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# Investigating the causal effect of cannabis use on cognitive function with a quasi-experimental co-twin design

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ABSTRACT

*Background:* It is unclear whether cannabis use causes cognitive decline; several studies show an association between cannabis use and cognitive decline, but quasi-experimental twin studies have found little support for a causal effect. Here, we evaluate the association of cannabis use with general cognitive ability and executive functions (EFs) while controlling for genetic and shared environmental confounds in a longitudinal twin study.
*Methods:* We first examined the phenotypic associations between cannabis initiation, frequency, and use disorder with cognitive abilities, while also controlling for pre-use general cognitive ability and other substance involvement. We tested the concurrent association between the cannabis use variables and cognitive abilities in late adolescence and young adulthood and the longitudinal association between cannabis use variables during adolescence and young adulthood cognitive abilities. Next, we used multilevel models to test whether these relations reflect between- and/or within-twin pair associations.
*Results:* Phenotypically, cannabis use was related to poorer cognitive functioning, although most associations were negligible after accounting for other substance use. Nevertheless, there were few significant within-family twin-specific associations, except that age 17 cannabis frequency was associated with worse age 23 Common EF and general cognitive ability.
*Conclusions:* We found little support for a potential causal effect of cannabis use on cognition, consistent with previous twin studies. Results suggest that cannabis use may not cause decline in cognitive ability among a normative sample of cannabis users.

## 1. Introduction

With increases in cannabis use and movement toward greater acceptance and legalization in the US (Johnston et al., 2018), it is critical to understand whether cannabis use causes long-term cognitive impairment. There is accumulating empirical evidence that cannabis is associated with cognitive decrements (Volkow et al., 2016), but despite the large number of studies on this topic, this research has several limitations. Perhaps the most important limitation is the difficulty of establishing causation with non-experimental designs. This difficulty arises because poor cognitive ability is a predisposing factor for drug abuse (e.g., Ridenour et al., 2009), and it is plausible that those most likely to show declines in cognitive performance also use cannabis to a greater extent. Though prospective studies that control for pre-use cognitive functioning can strengthen the case for causation, even these study designs are limited (e.g., Gonzalez and Swanson, 2012). Twin studies can be used to test whether associations conform to patterns expected in a causal and non-causal models: Specifically, that associations that hold phenotypically also hold within twin pairs who differ in cannabis exposure. Using a longitudinal twin study, we examined the phenotypic and the between- and within-twin-pair associations between cannabis and both intelligence and executive functions (EFs). EFs are higher-level cognitive processes used to control and regulate thoughts and actions during goal-directed behavior. While EFs correlate with intelligence, they are phenotypically and genetically separable from intelligence, and in many cases predict behavior and psychopathology even when controlling for intelligence (Friedman and Miyake, 2017).

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### 1.1. Existing studies

Numerous studies have reported negative associations of cannabis use with various measures of cognition, including intelligence (e.g., Fried et al., 2002). A widely cited study reported that persistent cannabis users who met criteria for cannabis dependence before age 18 had a greater decline in IQ than those who first met diagnostic criteria for cannabis dependence after age 18 (Meier et al., 2012). Although many researchers have concluded that cannabis causes impairment in cognition, there are alternative explanations. First, poor cognitive functioning is a risk factor for substance use. Specifically, EF measured in childhood predicts later substance use and substance use disorders (SUDs; Ridenour et al., 2009). Thus, studies need to control for prior cognitive functioning (Meier et al., 2012). Second, poor cognitive functioning and cannabis use may also be related, not because one causes the other, but because they share common risk factors, like lower SES (Rogeberg, 2013). Lynskey and Hall (2000) proposed that early use is likely to occur in a social context characterized by affiliations with substance using peers, poor school attendance, and precocious adoption of adult roles including dropping out of school; such an effect on educational participation may also influence later cognitive functioning.

### 1.2. Co-twin control designs

It is impossible to demonstrate causality in epidemiological studies, and an experimental study is not ethical. Although researchers can attempt to match cannabis users and controls on potential confounders, it is impossible to control for every variable that may contribute to cognition (e.g., Schweinsburg et al., 2008). Several different methods have been developed to test the direction of causality (DOC), which evaluates causal hypotheses by comparing fits of models with alternative causal directions between two variables. DOC has been examined in genetically informative samples, such as twin studies (Heath et al., 1993) and in population-based studies as well as using different analytic techniques (Duffy and Martin, 1994; Heath et al., 1993). For example, Gillespie et al. (2009) used this method to conclude that the association between deviant peer affiliation and cannabis use is best explained by a model in which cannabis use causes deviant peer group affiliation.

An alternative strategy is to use monozygotic (MZ) twins discordant for various indices of cannabis use, which controls for all genetic and shared environmental confounds as well as age, sex, cohort, and parental characteristics. Additionally, same-sex dizygotic (DZ) twins discordant for cannabis use exposure will control for all shared environmental confounds, age, sex, cohort, and parental characteristics, but only partially for genetic differences between families. To our knowledge, there have been three studies using this design to address the association between cannabis use and cognition. However, there has been extensive research using this design to examine causal associations with alcohol (Kendler et al., 2000; Prescott and Kendler, 1999; Young-Wolff et al., 2011). We choose to use the discordant twin design so that we can compare our results directly with previous studies on the association between cannabis use and cognition.

First, Lyons et al. (2004) examined MZ twins discordant for use 20 years after regular use, and found a significant difference between twins on only one of 50+ measures of cognition. Second, Jackson et al. (2014) found no evidence for a dose-dependent relationship or significant differences in cognition among MZ twins discordant for cannabis use. Similarly, Meier et al. (2017) found no evidence for differences in cognition among a combined sample of MZ and DZ twins discordant for cannabis dependence or use frequency. Thus, quasi-experimental, co-twin control designs have yielded little evidence that cannabis causes poorer cognition.

We expanded on these previous studies in several ways. First, we evaluated the association between cannabis use and EFs in addition to intelligence; specifically, we examined three EF components with factor scores derived from a well-validated latent variable model (Friedman et al., 2016; Miyake et al., 2000; Miyake and Friedman, 2012). Most of the discordant twin studies of the association between cannabis use and cognition have focused on general cognitive ability, not on EF. Second, we also considered whether cannabis–cognition associations are explained by other substance use, given the high frequency of poly-substance use (Kedia et al., 2007). Third, we assessed participants during adolescence and young adulthood, while the above-mentioned studies focused on twins up to age 20 and older than age 45.

## 2. Method

### 2.1. Participants

The Colorado Longitudinal Twin Study (Rhea et al., 2013) is an ongoing study of the cognitive, emotional, and behavioral development of same-sex twins from infancy to adulthood. A total of 856 individual twins (437 female, 419 male) from 428 families (232 MZ, 196 DZ) had data for one of the assessments in adolescence (Wave 1) and/or young adulthood (Wave 2). At Wave 1 (2003–2008), general cognitive ability was measured at mean age 16.6 (SD = 0.8, range 16.0–20.1), EF at mean age 17.3 (SD = 0.6; range 16.5–20.1), and substance use at mean age 17.3 (SD = 0.6; range 16.1–20.1). At Wave 2 (2009–2013), cognitive abilities and substance use were measured at mean age 22.8 (SD = 1.3; range 21.1–28.0). The sample is 91.9% Caucasian (including 9.4% Hispanic/Latino), 1.1% American Indian, 0.2% Native Hawaiian/Pacific Islander, 0.2% Asian, 5.3% multiracial, and 1.1% unknown/not reported. Zygosity was determined via repeated rater assessment and DNA genotyping. A more detailed description of participant characteristics, including attrition rate for the sample in adolescence, are included in Rhea et al., 2013.

The Institutional Review Board at the University of Colorado Boulder approved all study procedures. Participant assent and parental consent were obtained for all participants under the age of 18. Participant consent was obtained when participants turned 18 years old. Participant characteristics and descriptive statistics, including *N*s for each measure, are shown in Table 1.

### 2.2. Measures, design, and procedure

#### 2.2.1. Substance use

We used the Substance Abuse Module of the Composite International Diagnostic Interview (CIDI-SAM) to determine whether participants met diagnostic criteria for a SUD, based on DSM-IV criteria (Cottler et al., 1989). We added interview questions to assess other indices of substance use (see Salomonsen-Sautel et al., 2012). We created variables for age of initiation, frequency of use, and SUD diagnosis for cannabis, alcohol, tobacco, and other illicit drugs. For the illicit drug category, we collapsed across seven illicit drug categories by only including the highest (or lowest) score for any one drug category, given low endorsement for other individual substances. See supplemental materials (SM) for additional information.

*2.2.1.1. Frequency of substance use.* Participants were asked, "How many days have you used cannabis (and alcohol, tobacco, or other drugs) in the past six months (180 days)?" Thus, frequency of substance use was only collected for the past six months. Participants who denied ever using the substance were given a score of zero for that substance. To ease interpretation of unstandardized parameter estimates, we divided this variable by 6 so that a one unit increase would correspond to an additional day/month of use.

*2.2.1.2. Age of initiation.* We asked age of initiation if participants endorsed ever using a particular substance: "How old were you when you first used cannabis?" Only 248 participants and 466 participants endorsed ever using cannabis at the adolescent and young adult assessments, respectively. We took the youngest age of initiation for

**Table 1**
Descriptive Statistics.

| | Wave 1 (Adolescence) | | | | | Wave 2 (Young Adulthood) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | Mean | SD | Range | Reliability | N | Mean | SD | Range | Reliability |
| Age WAIS & Raven | 813 | 16.6 years | 0.8 | 16.0 – 20.1 | – | – | – | – | – | – |
| Age EF | 786 | 17.3 years | 0.6 | 16.5 – 20.1 | – | 749 | 22.8 years | 1.3 | 21.1 – 28.0 | – |
| Age substance use | 793 | 17.3 years | 0.6 | 16.1 – 20.1 | – | 757 | 22.8 years | 1.3 | 21.1 – 28.0 | – |
| Premorbid IQ | 809 | 103.5 | 11.1 | 70.4 – 138.4 | – | 809 | 103.5 | 11.1 | 70.4 – 138.4 | – |
| Cannabis initiation[a] | 248 | 14.9 years | 1.7 | 8 – 19 | – | 466 | 16.7 years | 2.4 | 8 – 23 | – |
| Alcohol initiation[a] | 409 | 14.5 years | 2.0 | 5 – 19 | – | 735 | 16.9 years | 2.5 | 5 – 22 | – |
| Tobacco initiation[a] | 256 | 14.1 years | 2.5 | 4 – 19 | – | 495 | 16.2 years | 3.0 | 5 – 22 | – |
| Other drug initiation[a] | 117 | 15.1 years | 2.8 | 5 – 18 | – | 370 | 18.9 years | 3.2 | 6 – 25 | – |
| Frequency cannabis[b] | 792 | 1.2 days | 4.5 | 0 – 30 | – | 755 | 3.0 days | 7.9 | 0 – 30 | – |
| Frequency alcohol[b] | 789 | 1.0 days | 2.5 | 0 – 25 | – | 757 | 4.9 days | 6.0 | 0 – 30 | – |
| Frequency tobacco[b] | 773 | 3.2 days | 8.6 | 0 – 30 | – | 756 | 6.1 days | 11.2 | 0 – 30 | – |
| Frequency other drug[b] | 791 | 0.4 days | 2.7 | 0 – 30 | – | 754 | 0.8 days | 3.9 | 0 – 30 | – |
| Cannabis use disorder[c] | 793 | 7.3 % | 0.3 | – | – | 740 | 12.7 % | 0.3 | – | – |
| Alcohol use disorder[c] | 793 | 14.4 % | 0.4 | – | – | 756 | 38.7 % | 0.5 | – | – |
| Tobacco use disorder[c] | 793 | 12.7 % | 0.3 | – | – | 755 | 25.3 % | 0.4 | – | – |
| Other drug use disorder[c] | 791 | 3.2 % | 0.2 | – | – | 754 | 12.9 % | 0.3 | – | – |
| WAIS – Full Scale IQ | 813 | 102.2 | 11.4 | 70.0 – 142.0 | .97[f] | – | – | – | – | – |
| Raven | 811 | 72.2 % | 14.7 | 20.7 – 100.0 | .84[g] | – | – | – | – | – |
| Raven-S | – | – | – | – | – | 745 | 62.2% | 19.3 | 11.1 – 100.0 | .78[h] |
| Antisaccade[d] | 779 | 1.04 | 0.20 | 0.47 – 1.57 | .89[h] | 748 | 0.62 | 0.16 | 0.20 – 0.96 | .90[i] |
| Stop-signal | 741 | 282 ms | 63 | 151 – 489 | .75[h] | 735 | 215 ms | 30 | 116 – 315 | .63[i] |
| Stroop | 759 | 214 ms | 90 | 0 – 488 | .91[h] | 737 | 156 ms | 74 | −73 – 387 | .96[h] |
| Keep track[d] | 774 | 0.94 | 0.18 | 0.38 – 1.49 | .65[i] | 749 | 0.72 | 0.09 | 0.44 – 0.96 | .66[i] |
| Letter memory[d] | 785 | 1.09 | 0.25 | 0.38 – 1.57 | .62[i] | 749 | 0.70 | 0.13 | 0.38 – 1.0 | .92[i] |
| Spatial *n*-back[d,e] | 777 | 1.17 | 0.17 | 0.65 – 1.57 | .90[i] | 749 | −0.01 | 0.91 | −2.74 – 2.70 | .75[h] |
| Number-letter | 776 | 331 ms | 183 | −14 – 923 | .86[h] | 748 | 246 ms | 157 | −241 – 735 | .91[h] |
| Color-shape | 768 | 331 ms | 189 | −196 – 916 | .85[h] | 743 | 221 ms | 182 | −239 – 792 | .90[h] |
| Category-switch | 768 | 333 ms | 181 | −34 – 899 | .83[h] | 747 | 198 ms | 161 | −81 – 735 | .94[h] |

*Note*: IQ = Intelligence quotient, WAIS = Wechsler Adult Intelligence Scale, Raven = Raven Progressive Matrices, Raven-S = Advanced Raven Progressive Matrices Short Form, dashes indicate that data were not applicable or not collected.

[a] Age of initiation. For participants who had not initiated substance use (i.e., cannabis, alcohol, tobacco, or other drug use) at the time of their assessment, age 30 was used in the analyses as their age of initiation. This included 283 participants for cannabis, 20 participants for alcohol, 253 participants for tobacco, and 367 participants for other drugs. These values are not included in these descriptive statistics.

[b] Number of days in past 180 days.

[c] Percent of individuals who met diagnostic criteria for either mild, moderate, or severe substance use disorder based on number of symptoms endorsed on the CIDI-SAM.

[d] Proportion correct. Wave 1 accuracy scores for all tasks, and Wave 2 accuracy scores for spatial 2- and 3-back, were arcsine transformed.

[e] Spatial 2-back at Wave 1, and the average of *z*-scores for spatial 2-back and 3-back at Wave 2. The mean arcsined accuracy for Wave 2 spatial 2-back was 1.08, and for spatial 3-back was 0.97.

[f] Internal reliability from Wechsler (1997).

[g] Internal reliability from DeFries et al. (1981).

[h] Internal reliability was calculated by adjusting split-half or Part 1–Part 2 correlations with the Spearman– Brown prophecy formula.

[i] Internal reliability was calculated using Cronbach's alpha.

each substance category (i.e., cannabis, alcohol, tobacco, and other drug) across all assessments and used the same variable to test for an association between age of initiation with adolescent and young adult cognitive outcomes. To include information from twins who reported initiating but whose co-twins did not, we set the age of initiation to one year above the highest reported age at the young adult assessments (age 30) for individuals who denied ever using cannabis, alcohol, tobacco, or other drugs.

*2.2.1.3. Substance use disorder diagnosis*. The CIDI-SAM asked about symptoms for each of 11 categories of substances used to criterion (detailed in the SM).We added abuse and dependence symptoms together and categorized each SUD diagnosis into none (0–1 symptoms), mild (2–3 symptoms), moderate (4–5 symptoms), or severe (6 or more symptoms), based on the DSM-V SUD criteria. The abuse and dependence symptoms from the DSM-IV are the same symptoms used in the DSM-V, except the DSM-IV legal symptom question was included and the new DSM-V craving symptom was not included. Participants who reported not using cannabis, alcohol, tobacco, and/or other drugs to criterion were scored as "none" for that SUD variable.

### 2.2.2. Intelligence

We assessed general cognitive ability/intelligence with the Raven Progressive Matrices (Raven; Raven, 1960) and the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997) in adolescence, and with a short form of the Advanced Raven Progressive Matrices (Raven-S, which included 18 odd-numbered questions; Raven, 1962) in young adulthood. The WAIS included 11 subtests, used to obtain a norm-referenced full-scale intelligence score. The Raven and Raven-S are non-verbal assessments of intelligence, scored as percent correct. Intelligence was also assessed throughout development at mean ages 4 (Stanford-Binet; Terman and Merrill, 1973), 7 (WISC-R; Wechsler, 1974), and 12 years (WISC-III; Wechsler, 1991). After rescaling the ages 4 and 7 scores so they had the same mean and standard deviation (SD) as the age 12 scores, we averaged scores from all three ages to obtain a premorbid intelligence score, excluding scores obtained after cannabis initiation if a participant reported initiating before age 12 ($n$ = 9). No participant reported cannabis initiation prior to age 8.

### 2.2.3. Executive functions

Participants completed 9 computerized EF tasks (3 each measuring response inhibition, working memory updating, and mental shifting) at

2 waves. We used standardized factor scores from the bifactor models reported by Friedman et al. (2016): at each wave, a Common EF factor predicted performance on all 9 tasks, and Updating-Specific and Shifting-Specific factors also predicted the updating and shifting tasks; there was no inhibiting-specific factor because Common EF explained all the covariance among the inhibition tasks. We briefly describe the task requirements below; for full details, see Friedman et al. (2016).

The response inhibition tasks required participants to withhold a dominant response. In the antisaccade task, participants avoided reflexively looking at a cue to look in the opposite direction in time to see the target stimulus before it was masked. In the stop-signal task, participants withheld a rote categorization response on a small number of signaled trials. In the Stroop task, participants named aloud the font color of incongruent color words (avoiding reading the word) or neutral stimuli (asterisks). Dependent variables were accuracy of target identification, estimated stop-signal reaction time, and interference effect (differences in mean response time between correct responses for the incongruent and neutral trials).

The working memory updating tasks required participants to remember and update information. In the keep-track task, participants saw a series of words from 6 categories and had to continuously update the most recent exemplars from 2 to 5 target categories. In the letter memory task, participants continuously rehearsed the last 3–4 letters from a series of consonants. In the spatial *n*-back task, participants indicated whether spatial locations matched those 2- or 3- trials back. Dependent measures were accuracy of target word recall, letter rehearsal, and n-back identification.

The set shifting tasks required participants to switch between two subtasks depending on a cue that appeared before each trial: number-letter, color-shape, and category-switch. The dependent measure was the local switch cost: the average response time for correct trials preceded by a different task (switch trials) minus correct trials preceded by the same task (repeat trials).

### 2.3. Analytic procedures

We used Mplus 8 to estimate regression and multilevel models, each with one cognitive dependent variable and one cannabis independent variable, as well as pre-use cognitive ability and sex as covariates. Dependent variables were EF factor scores, nonverbal intelligence (Raven and Raven-S), and general intelligence (WAIS). Independent variables were cannabis age of initiation, frequency of cannabis use in the past 180 days (transformed to days/month), and past-year cannabis use disorder (CUD) diagnosis. We tested the concurrent association of each cannabis use variable with each cognitive variable during adolescence and young adulthood. Then we tested the association of the adolescent cannabis variables with young adulthood cognitive variables. For each analysis, we first estimated the associations with cannabis alone (primary analyses), then added parallel phenotypic measures (including the multilevel models) of other substances as covariates (e.g., alcohol, tobacco, and other substances frequency when cannabis frequency was included; results presented in SMs). Only unstandardized coefficients are reported because standardized parameters are not recommended for multilevel models (e.g., see Nezlek, 2012), and variables are in interpretable units. Since the dependent variables were substantially correlated within and across time, as were independent variables, we corrected for multiple testing by setting the alpha level at $p < .01$, using a Bonferroni correction (.05/5 = .01) based on the 5 dependent cognitive constructs examined (i.e., Raven, WAIS, Common EF, Shifting-Specific, Updating-Specific).

#### 2.3.1. Model 1: phenotypic associations

Model 1 estimated the association between cannabis exposure and cognitive performance at the sample level (i.e., without accounting for familial confounds). These analyses accounted for nonindependence of twin pairs with the "type = complex" option, which provides the same estimates as a standard regression but corrects the standard errors for non-independence using a sandwich estimator.

#### 2.3.2. Model 2: within-family exposure

Model 2 estimated the association between cannabis exposure and cognitive performance within families (i.e., differential twin exposure in each family; Neuhaus and McCulloch, 2006), accounting for unmeasured familial factors that make twins alike. To index general familial risk, each cannabis measure was averaged across twin pairs. The average for each family (MCan), was used to model the between-family effect. To index twin-specific risk, we included each individual's deviation of the cannabis measure (DCan) from the twin pair's respective MCan for that measure. We included random between-family intercepts for cognitive performance, but fixed effects for each substance use variable on the cognitive outcome (MCan and DCan). In addition, we included a DCan-by-zygosity interaction term. We present simple DCan effects for each zygosity as well as the average across zygosity. Independent variables were grand-mean centered, except for DCan, which was centered within each twin pair.

Examining MZ and DZ twins together broadly accounts for environmental and genetic factors shared by twins. Both types of twins are reared together, and MZ twins share all of their genes, whereas DZ twins share on average half of their genes identical by descent. Thus, the within-family effect controls for shared environmental confounds in both twin types and fully controls for genetic confounds in MZ twins, but only partially controls for genetic confounds in DZ twins. Hence, we allowed the fixed within-family cannabis exposure effects to vary by between-family zygosity. A null interaction, in which the within-family effect of cannabis exposure is significant in both MZ and DZ twin pairs, would be consistent with the inference that cannabis use causes declines in cognition (controlling for genetic and environmental confounds).

Sex and premorbid IQ (grand-mean centered) were covariates in all models. When tobacco, alcohol, and other drug use were included as covariates, they were modeled as grand mean centered fixed-effect covariates (i.e., not at the between- or within-family level). For more details, see the SMs.

## 3. Results

### 3.1. Model 1: phenotypic associations

Table 2 displays the phenotypic associations between substance use and cognitive measures. The models are labeled model sets 1–9 to facilitate locating analyses in the table. Supplemental Table (ST) 1 includes corresponding phenotypic analyses controlling for other substance use. MZ twins were significantly correlated on measures of cognition and cannabis (e.g., MZ correlations: Age 17 Common EF $r = 0.73$, $p < .001$, age 23 Raven-S $r = 0.60$, $p < .001$, age of initiation $r = 0.72$, $p < .001$).

For the adolescent cognitive measures, a one year later onset for cannabis initiation was associated with 0.435 percentage point increase in Raven ($p < .001$; model set 1), a 0.128 point increase in WAIS ($p = .003$; model set 3), and an increase of 0.017 SDs in Common EF ($p = .005$, model set 4). An increase in one severity category of CUD was associated with a decrease of 0.198 SDs in Common EF ($p = .009$; model set 4). Only a one year later age of onset associated with an increase of 0.313 percentage points on the Raven remained significant after controlling for other substance use ($p = .003$; model set 1 in ST 1). No other adolescent phenotypic associations remained significant after controlling for other substance use.

For the adult cognitive measures, a one year later age of cannabis initiation was associated with 0.378 percentage point increase in Raven-S ($p < .001$; model set 2). An increase of one day per month of cannabis frequency was associated with 0.298 percentage point decrease in Raven-S (age 23; $p = .002$; model set 2). All other adult

**Table 2**
Unstandardized coefficients for the phenotypic analyses of the association between cannabis use variables with intelligence and executive functions.

| **Dependent (Cognitive)** and Independent (Cannabis) Variables | Path from Cannabis Variable |
|---|---|
| Model Set 1**: Raven (age 17)** | |
| Age of cannabis initiation ($N$ = 718) | 0.435** |
| Cannabis frequency (age 17; $N$ = 757) | −0.269 |
| CUD (age 17; $N$ = 758) | −2.449 |
| Model Set 2: **Raven-S (age 23)** | |
| Age of cannabis initiation ($N$ = 713) | 0.378** |
| Cannabis frequency (age 17; $N$ = 666) | −0.259 |
| CUD (age 17; $N$ = 667) | −1.982 |
| Cannabis frequency (age 23; $N$ = 710) | −0.298* |
| CUD (age 23; $N$ = 698) | −1.382 |
| Model Set 3: **WAIS (age 17)** | |
| Age of cannabis initiation ($N$ = 720) | 0.128* |
| Cannabis frequency (age 17; $N$ = 759) | −0.060 |
| CUD (age 17; $N$ = 760) | −0.552 |
| Model Set 4: **Common EF (age 17)** | |
| Age of cannabis initiation ($N$ = 706) | 0.017* |
| Cannabis frequency (age 17; $N$ = 751) | −0.020 |
| CUD (age 17; $N$ = 751) | −0.198* |
| Model Set 5: **Common EF (age 23)** | |
| Age of cannabis initiation ($N$ = 717) | 0.008 |
| Cannabis frequency (age 17; $N$ = 670) | −0.009 |
| CUD (age 17; $N$ = 671) | −0.094 |
| Cannabis frequency (age 23; $N$ = 714) | −0.004 |
| CUD (age 23; $N$ = 702) | −0.047 |
| Model Set 6: **Updating-Specific (age 17)** | |
| Age of cannabis initiation ($N$ = 706) | −0.001 |
| Cannabis frequency (age 17; $N$ = 751) | 0.006 |
| CUD (age 17; $N$ = 751) | 0.049 |
| Model Set 7: **Updating-Specific (age 23)** | |
| Age of cannabis initiation ($N$ = 717) | −0.008 |
| Cannabis frequency (age 17; $N$ = 670) | 0.008 |
| CUD (age 17; $N$ = 671) | 0.067 |
| Cannabis frequency (age 23; $N$ = 714) | 0.001 |
| CUD (age 23; $N$ = 702) | 0.079 |
| Model Set 8: **Shifting-Specific (age 17)** | |
| Age of cannabis initiation ($N$ = 706) | −0.004 |
| Cannabis frequency (age 17; $N$ = 751) | −0.011 |
| CUD (age 17; $N$ = 751) | −0.179 |
| Model Set 9: **Shifting-Specific (age 23)** | |
| Age of cannabis initiation ($N$ = 717) | 0.004 |
| Cannabis frequency (age 17; $N$ = 670) | −0.011 |
| CUD (age 17; $N$ = 671) | −0.134 |
| Cannabis frequency (age 23; $N$ = 714) | −0.008 |
| CUD (age 23; $N$ = 702) | −0.032 |

*Note.* Each row contains a separate model. All analyses controlled for sex and premorbid intelligence. Raven = Raven Progressive Matrices; Raven-S = Advanced Raven Progressive Matrices Short Form; WAIS = Wechsler Adult Intelligence Scale; EF = executive function; Cannabis frequency = number of days cannabis was used per month over the past six months; CUD = cannabis use disorder diagnosis (i.e., no use disorder, mild, moderate, or severe).
* $p < .01$.
** $p < .001$.

phenotypic associations between concurrent and prospective cannabis and intelligence measures were not significant, including those in analyses that controlled for other substance use.

### 3.2. Model 2: multilevel models

#### 3.2.1. Within-family exposure averaged across zygosity

Table 3 displays the between- and within-family effects of cannabis use on intelligence and EFs, (labeled model sets 1–9); see ST 2 for corresponding models controlling for other substance use. At the between-family level for adolescent cognitive measures, a one year later age of cannabis initiation (i.e., averaged between twin pairs) was associated with an increase of 0.482 percentage points in Raven (age 17: $p < .001$; model set 1), 0.149 points in WAIS (age 17: $p = .003$; model set 3), and 0.019 SDs in Common EF ability (age 17: $p = .007$; model set 4). An increase in one severity category of CUD was associated with 5.33 percentage point decrease in Raven (age 17: $p < .001$; model set 1).

Regarding adult cognitive measures, a one year later age of initiation was associated with an increase of 0.407 percentage points in Raven-S (age 23: $p < .001$; model set 2). A one day per month increase in cannabis frequency during young adulthood was associated with 0.342 percentage point decrease in Raven-S (age 23: $p = .005$; model set 2). After accounting for other substance use, the between-family effect of age of cannabis initiation on Raven (age 17: $p = .001$; model set 1 in ST 2) scores remained significant, but all other between-family effects became non-significant.

At the total within-family level, there were no statistically significant effects of age of cannabis initiation, cannabis frequency, or CUD on Raven, Raven-S, or WAIS at age 17 or age 23. There were some significant effects for only MZ or DZ twin pairs, which are discussed in section 3.2.2.

For Common EF, total within-family estimates suggested that after controlling for familial confounds, an increase of one day per month of cannabis frequency at age 17 was associated with a decrease of 0.023 SDs in Common EF at age 23 ($p < .001$; model set 5). This effect was significant in both MZ and DZ pairs, and was undiminished by including other substance use ($p < .001$; model set 5 in ST 2). Although the association for DZ twin pairs became non-significant when other substances were included in the model, the magnitude of the regression coefficient only changed slightly ($\beta = -0.020$, $p = .018$).

#### 3.2.2. Within-family exposure by zygosity interactions

First, there was one significant effect in DZ, but not MZ, twin pairs. However, the direction of this effect was opposite that of the significant between-family effect (i.e., for which severity of CUD was significantly associated with worse Raven performance at age 17), and was inconsistent with the hypothesis that cannabis use impairs cognition.

There were also some associations within MZ twin pairs, which would be consistent with a direct effect of cannabis exposure after accounting for all genetic factors and shared environmental factors. In addition to the aforementioned association between cannabis frequency and age 23 Common EF, which was significant for MZ and DZ pairs (model set 5), an increase in one day per month of cannabis frequency was associated with a decrease in 0.528 percentage points on the Raven-S at age 23 ($p = .001$; model set 2) in MZ pairs. However, this effect was not also significant in DZ pairs, and did not remain significant after controlling for other substance use.

### 3.3. Structural equation twin models

Although a multilevel approach was chosen to enhance comparability to previous research, we confirmed results of these models through estimating biometric (ACE) twin models as well, as described in the SM. These models decomposed the correlation of each cannabis variable with each cognitive variable into covariance explained by additive genetic (A) and nonshared environmental (E) influences. The within-family effect examined by the multilevel models is analogous to covariance of the E components for cannabis exposure and cognition, whereas the covariance of the A components reflects genetic confounding. Using this alternative approach (see ST3 and ST4), most significant phenotypic associations between cannabis and cognitive measures were due to significant genetic correlations, with only three nominally significant non-shared environmental correlations (i.e.,

**Table 3**
Within- and between-family unstandardized regression coefficients for the association between cannabis use variables with intelligence and executive functions.

| **Dependent (Cognitive)** and Independent (Cannabis) Variables | Total Within-Family Effect | MZ Within-Family Effect | DZ Within-Family Effect | Between-Family Effect |
|---|---|---|---|---|
| Model Set 1: **Raven (age 17)** | | | | |
| Age of cannabis initiation ($N$ = 718) | 0.238 | 0.264 | 0.209 | 0.482** |
| Cannabis frequency (age 17; $N$ = 757) | −0.065† | −0.365 | 0.273 | −0.417 |
| CUD (age 17; $N$ = 758) | 1.808† | 0.197 | 3.624* | −5.33** |
| Model Set 2: **Raven-S (age 23)** | | | | |
| Age of cannabis initiation ($N$ = 713) | 0.255 | 0.209 | 0.306 | 0.407** |
| Cannabis frequency (age 17; $N$ = 666) | −0.163† | −0.528* | 0.220 | −0.350 |
| CUD (age 17; $N$ = 667) | −0.949 | −0.669 | −1.246 | −2.309 |
| Cannabis frequency (age 23; $N$ = 710) | −0.159 | −0.075 | −0.250 | −0.342* |
| CUD (age 23; $N$ = 698) | 0.357 | −0.547 | 1.341 | −2.543 |
| Model Set 3: **WAIS (age 17)** | | | | |
| Age of cannabis initiation ($N$ = 720) | 0.039 | 0.023 | 0.057 | 0.149* |
| Cannabis frequency (age 17; $N$ = 759) | −0.031 | −0.020 | −0.043 | −0.075 |
| CUD (age 17; $N$ = 760) | 0.091 | −0.248 | 0.471 | −1.012 |
| Model Set 4: **Common EF (age 17)** | | | | |
| Age of cannabis initiation ($N$ = 706) | 0.002 | 0.010 | −0.006 | 0.019* |
| Cannabis frequency (age 17; $N$ = 751) | −0.019 | −0.016 | −0.022 | −0.003 |
| CUD (age 17; $N$ = 751) | −0.136† | 0.009 | −0.297 | −0.189 |
| Model Set 5: **Common EF (age 23)** | | | | |
| Age of cannabis initiation ($N$ = 717) | −0.009 | 0.000 | −0.019 | 0.012 |
| Cannabis frequency (age 17; $N$ = 670) | −0.023** | −0.023* | −0.023** | −0.001 |
| CUD (age 17; $N$ = 671) | −0.031 | 0.083 | −0.152 | −0.095 |
| Cannabis frequency (age 23; $N$ = 714) | −0.006 | −0.009 | −0.004 | −0.001 |
| CUD (age 23; $N$ = 702) | −0.010 | −0.052 | 0.035 | −0.079 |
| Model Set 6: **Updating-Specific (age 17)** | | | | |
| Age of cannabis initiation ($N$ = 706) | 0.019 | 0.029 | 0.008 | −0.004 |
| Cannabis frequency (age 17; $N$ = 751) | −0.002 | 0.003 | −0.007 | 0.002 |
| CUD (age 17; $N$ = 751) | −0.056 | −0.011 | −0.106 | 0.102 |
| Model Set 7: **Updating-Specific (age 23)** | | | | |
| Age of cannabis initiation ($N$ = 717) | −0.003 | −0.005 | −0.001 | −0.008 |
| Cannabis frequency (age 17; $N$ = 670) | 0.007 | −0.001 | 0.016 | 0.001 |
| CUD (age 17; $N$ = 671) | −0.007 | −0.032 | 0.018 | 0.105 |
| Cannabis frequency (age 23; $N$ = 714) | −0.005 | −0.002 | −0.008 | 0.001 |
| CUD (age 23; $N$ = 702) | 0.033 | −0.024 | 0.094 | 0.119 |
| Model Set 8: **Shifting-Specific (age 17)** | | | | |
| Age of cannabis initiation ($N$ = 706) | −0.023 | −0.016 | −0.031 | 0.000 |
| Cannabis frequency (age 17; $N$ = 751) | 0.002 | 0.010 | −0.008 | −0.003 |
| CUD (age 17; $N$ = 751) | −0.009 | 0.077 | −0.105 | −0.240 |
| Model Set 9: **Shifting-Specific (age 23)** | | | | |
| Age of cannabis initiation ($N$ = 717) | −0.006 | −0.019 | −0.033 | 0.005 |
| Cannabis frequency (age 17; $N$ = 670) | −0.003 | 0.009 | −0.017 | −0.002 |
| CUD (age 17; $N$ = 671) | 0.079 | 0.152 | 0.001 | −0.225 |
| Cannabis frequency (age 23; $N$ = 714) | −0.004 | −0.009 | 0.002 | −0.002 |
| CUD (age 23; $N$ = 702) | 0.070 | 0.067 | 0.072 | −0.113 |

*Note.* Each row contains a separate model. All analyses controlled for sex and premorbid intelligence . Factors scores were standardized prior to analysis. MZ = monozygotic; DZ = dizygotic; Raven = Raven Progressive Matrices; Raven-S = Advanced Raven Progressive Matrices Short Form; WAIS = Wechsler Adult Intelligence Scale; EF = executive function; Cannabis frequency = number of days cannabis was used per month over the past six months; CUD = cannabis use disorder diagnosis (i.e., no use disorder, mild, moderate, or severe).
† indicates parameter differed significantly for MZ and DZ twins.
* $p < .01$.
** $p < .001$.

analogous to within-family effects). Thus, these results agree with the multilevel model results in providing little to no evidence for a causal effect of these levels of cannabis exposure on these cognitive variables.

In addition to estimating biometric twin models, we examined direction of causation models (ST5). We compared model fit of the biometrical twin model to models in which cannabis use predicts cognition, cognition predicts cannabis use, and cannabis use and cognition bidirectionally predict each other. Focusing on the phenotypic associations reported in Table 2, we did not find converging evidence for one variable causing the other. For two of the five phenotypically associated variables, the unidirectional causal models fit significantly worse than the biometric twin model, and the bidirectional causal models had significant paths that were opposite in sign (i.e., a later age of cannabis initiation predicted worse cognition, but better cognition predicted later initiation). For two of the the other three phenotypes, the causal paths did not reach significance ($p < .01$) after multiple testing correction. For only one association, between age of initiation and Raven-S, was there a pattern suggesting with earlier cannabis use causing lower cognitive performance: Although the causal path was significant in either unidirectional model, in the bidirectional model only the path from cannabis to cognition was significant. However, given that this was the only combination of cannabis use and cognition

variables for which we observed both a phenotypic association and a suggestion of causal directionality, the evidence is weak. In general, there are no consistent patterns suggesting the cannabis or cognition are causal effects in the association. Thus, our conclusion remains the same, that the evidence is inconsistent with a causal model of cannabis use causing cognitive decline.

## 4. Discussion

We used a quasi-experimental co-twin control design to test the effect of cannabis on intelligence and EFs. While others have examined intelligence using this design, we are the first to examine multiple EF factors using an extensive and well-validated model of EF. Furthermore, our study includes a measure of intelligence prior to cannabis initiation. We found six associations of cannabis involvement with intelligence and Common EF at the phenotypic and between-family levels. However, five of these associations became negligible at the phenotypic or between-family levels after accounting for other substance use, with the exception of the effect between age of initiation and Raven performance during adolescence. There were few within-family effects consistent with a model in which cannabis exposure causes cognitive impairments. Only one effect — between age 17 cannabis frequency and age 23 Common EF —remained significant across all within-family levels and after accounting for other substance use. However, this effect was not significant at the phenotypic or between-family levels. Other effects provided weaker or inconsistent evidence for causal effects. A within-family prospective association between cannabis frequency during adolescence and Raven performance in young adulthood was significant only in MZ twins. Again, this association was not significant the phenotypic or between-family level. And an increase in CUD severity in adolescence was associated with an *increase* in adolescent Raven performance within DZ twin pairs, an effect that was in the opposite direction from the significant between-family association of higher severity with lower Raven performance. Although several significant within-twin effects were reported, these effect sizes were small, calling into question the clinical significance of these findings as well as the impact of the magnitude of this effect of lower cognitive functioning on “real-world” demands (Gonzalez and Swanson, 2012). In addition, we verified the results from the multilevel models using structural twin modeling analysis, finding that the significant correlations between cannabis use and cognition are explained by genetic factors (see ST 3).

These findings are consistent with previous co-twin controlled studies that have reported minimal evidence that cannabis use has a causal effect on cognitive deficits across various cognitive domains. Two of the previous twin studies found evidence of cannabis causing a greater decline in visual-spatial ability (Lyons et al., 2004) and visual-spatial working memory (Meier et al., 2017). However, each of these studies, including the current study, examined the association between cannabis use and numerous measures of cognitive functioning, only reporting significance with one or two cognitive outcomes. Furthermore, in our own study, we cannot rule out the possibility that poorer EF predated cannabis use initiation; although we controlled for pre-use IQ, we did not have EF measures collected prior to the Wave 2 assessment. Overall, our findings are consistent with previous twin studies that suggest cannabis use does not cause cognitive decline, with potentially two exceptions between adolescent frequency of cannabis use and young adult Common EF and Raven.

The phenotypic and between-family effects in the association between cannabis and cognition are consistent with studies conducted among singletons, which also suggest that cannabis use is associated with lower intelligence and other cognitive abilities (e.g., Fried et al., 2002; McHale and Hunt, 2008). The results from the current study are also consistent with those from a recent population-based study of adolescents reporting that both between-subject and within-subject changes in cannabis use were associated with response inhibition across four years (Morin et al., 2018). Of importance, individuals who initiate cannabis at a younger age are less likely to complete high school and enroll in college (Horwood et al., 2010), and heavy cannabis use during adolescence is associated with lower grade-point average (Meier et al., 2015). Thus, cannabis use is associated with lower educational achievements, which in turn hinders cognitive growth. Taken together with the sparseness of within-family effects, our results are most consistent with the possibility that these associations arise because of genetic influences and/or environmental influences shared by siblings, at least among a normative sample of cannabis users.

### 4.1. Limitations

Our study had several limitations. First, the sample was primarily White; thus results may not generalize to ethnically/racially diverse populations. Second, we had few daily cannabis users: 16 and 62 individuals reported daily or near daily cannabis use during adolescence and young adulthood, respectively. Thus, our results may not apply to heavy or daily users. Third, detailed information about cannabis use history, like method of ingestion, potency, or lifetime frequency of use were not collected. Fourth, EF data was not collected prior to initiation of cannabis use, thus we could not control for premorbid EF abilities. Although EF and intelligence are two distinct constructs, intelligence is highly correlated with EF, which provides a good, but not exact, control for pre-existing EF differences.

Finally, it is important to note the limitations specific to using a discordant twin design. These include confounding by factors not perfectly shared by the twins and random measurement error of cannabis exposure (Frisell et al., 2012). Furthermore, we may not have been sufficiently powered to detect within-twin effects for variables that showed a high intraclass correlation, as many cognitive variables do, particularly in MZ twins. However, the effect size at the within-twin level was small, suggesting that the differences that do exist within twin pairs have only small associations with cannabis exposure, at least in this normative sample. Thus, a relatively large sample size would be required to detect significance at the within-twin level, but it is not clear that such effects would be practically significant even if statistically significant.

Despite these limitations, this study also had several strengths. First, the measures of cognition included multiple EF factors from a well-validated latent model of EFs. Furthermore, our assessment battery included several measures of intelligence (WAIS, Raven, and Raven-S) and intelligence prior to cannabis initiation. Finally, our sample included assessments during both adolescence and young adulthood, while previous twin studies only included assessments up until age 20 or after age 45.

### 4.2. Conclusion

Although we found numerous associations between cannabis involvement and intelligence and EFs at the phenotypic and between-family levels, there was only one within-family effect consistent with a causal effect of cannabis use frequency on Common EF out of 70 (non-independent) within-family tests. However, this effect could also be explained by lower Common EF predating cannabis initiation. Thus, we found little support for a causal effect of cannabis use on cognition. This conclusion is consistent with those from previous twin studies, which suggest that cannabis use does not cause a decline in cognitive ability among a normative cannabis using sample.

## Contributors

JMR, JME, NPF, and RPC contributed to data preparation and analyses. JMR, JME, SHR, JML, and NPF participated in completing the manuscript. All authors contributed to the study design and questions and approved the final version of the manuscript.

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## Declaration of Competing Interest

The authors report no conflicts of interests.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107712.

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