Journal of Psychopathology and Clinical Science

ISSN: 2769-7541

2024, Vol. 133, No. 1, 115–128
https://doi.org/10.1037/abn0000867

Limited Psychological and Social Effects of Lifetime Cannabis Use Frequency: Evidence From a 30-Year Community Study of 4,078 Twins

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Background: Cannabis use is associated with outcomes like income, legal problems, and psychopathology. This finding rests largely on correlational research designs, which rely at best on statistical controls for confounding. Here, we control for unmeasured confounders using a longitudinal study of twins. ***Method:*** In a sample of 4,078 American adult twins first assessed decades ago, we used cotwin control mixed effects models to evaluate the effect of lifetime average frequency of cannabis consumption measured on substance use, psychiatric, and psychosocial outcomes. ***Results:*** On average, participants had a lifetime cannabis frequency of about one to two times per month, across adolescence and adulthood. As expected, in individual-level analyses, cannabis use was significantly associated with almost all outcomes in the expected directions. However, when comparing each twin to their cotwin, which inherently controls for shared genes and environments, we observed within-pair differences consistent with possible causality in three of the 22 assessed outcomes: cannabis use disorder symptoms ($\beta_{W\text{-}Pooled} = .15$, $SE = .02$, $p = 1.7 \times 10^{-22}$), frequency of tobacco use ($\beta_{W\text{-}Pooled} = .06$, $SE = .01$, $p = 1.2 \times 10^{-5}$), and illicit drug involvement ($\beta_{W\text{-}Pooled} = .06$, $SE = .02$, $p = 1.2 \times 10^{-4}$). Covariate specification curve analyses indicated that within-pair effects on tobacco and illicit drug use, but not cannabis use disorder, attenuated substantially when covarying for lifetime alcohol and tobacco use. ***Conclusions:*** The cotwin control results suggest that more frequent cannabis use causes small increases in cannabis use disorder symptoms, approximately 1.3 symptoms when going from a once-a-year use to daily use. For other outcomes, our results are more consistent with familial confounding, at least in this community population of twins.

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This work was supported by National Institutes of Health Grants DA042755 (Christian J. Hopfer, John K. Hewitt, Matt K. McGue, Scott Vrieze), DA046413 (Scott Vrieze), DA005147 (William Iacono), DA013240 (William Iacono), DA036216 (William Iacono), DA037904 (Scott Vrieze), DA032555 (Christian J. Hopfer), DA035804 (Christian J. Hopfer), DA011015 (John K. Hewitt), DA012845 (John K. Hewitt), DA038065, AA023974 (Scott Vrieze), AA009367 (Matt K. McGue), and MH066140 (Matt K. McGue). We have no known conflicts of interest to disclose. Prior dissemination of data: These hypotheses and results have not been presented at a conference or as a preprint; however, we have published two related manuscripts that focus on recreational cannabis legalization and the same outcomes (Zellers et al., 2022; Zellers, Ross, Saunders, Ellingson, Anderson, et al., 2023). The authors complied with American Psychological Association ethical standards. The University of Minnesota Institutional Review Board (IRB) determined this work was not research involving human subjects as defined by Worksheet HRP-310 and therefore did not require ongoing IRB approval. All deviations from the preregistration are also documented at the same link. Study data are not publicly available due to privacy concerns and limitations of the informed consent provided by participants at each assessment. Archiving of the outcome assessments is in progress via the Inter-university Consortium for Political and Social Research at the University of Michigan. Study materials (including code) are available upon reasonable request from the corresponding author.

The analysis plan was preregistered on April 21, 2022, and is available at https://osf.io/dtqg7/.

Stephanie Zellers served as lead for conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, writing–original draft, and writing–review and editing. Jordan Alexander served in a supporting role for conceptualization, methodology, and writing–review and editing. Jarrod M. Ellingson served in a supporting role for methodology and writing–review and editing. Jonathan D. Schaefer served in a supporting role for conceptualization, methodology, and writing–review and editing. Robin P. Corley served in a supporting role for data curation, funding acquisition, and writing–review and editing. William Iacono served in a supporting role for formal analysis, supervision, and writing–review and editing. John K. Hewitt served in a supporting role for writing–review and editing. Christian J. Hopfer served in a supporting role for conceptualization and writing–review and editing. Matt K. McGue served in a supporting role for conceptualization and writing–review and editing. Scott Vrieze served as lead for supervision and served in a supporting role for conceptualization and writing–review and editing. William Iacono, John K. Hewitt, Christian J. Hopfer, Matt K. McGue, and Scott Vrieze contributed equally to funding acquisition. Christian J. Hopfer and Matt K. McGue contributed equally to supervision.

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General Scientific Summary
This study suggests that lifetime exposure to cannabis has few persistent effects on mental health and other psychosocial outcomes. The notable exceptions are cannabis use disorder, tobacco frequency, and illicit drug use, for which lifetime cannabis frequency causes small increases.

Keywords: substance use disorder, discordant twin, causal inference, cannabis, mental health

Supplemental materials: https://doi.org/10.1037/abn0000867.supp

Over the past decade, many U.S. states have legalized medical and recreational cannabis use. As of January 2023, recreational cannabis use is fully legal in 20 states and the District of Columbia and cannabis is fully illegal in only four states. Correspondingly, attitudes in the United States toward cannabis use have rapidly changed; fewer than one quarter of adults now perceive occasional cannabis use as a substantial health risk (SAMHSA, 2021; Van Green, 2021). Proponents of recreational cannabis legalization argue that cannabis use is no more dangerous than other legal recreational drugs, like alcohol or tobacco, and that legalizing and taxing cannabis can increase state tax revenue (Resko et al., 2019).

Nonetheless, amidst this environment of increased cultural permissiveness and rapid legalization, policy makers and public health officials have raised concerns that cannabis legalization may carry substantial public health risks. Research thus far suggests cannabis legalization is associated with increased adult cannabis use and rates of cannabis use disorder (O'Grady et al., 2022; Smart & Pacula, 2019). Additionally, cannabis use is correlated with a multitude of adverse health, cognitive, and psychosocial consequences. These include poorer executive functioning and working memory (Scott et al., 2018; Volkow et al., 2016), greater rates of psychiatric and psychotic symptoms (Hjorthøj et al., 2023; Schaefer, Hamdi, et al., 2021; Volkow et al., 2014), and poorer academic and job outcomes (Schaefer, Hamdi, et al., 2021; Volkow et al., 2014, 2016). Critics of cannabis legalization hence argue that these policies will increase both cannabis use and the many health and psychosocial harms associated with it.

These claims presume a causal relationship between cannabis use and these adverse consequences. However, the claims are largely supported by correlational research that is of limited use in inferring causality as it is prone to confounding (Lu, 2009). Observed correlations between two variables (i.e., greater cannabis use predicts poorer job outcomes) may reflect causal effects of one variable on the other, but they may also reflect the effects of confounding variables, often genetic and environmental influences that affect both variables (McGue et al., 2010). These unmeasured genetic and environmental confounds are difficult to address with observational data of unrelated individuals, and it is rarely straightforward to control for even measured confounders (Meehl, 1971). Randomized, controlled experiments can address these conditions for causal inference, but such studies on the consequences of cannabis use are infeasible for both practical and ethical reasons. However, quasiexperimental designs, which can control for the effects of potential confounders, offer one useful avenue to test causal claims made about the effects of cannabis use.

One quasi-experimental research design is the cotwin control study, also called a discordant twin study. Monozygotic twins share essentially 100% of their genome, are typically raised in a common environment, and share many important demographic features (age, ethnicity, birth year, etc.), so this quasi-experimental design naturally controls for additive genetic influences and partially controls for environmental influences that may otherwise confound an observed relationship between a risk factor and some outcome (McGue et al., 2010; Saunders et al., 2019). In other words, cotwin control designs test whether twins who differ on an exposure, here cannabis use, also differ on some outcome, naturally controlling for all the unmeasured genetic and environmental confounders shared by twins within a family.

Other substance involvement, psychotic symptoms, and socioeconomic outcomes are among the largest concerns with respect to cannabis consumption. Cotwin control research on the effects of cannabis use suggests that many of these suspected consequences of cannabis use are better explained by common genetic liabilities and confounded environmental influences than by a causal effect of cannabis ingestion, though definitions of cannabis exposure vary. On the one hand, many cotwin control studies have found evidence consistent with causal influences of any adolescent use or early-onset cannabis consumption on some phenotypes, such as substance abuse/dependence or illicit substance involvement (Agrawal et al., 2004; Grant et al., 2010; Lessem et al., 2006; Lynskey et al., 2003, 2006). On the other hand, a study of monozygotic twins suggests that former heavy cannabis use was not associated with current alcohol or tobacco use and dependence, nor other health outcomes (Eisen et al., 2002).

Other studies have found mixed evidence for a causal relationship between frequent cannabis use or cannabis use disorder symptoms and psychotic-like experiences (Karcher et al., 2019; Nesvåg et al., 2017; Schaefer, Hamdi, et al., 2021; Schaefer, Jang, et al., 2021). Additionally, studies have repeatedly demonstrated that cannabis exposure (operationalized as any lifetime use, early use, cumulative adolescent use, frequency of use, regular use, age of initiation, or cannabis use disorder symptoms) does not appear to cause the observed associations between cannabis use and socioeconomic outcomes, lower verbal IQ, or lower cognitive ability (Grant et al., 2012; Jackson et al., 2016; Lyons et al., 2004; Meier et al., 2018; Ross et al., 2020; Schaefer, Hamdi, et al., 2021). These studies suggest that shared genetic and/or environmental variables better explain many of the observed relationships between cannabis use and adverse outcomes, though for some outcomes there is mixed evidence for a causal influence of cannabis consumption.

While this body of research has indicated that many purported consequences of cannabis in fact appear to arise from other sources, several issues remain unresolved. First, many studies have largely focused on the effects of adolescent cannabis use initiation on later outcomes. While this is understandable given the substantial concerns that public health officials have raised about the consequences

of youth cannabis use on the developing brain (CDC, 2022a), such studies have not investigated the effects of lifetime cannabis intake on outcomes in young adulthood and middle age. It would be informative to understand if cannabis exerts acute effects, or effects that vary depending on timing of exposure, or rather if cannabis has cumulative effects that persist through adulthood. For example, Schaefer, Hamdi, et al. (2021) finds some persistence of effects of cumulative adolescent cannabis use on some young adult outcomes, highlighting an area for future work.

Secondly, existing cotwin control studies often rely on coarse measures of cannabis exposure (e.g., "have you ever used cannabis" and analogous measures), rendering them unable to differentiate between the effects of any consumption and effects of amount of consumption. Lastly, retrospective measures are subject to recall bias more so than prospective reports, a factor that is particularly important when measuring more fine-grained outcomes (e.g., amount of consumption in a particular time period) as compared to coarser measures (e.g., any lifetime use).

We aimed to address some of these limitations using data from a longitudinal population sample of twins. We analyzed data from approximately 4,000 twins with prospectively assessed data on frequency of cannabis consumption from adolescence to midadulthood, as well as prospectively assessed covariates, and outcomes assessed in adulthood. The present study had two aims: (a) measure relationships between prospectively assessed, cumulative, lifetime cannabis exposure and later substance use, psychiatric, and psychosocial outcomes, and (b) further test these relationships with cotwin control analyses to control for unmeasured genetic and shared-environmental confounders influencing the relationships. If cannabis use has a causal effect on subsequent psychosocial functioning, we would expect significant prospective associations between cannabis use and subsequent outcomes, and familial confounds would not explain these effects in cotwin control analyses. We additionally evaluated many outcomes and definitions of cannabis exposure, to ensure a broad understanding of the impacts of cannabis use as well as evaluate different conceptual explanations for cannabis's effects (cumulative use, heavy use, developmentally sensitive periods).

Method

Participants

We analyzed data from $N = 4{,}078$ individuals from two longitudinal community twin samples maintained by the Minnesota Center for Twin Family Research (Wilson et al., 2019), and the Colorado Center for Antisocial Drug Dependence (Corley et al., 2019). Both samples were recruited in adolescence via birth records; additional recruitment and sample details have been extensively described previously (Corley et al., 2019; Wilson et al., 2019). In brief, participants were born between 1972 and 1994 and first assessed between ages 11 and 19. We utilized data from up to four assessment waves for Colorado and up to six assessment waves for Minnesota. Cannabis use was prospectively measured across ages 11–35 during the years 1994–2014 (up to three prospective cannabis assessments in Colorado and up to five prospective cannabis assessments in Minnesota). Outcomes were assessed during the years 2018–2021; participants ranged in age from 25 to 49 at this assessment. Assessments from 1994 to 2014 were conducted independently and later harmonized between sites, but the final wave of assessment was conducted from 2018 to 2021, in a coordinated effort across sites. Table S1 in the online supplemental materials indicates how many participants had data for each number of assessments, as well as more details on the ages, sample sizes, and years of assessment. Additional details on previous work in overlapping samples are addressed in the Supplemental Methods in the online supplemental materials.

Measures

The Supplemental Methods section in the online supplemental materials contain full descriptions of each predictor, covariate, and outcome, as well as the methods utilized to harmonize the measures across sites (see also Tables S2 and S3 in the online supplemental materials).

Lifetime Average Cannabis Frequency Measure

Frequency of cannabis consumption was harmonized to represent "number of days used in the last 180" at each assessment. Our primary cannabis use predictor, which we will refer to as "lifetime average cannabis frequency," was measured by computing an average frequency for each individual across all waves of assessment available (up to three waves for Colorado participants, and up to five waves for Minnesota participants). This primary exposure was preregistered and designed to evaluate the cumulative effects of cannabis use across adolescence and young adulthood.

Alternative Measures of Cannabis Exposure

To evaluate alternative definitions of lifetime exposure to cannabis, we constructed five additional cannabis use variables that map onto different conceptual framework of cannabis effects. The simplest measure of use was lifetime ever use, defined as "no use" if the participant reported never using cannabis in their lifetime at every assessment prior to outcome measurement, and "lifetime use" if the participant reported ever having used cannabis at any assessment prior to outcome measurement. Significant effects from this exposure would suggest that trying cannabis, even once, was associated with consequences of cannabis use. We also defined an alternative frequency of consumption, using maximum last 12 months frequency reported across all waves prior to the final assessment, designed to evaluate the effects of heavier but time-limited cannabis use on these outcomes.

We also defined three measures of use related to age of onset. First, we defined age of onset as age in years that the participant first used cannabis by averaging the reported age of onset across all waves of assessment prior to the final assessment at which outcomes were measured. All reported ages of onset younger than 10 years were redefined as 10 years old. From this age of onset in years, we created two additional binary variables capturing early age of onset. While dichotomizing inherently continuous phenomena throws away information, these variables were created to improve comparability to existing cotwin control literature. We defined one early onset variable as whether the participant had an age of onset prior to the age of 18, an age commonly used in the existing cotwin control literature on early onset (ex., Grant et al., 2012; Verweij et al., 2013). Our second early onset variable was defined as having an age of onset in the bottom quartile (here 15.3 years) as this method for defining "early" based on the distribution

is also used in the existing literature (Agrawal et al., 2017; Few et al., 2016). These three age of onset exposures were created to evaluate developmental timing effects with respect to cannabis consumption and its outcomes. These secondary exposures were not preregistered.

Substance Use, Psychiatric, and Psychosocial Outcomes

Substance use, psychiatric, and psychosocial outcomes were measured at the final assessment wave with a reporting period of the last 12 months via an online self-report survey and telephone structured clinical interview. Substance use outcomes included consumption of alcohol and tobacco, which were assessed as "number of days used in the last 180." We also measured the number of noncannabis illicit substances consumed across 11 categories of substances (e.g., stimulants, hallucinogens, steroids, etc.). Psychiatric outcomes included *Diagnostic and Statistical Manual of Mental Disorders-5th Edition* (*DSM-5*) alcohol, tobacco, and cannabis use disorder symptom counts, and *DSM-5* disordered personality traits assessed at the domain level: negative affectivity, detachment, psychoticism, and disinhibition (Krueger et al., 2012). Other psychosocial outcomes included the following adapted scales: Externalizing Spectrum Inventory (Patrick et al., 2013), Dyadic Adjustment Scale (Spanier & Thompson, 1982), Occupational Citizenship and Counterproductive Work Behavior checklists (Spector et al., 2010), Civic Engagement Scale (Doolittle & Faul, 2013), and the International Cognitive Ability Resource (Condon & Revelle, 2014). We also assessed some psychosocial outcomes through scales created specifically for this particular study assessment: financial problems (e.g., I have found it difficult to meet the cost of major repairs to my home or car), savings habits (e.g., I regularly save some of the money I earn by placing it in a special account), legal consequences (e.g., I have received some form of driving citation), and degree of unemployment (e.g., I have been demoted at work). Details on the reliability and validity of these created scales are available in the Supplemental Methods in the online supplemental materials.

Covariates

All models included covariates of age and sex. We also explored the effects of additional covariates including birth state (Colorado or Minnesota), intake cohort, current residence, adolescent externalizing symptoms, parental education, and earlier use of alcohol and tobacco. More details on the operationalization of current residence, parental education, adolescent externalizing symptoms, and earlier tobacco and alcohol use are presented in the Supplemental Methods in the online supplemental materials.

Current residence was included as some participants resided in recreationally legal states and others in recreationally illegal states at the time of outcome assessment. Participants were classified as living in a recreationally legal or illegal state based on five digit postal code and date of assessment. We evaluated both current residence and birth state, as these two variables are highly correlated but provide different information. Current residence has been previously identified as significantly related to some of the included outcomes in our previous work on recreational cannabis legalization, whereas birth state is significantly related to some of the included outcomes via effects of ascertainment and attrition (Zellers, Ross, Saunders, Ellingson, Walvig, et al., 2023).

Intake cohort was defined as belonging to a small group ($N = 308$; 7.6% of the sample) selected at age 10–11 to have a higher likelihood of developing childhood externalizing symptoms as compared to the other nonselected community members (Keyes et al., 2009). Parental education was evaluated as a proxy for socioeconomic status in the rearing environment, also established to relate to substance use and other psychosocial factors (Bachman et al., 2011; Hanson & Chen, 2007; Lee et al., 2018; Lemstra et al., 2008). Adolescent externalizing was included given the evidence supporting a general genetic vulnerability to externalizing and substance use behaviors (Krueger et al., 2002; McGue et al., 2014; Vanyukov et al., 2012; Young et al., 2000). Lastly, to evaluate whether cumulative cannabis intake predicted deviations in substance use outcomes from earlier behavior, we also evaluated prospectively assessed substance use and use disorder covariates in conjunction with their respective outcome (e.g., lifetime alcohol use disorder symptoms included as a covariate for analyses of current alcohol use disorder symptoms).

Analyses

Data cleaning, analyses, and plotting were conducted in RStudio 1.4.1106 using lme4 1.1-23 (Bates et al., 2015), lmerTest 3.1-3 (Kuznetsova et al., 2017), specr 1.1.0 (Masur & Scharkow, 2023), and ggplot2 3.3.5 (Wickham, 2016). We chose an α cutoff of .001 to account for the number of predictors and outcomes. We ran post hoc power analyses to determine what effect size we could detect given our sample size, power of 80%, and α level of .001. We are able to detect fixed effects at the local effect size of Cohen's $f^2 = .004$ (Selya et al., 2012), which corresponds to the amount of variance explained by one fixed effect over and above the variance accounted for by other variables in the model, akin to change in R^2.

Individual and Cotwin Analyses

To first measure the effect of lifetime average cannabis frequency on other substance use, psychiatric, and psychosocial outcomes (without controlling for the influence of shared genetic and environmental influences) we fit individual-level mixed effects models which included a family-level random intercept. In the individual model, $Y = \beta_0 + X\beta_I + Zu + \epsilon$, the outcome Y is a function of X, the design matrix that includes fixed effects, Z, the random effect of individual nested within family u, and ϵ, the error term. All predictor and outcome variables were standardized to have M 0 and SD 1 ("z-scored") to facilitate interpretation of effects in SD units.

Next, to control for a wide variety of unmeasured confounders, we used a mixed effects models that decomposed the effect of the cannabis use into within-pair and between-pair effects using the following model: $Y_{ij} = \beta_0 + \beta_B \bar{X}_{.j} + \beta_w(X_{ij} - \bar{X}_{.j}) + Zu + \epsilon_{ij}$. Each outcome Y is a function of the average cannabis use for a given twin-pair (the between-pair effect β_B) and the difference in cannabis use between twins in the same family (the within-pair effect β_w). The cotwin control model naturally controls for unmeasured shared genetic and environmental confounders by evaluating whether twins from the same family who use cannabis at different rates are also different on a relevant outcome. To maximize power due to sample size while also capitalizing on the improved genetic control offered by the monozygotic-only analyses, we ran both zygosity-pooled models, which included both monozygotic and dizygotic pairs, and zygosity-stratified models: all dizygotic pairs, same-sex dizygotic pairs only, and monozygotic pairs. The analysis on the subset of monozygotic twins offers the estimate of β_w least affected by unmeasured confounds, as monozygotic twins share all of their

genes, as compared to dizygotic pairs who share half of their segregating genes on average (McGue et al., 2010; Saunders et al., 2019). Comparing the estimates from the individual-level model, pooled cotwin model, and monozygotic-only cotwin model allows us to determine if the observed effect is completely due to confounding by genetic and shared environmental effects, due to both confounding and causal influences, or entirely causal.

To formally compare $\beta_{W\text{-}Pooled}$ to β_I we computed the mean difference between $\beta_{W\text{-}Pooled}$ and β_I and the 95% confidence interval around the difference across 1,000 bootstrap replicates. If $\beta_{W\text{-}Pooled}$ is significantly different from zero and the magnitude of $\beta_{W\text{-}Pooled}$ is comparable in magnitude to β_I, this is consistent with a causal impact of cannabis consumption. On the other hand, if $\beta_{W\text{-}Pooled}$ is completely attenuated as compared to β_I, this is consistent with an effect of lifetime average cannabis frequency completely due to genetic and/or environmental confounders. Lastly, if there are significant within-pair differences that are smaller in magnitude than the individual-level effect (i.e., $\beta_{W\text{-}Pooled} < \beta_I$), this is consistent with the presence of both causal influences and confounders. As $\beta_{W\text{-}Pooled}$ does not control for all shared genetic factors, as the estimate of $\beta_{W\text{-}MZ}$ does, the case where $\beta_{W\text{-}MZ} < \beta_{W\text{-}Pooled}$ is also suggestive of mixed causal and confounding influences. Therefore, we also computed the mean difference between $\beta_{W\text{-}Pooled}$ and $\beta_{W\text{-}MZ}$ and the 95% confidence interval around the difference across 1,000 bootstrap replicates.

Secondary Cotwin Control Analyses

To assess the robustness of our analyses to alternative ways of measuring cannabis exposure, we conducted the same analyses on the five secondary cannabis exposure phenotypes as well (binary initiation, continuous maximum reported frequency, continuous age of onset, and two binary definitions of early use). As our sample is characterized as low-using and therefore also low-discordance, we also ran the primary analysis on two reduced samples to investigate more extreme use and discordance. One subsample analyses was in a subset of pairs where at least one twin was using approximately weekly (average frequency greater than 30 days, $N = 269$ pairs included) and a second in only pairs that had high discordance (approximately top quartile, discordance of 30 days or more, $N = 198$ pairs included). Lastly, as a sensitivity analysis, we reran the primary analyses with binary diagnoses of substance dependence instead of symptom counts.

Analysis of Covariate Effects via Specification Curve Analysis

It is frequently unclear whether a given covariate should be statistically controlled (Glymour et al., 2005; Meehl, 1971), so we also systematically evaluated the effects of covariates, other than age and sex, on the individual-level and cotwin analyses via specification curve analysis. The specification curve analysis is designed to evaluate the impact of analytical decisions on results, as these decisions may introduce bias in the results (Simonsohn et al., 2020). Inclusion, or lack of inclusion, of certain covariates is one such decision. Here we implement specification curve analysis by systematically including each covariate in the model and evaluating changes in effect size for the effect of interest (i.e. effect of cannabis consumption or within-pair differences in cannabis consumption). The covariates examined are birth state, current residence, intake cohort, earlier substance use and abuse (for corresponding outcomes), adolescent externalizing symptoms, and parental education. Models tested included a model with no additional covariates (i.e., the base model with only age and sex), models with each additional covariate included individually, and one final model with all additional covariates included simultaneously. We ran the specification curve analysis at the individual and zygosity-pooled levels. The chosen covariates were preregistered but specification curve analysis itself was not preregistered.

Transparency and Openness

The analysis plan was preregistered on April 21, 2022, and is available at https://osf.io/dtqg7/ (Zellers, Ross, Saunders, Ellingson, Anderson, et al., 2023). All deviations from our preregistration are also described in detail, available at the same link. Study data are not publicly available due to privacy concerns and limitations of the informed consent provided by participants at each assessment. Archiving of the outcome assessments are in progress via the Interuniversity Consortium for Political and Social Research at the University of Michigan. Study materials (including code) are available upon reasonable request from the corresponding author.

Results

Descriptives

The analytic sample was 57.5% female and 53.0% monozygotic pairs. At the time of outcome assessment, 40% of individuals resided in recreationally legal states and 60% lived in states without recreational cannabis. The majority (92%) of participants were White and 5% of the sample reported Hispanic ethnicity, consistent with the birth cohorts and states from which these participants were drawn.

Table 1 presents sample sizes, means, *SD*s, and ranges for variables in the main text. Sample sizes and descriptives for twin discordance on the primary and secondary cannabis variables are presented in Table S4 in the online supplemental materials. Individual-level correlations between all continuous variables are presented in Figure S1 in the online supplemental materials and twin correlations are presented in Table S5 in the online supplemental materials. Twin correlations were generally significantly positive and larger in monozygotic twins as compared to dizygotic twins, an indication of approximately moderate heritability of all variables. Lastly, prevalences for the *DSM-5* diagnoses analyzed in sensitivity analyses are presented in Table S6 in the online supplemental materials.

Individual and Cotwin Analyses

Results from the individual-level models are presented in Figure 1. At the individual-level, lifetime average cannabis frequency was associated with nearly all outcomes in the expected directions. All effects indicated small but harmful consequences of use. The only outcomes not associated with cannabis frequency at the individual level were negative affectivity and occupational citizenship behavior.

The pooled cotwin results are also presented in Figure 1, and Table 2 presents the zygosity-stratified results. While the majority of phenotypes had significant individual-level relationships with

Table 1
Variable Descriptives for Primary Analyses

Phenotype	*M*	*SD*	*Mdn*	Description	Range	*N*
Predictors and covariates measured at past assessments						
Lifetime average cannabis use frequency	9.0	24.1	0	Days in last 180	0–180	4,073
Max. reported cannabis use frequency	20.1	49.1	0	Days in last 180	0–180	4,073
Age of cannabis initiation	17.1	2.6	17	Years	10–30	249
Lifetime average tobacco use frequency	38.0	59.5	2	Days in last 180	0–180	4,056
Lifetime average alcohol use frequency	19.0	21.0	12	Days in last 180	0–180	4,073
Lifetime cannabis use disorder	0.8	1.8	0	Symptom count	0–9	4,077
Lifetime alcohol use disorder	1.6	2.2	1	Symptom count	0–9	4,077
Lifetime nicotine dependence	1.2	1.8	0	Symptom count	0–6	4,077
Adolescent externalizing	1.6	2.4	1	Symptom count	0–18	3,970
Lifetime adult ASPD	1.3	1.6	1	Symptom count	0–7	4,077
Outcomes measured at final assessment						
Current alcohol frequency	39.7	47.9	20	Days in last 180	0–180	3,960
Current nicotine frequency	29.4	62.8	0	Days in last 180	0–180	3,961
Other illicit drug use	0.2	0.6	0	Count	0–8	3,954
Current cannabis use disorder	0.2	0.9	0	Symptom count	0–11	3,948
Current alcohol use disorder	0.5	1.3	0	Symptom count	0–11	3,961
Current nicotine dependence	0.3	1.0	0	Symptom count	0–9	3,964
Negative affect	3.7	3.2	3	Sum score	0–12	3,941
Detachment	6.4	7.0	4	Sum score	0–45	3,939
Psychoticism	4.0	4.8	2	Sum score	0–31	3,938
Disinhibition	16.6	6.2	15	Sum score	0–47	3,939
Current externalizing	0.3	0.9	0	Sum score	0–4	3,957
Savings behavior	4.7	1.3	5	Sum score	0–6	3,943
Financial distress	1.9	2.8	1	Sum score	0–15	3,218
Income	7.2	3.6	7	Ordinal	1–16	3,922
Unemployment	0.3	0.7	0	Ordinal	0–4	3,967
Relationship agreement	87.0	10.7	88	Sum score	37–111	3,135
Legal issues	0.8	1.5	0	Sum score	0–6	3,958
Occupational citizenship	21.8	8.1	22	Sum score	0–40	3,654
Counterproductive work behavior	2.8	2.9	2	Sum score	0–11	3,653
Community attitude	33.9	5.5	34	Sum score	9–45	3,955
Community behavior	22.7	6.3	23	Sum score	8–40	3,956
Cognitive ability	8.7	3.8	9	Sum score	0–16	3,952

Note. Range refers to actual range in data, rather than theoretical range. ASPD = antisocial personality disorder.

cannabis consumption, few associations survived the cotwin control. The within-pair association between cannabis use disorder symptoms and frequency of cannabis consumption was robust across all pooled and zygosity-stratified analyses, supporting some causal influence of lifetime average cannabis frequency on cannabis use disorder ($\beta_{W\text{-}Pooled} = .15$, $SE = .015$, $p = 1.7 \times 10^{-22}$). This is a modest effect, approximately an increase of ~1 *SD* units, or ~1 symptoms, when going from using cannabis once per year to using daily. This within-pair effect ($f^2 = .03$) is a small effect according to local effect size conventions (Selya et al., 2012). This can be interpreted as change in R^2 from the within-pair effect above and beyond the other effects in the model (between-pair effect, age, sex, and random effect of family).

There was also evidence that lifetime average frequency of cannabis consumption caused higher frequency of tobacco use ($\beta_{W\text{-}Pooled} = .06$, $SE = .014$, $p = 1.2 \times 10^{-5}$). This is a modest effect, approximately an increase of ~.04 *SD* units, or ~27 days, when going from using cannabis once per year to using daily. This within-pair effect ($f^2 = .004$) is a very small effect according to local effect size conventions (Selya et al., 2012). Lastly, increased cannabis frequency caused higher illicit drug involvement ($\beta_{W\text{-}Pooled} = .06$, $SE = .015$, $p = 1.2 \times 10^{-4}$) though this was also a small effect in practical terms as it represents an increase of ~.04 *SD* units or ~.3 illicit substances when going from using cannabis once per year to using daily. This within-pair effect ($f^2 = .004$) is a very small effect according to local effect size conventions (Selya et al., 2012).

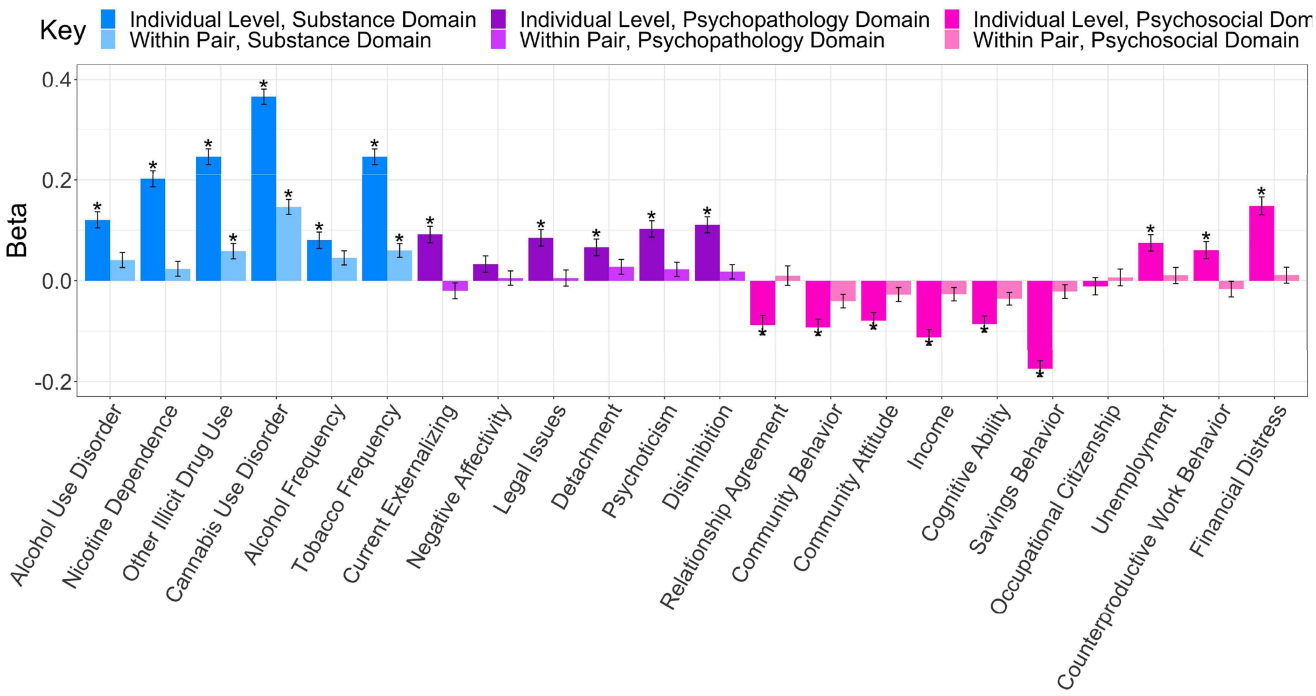
Bootstrapped comparisons of the individual level, pooled cotwin, and monozygotic cotwin estimates indicated that the effects of lifetime average cannabis frequency on cannabis use disorder, tobacco frequency, and illicit drug use were attenuated in the cotwin control models but there was no attenuation of within-pair effect with increasingly stringent cotwin analyses (i.e., $\beta_{W\text{ - }MZ} = \beta_{W\text{ - }Pooled}$; $\beta_{W\text{ - }MZ}$ and $\beta_{W\text{ - }Pooled} < \beta_{I}$; see Table 3). This attenuation suggests the observed effects of cannabis use on cannabis use disorder, tobacco frequency, and illicit drugs use represent a combination of causal influences and familial confounding.

Secondary Cotwin Control Analyses

We conducted five additional analyses utilizing alternative definitions of lifetime exposure to cannabis: ever use (Table S7 in the online supplemental materials), maximum last-12 months frequency of use (Table S8 in the online supplemental materials), age of onset (Table S9), and two definitions of early use (Tables S10 and S11 in the online supplemental materials). Broadly speaking, the results of each alternative cannabis use measure analysis agreed with the primary analysis of lifetime average frequency of cannabis consumption,

Figure 1

Bar Chart Illustrating the Effect Estimates From the Individual-Level and Zygosity-Pooled Cotwin Analyses of Prospective Average Frequency of Cannabis Consumption on a Variety of Outcomes (Grouped Here by Domain: Substances, Psychiatric, and Psychosocial)



Note. All predictor and outcome variables were standardized to have *M* 0 and *SD* 1 ("*z*-scored") to facilitate interpretation of effects in *SD* units. Error bars indicate *SE*. Positive betas indicate increased scores on the outcome with increasing frequency of cannabis consumption. See the online article for the color version of this figure.

in that each measure of cannabis use was associated with most outcomes at the individual level in the expected directions, but there were limited significant within-pair effects beyond those identified in the primary analysis. There were two exceptions. Age of onset within the first quartile of our sample (before 15.3) was significantly associated with current disinhibition within pairs ($\beta_{\text{W-Pooled}} = .20$, $SE = .04$, $p = 1.7 \times 10^{-6}$). Initiating cannabis use prior to age 18 was significantly associated with nicotine dependence within pairs ($\beta_{\text{W-Pooled}} = .15$, $SE = .04$, $p = 9.9 \times 10^{-5}$).

We also conducted secondary analyses in reduced samples to evaluate more extreme use and discordance. The analysis in the subset of pairs where at least one twin was using approximately weekly (Table S12 in the online supplemental materials) and the analysis of only pairs that had high discordance (Table S13 in the online supplemental materials) did not differ from the primary analysis with respect to cannabis use disorder, but within-pair effects on tobacco use and illicit substance attenuated significantly. Sensitivity analyses on binary diagnostic outcomes were in agreement with the corresponding symptom count results (Table S14 in the online supplemental materials).

Analysis of Covariate Effects via Specification Curve Analysis

Full results from the specification curve analysis are presented in Table S15 in the online supplemental materials. The results generally agreed with the results of the primary analysis, in the sense that adding covariates did not result in individual or within-pair effects where there previously were not significant effects. Of most interest are the three variables for which there were significant within-pair effects in the primary analysis: cannabis use disorder, tobacco frequency, and illicit drug use. The inclusion of any additional covariates did not result in attenuation of effect sizes for cannabis use disorder; the effect of cannabis use on cannabis use disorder remained significant in each model. In other words, within-pair differences in lifetime cannabis consumption predict current cannabis use disorder symptoms, even after accounting for earlier symptoms of cannabis use disorder. Only inclusion of prospective alcohol frequency resulted in attenuation of the effect sizes for illicit drug use to nonsignificance at our corrected alpha, though attenuation was incredibly small ($\beta_{\text{W-Pooled}} = .06$, $p = 1.2 \times 10^{-4}$ without inclusion of alcohol frequency covariate, $\beta_{\text{W-Pooled}} = .05$, $p = 1.3 \times 10^{-3}$ after inclusion). Likewise for tobacco frequency only the inclusion of prospective tobacco frequency resulted in significant attenuation of effect, though the attenuation was more pronounced ($\beta_{\text{W-Pooled}} = .06$, $p = 1.2 \times 10^{-5}$ without inclusion of alcohol frequency covariate, $\beta_{\text{W-Pooled}} = .01$, $p = .60$ after inclusion). In other words, within-pair differences in lifetime cannabis consumption do predict current tobacco use, but they do not predict current deviations in tobacco use as compared to earlier tobacco consumption. Specification curve plots for these three variables are presented in Figure 2.

Table 2
Individual and Within-Pair Estimates From Primary Cotwin Control Analysis

	Individual			Pooled zygosity			All dizygotic			Same-sex dizygotic			Monozygotic		
Phenotype	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Alcohol freq.	**.08**	**.016**	**8.3E−07**	.05	.014	1.2E−03	.04	.020	.08	.04	.024	.10	.06	.020	2.5E−03
Tobacco freq.	**.25**	**.016**	**1.7E−53**	**.06**	**.014**	**1.2E−05**	.06	.021	2.8E−03	.06	.025	.01	.06	.018	1.4E−03
Illicit drugs	**.25**	**.016**	**3.7E−53**	**.06**	**.015**	**1.2E−04**	.07	.023	1.4E−03	.08	.027	2.1E−03	.04	.021	.06
CUD	**.37**	**.015**	**4.7E−121**	**.15**	**.015**	**1.7E−22**	**.13**	**.021**	**4.4E−10**	**.13**	**.024**	**9.0E−08**	**.16**	**.021**	**2.6E−14**
AUD	**.12**	**.016**	**5.2E−14**	.04	.015	5.7E−03	.04	.020	.03	.05	.025	.05	.04	.022	.08
ND	**.20**	**.016**	**1.4E−36**	.02	.015	.11	.06	.022	.01	.06	.027	.03	−.02	.020	.28
Negative affectivity	.03	.016	.04	.01	.014	.71	.00	.020	.92	.00	.024	1.00	.02	.021	.44
Detachment	**.07**	**.017**	**5.9E−05**	.03	.015	.06	.03	.021	.24	.03	.026	.22	.03	.020	.12
Psychoticism	**.10**	**.016**	**1.9E−10**	.02	.014	.11	.02	.021	.27	.03	.025	.25	.02	.019	.29
Disinhibition	**.11**	**.016**	**7.1E−12**	.02	.014	.21	.02	.021	.37	.00	.025	.93	.02	.020	.44
Externalizing	**.09**	**.016**	**1.9E−08**	−.02	.016	.20	−.03	.021	.20	−.05	.025	.07	−.01	.023	.74
Savings	**−.17**	**.016**	**1.4E−27**	−.02	.014	.12	−.03	.020	.08	−.03	.023	.19	.00	.020	.83
Financial distress	**.15**	**.018**	**1.4E−16**	.01	.016	.49	.01	.023	.57	.02	.029	.54	.01	.023	.64
Income	**−.11**	**.016**	**6.6E−13**	−.03	.013	.04	−.03	.019	.19	−.03	.023	.13	−.03	.018	.12
Unemploy.	**.08**	**.016**	**4.1E−06**	.01	.016	.51	.04	.021	.09	.04	.026	.14	−.03	.025	.29
Relationship agreement	**−.09**	**.020**	**6.9E−06**	.01	.019	.60	.02	.027	.38	.01	.031	.65	−.01	.028	.77
Legal issues	**.09**	**.016**	**2.0E−07**	.01	.016	.74	.00	.023	.85	−.01	.028	.76	.01	.023	.76
OCB	−.01	.017	.53	.01	.017	.69	.01	.022	.58	.00	.027	.89	−.01	.025	.82
CWB	**.06**	**.017**	**3.6E−04**	−.02	.016	.29	−.02	.022	.31	−.01	.026	.62	−.01	.023	.65
Community attitude	**−.08**	**.016**	**1.2E−06**	−.03	.014	.05	−.02	.019	.19	−.04	.022	.05	−.03	.021	.14
Community behavior	**−.09**	**.016**	**9.6E−09**	−.04	.013	.00	−.04	.019	.04	−.05	.022	.04	−.04	.020	.03
ICAR	**−.09**	**.016**	**8.0E−08**	−.04	.013	.00	−.04	.019	.02	−.06	.023	.01	−.02	.017	.15

Note. CUD = cannabis use disorder; AUD = alcohol use disorder; ND = nicotine dependence; OCB = occupational citizenship; CWB = counterproductive work behaviors; ICAR = cognitive ability. Bolded values indicate $p < .001$.

Table 3
Results From 1,000 Bootstrap Replicates Comparing Individual and Within-Pair Effects

Phenotype	Parameter	Mean estimate of effect	Estimates compared	Mean diff between estimates	95% confidence interval
Cannabis use disorder	β_I	.337	$\mathbf{\beta_I - \beta_{W\text{-}Pooled}}$	**.193**	**[.162, .224]**
	$\beta_{W\text{-}Pooled}$	.143	$\mathbf{\beta_I - \beta_{W\text{-}MZ}}$	**.178**	**[.104, .252]**
	$\beta_{W\text{-}MZ}$	.159	$\beta_{W\text{-}Pooled} - \beta_{W\text{-}MZ}$	−.015	[−.089, .059]
Tobacco use	β_I	.203	$\mathbf{\beta_I - \beta_{W\text{-}Pooled}}$	**.146**	**[.126, −.166]**
	$\beta_{W\text{-}Pooled}$	.058	$\mathbf{\beta_I - \beta_{W\text{-}MZ}}$	**.147**	**[.091, .203]**
	$\beta_{W\text{-}MZ}$	.057	$\beta_{W\text{-}Pooled} - \beta_{W\text{-}MZ}$	.001	[−.049, .051]
Illicit drug use	β_I	.201	$\mathbf{\beta_I - \beta_{W\text{-}Pooled}}$	**.145**	**[.112, .178]**
	$\beta_{W\text{-}Pooled}$	.056	$\mathbf{\beta_I - \beta_{W\text{-}MZ}}$	**.166**	**[.085, .247]**
	$\beta_{W\text{-}MZ}$	.035	$\beta_{W\text{-}Pooled} - \beta_{W\text{-}MZ}$	.021	[−.055, .097]

Note. The differences in parameter estimates measure the attenuation of effect between individual and cotwin control models. The pattern of effect attenuation informs the meaning of the individual and within-pair effects in these models. Fully causal relationships are indicated when there is no attenuation of effect across all estimates. Partial attenuation of individual effects in the cotwin control models suggests a partly causal relationship that is magnified by genetic/environmental confounding. Full attenuation of effect across all estimates indicates the effect is fully explained by genetic/environmental confounding. Bold indicates significant mean differences as indexed by 95% confidence intervals that do not overlap 0; in other words, significant attenuation of effect between the individual and cotwin estimates. Here, we see significant attenuation in the cotwin effects as compared to the individual-level models, but no attenuation between the combined and MZ-only analyses; this pattern of results suggests partial genetic and environmental confounding of a causal effect. MZ = monozygotic.

Discussion

In a sample of 4,078 American adult twins, we evaluated the causal influences of lifetime average cannabis frequency on substance use, psychiatric, and psychosocial outcomes in a community sample. Our work replicates and extends existing cotwin control studies of cannabis use. Almost all outcomes included in this study were significantly associated with lifetime average cannabis frequency at the individual level. In other words, those who used more cannabis had more negative outcomes. On the other hand, few outcomes remained significant in the cotwin analysis. This suggests the relationships between lifetime prospectively assessed cannabis use and adult outcomes were largely attributable to shared genetic and shared environmental risk, not by impairments attributable to any cumulative and persistent effects of cannabis use itself.

This result was not uniform, with important exceptions including small effects on cannabis use disorder (perhaps considered a positive control), tobacco frequency, and illicit substance use, in which the heavier-using twin had higher cannabis use disorder symptoms ($\beta_{W\text{-}Pooled} = .15$, about an increase of ∼1 *SD* units or ∼1 symptoms when going from a once-a-year use to daily use), higher tobacco frequency ($\beta_{W\text{-}Pooled} = .06$, going from a once-a-year use to daily use would increase tobacco frequency used by ∼.4 *SD* unit or ∼27 days), and higher illicit substance use ($\beta_{W\text{-}Pooled} = .06$, going from a once-a-year use to daily use would increase illicit drugs used by ∼.4 *SD* unit or .3 additional drugs) than their lesser-using cotwin.

Further examination of the individual, zygosity-pooled, and monozygotic-only results indicate that the within-pair effects significantly attenuate as compared to the individual-level effects. This means the observed individual-level effects are composed of both familial confounding as well as causal influences of cannabis consumption on these three phenotypes. The within-pair effects for cannabis use disorder were robust to alternative definitions of cannabis use and subsample analyses (maximum frequency of use, heavier using twins, and more discordant pairs) though the within-pair effects for illicit drug use and tobacco frequency were not.

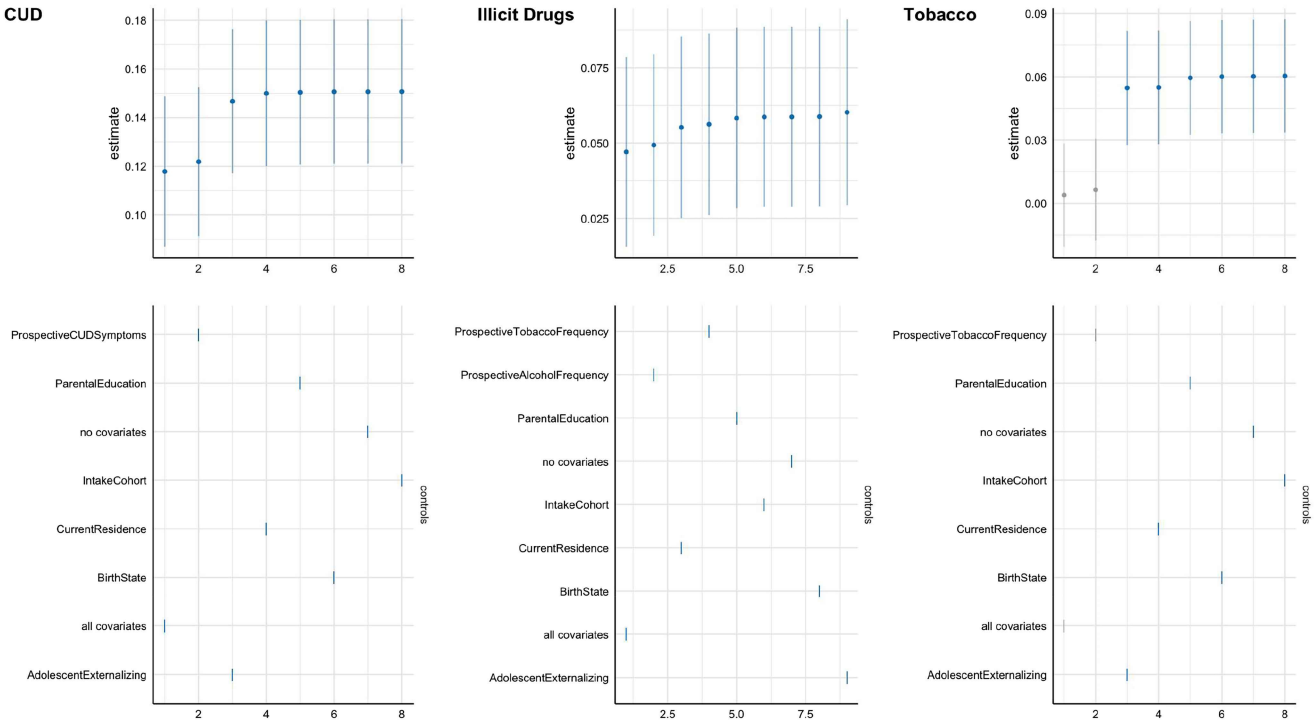
Furthermore, within-pair effects on cannabis use disorder, illicit drug use, and tobacco frequency were generally robust to the inclusion of additional covariates, with the exception of prospective alcohol use as a covariate for illicit drug use and prospective tobacco use for current tobacco frequency. As is often the case with researcher choices around exposure definitions and covariates, these results are difficult to interpret. Broadly speaking, the effect of cannabis use on cannabis use disorder symptoms is our most robust finding across all possible changes to our analysis. The evidence for effects on illicit drug use and tobacco frequency was more mixed. It could be that the relationship between cannabis use and use of other substances is better explained by a general vulnerability to substance use, rather than cannabis-specific effects (Vanyukov et al., 2012). Alternatively, there are theorized causal chains in which cannabis use does cause tobacco use or illicit drug use (i.e., gateway theory), but controlling for alcohol and tobacco use during the same time period could mask a causal effect of cannabis (Agrawal et al., 2010; Huizink et al., 2010). Further work is necessary to disentangle these causal chains, though broadly speaking the gateway theory lacks empirical support as compared to general vulnerability models (CDC, 2022b; Kleinig, 2015; Vanyukov et al., 2012).

This result is somewhat consistent with other cotwin control studies examining the relationships between cannabis consumption and illicit substance use. For example, several studies identified causal influences of early cannabis initiation (before age 17) on lifetime use of illicit substances as well as cannabis dependence (Lessem et al., 2006; Lynskey et al., 2003, 2006). We did not replicate these associations, instead our work is consistent with other studies that have found that early initiation confers minimal risk for later illicit substance use or dependence (Agrawal et al., 2004; Grant et al., 2010). Our work and these studies instead suggest that correlated liabilities explain the majority of the associations between early use and later substance outcomes.

With respect to existing work on cognitive ability, Ross et al. (2020) and Jackson et al. (2016) both did not identify robust evidence that adolescent cannabis use caused deficits in early adult executive functioning or IQ. We similarly did not identify within-pair differences in

Figure 2

Specification Curve Analyses for Outcomes With Significant Within-Pair Effects (Cannabis Use Disorder, Illicit Drug Use, and Tobacco Frequency)



Note. The top row presents the estimates of within-pair effect of cannabis consumption with varied covariates, beyond those of age and sex. The bottom row indicates correspondence between estimates and covariates included in the model the estimate was derived from. CUD = cannabis use disorder. See the online article for the color version of this figure.

cognitive ability. Also in agreement with earlier work in a subset of the current sample, cannabis consumption did not predict within-pair differences in psychoticism, at least in community samples (Schaefer, Jang, et al., 2021). Other cross-sectional studies suggest both shared genetic and environmental factors and direct causal influences underlie the relationship between cannabis intake and psychotic-like experiences (Karcher et al., 2019; Nesvåg et al., 2017). Differences in timing of exposure, as well as in the measures of psychoticism and cannabis use, and the use of a representative birth cohort could explain differences in results between the present work and previous studies.

Lastly, we did not replicate some within-pair associations identified by Schaefer, Hamdi, et al. (2021) in an overlapping but younger sample; namely, within-pair differences in occupational status and income. We identified individual, but not within-pair effects in income and unemployment. Schaefer, Hamdi, et al. (2021) indicated their observed young adult socioeconomic effects were driven by adolescent (ages 11–17), rather than adult (ages 24–29) cannabis use, so perhaps the effects of adolescent cannabis intake are limited to young adulthood, and the effects do not persist as individuals mature further. Alternatively, there could be different factors influencing socioeconomic outcomes in adolescence and adulthood, such that cannabis intake is only relevant to those influences occurring earlier in life. There are also a few methodological differences between the present study and Schaefer, Hamdi, et al. (2021): the two studies used different measures of occupational status (degree of unemployment vs. prestige of occupation) and the present study utilized a stricter p-value threshold. The effect identified here for income ($\beta_{\text{W-Pooled}} = -.03$, $SE = .013$, $p = .042$) is considered non-significant per our adjusted α level, but it is below the conventional threshold of .05.

In summary, we identified limited evidence consistent with causal influences of lifetime cannabis consumption, with the major exceptions being cannabis use disorder, tobacco frequency, and illicit drug use, for which the modest effects may be partially causal. For all other phenotypes associated with cannabis consumption, genetic and environmental confounds likely best explain the observed associations. These results, taken as a whole, suggest that cannabis use, at the frequency at which it occurs in a broad-based community sample, does not cause substantial harm with respect to other substance use, psychiatric, and psychosocial outcomes in adulthood.

Broadly speaking, these results are in agreement with existing literature suggesting that cannabis use, and substance use more broadly, is one phenotypic manifestation of a broader underlying vulnerability. This vulnerability is often referred to in the literature as externalizing, behavioral disinhibition, or common liability to addiction. It is a general genetic risk to substance use, externalizing psychopathology, and nonpathological manifestations of behavioral impulsivity; this framework is supported by evidence from twin and family studies, as well as large genetically informative studies of unrelated individuals (Hicks et al., 2004, 2011; Karlsson Linnér et al., 2021; Krueger et al., 2002; Kuo et al., 2021; McGue et al., 2014;

Vanyukov et al., 2012; Young et al., 2000, 2009). It is theorized to underly the observed covariation between these phenotypes, including cannabis use and the consequences it is correlated with. Here this is reflected in the wide variety of individual-level effects that do not persist within pairs, we see familial aggregation of externalizing spectrum behaviors independent of their exposure to cannabis. This in turn suggests that the relationship between cannabis use and most outcomes is better explained by genetic and familial confounds (i.e., externalizing), the major exception being cannabis use disorder, which is modestly causally impacted by increasing cannabis use frequency.

Limitations

Our sample was a large sample of twins, representative of the birth cohorts from which they were drawn, which resulted in levels of cannabis use reflective of the broader population, namely, moderate prevalence of lifetime use and relatively low average frequency of use. That said, racial and socioeconomic diversity are limited in our sample, which limits generalizability. It has been established that people of color experience health disparities and substance-related legal consequences at higher rates than white individuals (Beckett et al., 2005; Wu et al., 2016), though rates of cannabis use are highest in non-Hispanic white samples (Martins et al., 2021). Additionally, we analyzed alternative definitions of use (highest frequency reported) and analyzed the outcomes in a subsample of heavier users and our results were robust to these changes. Even still, heavy and persistent use was not widely represented in these data, and heavier patterns of use may have larger and more profound psychiatric, psychosocial, and cognitive effects. It is therefore possible that our individual-level associations are underestimated due to range restriction, which would, in turn, result in underestimation of within-pair effects.

We also have several methodological limitations. The measurement of multiple outcomes is a strength of this study, but the majority of outcomes were assessed via self-report and therefore there is the potential for mono-method bias and shared method variance. Additionally, statistical power decreases with sample size. The zygosity-pooled analyses offer the greatest power for detecting within-pair effects, but these effects are not as precisely controlled as those of the monozygotic analyses; however, the monozygotic analyses are the least well powered in terms of sample size. Furthermore, we do not have measures of some exposures and outcomes of interest, such as symptom count for internalizing disorders like generalized anxiety or major depression, or measures of cannabis potency. Importantly, it is well established that cannabis potency has changed across the time frame included in our study (ElSohly et al., 2016). We are unable to address time period effects around changing cannabis potency, but future work should investigate higher potency cannabis in the context of these psychological outcomes.

While our study reflects up to 30 years of longitudinal assessments, pushing our understanding of the effects of cannabis use on midlife outcomes, the study was not designed to assess acute effects that may be relevant for understanding the broad impacts of cannabis consumption. For example, cannabis may not have long term causal effects on cognitive ability, but could have shorter term causal effects on cognitive processes, motor coordination or memory either during acute intoxication or during periods of frequent or heavy use (Scott et al., 2018; Volkow et al., 2014). Lastly, the longitudinal data is an advantage of this data that can be further explored; we elected to look at exposures from one assessment or averages across many assessments for simplicity and comparability to previous work, but future work could evaluate developmental trends in cannabis use and their relation to various outcomes.

Conclusions

Broadly speaking, our results do not support a causal relationship between lifetime average cannabis frequency and most of the substance use, psychiatric, and psychosocial outcomes assessed here. Rather, genetic and familial confounding most likely explain the relationships between cannabis use and the negative outcomes associated with it, in a community sample characterized by low use. The major exceptions to this pattern are cannabis use disorder, tobacco frequency, and illicit drug use, for which there were small but significant within-pair differences consistent with partially causal effects. Effect sizes were very modest, with the largest significant within-pair effect ($\beta_{W\text{-}Pooled} = .15$ for cannabis use disorder) represents about an increase of $\sim$1 *SD* units or $\sim$1 symptoms when going from a once-a-year use to daily use. Though the effect is modest, harm reduction and psychoeducational materials aimed at decreasing individuals' frequency of cannabis consumption may be a viable strategy to reducing the burden of cannabis use disorder. Future research as well, could focus on other conceptualizations of cannabis exposure. As frequency of cannabis consumption is causally related to cannabis use disorder, it is possible that other metrics, like quantity consumed, mechanism of consumption, or cannabis potency, could also be relevant to the development of cannabis use disorder.

The lack of within-pair effects, or small effects for those existing within-pair differences, in our primary outcome suggest that cumulative cannabis use does not have large, or lasting effects on many psychosocial outcomes. We additionally tested alternative exposures, such as maximum frequency reported, age of onset, and early onset use that map onto different conceptual frameworks of cannabis effects. The maximum use exposure suggests that heavier time-limited use may also not have large or lasting effects. Lastly, several ways of conceptualizing age of onset and early onset suggest a lack of causal developmental timing effects on consequences of cannabis use in adulthood.

That said, our results cannot conclusively tease apart the causal influences of cannabis on tobacco and illicit drug use from the causal effects of broader substance involvement or shared preexisting liability for use of various substances, nor can they generalize to heavier use. These findings on psychosocial outcomes in adults can be informative to the practical risks of cannabis consumption in our rapidly changing and permissive cannabis environment. Additional work examining acute effects of cannabis consumption as well as heavy and persistent use are necessary to understand broader consequences of cannabis use on adult health.

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Received February 3, 2023
Revision received June 28, 2023
Accepted June 30, 2023 ■