes in common, offer a particularly strong test of causality as they control fully for shared genetic liability (37, 38). If cannabis is a causal contributor to psychiatric, cognitive, and socioeconomic problems, twins who use more cannabis than their cotwins should experience poorer outcomes in these domains. If this "twin difference" in outcomes is not observed, it suggests that cannabis–outcome associations may be due to familial confounding. It is important to note, however, that either of these results could also reflect confounding by unmeasured, individual twin-specific factors. For example, twin differences in outcomes could arise because of differences in other substance use (e.g., alcohol or nicotine), or a true twin difference could be suppressed by compensatory allocation of resources to the more-cannabis-using twin (e.g., treatment for drug use, academic tutoring, etc.).

To date, twin studies of cannabis use have examined varied outcomes and returned somewhat mixed findings. Studies examining associations between cannabis use and psychopathology find that the twin who uses cannabis is at greater risk of alcohol and drug misuse, (see refs. 26, 39–41, but see also ref. 42) psychosis (43, 44), and suicidal ideation or attempts (45, 46). However, findings for depression are mixed (45, 46). Studies examining associations between cannabis use and cognitive ability or educational attainment, on the other hand, have consistently indicated that these associations disappear after controlling for shared familial factors or other substance use (27, 39, 47–49).

Limitations of Previous Research

Although twin studies have made substantial contributions to our understanding of cannabis–outcome associations, this body of knowledge is still characterized by three important limitations. First, twin studies that test each individual cannabis–outcome association are few in number, and findings from these early reports must be replicated in independent samples. Second, many of the twin samples used in these studies have been relatively small (i.e., involving only 200 to 400 twin pairs), which limits their power to detect modest effects (39–41). Third, although several twin studies have focused on understanding the long-term consequences of adolescent cannabis use, the majority have been cross-sectional studies of adult twins. Thus, these studies have used either very coarse, retrospective measures of early cannabis use (e.g., a dichotomous indicator representing use versus no use prior to age 18) or retrospective measures that assume adult participants will correctly recall details of cannabis use that occurred years (or sometimes decades) earlier. Use of fine-grained cannabis-exposure measures in retrospective studies is particularly problematic given that exposure measurement error tends to attenuate within-pair estimates more dramatically than corresponding unpaired associations, potentially leading to false-negative findings (50). Twin studies that assess cannabis prospectively with repeated, high-quality assessments over time are thus needed to address this concern.

The Present Study

We examined associations between adolescent cannabis use and young-adult outcomes in a twin sample (n = 3,762) that combines data from three longitudinal studies at the Minnesota Center for Twin and Family Research (MCTFR) (51). The timing of assessments across all three cohorts is shown in Table 1. When twins were in their teens, they reported on the frequency and severity of multiple types of substance use, including cannabis. We created a continuous index measuring cumulative cannabis use prior to and during adolescence ("adolescent cannabis use index"). We next tested the hypothesis that individuals who used more cannabis in adolescence would experience more negative outcomes in young adulthood—specifically, poorer psychiatric, cognitive, and socioeconomic functioning. We leveraged our relatively large number of MZ twins (n = 2,410) to test whether observed associations were attributable to shared environmental and genetic factors or consistent with a causal effect of cannabis exposure. Finally, we ran a series of planned follow-up analyses testing whether specific twin differences might confound the within-pair associations observed in our cotwin control models.

Results

Descriptive data for our measures of cannabis use, including percentage of twins with data on each measure, are presented in Table 2. Cannabis use was relatively prevalent in our sample, with 29% of participants reporting at least some cannabis use in adolescence and 11% meeting criteria for an adolescent cannabis-use disorder.

Is Greater Cannabis Use in Adolescence Associated with Poorer Young-Adult Outcomes? Results from individual-level analyses, comparable to linear regression models in a sample of singletons, are summarized in Table 3. Broadly, greater cannabis use in adolescence was associated with multiple negative psychiatric and socioeconomic outcomes in young adulthood, including greater rates of major depressive, anxiety, antisocial personality, and noncannabis illicit drug–use disorders, as well as lower educational attainment, occupational status, and annual income. Negative cognitive outcomes associated with adolescent cannabis exposure, on the other

Table 1. Timing of assessments and descriptive statistics for each of the three twin studies constituting the combined sample

	ES			Younger			Older		
Target age	Age (in years)	Years	Percent	Age (in years)	Years	Percent	Age (in years)	Years	Percent
Age 11	10.9 to 13.0	1999 to 2006	100%	10.7 to 12.8	1990 to 1996	100%	—	—	—
Age 14	13.6 to 17.0	2003 to 2010	93.2%	13.6 to 16.8	1993 to 2000	92.6%	—	—	—
Age 17	16.8 to 19.8	2006 to 2012	91.5%	16.6 to 20.3	1996 to 2004	87.3%	16.6 to 18.5	1990 to 1996	100%
Age 24	22.6 to 28.1	2013 to 2017	81.1%	23.7 to 28.0	2004 to 2011	87.8%	22.6 to 29.3	1996 to 2005	93.2%
Age 29	—	—	—	28.2 to 33.2	2007 to 2014	87.6%	28.4 to 32.4	2002 to 2010	93.3%
% male		47.9%			49.7%			46.2%	
MZ/DZ twin pairs		303/196			486/270			416/210	

This table displays descriptive statistics for each of the cohort-specific assessment waves that provided data used in the present study. Descriptive statistics in the bottom half of the panel (i.e., "% male" and "MZ/DZ twin pairs") describe the composition of each cohort at intake. We defined "adolescent" assessments as those taking place when the mean age of the cohort was ~17 y of age or younger (i.e., target age 11, 14, and 17 in ES and Younger cohorts or target age 17 only in the Older cohort). "Young-adult" assessments were defined as those taking place when the target age of the cohort was 24 and 29 (target age 24 assessment only in the ES cohort or target age 24 and 29 assessments in the Younger and Older cohorts). Target age = targeted age of assessment wave. Age (in years) = range of participant ages at each cohort-specific assessment wave. Years = calendar years during which each cohort-specific assessment wave took place. Percent = percent of the original sample that participated in each cohort-specific assessment wave.

hand, were limited to lower scores on a test of vocabulary (i.e., associations with performance on Block Design, Digit Span Forward, and Digit Span Backward were not significant). Overall, these results are consistent with those of previous studies, which indicated that adolescent cannabis use is associated with poorer adult outcomes across multiple domains (for full model results, reference *SI Appendix*, Table S1; mean outcome scores for twins with no, light, moderate, and heavy adolescent cannabis use are shown in *SI Appendix*, Fig. S1).

Is Cannabis Use Associated with Poorer Young-Adult Functioning Independent of Shared Environmental and Genetic Factors, Consistent with a Causal Effect? We next examined whether associations from these individual-level analyses would survive the introduction of cotwin controls (reference *SI Appendix*, *Supplemental Methods* for a more detailed overview of this approach). Twin correlations for our exposure and outcome measures are presented in *SI Appendix*, Table S2. 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 the result of measurement error). Similarly, the higher within-trait twin correlations in MZ twins relative to DZ twins indicated that phenotypic variation was also influenced by additive genetic factors. Of the 1,881 twin pairs in the combined sample, 623 pairs (364 MZ/259 DZ) (33%) were discordant on our measure of cumulative adolescent cannabis use (i.e., had different index scores), whereas 184 pairs (93 MZ/91 DZ) (10%) were discordant in terms of adolescent cannabis-use disorder diagnosis (i.e., with one twin meeting criteria for the diagnosis and the other not). The mean level of discordance on the cannabis-use index across discordant pairs was 0.69 (SD = 0.62). Because our cannabis-use index combines ordinal measures of cannabis use and frequency, a difference of 1 between twins would be consistent with one twin using <1×/month and the other twin using 1 to 3×/month, or one twin using 1 to 4×/week and another twin using every day or nearly every day. Alternatively, it would also be consistent with one twin reporting 1 to 4 uses of

Table 2. Descriptive statistics for adolescent cannabis exposure

	ES			Younger			Older		
	Mean (SD)/%	Range	% present	Mean (SD)/%	Range	% present	Mean (SD)/%	Range	% present
Age 11									
Cannabis use index	0.00 (0.03)	0.00 to 0.50	99.8%	0.00 (0.03)	0.00 to 1.00	99.9%			
Frequency of use*	0.33 (0.58)	0.00 to 1.00		0.00 (0.00)	0.00 to 0.00				
Number of uses*	0.67 (0.58)	0.00 to 1.00		1.33 (0.58)	1.00 to 2.00				
% with CUD	0%	—	91.0%	0%	—	100%			
Age 14									
Cannabis use index	0.13 (0.52)	0.00 to 5.00	93.2%	0.19 (0.63)	0.00 to 5.00	92.7%			
Frequency of use*	1.22 (1.27)	0.00 to 4.00		1.54 (1.12)	0.00 to 4.00				
Number of uses*	1.62 (1.19)	0.00 to 5.00		1.70 (1.11)	0.00 to 5.00				
% with CUD	2%	—	93.0%	2%	—	93.8%			
Age 17									
Cannabis use index	0.58 (1.17)	0.00 to 5.00	91.4%	0.76 (1.26)	0.00 to 5.00	86.5%	0.34 (0.81)	0.00 to 5.00	99.1%
Frequency of use*	1.59 (1.44)	0.00 to 5.00		1.60 (1.36)	0.00 to 5.00		1.26 (1.11)	0.00 to 5.00	
Number of uses*	2.36 (1.48)	1.00 to 5.00		2.34 (1.43)	0.00 to 5.00		1.82 (1.17)	1.00 to 5.00	
% with CUD	12%	—	92.2%	14%	—	89.7%	6%	—	99.2%
Cumulative									
Cannabis use index	0.23 (0.49)	0.00 to 3.17	100%	0.29 (0.53)	0.00 to 3.00	100%	0.34 (0.81)	0.00 to 5.00	99.1%
% with CUD	12%	—	92.2%	14%	—	90.3%	6%	—	99.2%

CUD = cannabis-use disorder (i.e., abuse or dependence). "Range" indicates the range of responses given at each time frame (the full range of possible values on each use measure was 0 to 5).

*Summary statistics for these measures refer only to the subset of participants who endorsed using cannabis during this assessment wave (i.e., individuals scoring "0" on both frequency of use and number of uses at this wave are excluded).

Table 3. Individual-level associations between cumulative adolescent cannabis use and young-adult outcomes

Functional domain	Young-adult outcome	*n*	OR (95% CI)	*P* value
Psychiatric	Major depressive disorder	3,284	1.16 (1.07, 1.25)	<0.001
	Anxiety disorder	2,422	1.26 (1.11, 1.43)	<0.001
	Antisocial personality disorder	3,286	1.75 (1.57, 1.95)	<0.001
	Noncannabis illicit drug– use disorder	3,284	1.80 (1.62, 2.00)	<0.001
			β (95% CI)	
Cognitive	WAIS-R vocabulary	2,585	−0.11 (−0.16, −0.07)	<0.001
	WAIS-R block design	2,739	−0.03 (−0.07, 0.01)	0.172
	WAIS-III digit span forward	1,689	0.01 (−0.06, 0.07)	0.866
	WAIS-III digit span backward	1,681	−0.03 (−0.09, 0.03)	0.371
Socioeconomic	Educational attainment	3,282	−0.22 (−0.27, −0.18)	<0.001
	Occupational status	2,927	−0.16 (−0.20, −0.11)	<0.001
	Annual income	2,910	−0.06 (−0.09, −0.03)	<0.001

All models included participant age, sex, cohort, and zygosity as covariates. *n* = sample size; OR = odds ratio.

cannabis since their last assessment and the other twin reporting 5 to 30 uses, or one twin reporting 31 to 100 uses and the other twin reporting 101 to 400 uses (see *Methods* section for additional details).

Results from MZ-only cotwin control models of cannabis use are displayed in Table 4. (Between- and within-pair estimates from full-sample and DZ-only cotwin control analyses are shown in *SI Appendix*, Tables S3 and S4; mean outcome scores by MZ-twin discordance are shown in *SI Appendix*, Fig. S2). Significant within-pair associations between cannabis use and educational attainment, occupational status, and income indicated that higher levels of adolescent use remained associated with poorer socioeconomic outcomes even after accounting for the genetic and environmental factors shared by twins that confer liability toward both cannabis use and these outcomes. In contrast, within-pair associations between cannabis use and all psychiatric and cognitive outcomes were consistently nonsignificant. As shown in Table 4, within-pair associations for antisocial personality disorder, noncannabis illicit drug–use disorder, and vocabulary were significantly reduced (falling outside the 95% confidence interval of the corresponding between-pair estimates), suggesting confounding by shared familial liability. In contrast, within-pair associations for major depressive and anxiety disorders were comparable to corresponding between-pair and individual-level associations, suggesting that the higher *P* values for these tests (relative to individual-level models shown in Table 3) may have been driven primarily by reductions in statistical power rather than by accounting for familial confounding (for full MZ-only model results, reference *SI Appendix*, Table S5).

As a sensitivity analysis, we also ran parallel individual-level and MZ-only cotwin control analyses using a binary indicator of adolescent cannabis-use disorder in place of our continuous measure of cumulative cannabis use. Results from these analyses largely mirror those reported for cumulative adolescent cannabis use and are shown in *SI Appendix*, Tables S6 and S7.

Do the Significant within-Pair Associations between Cannabis Use and Socioeconomic Outcomes Survive Statistical Adjustment for Potential Confounds? A significant limitation of cotwin control models is that they do not account for potential differences between twins that are nongenetic in origin. It is possible, therefore, that observed within-pair associations could be driven by twin differences in attributes other that adolescent cannabis use. One particularly relevant potential confound is other externalizing problems (i.e., disruptive behavior problems and noncannabis drug use), given previous research reporting considerable polysubstance use and comorbidity among adolescent cannabis users (52, 53) and that many cannabis–outcome associations are dramatically attenuated

Table 4. MZ-only cotwin control analyses of cumulative adolescent cannabis use and young-adult outcomes

			MZ-only cotwin control analyses			
			Between-pair estimate		Within-pair estimate	
Functional domain	Young-adult outcome	*n*	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Psychiatric	Major depressive disorder	2084	1.14 (1.01, 1.29)	0.040	1.11 (0.90, 1.36)	0.341
	Anxiety disorder	1551	1.25 (1.04, 1.51)	0.017	1.58 (0.98, 2.54)	0.062
	Antisocial personality disorder	2086	2.07 (1.71, 2.50)	<0.001	1.18 (0.93, 1.50)	0.184
	Noncannabis illicit drug–use disorder	2088	1.85 (1.54, 2.21)	<0.001	1.09 (0.82, 1.44)	0.558
			β (95% CI)		β (95% CI)	
Cognitive	WAIS-R vocabulary	1582	−0.19 (−0.26, −0.11)	<0.001	−0.04 (−0.12, 0.05)	0.373
	WAIS-R block design	—	—	—	—	—
	WAIS-III digit span forward	—	—	—	—	—
	WAIS-III digit span backward	—	—	—	—	—
Socioeconomic	Educational attainment	2083	−0.22 (−0.30, −0.15)	<0.001	−0.15 (−0.23, −0.06)	<0.001
	Occupational status	1862	−0.18 (−0.25, −0.11)	<0.001	−0.11 (−0.21, −0.01)	0.030
	Annual income	1854	−0.07 (−0.11, −0.02)	0.002	−0.06 (−0.11, −0.01)	0.023

Cotwin control analyses were conducted following up on only significant individual-level associations (outcomes not significantly associated with cannabis exposure in these individual-level models are marked with "—"). All models included participant age, sex, cohort, and zygosity as covariates. *n* = sample size; OR = odds ratio.

once these other problems are accounted for (49, 54). A second potential confound is cannabis use in adulthood, given that adolescents who use cannabis are likely to continue using as adults. To rule out these potential confounds, we conducted two sets of follow-up analyses that included covariates capturing twin differences in (1) adolescent alcohol use, tobacco use, and disruptive behavior problems and (2) adult cannabis use.

In the first set of follow-up analyses, the magnitude of within-pair associations between cannabis use and all three socioeconomic outcomes remained relatively unchanged, suggesting that twin differences in adolescent alcohol use, tobacco use, and disruptive behavior problems likely do not account for these associations (*SI Appendix*, Table S8). Similarly, within-pair associations between adolescent cannabis use and all three socioeconomic outcomes were also largely unchanged in our second set of follow-up analyses, which introduced covariates capturing adult cannabis use. Within-pair associations between adult cannabis use and each outcome, however, were consistently nonsignificant and either smaller than or roughly equivalent to their adolescent within-pair counterparts across models, suggesting that associations between cannabis and socioeconomic outcomes were driven primarily by adolescent use (*SI Appendix*, Table S9).

What Pathways Might Explain the Association between Adolescent Cannabis Use and Young-Adult Socioeconomic Outcomes? Finally, we explored how adolescent cannabis exposure might affect young-adult socioeconomic status without detectable effects on mental health or cognitive ability. One possibility is that cannabis use impairs academic functioning in adolescence, captured by measures of grade point average (GPA), academic motivation, academic problem behaviors, school discipline problems, and affiliation with antisocial peers. Individual-level analyses showed that adolescent cannabis use was consistently associated with poorer academic functioning across all five of these outcomes. We also observed uniformly significant within-pair associations in MZ-only cotwin control models, consistent with a causal effect of cannabis exposure (Table 5) (mean scores on academic functioning variables for twins with no, light, moderate, and heavy adolescent cannabis use are shown in *SI Appendix*, Fig. S3; mean scores on academic functioning variables by MZ-twin discordance are shown in *SI Appendix*, Fig. S4).

To rule out the possibility that these associations reflect a causal effect of poor academic functioning on greater cannabis use (i.e., reverse causation), we additionally tested whether academic functioning at age 11 (before the onset of nearly all cannabis use) predicted subsequent cannabis use in adolescence. We found that twins with poorer academic functioning at age 11 reported greater cumulative adolescent cannabis use but also that nearly all of these associations became nonsignificant in MZ-only cotwin control models, suggesting they were attributable to shared environmental or genetic influences rather than a causal effect of academic functioning on use (*SI Appendix*, Table S10). To further strengthen causal inference, we also tested whether adolescent cannabis use continued to predict academic functioning at age 17 after adjusting for baseline academic functioning assessed at age 11. Individual-level analyses indicated that they did, and significant within-pair estimates in MZ-only cotwin control models suggested that greater cannabis use was associated with deleterious changes in GPA, academic motivation, and school discipline problems from age 11 to 17 independent of shared genetic and environmental liability (*SI Appendix*, Table S11). Finally, we used structural equation modeling to test whether any of our five measures of academic functioning mediated associations between MZ-twin differences in adolescent cannabis use and educational attainment. Results supported indirect paths from cannabis use to reduced educational attainment via lower GPA (β [95% CI] = −0.04 [−0.06, −0.02] and $P < 0.001$) and lower academic motivation (β [95% CI] = −0.01 [−0.01, 0.00] and $P = 0.021$); indirect paths through other potential academic mediators were nonsignificant (*SI Appendix*, Fig. S5).

Discussion

The belief that cannabis use in adolescence has pronounced, negative effects on the developing brain has cast a long shadow, animating both well-meaning objections to cannabis legalization (6) as well as public health campaigns designed to acquaint parents and teens with the dangers of adolescent use (7). Although the present set of analyses supports the existence of a possible causal relationship between adolescent cannabis use and young-adult socioeconomic outcomes, we observed few instances in which cannabis use remained associated with difficulties in other domains once familial factors were accounted for. These findings thus provide evidence against the notion that adolescent cannabis use has substantial, long-term effects on emotional and cognitive functioning, suggesting instead that most negative effects on young-adult well-being are likely to proceed through educational pathways.

Because our twin studies were designed specifically to examine associations between adolescent substance use and later functioning, our analyses are characterized by several strengths. One is that we used gold-standard, interview-based measures of both cannabis exposure and various young-adult outcomes. Assessments of cannabis use were also administered repeatedly over time, minimizing many of the well-known limitations of retrospective data (e.g., normal forgetting, revisionist recall, or forward telescoping of recalled events) (55, 56) as well as measurement error that could bias our within-pair estimates (50). A second advantage is that we combined data from multiple cohorts, which together cover adolescent cannabis use occurring over three decades. In addition to providing sufficient numbers of MZ twin

Table 5. Individual-level and MZ-only cotwin control analyses of cumulative adolescent cannabis use and age-17 academic functioning

				MZ-only cotwin control analyses				
	Individual-level models			Between-pair estimate			Within-pair estimate	
Academic functioning	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value	β (95% CI)	*P* value
GPA	3290	−0.24 (−0.29, −0.20)	<0.001	2108	−0.26 (−0.33, −0.19)	<0.001	−0.13 (−0.21, −0.05)	<0.001
Academic motivation	3265	−0.27 (−0.32, −0.23)	<0.001	2096	−0.31 (−0.38, −0.25)	<0.001	−0.16 (−0.25, −0.08)	<0.001
Academic problem behaviors	3262	0.25 (0.20, 0.29)	<0.001	2095	0.31 (0.23, 0.38)	<0.001	0.10 (0.02, 0.18)	0.015
School discipline problems	2693	0.43 (0.36, 0.51)	<0.001	1702	0.43 (0.31, 0.55)	<0.001	0.25 (0.13, 0.37)	<0.001
Antisocial peer affiliation	2093	0.65 (0.58, 0.71)	<0.001	1311	0.74 (0.63, 0.85)	<0.001	0.40 (0.24, 0.55)	<0.001

Individual-level analyses examined associations between adolescent cannabis use and scores on five measures of academic functioning at target age 17. Cotwin control analyses decompose associations from individual-level models into between-pair (reflecting preexisting, shared familial liability) and within-pair (cannabis exposure) estimates. All models included participant age, sex, and cohort as covariates. Individual-level models also included a covariate controlling for twin zygosity. Estimates are reported in standardized betas. *n* = sample size.

pairs to permit cotwin control analyses, this design feature also allowed us to examine the consistency of results across cohorts.

Our findings replicate and extend those of previous studies examining the consequences of adolescent cannabis use in several ways. Consistent with previous twin studies, we found that associations between adolescent cannabis use and young-adult depression (45), anxiety, and cognitive ability were either attributable to shared familial confounds or too modest to reach statistical significance in MZ-only cotwin control models (47–49). We found that shared environmental and genetic factors were also responsible for associations between cannabis and both antisocial behavior and noncannabis illicit drug–use disorder in young adulthood. Interestingly, our drug-use disorder finding is somewhat at odds with most—though not all (42)—previous twin studies, which have generally found evidence supporting a role for these shared factors but also evidence of independent causal effects (26, 39–41). It is possible that the relatively greater size and longitudinal nature of the current study partially accounts for these differences. In addition, it is also possible that cohort effects play a role, as the twin participants in the present study belong to more contemporary cohorts than those used in previous studies.

Our finding of a potential causal relationship between adolescent cannabis use and young-adult socioeconomic status is in line with findings from multiple epidemiological studies, which have reported similar associations that survive adjustments for measured preexposure confounds as well as propensity score analyses (18, 54, 57, 58). Indeed, comparative studies have suggested that adolescent cannabis use is a better marker for lower educational attainment than adolescent alcohol use (57). Although two previous twin studies of cannabis and education failed to find similar effects (27, 39), ours uses a longitudinal design with repeated, prospective measures of adolescent use. Our analyses also used continuous measures of both cannabis use and socioeconomic outcomes, which are characterized by greater variability than the relatively coarse, dichotomous indicators of both cannabis exposure (i.e., ever used, initiated use before age 18, lifetime cannabis-use disorder) and educational attainment (i.e., completed high school or undergraduate degree) used in previous reports, and thus has greater power to detect true effects.

A final advantage of the present analyses is that our data included repeated measures of adolescent academic functioning, allowing us to conduct exploratory analyses examining whether these more proximal outcomes might also be impacted by cannabis use. MZ-only cotwin control models using age-17 measures of academic functioning indicated that greater adolescent cannabis use was consistently associated with decreased GPA and academic motivation as well as increased academic problem behaviors, school discipline problems, and antisocial peer affiliation, independent of shared genetic and environmental factors. Although introducing covariates that captured age-11 scores on these measures reduced associations with academic problem behaviors and antisocial peer affiliation to nonsignificance, remaining significant associations indicated that many of these differences could not be attributed to preexisting differences in academic functioning that preceded cannabis-use onset. Given that cannabis use had no detectable causal effect on young-adult cognitive performance in our sample, these academic functioning findings, combined with results from our test of statistical mediation, raise the possibility that adolescent cannabis use might instead reduce socioeconomic attainment in young adulthood through subtler effects on academic performance and motivation (59).

Findings from this study should be interpreted in light of several limitations. First, although our study presents results from models spanning multiple domains of young-adult functioning, we could not examine all relevant outcomes. It remains possible, therefore, that cannabis could influence important psychiatric or cognitive outcomes not considered by our study, such as psychotic illnesses or executive functioning. Second, it is also possible that some of the "null" findings in our MZ-only cotwin control models reflect weak causal effects of cannabis on these outcomes, which might approach statistical significance had we an even larger sample. Results from our analyses of psychiatric outcomes, in particular, should be interpreted with this limitation in mind, given that our use of binary diagnostic outcomes means these analyses are characterized by reduced power relative to tests of association with continuous outcomes (e.g., measures of cognitive performance or socioeconomic status). On the other hand, these same analyses do not control for psychiatric symptoms present before cannabis use initiation, doing so would likely attenuate observed associations further. Third, because the samples used in our analyses all consisted of predominantly white participants born and raised in Minnesota between the 1970s and early 2000s, results from this study may not generalize to communities with different demographic characteristics or to present-day cannabis users, who tend to use cannabis products both more frequently and with higher potency (60). We note, however, that our findings were largely consistent across cohorts, even though each was born into a different era with corresponding differences in drug potency and societal attitudes toward cannabis (*SI Appendix*, Figs. S6 and S7). Fourth, our analyses were right censored at young adulthood. It is therefore possible that cannabis use could affect the functioning of adults at older ages or following multiple decades of routine, heavy use. It will be important to continue following twin cohorts with prospective assessments of cannabis use into middle and old age to address this limitation. Finally, we acknowledge limitations to the cotwin control approach, including heightened vulnerability to measurement error relative to individual-level analyses and an inability to conclusively rule out confounding due to nonshared environmental influences (50, 61). We attempted to address these limitations using repeated, prospective assessments and by including covariates capturing other adolescent externalizing problems and adult cannabis use in our follow-up analyses, but it is impossible to eliminate measurement error entirely and possible that twins differ on other confounding factors.

Despite these limitations, our findings have several implications for public health and clinical practice. First, they suggest the testable hypothesis that public health initiatives aimed at reducing youth cannabis exposure may lead to improved socioeconomic outcomes, even if these programs are unlikely to significantly reduce rates of young-adult mental disorder or cognitive impairment. Second, our findings reinforce the notion that most effects of cannabis on functioning are temporary in nature. Indeed, rather than finding evidence suggesting that adolescent cannabis users experienced reductions in socioeconomic status alongside compromised cognitive ability or mental health in young adulthood, our results instead suggest their poorer socioeconomic outcomes were more likely due to impairments in academic functioning that occurred contemporaneously with adolescent use. Future twin studies examining academic and occupational behaviors beyond the secondary school years could strengthen this hypothesis by examining the extent to which these functional impairments persist into adulthood or dissipate with abstention from use. Finally, our results emphasize that although early cannabis use is strongly associated with multiple types of future problems, it is causally implicated in far fewer. Accordingly, our results bolster the already widely shared perspective that actions or treatments aimed solely at reducing teen cannabis use without addressing other psychological or contextual issues are generally unlikely to produce long-term positive effects (62). Our results also encourage intervention at the level of the family, given that familial influences contribute both to cannabis use and many negative outcomes.

Methods

Participants and Procedures. Participants were a combined twin sample (n = 3,762) from three longitudinal studies at the MCTFR. Twin pairs were identified from Minnesota birth records. 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 completing of a day-long, in-person assessment. The "Enrichment Sample" (ES) cohort ($n = 998$) and "Younger" cohort ($n = 1{,}512$) were first assessed with their parents at age 11, and the "Older" cohort ($n = 1{,}252$) was first assessed with their parents at age 17. Follow-up assessments were conducted approximately every 3 y into young adulthood (see Table 1 for the timing of assessments across all three cohorts). Detailed overviews of the MCTFR, twin samples, inclusion/exclusion criteria, and procedures and assessments are provided in previous articles (51, 63, 64). We observed no significant association between cumulative adolescent cannabis use and likelihood of contributing data to at least one of the young-adult assessment waves (odds ratio: 0.93, 95% CI: [0.85, 1.02], and $P = 0.121$).

The Institutional Review Board of the University of Minnesota approved these studies at each wave. After the study protocol was explained, caregivers provided permission for their minor children to participate, and children provided written assent. Informed consent was obtained from the participants during each assessment wave conducted when participants were 18 y or older.

Measures.

Cannabis use. Cannabis use was assessed at ages 11, 14, 17, 24, and 29 using either a Computerized Substance Use Inventory (CSU), the Diagnostic Interview for Children and Adolescents-revised edition (DICA-R) (65), the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (66, 67), 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. Both the DICA-R and SAM assess Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for cannabis-use disorders, whereas all three measures assess frequency of cannabis use or number of uses since the last assessment (or lifetime number of uses at intake).

We computed cannabis use indices at ages 11, 14, 17, 24, and 29 as twins' mean scores on items assessing frequency of use and number of uses. Because responses were skewed and sparse, they were transformed into ordinal measures (with six categories per item) prior to averaging. For frequency of use, twins scored either 0 (no use), 1 (<1×/mo), 2 (1 to 3×/mo), 3 (1 to 4×/wk), 4 (every day or nearly every day), or 5 (>1×/d). For number of uses, twins scored either 0 (no uses), 1 (1 to 4 uses), 2 (5 to 30 uses), 3 (31-100 uses), 4 (101 to 400 uses), or 5 (>400 uses or "too many to count"). We derived an index of cumulative cannabis use in adolescence by averaging these scores across all adolescent assessment waves (i.e., ages 11, 14, and 17) available in each cohort. Although this method means we used data from all three assessment waves to derive indices in the "ES" and "Younger" cohorts, and only data from the age-17 assessment to derive indices in the "Older" cohort, the reporting period covered by these assessments (birth to age 17) was equivalent across cohorts. We also derived an index of total adult use by averaging across use indices computed for our two adult assessment waves (i.e., ages 24 and 29 in the "Younger" and "Older" cohorts and age 24 only in the "ES").

For sensitivity analyses, we also derived a measure of adolescent cannabis-use disorder. Diagnoses were based on a "best estimate" approach that combined information from twins' self-report and parent report and were made according to the DSM, fourth edition (DSM-IV) (68), or, in the "Older" cohort, according to the DDSM, third edition-revised (DSM-III-R) (69). Kappa reliabilities exceeded 0.90 (70).

Outcomes in young adulthood. Across cohorts, outcomes were assessed at either age 24 or 29 (or in the case of certain psychiatric diagnoses, at both ages). For psychiatric outcomes assessed at both age-24 and age-29 assessments, we coded the disorder as "present" if the twins met criteria for the condition at either wave. The exact schedule of outcome assessments in each cohort is shown in *SI Appendix*, Table S12.

Psychiatric disorder. Twins were assessed for common forms of psychopathology in young adulthood via clinical interview. Psychiatric disorders assessed included major depressive disorder, anxiety disorders, antisocial personality disorder, and noncannabis illicit drug–use disorders. Anxiety disorders comprised generalized anxiety disorder, social phobia, specific phobia, panic disorder, and agoraphobia. Noncannabis illicit drug–use disorders comprised amphetamine-, cocaine-, sedative-, phencyclidine-, opiate-, inhalant-, and hallucinogen-use disorder. Major depressive disorder and anxiety disorders were assessed with the Structured Clinical Interview for the DSM (SCID) (71), antisocial personality disorder was assessed with an MCTFR variation of the SCID-II, and drug-use disorders were assessed with a modified version of the expanded SAM (66, 67). All diagnoses were based on full DSM-IV criteria except antisocial personality disorder, which was diagnosed regardless of whether participants had evidence of conduct disorder prior to age 15, consistent with our focus on adult functioning (68). Kappa reliabilities for all diagnoses exceeded 0.80 (70).

Cognitive ability. Measures of cognitive ability included the Vocabulary and Block Design subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (72) and the Digit Span Forward and Digit Span Backward subtests from the WAIS-III (73). The Vocabulary subtest asks participants to name objects in pictures or define words presented to them and taps semantic knowledge as well as verbal comprehension and expression. The Block Design subtest asks participants to rearrange blocks that have various color patterns on different sides to match a pattern and taps both motor and visuospatial skills. The Digit Span Forward and Digit Span Backward subtests ask participants to listen to sequences of numbers presented orally and to repeat them as heard and in reverse order, tapping working memory, attention, and auditory processing abilities.

Socioeconomic outcomes. Socioeconomic outcomes included educational attainment (coded as a 6-category ordinal variable where 1 = less than high school and 6 = graduate/professional degree), occupational status (a Hollingshead-type scale with higher values indicating occupations requiring more skill), and personal annual income before taxes (in US dollars). Information about these outcomes came from the Social Adjustment Interview, in which twins reported on their academic and professional functioning (74). Analyses for occupation and income excluded students and homemakers.

Covariates.

Alcohol use. Alcohol use was assessed at ages 11 and 14 using the CSU (75) and at age 17 using our expanded version of the SAM (66, 67). We computed alcohol use indices at ages 11, 14, and 17 as twins' mean scores on four items (frequency of drinking in the preceding 12 mo, number of drinks typically consumed per occasion in the preceding 12 mo, maximum number of drinks consumed in a single 24 h period since the last assessment 3 to 7 y prior, and number of times intoxicated in their lifetime). Because responses were skewed and sparse, they were transformed into ordinal measures (five to six categories per item) prior to averaging. We then derived an index of cumulative alcohol use in adolescence by averaging these scores across all adolescent assessment waves available in each cohort. Comprehensive data on the psychometric properties and validity of the alcohol index have been described previously (75).

Tobacco use. Lifetime tobacco use was assessed at age 17 using our expanded version of the SAM (66, 67) in much the same way as alcohol and cannabis use. We computed a tobacco use index as twins' mean scores on items assessing frequency of use (days per month) and typical amount used (summing across cigarettes, cigars, pipes, and chewing tobacco). Because responses were skewed and sparse, they were transformed into ordinal measures (two to three categories per item) prior to averaging.

Disruptive behavior problems. Lifetime symptoms of conduct disorder and oppositional defiant disorder were assessed at intake in each cohort using a best-estimate approach that combined both parent and child responses to items on the DICA-R (65). Disorders were assessed using DSM-IV criteria in the "ES" cohort (68) and DSM-III-R criteria in the "Younger" and "Older" cohorts (69). Adolescent disruptive behavior problems were defined as a count of the diagnostic criteria met for each of these disorders.

Academic functioning. Interview-based measures of academic functioning were administered to twin participants in each of the three cohorts at age 17. These measures have been described previously (76, 77). Twins in the "ES" and "Younger" cohorts also completed identical measures at baseline assessments targeting age 11. GPA was assessed by asking participants for past-academic-year grades in four core subjects (reading/English, arithmetic/math, science, and social studies/history). Academic motivation (e.g., "enjoys attending school," "motivated to earn good grades," etc.) and academic problem behaviors (e.g., "turns in homework on time," "easily distracted in class," etc.) were each assessed with six items rated on a four-point scale ranging from "definitely false of me" to "definitely true of me." Twins' school discipline problems were assessed with seven items (e.g., were they sent to detention or held after school, suspended, etc.) that also asked for the frequency of each problem. Twins received a score of "0" on each item if they reported the consequence never happened to them, "1" if they reported the consequence happened one time in the past school year, and a "2" if they reported experiencing the consequence multiple times. Antisocial peer affiliation was assessed with nine items (e.g., "my friends break the rules," "my friends get into trouble with the police," "my friends use drugs," etc.) rated on a four-point scale ranging from "none of my friends are like that" to "all of my friends are like that." Age-17 versions of each of these measures were all moderately correlated, with the strength (i.e., absolute value) of each pairwise correlation ranging from 0.34 (GPA and antisocial

peer affiliation) to 0.58 (academic problems and academic motivation) (all $Ps < 0.001$).

Statistical analyses. Our analyses consisted of three steps. First, we tested pooled individual-level associations. Second, we followed up significant individual-level associations using a cotwin control model, conducted using MZ twins to stringently control for all sources of familial confounding (i.e., genes and shared environment) and evaluate an especially robust test of exposure effects (for additional details regarding this method, reference *SI Appendix, Supplemental Methods*) (37, 38). Finally, we followed up significant within-pair estimates from our MZ-only cotwin control models with a set of planned analyses controlling for twin differences in externalizing behavior problem and adult cannabis use.

All models were run including sex and age at time of outcome assessment as covariates. Because twins in each cohort reached adulthood in different eras, and because of slight differences in the timing of assessments across cohorts, all models also included dummy variables designed to capture cohort effects. Models run in the full sample (i.e., not restricted to only MZ or DZ twins) included a further covariate for zygosity. To examine whether the associations between cannabis and each outcome were similar across cohorts, we also ran a separate set of models that included covariates capturing the interaction of cohort and cannabis exposure. Although these interaction terms were statistically significant in a small number of cases, comparison of coefficients from cohort-specific models indicated that most estimates were roughly equivalent in magnitude and that significant associations were always in the same direction (reference *SI Appendix*, Figs. S6 and S7 for details). Consequently, we conducted all analyses pooling across cohorts.

Analyses were conducted in R Studio version 1.2.5019 using the "geeglm" function from the "geepack" package (78), which implements the generalized estimating equation approach for fitting marginal generalized linear models to clustered data. In these models, we specified a binomial distribution for diagnostic outcomes and a normal distribution for continuous outcomes. We also specified an exchangeable correlation matrix and robust SEs to account for the nested family structure.

Data Availability. Anonymized quantitative data have been deposited in Open Science Framework, https://osf.io/5nfxk (79).

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