# Cannabis use and cognition from adolescence to young adulthood: exploring cause, consequence, and influencing factors

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## General Abstract

There are two overarching themes of this dissertation. The first is to evaluate the robustness of unique relationships between nonacute cannabis use occurring across adolescence and young adulthood and young adult cognitive outcomes. The second is to explore possible alternative explanations for associations found and separate the potential causal influences of nonacute cannabis on cognition from pre-existing shared familial or environmental factors.

Research in this area has predominantly relied upon cross-sectional studies, and critics have raised concerns regarding the impact of extraneous factors insufficiently addressed within prior research, leaving the true relationship between cannabis and cognition uncertain. To address this and other limitations in the literature, this dissertation was designed to examine the relationship between nonacute cannabis use across adolescence and young adulthood and young adult cognitive outcomes. We used a large population-based twin sample (N = 801) with longitudinal tracking of cannabis use at multiple time points along with extensive neuropsychological assessment and interviewing and a quasi-experimental research design (cotwin control design) to draw stronger causal inferences regarding the relationship between nonacute cannabis use and cognition.

Across the two studies, consistent with prior research, nonacute cannabis use was associated with deficits in neurocognitive outcomes. Study 1 highlighted the importance of controlling for confounding as many of the associations did not survive covariate analyses, such that cannabis did not uniquely predict cognitive outcomes. However, beyond other factors, heavier and early cannabis use was related to persistent deficits in

domains, such as decision-making, processing speed, visuospatial attention, and general cognitive abilities. A pattern of sex-specific effects emerged such that males performed more poorly than females on decision-making and processing speed tasks with cannabis use. Converging on conclusions from Study 1 to explore the etiology of the most robust relationships, Study 2 found evidence that deficits in neurocognitive performance indexed pre-existing familial or environmental liability toward cannabis use but may also in turn be adversely impacted by heavy and early cannabis use, specifically for IQ and, in males, decision-making performance.

Collectively, this work suggests a complex relationship between nonacute cannabis use and cognition, with differences in cognition reflecting a mixture of premorbid familial risk factors and possible adverse consequences of cannabis exposure. This information has implications for shaping policy decisions and targeting preventative and intervention efforts to reduce negative consequences of cannabis exposure in adolescents and young adults.

Table of Contents

## List of Tables

## List of Figures

## General Introduction

The overarching theme of this dissertation is to examine the relationship between nonacute cannabis use and neurocognitive outcomes during the sensitive neurodevelopmental period of adolescence and young adulthood. Cross-sectional research has consistently found an association between nonacute cannabis use and cognition. This relationship is often assumed to represent a neurotoxic consequence of cannabis on the brain, but the relationship between cognition and cannabis is complex. Several avenues may account for associations demonstrated between cannabis use and cognition, including a) cannabis exposure has a direct adverse impact on cognition, b) unmeasured variables explain cannabis use and cognitive deficits, and c) cognitive deficits predate cannabis initiation and index shared familial or environmental risk toward later cannabis use. Indeed, it may be a combination of one, two, or all of these factors.

Understanding the nature of the relationship between cannabis and cognition is imperative to inform policy decisions regarding the legalization of cannabis and targeting prevention or harm reduction efforts. However, the extant literature has not yet come to a clear consensus on the exact nature of this association. To address this open question, the studies presented here used a large, population-based twin sample to assess the association between cannabis and neurocognitive performance, capitalizing on the robust, multi-assessment longitudinal study design and the causally informative nature of twins using the cotwin control analysis. Cotwin control designs allow for more stringent control of shared familial and environmental factors through the genetic and environmental similarities of reared-together twins.

As reiterated in studies 1 and 2, adolescence and young adulthood are critical periods for neuromaturation and neuronal restructuring but are also periods of peak substance use. During these time frames, exposure to substances, such as cannabis, may disrupt brain developmental processes and produce harmful and potentially lasting effects that would otherwise not be seen if maturation was complete, pointing to youth as a time of possible vulnerability for neurocognitive insults. There are also numerous neurobiological reasons that sex-specific effects would be expected in the relationship between cannabis exposure and neurocognitive outcomes due to differences in the pharmacologic effects of Δ9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis, in males and females. Cannabis exposure during adolescence or young adulthood, in particular, may result in sex-specific effects as brain maturational trajectories vary, such that males undergo a protracted neurodevelopmental course compared to females. Maturational restructuring of the brain during adolescence and young adulthood might provide the necessary environment for sex-specific effects to emerge.

The two studies presented in this dissertation share several strengths that address gaps in the literature (described in more detail in Study 1). First, we used a large, population-based longitudinal sample of males and females with multiple, comprehensive follow-up assessments over the critical neurodevelopmental period of adolescence to young adulthood and peak substance use. We also used several dimensional measures to characterize cannabis use across adolescence and young adulthood, which are more reliable and valid than discrete group comparisons typically used in the cannabis literature. Our extensive neurocognitive battery allowed us to address a full spectrum of

cognitive domains, including those often under-represented in the longitudinal and twin literature and measured pre-exposure cognitive ability to address questions regarding temporal sequencing of the association. More exhaustive interviewing regarding psychosocial, environmental, and participant-specific factors allowed us to better address possible confounding variables, increasing confidence in findings and causal inferences.

Study 1 examined the phenotypic link between dimensional measures of nonacute cannabis use across adolescence to young adulthood and an extensive battery of young adult cognitive outcomes. We focused on the evaluation of cannabis-related associations, independent of common confounding variables (e.g., pre-exposure cognitive ability, socioeconomic status, alcohol/nicotine use, education, recent cannabis use), along with more nuanced factors, such as sex-specific effects, implications of recency of last cannabis use, and exploratory analyses of effects unique to cannabis users. The conclusions drawn from Study 1 were used to hone the focus of Study 2 to the most relevant and robust nonacute cannabis use and cognitive associations. Study 2 built on the results of Study 1 by assessing the causal association between nonacute cannabis use and cognitive performance, disentangling pre-existing liability, and exposure-related consequences of cannabis use across adolescence.

## General Study Characteristics

### Sample

Participants for both studies comprised monozygotic and same-sex dizygotic twins drawn from the Enrichment Study (ES), a component of the Minnesota Twin Family Study (MTFS) at the Minnesota Center for Twin and Family Research (MCTFR). The ES sample is one of several population-based, longitudinal studies of reared-together

twins conducted at the MCTFR (Keyes et al., 2009; Wilson et al., 2019). The ES twins were recruited and assessed at age 11 and were followed at ages 14, 17, and 24. A small subset of ES twins (n=265) were assessed at age 20; however, this follow-up was discontinued early and was not included in the current studies due to its comparatively small size to the larger sample. Years for intake recruitment and follow-ups included: 1999-2001 (age-11), 2003-2010 (age-14), 2006-2012 (age-17), 2013-2018 (age-24).

Of the original 998 twins recruited for the ES sample at the age-11 intake, 81% (n = 809) participated in the most recent age-24 follow-up in some capacity. Twin participation at the age-24 assessment was not uniform across all neurocognitive assessments due to logistic factors, such as time constraints during interviewing or impractical travel distances to participate in-person that necessitated phone interviews (n = 111). Eight individuals were excluded as they reported cannabis exposure before their intake assessment. Sample sizes for initial analyses will be reported in tables provided for each study, and the possible impact of attrition was examined in study 1.

For participants included in this project, mean age (SD) for each assessment wave were as follows: 11.86 (0.43), 15.04 (0.55), 17.89 (0.47), 24.43 (0.90). Age at the most recent follow-up (age-24) break down included: 22 (22), 23 (229), 24 (351), 25 (150), 26 (40), 27 (7), 28 (2). Given age dispersion at the most recent assessment, age was included as a covariate in all models. Racial and ethnic backgrounds mimicked that of the general population in Minnesota at the time of recruitment; as such, the ES sample was predominantly white (93%). Cannabis use data was pulled from all four assessment waves. Neurocognitive outcomes were obtained from the age-24 assessment wave and are described in detail in the section below.

**Cannabis use measures**

Cannabis use was assessed at ages 11, 14, 17, and 24. Six variables were used to characterize cannabis use. Variables included frequency of use (past 12 months), number of uses (since last assessment), heaviest frequency (lifetime), age of initiation, recent use (past 24-hour), and length of abstinence (time since last use from age-24 assessment). Two of these variables (frequency of cannabis (past 12 months) and the number of uses (since last assessment)) were combined at each follow-up assessment wave (i.e., 14, 17, and 24) and then averaged to form a single cumulative measure of cannabis exposure across adolescence to young adulthood (cannabis index). A similar approach has been used in several other studies from our group that have examined the impact of cannabis use on cognition (Malone et al., 2021; Schaefer et al., 2021). The other four variables (lifetime heaviest frequency, age of initiation, recent cannabis use, length of abstinence) were examined individually. Our primary variables of interest were the cannabis index, lifetime heaviest frequency, and age of initiation. Recent use and length of abstinence were utilized as covariates and are detailed in each study's method section.

Cannabis was assessed using the Computerized Substance Use (CSU; McGue et al., 2014) questionnaire and a revised version of the drug supplement from the Diagnostic Interview for Children and Adolescents – Revised (DICA-R; Reich, 2000; Welner et al., 1987). A modified version of the Substance Abuse Module (SAM; Robins et al., 1987) from the Composite International Diagnostic Interview (CIDI; Robins et al., 1988) was used to assess substance use at ages 17 and 24. Assessments were administered by interviewers with at least a bachelor-level degree in psychology or a related discipline who had completed intensive training in psychiatric assessment. The DICA-R and the

SAM assess Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for cannabis use disorder (CUD). The number of uses was obtained from the DICA-R (age 11, 14) and the SAM (age 17, 24). Frequency of use (past 12 months) was obtained from the CSU (age 11, 14) and the SAM (age 17, 24). Heaviest frequency was only asked on the SAM and was asked for lifetime (age 17) and since the last assessment (age 24) to cover the entirety of the lifespan (i.e., birth to age 24). Age of initiation was pulled from the DICA-R (age 11, 14) and the SAM (age 17, 24). Length of abstinence (time since last use) was asked on the SAM (age 24).

*Cannabis index.* To obtain our cannabis index, which characterized cumulative cannabis exposure from adolescence to young adulthood, separate cannabis indices were first calculated for each follow-up wave (i.e., 14, 17, and 24) by averaging two items: (1) frequency of use in the past 12 months, and (2) number of times used since last assessment. Due to skew and spareness, we transformed responses of frequency and number of uses into ordinal measures before averaging these two items, with six categories per item. For frequency of use in the past 12 months, categories included: 0 (no use), 1 (<1x/month), 2 (1-3x/month), 3 (1-4x/week), 4 (every day or nearly every day), or 5 (>1x/day). For number of uses since last assessment, categories included: 0 (no use), 1 (1-4 uses), 2 (5-30 uses), 3 (31-100 uses), 4 (101-400 uses), or 5 (>400 uses or "too many to count"). After we obtained individual indices for each follow-up assessment wave, we computed our cannabis index by averaging each of the separate indices into a single composite measure to summarize overall exposure from adolescence to young adulthood. Consistent with prior research using similar composite measures (Malone et al., 2021), we did not include the age-11 intake when computing the cannabis index as we

had purposefully excluded individuals who had used cannabis before their intake assessment and, as such, age-11 cannabis use was zero for all participants.

*Lifetime heaviest frequency.* Participants were asked to think about the period when they were using cannabis the most, either in their lifetime (asked at age 17) or since their last assessment (asked at age 24), and then asked to report the frequency of their cannabis use during that time. We used the max value reported at either their age-17 or age-24 evaluation to assess for heaviest frequency in the participant's lifetime (i.e., birth to age 24). Mimicking procedures used to develop the cannabis index, we transformed lifetime heaviest frequency into an ordinal measure containing six categories to reduce skew and spareness of responses. Categories included: 0 (no use), 1 (<1/year), 2 (>1x/year to 2 to 3x/month), 3 (1 to 2x/week to nearly every day), 4 (1 to 2x/day), 5 (≥3x/day).

*Age of initiation.* Age of initiation was defined as the first exposure to cannabis regardless of the amount used. We asked participants how old they were when they first tried cannabis at each assessment wave to obtain this value. The age reported at the earliest assessment was used, as this was the report most proximal to when use occurred, likely reducing measurement error due to retrospective reporting over more extended periods.

To illustrate the variation in normative cannabis use behaviors, descriptive statistics for our cannabis use variables are presented in Table. 1 with distributions presented for our three cannabis variables in Figure 1. Of the 801 participants used in our studies, 162 (20%) qualified for a cannabis use disorder (CUD) at some point in the previous seven years. Data was unavailable for CUD in the 12 months preceding the age-

24 assessment as DSM criteria for CUD were only asked since the last assessment (e.g., past seven years). However, this is generally commensurate with national prevalence rates (Waddell, 2021). At the age-24 assessment, 293 participants reported never using cannabis in their lifetime. Sixty-four individuals reported using cannabis within the 24-hours preceding their age 24 assessment. Consistent with national data (Johnston et al., 2021), males typically used cannabis more heavily and began using at an earlier age.

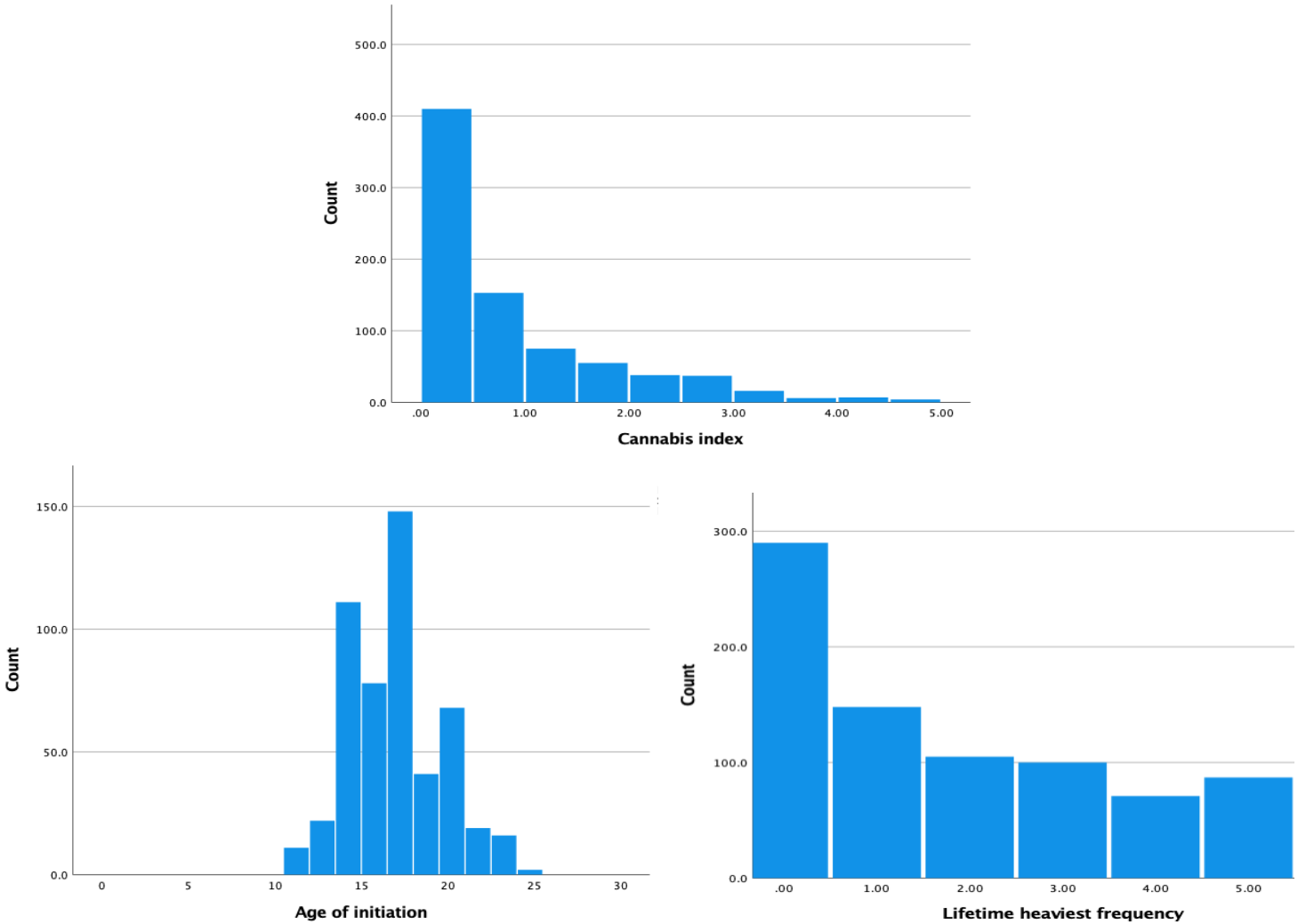


**Figure 1.** Histograms of the three primary cannabis use measures.

## Cognitive outcomes

A comprehensive neuropsychological battery was administered at the age-24 follow-up, assessing various cognitive domains, including verbal learning and memory, processing speed, verbal attention and working memory, visuospatial attention and working memory, decision-making, cognitive inhibition, and general cognitive abilities (see Table 2 for descriptive statistics of cognitive variables). Tests were selected given their strong psychometric properties, frequent use within research and/or clinical settings, and previous use within the cannabis use literature specifically. Scores derived from the completed neurocognitive battery are used to evaluate for possible implications of cannabis exposure on cognitive functioning.

### *Verbal learning and memory*

*Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996).* The RAVLT measures an individual's ability to acquire, consolidate, and retrieve verbal information. In past research, cannabis users were found to learn (Lamers et al., 2006; Solowij et al., 2011) and recall (Becker et al., 2014; Lamers et al., 2006; Pujol et al., 2014) fewer words on the RAVLT compared to controls. The test began with an initial learning phase, in which the participants were read a list containing 15 words five times (Trial 1-5) at a pace of approximately one word per second. After each list presentation, they were asked to repeat as many words as possible from the list. Next, as part of an interference trial (Trial B), individuals were read a new list of 15 words a single time and asked to recall as many words as possible from this new list. After this, there was an immediate recall trial (Trial 6), during which the participants were asked to recall as many words as possible from the first list presented without prior warning. Subsequently, following a 30-minute delay, a

delayed recall trial was undertaken (Trial 7), and the participants were again asked to recall as many words as possible from the first word list without prior warning. Three scores are derived from this task to assess verbal learning and memory, including: *(1)* a total learning score calculated as the summation of the number of words an individual was able to repeat back across all five learning trials (total learning), *(2)* a measure of retention over a short delay adjusted for overall learning represented by the difference between the number of words repeated on Trial 5 and the number of words recalled on Trial 6 (short-delay recall), and *(3)* a measure of retention over a long delay adjusted for overall learning represented by the difference between the number of words repeated on Trial 5 and the number of words recalled on Trial 7 (long-delay recall).

***Processing speed***

*Digit Symbol-Coding (Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol-Coding; Wechsler, 1997a).* Digit symbol-coding assesses processing speed and psychomotor functioning. Performance on this measure has been shown to be lower in cannabis users compared to controls (Winward et al., 2014), and earlier-onset users have shown more significant deficits compared to late-onset cannabis users in a prior longitudinal study (Jacobus et al., 2015). For this task, a subject was shown a key that displays a set of symbols that are matched with numbers. Using the key, the subject was asked to subsequently fill in as many empty boxes with the appropriate symbol under its corresponding number as quickly and accurately as possible in a 120-second time frame. A participant's raw score represented the number of accurately documented symbols in the designated timeframe. Raw scores were then converted to scaled scores following WAIS-III instructions utilizing age-corrected normative data.

*Symbol Search (WAIS-III Symbol Search; Wechsler, 1997a).* This test is also primarily a measure of mental processing speed and visual scanning. Subjects were asked to visually scan a row of symbols (search group) and compare these symbols to a set of two additional symbols (target group). They are then asked to mark as rapidly and accurately as possible whether or not a symbol in the search group was identical to one of the symbols in the target group. If no symbols in the search group were identical to the target group, they were instructed to mark the "no" box at the end of the row. Participants were given 120 seconds to complete as many items as possible. A participant's raw score represented the number of accurately marked symbols or "no" boxes less any errors executed in the designated time period. Like digit symbol-coding, raw scores were then converted to scaled scores following WAIS-III instructions utilizing age-corrected normative data.

*Processing Speed Index (WAIS-III Symbol Search; Wechsler, 1997a).* The processing speed index is a summary measure of an individual's overall speed of information processing. Both chronic and occasional adolescent cannabis users have been found to have deficits in processing speed index scores compared to non-consumers (Frolli et al., 2021). In prior longitudinal studies, current heavy cannabis users demonstrated lower mean scores on the processing speed index when compared to controls (Fried et al., 2005). An index score was derived from administering the digit symbol-coding and symbol search subtests described above using WAIS-III instructions and scoring procedures to obtain a standard score.

***Verbal attention and working memory***

*Digit Span Forward and Backward (WAIS-III Digit Span; Wechsler, 1997a).* Digit span forward is a measure of basic verbal attention abilities and maintenance component of working memory. Prior research demonstrated deficits on both digit span forward (Croft et al., 2001) and digit span backward (Croft et al., 2001; Jacobus et al., 2015) task in cannabis users compared to controls and found associations between an earlier age of onset and poorer performance on digit span backward (Gouzoulis-Mayfrank et al., 2000). For this task, participants were orally presented a string of digits at a pace of approximately one digit per second and then asked to immediately verbally repeat back the digits in the same order previously listed. Digit span backward reflects an individual's ability to maintain verbal information online and manipulate that information based on the task demands. The presentation was the same as the forward condition; however, after the presentation, participants were instead asked to repeat the number string in the reverse order than they were initially presented. In both the forward and backward conditions, digit strings became progressively longer as the participant continued to correctly repeat digit strings, with the max length being nine digits. Two variables were derived from the digit span subtest, including: *(1)* longest digit span forward, or the max number of digits that a participant was able to repeat back in the original order, and *(2)* longest digit span backward, or the max number of digits a participant was able to repeat back in reverse order.

*RAVLT Trail 1 (RAVLT; Schmidt, 1996).* Trial 1 of the RAVLT is a measure of attention span for a list of words. Several studies have found impairments in cannabis users' performance on the first list learning trial of the RAVLT when contrasted with controls (Jacobus et al., 2015; Pujol et al., 2014; Takagi et al., 2011). As part of the

RAVLT test administration, a score was obtained based on the number of words repeated back on the first trial presentation of the 15-word list (Trial 1; see above for further details on RAVLT administration).

***Visuospatial attention and working memory***

*Spatial Span Forward and Backward (Spatial Span; Wechsler, 1997b).* The spatial span test is a measure of basic visuospatial attention, information maintenance, and mental manipulation. Spatial span forward and backward have both been associated with cannabis dependence and frequency of cannabis use in prior research (Meier et al., 2018). It is considered the visuospatial analog to the digit span test. Participant's spatial span was measured using an irregular array of ten blocks similar to the Weschler Memory Scale-3rd edition spatial span task and modified for display on a PC monitor utilizing E-prime task presentation software (version 2.0; Schneider et al., 2002). Before beginning the forward and backward conditions, participants were given a practice trial. During both the spatial span forward and backward condition, the computer lit up a series of blue-colored squares one by one placed in various locations on a white background screen at a pace of approximately one square per second. When the computer stopped, during the spatial span forward condition, participants were instructed to use the mouse to click on the squares in the same order they lit up on the screen. During the spatial span backward condition, participants were instructed to click on the squares in reverse order. Two variables were derived from the spatial span task, including: *(1)* longest spatial span forward, or the max number of correctly identified squares selected in the original presentation order, and *(2)* longest spatial span backward, or the max number of correctly identified squares, selected in reverse order.

### *Decision-making*

*Iowa Gambling Task (IGT; Bechara et al., 1994).* The Iowa Gambling Task was originally developed to quantify poor judgment and impulsive decision-making. Several studies have found poorer performance on the IGT when compared to controls (Becker et al., 2014; Gonzalez et al., 2012; Solowij et al., 2012; Verdejo-García et al., 2013). Participants completed a computerized version of the IGT using E-prime task software (version 2.0; Schneider et al., 2002). There were 100 total trials across five blocks. This computer task presents four decks of cards face down on the screen (Decks 1, 2, 3, and 4). The participant was instructed to choose one card at a time from one of the four card decks. Each time they chose, they were given feedback about winning and/or losing some money. There was no limit to how often a participant could select from each deck. For each selection from Decks 1 and 4 ("advantageous decks"), participants would win either $0.10 or $0.15. Decks 1 and 4 differed in that with Deck 1, participants had a 50% chance of losses that varied from $0.05 to $0.20, whereas with Deck 4, there was a 10% chance of losses that varied from $0.60 to $0.65. Decks 1 and 4 were considered "advantageous" as losses were organized so that participants would accrue a net gain of $1.25 over 20 selections from these decks. For each selection from Decks 2 and 3 ("disadvantageous decks"), participants would win $0.25; however, losses were structured so that participants would incur a net loss of $1.25 over 20 selections from these decks, hence their label of "disadvantageous decks." Decks 2 and 3 differed in that with Deck 2, participants had a 50% chance of losses that varied from $0.35 to $0.90, whereas with Deck 3, there was a 10% chance of losses that varied from $3.00 to $3.25. Participants needed to select cards from the decks in a way that would lead to the most

money at the end of the task. Participants were paid their winnings in cash at the end of the day. Three measures were derived to evaluate IGT performance, including *(1)* overall performance, which was computed by subtracting the number of deck selections from the disadvantageous decks (2 and 3) from those from the advantageous decks (1 and 4) across all 100 trials (DM overall; Tolpak et al., 2010), *(2)* decision-making under ambiguity, characterized by the difference between advantageous and disadvantageous selections over the first two blocks (DM ambiguity; i.e., first 40 trials), and *(3)* decision-making under risk, defined as the difference between advantageous and disadvantageous sections across the remaining three blocks (i.e., last 60 trials) (DM risk; Almy et al., 2018).

***Cognitive inhibition***

*Go/No-Go Task (Go/No-Go Task; Roche, Garavan, Foxe, & O'Mara, 2005).* The 1-back go/no-go task was used to assess inhibitory control, or the ability to rapidly cancel a behavior or action even after it was initiated. Prior research has found trends for poorer performance on Go/No-go tasks with an earlier age of onset of cannabis use and that cannabis users make a greater number of errors (Hester et al., 2009; Tamm et al., 2013). This computerized task encompassed three blocks of 144 pseudorandomized trials. During this task, two white letters were alternately presented over a black background for 300ms. Letter combinations (X-Y, D-U, O-P) were different across each of the three blocks. Participants were instructed to press a button when the stimulus presented followed a different stimulus ("go" trials) but were asked to withhold their response when the stimulus was preceded by an identical stimulus ("no-go" trials). Participants were given 1150 milliseconds to respond, and a 900 millisecond intertrial interval separated

each trial following the response window. Participants were also given twenty practice trials before beginning the full task. Within each block, 25% of trials were no-go trials. Two variables were derived from task performance, including: *(1)* false alarm rate (No-go Error Rate), or frequency of responding to no-go trials, which is conceptualized as a measure of response inhibition specifically, and *(2)* d-prime, which refers to the z-transformed hit rate minus the z-transformed false-alarm rate and is considered the most comprehensive measure of overall task performance (Wickens, 2002).

***General cognitive ability***

*Block Design (Wechsler Adult Intelligence Scale-Revised (WAIS-R) Block Design; Wechsler, 1981).* Block design is broadly utilized as a measure of an individual's perceptual reasoning and problem-solving abilities. Worse block design performance has been found to be associated with greater mean levels of percent days of cannabis use across time (Infanted et al., 2019) and cannabis use predicted poorer block design performance in a sample of school age children (Morin et al., 2019). For this task, participants were presented with either two, four, or nine identical blocks with all white, all red, or half red and half white surfaces. Using the blocks provided, the subject was asked to duplicate a pattern as quickly as possible that the administrator presented. As the individual progressed, the patterns would require more blocks and become increasingly more difficult. Raw scores were then converted to an age-correct scaled score following WAIS-R scoring guidelines.

*Vocabulary (WAIS-R Vocabulary; Wechsler, 1981).* This test is a measure of verbal knowledge and concept formation. Phenotypic associations were found in a recent twin study for a relationship between cumulative cannabis use and worse performance on

a vocabulary task (Schaefer et al., 2021). For this task, participants were presented a word both orally and visually. The participant was then asked to define the word. The test includes 66 words that increased in difficulty as items were successfully completed. Raw scores were then converted to an age-correct scaled score following WAIS-R scoring guidelines.

*Prorated Full Scale Intelligence Quotient (WAIS-R Prorated FSIQ; Wechsler, 1981).* FSIQ is a measure of an individual's general cognitive and intellectual functioning. A recent meta-analysis of longitudinal studies found declines in intelligence quotient (IQ) scores were associated with cannabis use (Power et al., 2021). An estimate of the FSIQ summary score was derived from the administration of the block design and vocabulary subtests described above using WAIS-R instructions for pro-rating the FSIQ score.

## Study 1. Young Adult Neuropsychological Outcomes Associated with Cannabis Use from Adolescence to Young Adulthood


### Abstract

**Background.** The perceived risks of cannabis use have been steadily declining, particularly among adolescents and young adults. However, the potency of cannabis products has increased over recent decades, raising concerns regarding the consequences of cannabis exposure. Research suggests nonacute cannabis exposure is associated with impairments in cognition and highlights adolescence to young adulthood as a vulnerable period for adverse consequences. However, the robustness and strength of the connections between nonacute cannabis and cognition, including how well these connections hold after accounting for relevant variables, remains to be fully elucidated given methodologic limitations within the literature. Limitations comprised inconsistent control of confounders, over reliance on discrete group comparisons (e.g., "user" vs. "non-users") despite dimensional nature of data without a consistent definition of groups between studies, and narrow representation of cannabis behaviors (e.g., focus on user status or frequency of use) within a primarily cross-sectional literature base. Additionally, less focus has been placed on understanding nuances of the relationship between cannabis use and cognition that may confer additional risk for adverse cognitive outcomes (e.g., sex-specific effects). We sought to characterize the relationship between cannabis use occurring across adolescence into young adulthood and young adult cognitive outcomes and examine alternative explanations, confounding factors, and nuances, such as the interaction between sex and cannabis use behaviors.

**Method.** Dimensional measures of cannabis and other substance use were obtained across four assessment waves from age 11 to 24 in a population-based sample of 801 twins (55% female). Primary variables of interest were a summary measure of cumulative cannabis exposure across all assessment waves (cannabis index), lifetime heaviest frequency, and age of cannabis initiation. Participants completed a battery of cognitive assessments at age 24, and pre-exposure IQ was assessed at age 11. Linear mixed models (LMMs) were used to explore the relationships between cannabis use variables of interest and cognitive outcomes. Covariates of interest included pre-exposure IQ, parental socioeconomic status, alcohol and nicotine use, years of education, recent cannabis use, and length of abstinence from cannabis. All models include covariates for age, sex, and zygosity.

**Results.** Several significant associations were found in initial analyses between cannabis use and cognition; however, many of these were attenuated once relevant confounding factors were covaried. Independent of covariates, significant effects remained between an earlier age of cannabis initiation and lower prorated FSIQ scores and weaker visuospatial attention performance. Sex-specific effects emerged on a processing speed and decision-making task, such that males demonstrated greater processing speed deficits with an earlier age of cannabis initiation and greater decision-making impairments with higher lifetime heaviest frequencies than females. Impairments on a block design task appeared to be most strongly related to cumulative cannabis use, but no other significant effects were found with our cumulative cannabis use measure. Findings for age of initiation rose above a composite measure of frequency and quantity of cannabis use to uniquely predict cognitive deficits. Lower verbal working memory

scores were also evidenced with higher lifetime heaviest frequencies when assessing for deficits in cannabis users only. Differences in performance did not emerge when comparing cannabis users with less than a month of abstinence to those that had not used in at least a year, and abstinence length did not predict performance on our cognitive measures

**Conclusions.** Results from this longitudinal study suggest that individuals who use cannabis earlier during adolescence and have heavier peak frequencies of use are more vulnerable to persistent deficits in cognition even with prolonged abstinence, particularly males. Results suggest that more diffuse moderate levels of cannabis use, mainly occurring later into young adulthood, may be associated with fewer long-term negative outcomes.

## Introduction

Cannabis is currently the most used illicit substance in the United States. High rates of use are unsurprising given the steady decline since the mid-2000s in the public's perceived risk associated with cannabis use and, as is often the case with a downward shift in perceived risk, personal disapproval rates have also been falling over the last decade (Johnston et al., 2021). These changes in perception surrounding cannabis have been accompanied by shifts in policy and cannabis potency as well. For instance, at the time of writing this paper, 37 states have legalized cannabis use at the medicinal level, and 18 states, plus the District of Columbia, have legalized it at the recreational level (Berke et al., 2021). Alongside legalization, the cannabis products produced within the recreational and medicinal markets have seen a significant increase in delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis, with some products containing up to +80% THC content (Chandra et al., 2019; Russo, 2016). This increase has raised concerns given that THC exposure has been linked with several adverse outcomes, including interference with normal neurophysiological processes (Bossong & Niesink, 2010; Mizrahi et al., 2017). The changes in potency and push for legalization have placed additional expediency on the need for research on the enduring impacts of cannabis exposure on the brain to better inform policy.

### Risk conferred within youth

There is a particular urgency for research focusing on the ramifications of cannabis use in youth. The necessity to understand the consequences of cannabis exposure on the adolescent and young adult brain is salient for two reasons. First, adolescence and young adulthood are notable for peak substance exposure and are

characterized by behavioral changes, such as increased risk-taking (Dayan et al., 2010). The 2020 Monitoring the Future survey conducted on youth substance use found that daily marijuana use levels in 8th to 12th graders were at or near the highest level recorded since 1991, with 6.9% of 12th graders reporting smoking cannabis daily (Johnston et al., 2021).

Second, these periods of peak substance use occur during a time of substantial neuroanatomical development, with changes in both gray and white matter occurring well into early adulthood (Andersen et al., 2000; Lenroot et al., 2007; Sowell et al., 2002). It is hypothesized that, due to this ongoing neuroanatomical restructuring, adolescents and young adults, relative to older cohorts, are more vulnerable to potential cannabis exposure-related insults to brain structure and function. Interruption to developmental processes may result in lasting impairments in critical mechanisms, particularly those involved with the pharmacological effects of cannabis (Ellgren et al., 2008; Lubman et al., 2015).

Animal studies have supported this hypothesis. Rodent studies have found lasting alterations in glutamatergic functioning following adolescent THC exposure (Gleason et al., 2012). Other rodent studies have noted that adult rats, exposed to THC during adolescence or young adulthood, demonstrated diminished social interaction and recognition (O'Shea et al., 2006; Leweke & Schneider, 2011) and altered motivational processes (Rubino et al., 2008). Research has highlighted deficits in working memory in adolescent, but not adult, rats with the same amount of THC exposure (Quinn et al., 2008). Impairments were also found in sensorimotor gating and recognition memory in adolescent rats exposed to THC, but not adult rats (Schneider & Koch, 2003). Adult rats

exposed to chronic doses of THC during adolescence demonstrated lasting deficits in learning (Harte and Dow-Edwards, 2010).

The human literature generally converges on similar findings. For instance, a large longitudinal study found that cannabis use during adolescence was associated with altered cerebral cortical development, particularly in brain regions rich in cannabinoid receptors, and was associated with greater attentional impulsiveness (Albaugh et al., 2021). Decreasing resting functional connectivity with dorsolateral prefrontal and orbitofrontal cortices, as well as a lack of increase of resting functional connectivity with the superior frontal gyrus, have also been demonstrated in adolescence with a cannabis use disorder compared to those without, which overlapped with deficits in executive functioning performance (Camchong et al., 2017). An earlier age of initial cannabis exposure has been associated with protracted verbal learning and memory (Barthelemy et al., 2020; Jacobus et al., 2015), processing speed (Ehrenreich et al., 1999; Jacobus et al., 2015), cognitive disinhibition (Gruber et al., 2011; Solowij et al., 2012), poor working memory (Becker et al., 2010), and deficits in decision-making task performance (Castellanos-Ryan et al., 2017); however, other studies have not replicated these results (Ross et al., 2020; Scott et al., 2018). Exploration of risk conferred by the age of cannabis exposure warrants further exploration.

## Existing literature

### *Cross-sectional literature*

Given concerns that adolescence and young adulthood may represent periods of increased risk for adverse brain-related outcomes, it is unsurprising that there is a

substantial cross-sectional literature base focused on the implications of nonacute cannabis use and cognitive function during these developmental time points.

Within cross-sectional studies, evidence has emerged that adolescent and young adult cannabis users demonstrate a relatively consistent pattern of deficits in verbal learning and memory (Becker et al., 2014; Hanson et al., 2010; Lamers et al., 2006; Solowij et al., 2011), processing speed (King et al., 2011; Medina et al., 2007; Tapert et al., 2007; Winward et al., 2014), and decision-making performance (Becker et al., 2014; Clark et al., 2009; Grant et al., 2012; Gonzalez et al., 2012; Hanson et al., 2014; Lamers et al., 2006; Solowij et al., 2012; Tamm et al., 2013; Verdejo-García et al., 2007; Verdejo-García et al., 2013). Significant effects typically occurred in heavy, frequent cannabis users (Scott et al., 2018), with some evidence for persistent deficits despite abstinence (Bolla et al., 2002; Medina et al., 2007; Winward et al., 2014; Wallace et al., 2020) and more pronounced impairments seen in early-onset cannabis users (Ehrenreich et al., 1999; Pope et al., 2003; Schweinsburg et al., 2008; Solowij et al., 2011). Less consistent evidence has emerged for deficits in attention (Becker et al., 2014; Lisdahl & Price 2012; Medina et al., 2007; Petker et al., 2019;), working memory (Becker et al., 2010; Hanson et al., 2014; Parlar et al., 2021; Petker et al., 2019), and cognitive inhibition (Dougherty et al., 2013; Gonzalez et al., 2012; Takagi et al., 2011) within adolescents and young adults.

Meta-analyses have attempted to address some of the inconsistencies. In an early meta-analysis of 11 studies, Grant and colleagues (2003) demonstrated small but discernable deficits in the domains of learning and memory but not attention, executive functioning, or processing speed in chronic cannabis users, noting that 24-hours of

abstinence did not moderate the effects. Schreiner and Dunn (2012) similarly found small but significant effects sizes for poorer learning and memory performance in cannabis users compared to controls; however, unlike Grant et al. (2013), they also found deficits in attention and executive functioning domains. Differences in results could be attributable to sample size as Schreiner and Dunn included 33 studies and effect sizes were characterized as small, suggesting that the earlier meta-analysis may have been underpowered to decern effects.

Scott et al. (2018) reaffirmed this in a large meta-analysis of 69 studies focusing on adolescents and young adults, documenting small effect sizes for reduced cognitive functioning with frequent, heavy cannabis use in learning and memory, processing speed, inhibition, working memory, and attention. However, they noted that effect sizes were no longer significant when analyses were constrained to studies with at least 72-hour abstinence periods, which the author interpreted as evidence that deficits seen in cannabis users may be due to residual effects of recent use or withdrawal rather than persistent effects. There was no association with age of onset of cannabis use, although definitions within individual studies for "early-onset" ranged from use before age 15 to age 18 when looking at discrete groups. A meta-analysis examining the impact of abstinence on the association between nonacute cannabis use and verbal learning and memory also noted some amelioration of deficits related to cannabis, with deficits appearing to resolve between 7 and 28 days of abstinence (Krzyzanowski & Pudon, 2019).

Lovell et al. (2020) analyzed 30 young adult and adult studies, comparing 849 cannabis users to 764 controls, and found cannabis use was associated with small-magnitude deficits in executive functioning, learning and memory, global cognition, and

moderate deficits for decision-making and, unlike Schreiner and Dunn (2012) and Scott et al., (2018), prolonged abstinence (≥ 25 days) did not influence outcomes, except for executive functioning. No significant group differences were noted for simple reaction speed, working memory, or attention, nor did age of onset (defined as <16 years of age) influence outcomes. Consistent with this, in a meta-analysis of adolescents and adults, Ganzer and colleagues (2016) assessed the role of sustained abstinence of at least 14 days. Even with abstinence, they found moderate deficits in learning and memory and executive functioning (e.g., inhibitory control/decision-making) in cannabis users compared to controls (Ganzer et al., 2016). A meta-analysis of 13 studies of young adult chronic cannabis users partially affirmed these results, noting an association between chronic cannabis use and short- and long-delay memory, decision-making, and attention tasks, but not inhibition (Figueiredo et al. 2020).

Altogether, meta-analyses consistently report neurocognitive deficits in cannabis users, particularly with heavy, frequent cannabis use. Reviews indicate that learning and memory impairments appear to be the most consistent findings (Broyd et al., 2016; Duperrouzel et al., 2020). More moderate evidence is seen for deficits in processing speed and attention. Aspects of executive functioning, such as decision-making, also have support, but comparatively fewer cross-sectional studies have examined decision-making specifically, and most of those studies focus on young adulthood. Results for other cognitive domains continue to be characterized as mixed (Broyd et al., 2016; Ajmer et al., 2021), nor is it clear whether deficits resolve with abstinence.

Scott et al. (2018) cites limitations due to heterogeneity in the characterization of cannabis use and potential third variable confounding, particularly regarding other

substance use and the possibility of reverse causation. Duperrouzel et al. (2020) noted that because meta-analyses are based on cross-sectional research, they are limited in their ability to conclude causality and may also have trouble speaking to the impact of age of onset. Retrospective reports of the age of onset may be particularly susceptible to measurement error with cross-sectional cohorts as participants may be reporting on events occurring over decades prior. Other identified limitations included the small sample sizes of included studies ($n < 100$; Duperrouzel et al., 2020), variability in neurocognitive tasks used (Figueiredo et al., 2019; Lovell et al., 2020), and over-reliance on group comparisons (e.g., "user" vs. "non-user," "heavy" vs. "light") despite the dimensional nature of the data (Infante et al., 2020). Large longitudinal studies should focus on addressing these limitations.

***Longitudinal and twin studies***

In longitudinal cohort studies following adolescents and young adults post-initiation of cannabis use, cannabis users demonstrated worse learning and delayed recall for list-learning and story memory tasks compared to controls (Becker et al., 2018), with evidence of persistent deficits through three weeks of abstinence (Jacobus et al., 2015) but possible amelioration of impairments after 12 months of abstinence (Tait et al., 2011). More significant deficits were also noted in early-onset cannabis users (defined < age 16; Jacobus et al., 2015) and with greater cannabis use frequencies (Pacheco-Colón et al., 2021). These are partially consistent with a longitudinal study with pre-and post-initiation cognitive measures, such that current, heavy users had lower mean scores on immediate and delayed recall tasks in a sample of 113 adolescents followed over eight years compared to controls. However, differences were not significant for former users (three

months abstinence) regardless of frequency of use (Fried et al., 2005). In another project from our group, Malone et al. (2021) found that propensity to use alcohol (e.g., academic problems and family occupation) accounted for the relationship between cumulative cannabis use and verbal learning in a large sample of twins, and no relationship was found between cannabis and memory performance, which was replicated in a more modest sample of 175 adolescents followed into adulthood (Infante et al., 2019). However, in a sample of African American youth, early-onset cannabis users evidenced declines in story-memory performance across adolescence (Barthelemy et al., 2019), and another study found familial effects in sibling pairs, not alcohol use, accounted for the relationship between cannabis use and delayed recall (Ellingson et al., 2021).

Despite three weeks of abstinence, early-onset cannabis users performed more poorly on a speeded coding task than controls (Jacobus et al.,2015). But this was not replicated in other post-cannabis initiation longitudinal studies (Becker et al., 2018). A longitudinal study with pre-and post-initiation cognitive measures suggested that processing speed deficits associated with current, heavy cannabis use resolved after three months of abstinence as former users performed similarly to controls (Fried et al., 2005). Infante and colleagues (2019), who confirmed 24-hour abstinence from cannabis with drug screening before cognitive assessment, did not find a relationship between processing speed and cannabis use. As suggested by Scott et al. (2018), effect sizes for processing speed may diminish when accounting for abstinence length.

When verbal attention was assessed with a list-learn task, evidence was found for deficits in a cannabis and alcohol using group and early-onset cannabis users with three weeks abstinence compared to controls (Jacobus et al., 2015). A twin study found

evidence for an association between initial learning on a list-learning task, but this relationship was attenuated when accounting for propensity to use alcohol (e.g., risk factors for later substance use; Malone et al., 2021). Conversely, longitudinal studies using a digit-span task found no evidence of deficits in cannabis users (Becker et al., 2018; Fried et al., 2005; Jacobus et al., 2015) or associations with the age of initiation (Castellanos-Ryan et al., 2017), frequency of use in the last year (Castellanos-Ryan et al., 2017; Infante et al., 2019), or cumulative use (Schaefer et al., 2021). In a younger, more moderately using sample of twins, Meier et al. (2018) found pre-exposure IQ accounted for the relationship between cannabis dependence and a sustained attention task using digit sequences.

Verbal working memory deficits were evidenced in a group of alcohol and marijuana users, followed post-initiation of cannabis use, compared to controls (Jacobus et al., 2015). However, pre-initiation performance accounted for differences between cannabis users and control subjects in another study (Fried et al., 2005). In line with this, no associations were found between frequency of use or cumulative use and verbal working memory performance (Castellanos-Ryan et al., 2017; Schaefer et al., 2021); however, early-onset, regular cannabis users (typically with use before age 15) demonstrated deficits compared to never-users in a large longitudinal study (Mahedy et al., 2021), but the covariate for alcohol use may have under-represented alcohol exposure levels as it characterized alcohol use as whether or not an individual had a “whole drink” prior to age 13.

Relatively few longitudinal studies have focused on visuospatial attention. When assessed over a short follow-up period from age 14 to 19, no differences were

demonstrated between cannabis users and controls (Wendel et al., 2021), consistent with a previous investigation (Fried et al., 2005). In a longitudinal study with more follow-ups, poorer performance on a spatial span task was related to both cannabis dependence and frequency of cannabis use in the past year. However, differences in performance were not demonstrated between twins discordant for cannabis use, which was not consistent with a causal effect of cannabis use on visuospatial attention (Meier et al., 2018).

Mixed findings emerged for visuospatial working memory. In post-cannabis initiation cohort studies, young adult cannabis users demonstrated poorer efficiency on a visuospatial working memory task compared to controls (Becker et al., 2018), and in a sample of school-age children, cannabis use predicted impairment on a working memory task assessed one year later (Morin et al., 2019). However, worse visuospatial working memory performance at earlier time points also conferred risk for greater substance use in subsequent follow-up years. In their twin analyses, Meier et al. (2018) found differences in performance on a spatial span working memory task between twins discordant for frequency of cannabis use in the previous year, but twins discordant for cannabis dependence did not evidence differences in working memory performance. It may be that visuospatial working memory performance both confers risk for later substance use behaviors and could be adversely impacted by cannabis exposure, although other longitudinal studies found no association between visuospatial working memory and cannabis user status, frequency of use in the past six months, or age of initiation (Wendel et al., 2021; Ross et al., 2020).

Longitudinal investigations of decision-making tended to cover tighter age ranges beginning somewhat later in adolescence. In a cohort study following college students

post-cannabis initiation, cannabis users demonstrated deficits in risky decision-making at their baseline assessment compared to controls, but not at their 2-year follow-up assessment, which the authors attributed to possible recovery of function with reduced use or behavioral tolerance with regular use (Becker et al., 2018). In a sample of adolescent males followed for a longer period from age 13 to 20, past-year cannabis use frequency reported at age 14 predicted declines in performance on a reward-based decision-making task, which appeared to persist even with a year of abstinence (Castellanos-Ryan et al., 2017). Other studies with shorter follow-up periods (e.g., two years and five years, respectively) found no relationship between decision-making and cannabis use (Pacheco-Colón et al., 2021; Wendel et al., 2021). Longer follow-up periods may be needed to assess the full extent of the association between cannabis use and decision-making in adolescents and young adults.

In school-aged children, individuals more likely to use cannabis showed worse inhibitory control performance; however, greater cannabis use in a given year was also associated with poor inhibitory control one year later (Morin et al., 2019), suggesting at least some impact of cannabis exposure on cognitive inhibition. Consistent with this, greater mean levels of cannabis use were associated with poorer inhibitory control (Infante et al., 2019), and early-onset, regular cannabis users had a lower mean performance on a response inhibition task (Mahedy et al., 2021). In their twin study, Ross and colleagues (2020) found potential evidence for an exposure-related effect of frequency of cannabis use in the past six months reported at age 17 and worse scores on a summary score of executive functioning, which accounted for cognitive inhibition; however, no other relationships were consistent with an exposure-related effect.

Conversely in a recent sibling study, Ellingson and colleagues' (2021) results suggested that familial factors associated with greater cannabis use were associated with poorer inhibitory.

In an often-cited study, Meier and colleagues (2012) examined the association between cannabis dependence and intelligence scores in a large longitudinal study following individuals from early adolescence and well into adulthood. Results revealed that cannabis dependence was associated with a decline in intelligence scores from age 13 to 38. Impairments were concentrated in adolescent-onset cannabis users (weekly use or cannabis dependence before age 18), with more persistent use associated with greater decline. Other studies have demonstrated similar declines in intelligence scores in adolescent and young adult cannabis users (Boccio & Beaver, 2017) and poorer performance on a perceptual reasoning task with greater mean levels of percent days of cannabis use (Infante et al., 2019). Prior investigations also suggest deficits in intelligence and perceptual reasoning scores with heavier frequencies of cannabis use or early-onset cannabis use but note that deficits appeared transient and may resolve with abstinence (Fried et al., 2005; Infante et al., 2019). However, the causal nature of these associations has been questioned.

Regarding Meier et al.'s (2012) study, critics have suggested that the associations seen were better accounted for by confounding factors such as socioeconomic status (Rogeberg, 2013) or personality factors (Daly, 2013). In response, several twin studies have investigated the relationship between cannabis and general cognitive ability. Twin studies found evidence to suggest that deficits in general cognitive ability scores of cannabis users likely reflect shared familial confounding instead of exposure-related

effects of cannabis use (Jackson et al., 2016; Meier et al., 2018; Schaefer et al., 2021). Similarly, Castellanos-Ryan et al. (2017) found that the association between cannabis use and decline in verbal IQ was accounted for by high school graduation status and Mokrysz and colleagues (2016) found that after covarying for group differences in cigarette smoking, cannabis users no longer differed from non-users on IQ scores. A recent meta-analytic review of longitudinal studies of intelligence found significant associations between frequent or dependent cannabis use in youth and IQ change (Power et al., 2021). The author cited concerns regarding possible confounding; however, they felt that the hypothesis that family-level vulnerability predisposing to IQ decline, while possible, seemed less likely to be fully explanatory (Ellingson et al., 2020; Power et al., 2021).

As demonstrated in the above summary, longitudinal and twin studies to date do not necessarily converge on a single conclusion regarding the relationship between nonacute cannabis use and neurocognitive functioning in youth. However, they concur with the importance of examining the role of confounders, such as pre-exposure IQ, education, socioeconomic status, and other substance use (Castellanos-Ryan et al., 2017; Malone et al., 2021; Meier et al., 2018; Mokrysz et al., 2016). Prior research also highlights the need to use large, longitudinal investigations with multiple follow-ups across both adolescence and young adulthood to better assess nuances of the association between cannabis use and cognition along with abstinence from cannabis (Castellanos-Ryan et al., 2017; Infante et al., 2019; Jacobus et al., 2015; Pacheco-Colón et al., 2019). Evidence can be seen for possible task-dependent effects (Jacobus et al., 2015; Becker et al., 2018; Schaefer et al., 2021), as well as continued reliance on group comparisons (Wendel et al., 2021; Infante et al., 2020) that predominantly focus on the frequency of

use within a constrained period of six months to a year. It will be imperative that future studies consider these factors.

**Influence of sex on vulnerability to adverse cannabis consequences**

An often under-considered factor within the context of cannabis' impact on the brain, developmental processes, and cognition has been the role of sex. Accumulating evidence suggests sex-specific effects of cannabis exposure, including differences in pharmacokinetics and behavioral effects of cannabis compounds (Cooper & Craft, 2018; Ruiz et al., 2021). Animal studies have demonstrated that female rats metabolize THC to its most highly active metabolite, whereas male rats metabolize into multiple compounds (Narimatsu et al., 1991). Cannabinoid receptor type 1 (CB1) density also varies by sex, such that CB1 density, where THC binds in the brain, was greater for males than females (Burston et al., 2010; Mateos et al., 2011). Further, adolescent female rats evidenced greater CB1 desensitization than male rats following THC exposure in brain regions such as the prefrontal cortex and hippocampus (Burston et al., 2010). Different behavioral pictures have emerged within the animal literature as well, such that male rats presented with greater anhedonia while female rats presented with significant behavioral despair (Rubio et al., 2008). Females rats also showed increased locomotor activity after acute THC exposure compared to male rats (Wiley, 2003).

Human studies converge on sex-related differences in the implications of cannabis use as well. For instance, females have been shown to develop less tachycardia than males after smoking (Cocchetto et al., 1981) and may experience greater reinforcement from cannabis use than males (Fattore et al., 2007). Additionally, a telescoping effect has been noted, such that females escalate from initial drug use to compulsive drug-taking

more rapidly than men and enter treatment for cannabis use disorder sooner and after less cannabis use compared to males (Greenfield et al., 2010; Hernandez-Avila et al., 2004). Within the cross-sectional literature on nonacute cannabis use, heavy cannabis-using females performed worse than light cannabis using females on a visuospatial task, but no differences were found between heavy and light cannabis using males (Pope et al., 1997). Other studies of adolescents and young adults have found greater deficits in male cannabis users on measures of memory, processing speed, cognitive flexibility, and decision-making compared to their female counterparts (Crane, Schuster, & Gonzalez, 2013; King et al., 2011; Lisdahl & Price, 2012; Petker et al., 2019; Pope and Yurgelun-Todd, 1996). A recent cross-sectional study in adolescents and young adults found domain-specific sex effects such that females performed worse with an earlier age of initiated use on attention and cognitive switching tasks than males, but more cannabis use was associated with worse memory in males than females (Savulich et al., 2021). However, other studies report no sex-specific effects (Solowij et al., 2011). Few longitudinal studies reported examining sex-specific effects of cannabis on cognition in adolescents and young adults but did not find evidence for an interaction between sex and cannabis use (Fried et al., 2005; Meier et al., 2018; Tait et al., 2011).

Neurodevelopmental considerations need to be made when understanding the implications of sex-specific effects of cannabis exposure. Trajectories of neurodevelopment vary by sex in that females typically undergo earlier neuromaturation than males (Lenroot et al., 2007; Giedd et al., 1999). In females, total brain size typically peaks between 10 and 11 years of age, whereas total brain size peaks somewhat later at 14 to 15 years of age in males (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Lenroot

et al., 2007). Additionally, gray matter volume in the prefrontal cortex has been found to peak one to two years earlier in females than males, while males demonstrated greater age-related increases in white matter (Giedd et al., 1999). The endocannabinoid system plays a critical role in normal neurodevelopment and mediates processes, such as synaptogenesis, immune processes, and memory formation, and may be sensitive to alterations caused by exogenous cannabinoids, such as THC (Atkinson & Abbott, 2018).

As such, sex differences in neuromaturation may create a variable environment for THC exposure to occur and thus, depending on the timing of exposure, could result in further differentiation of cannabis consequences. Preliminary evidence within humans supports this assertion. Specifically, a cross-sectional study of young adult regular cannabis users found that an earlier age of regular initiated use was related to poorer episodic memory in females but not in males (Crane et al., 2015). Taken together, research suggests a unique relationship regarding the sex-specific effects of cannabis use on cognitive functioning and biological mechanisms. This area warrants further consideration, particularly in longitudinal studies, given the paucity of research.

**Purpose and strengths of the current study**

The aim of the current project was to assess the robustness of the relationship between nonacute cannabis use during adolescence and young adulthood and young adult neurocognitive function and examine nuances that may confer additional risk for adverse outcomes. Focus was placed on addressing the aforementioned gaps in the literature, including third variable confounding and over-reliance on discrete group comparisons with a narrow focus of cannabis use behaviors, sex-specific effects, and persistence of deficits with abstinence.

We were well situated to address these gaps for several reasons: a) we used a large, population-based longitudinal sample of males and females with multiple, comprehensive follow-up assessments over the critical neurodevelopmental period of adolescence to young adulthood and peak substance use (Johnston et al., 2021); b) using this longitudinal dataset, we computed continuous measures of cumulative cannabis use (cannabis index), lifetime heaviest frequency, and age of cannabis initiation, using information from multiple timepoints, likely reducing measurement error of retrospective reporting; c) in addition to an extensive neurocognitive battery assessed at the most recent follow-up (age 24), intelligence was assessed at intake prior to exposure to cannabis, establishing baseline cognitive abilities; d) assessment waves included comprehensive interviewing regarding psychosocial, environmental, and participant specific factors that have been identified in the literature as relating to nonacute cannabis use and cognition, which included socioeconomic status (Mills et al., 2019; Peters et al., 2018), education (Esch et al., 2014; Silins et al., 2015), alcohol and nicotine use (Agrawal et al., 2004; Malone et al., 2021), recent cannabis use (Curran et al., 2020; Kroon et al., 2021) and time since last use of cannabis (Fried et al., 2005; Scott et al., 2018; Schreiner & Dunn, 2012).

We included measures for cognitive domains previously shown to be associated with cannabis use in either the cross-sectional or longitudinal literature as noted above, including verbal learning and memory, processing speed, decision-making, verbal attention and working memory, visuospatial attention and working memory, cognitive inhibition, and general cognitive abilities. The extensive neurocognitive battery was particularly advantageous for examining domains under-represented in the longitudinal

literature with pre-exposure measures of cognitive ability (e.g., visuospatial attention, processing speed, decision-making, cognitive inhibition).

Differential risk for poor neurocognitive outcomes related to cannabis exposure may be conferred based on an individual's sex. Age of cannabis onset, in particular, may interact with sex producing differential effects depending on the timing of use given discrepant neurodevelopmental trajectories of males and females (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013). To the best of our knowledge, sex-specific effects have not yet been explored for cumulative cannabis use across both adolescence and young adulthood or age of initiation on cognitive outcomes within the adolescent or young adult longitudinal literature. Prior literature identified sex and its association with cannabis use as an area for further consideration given the limited research (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Figueiredo et al., 2020; Greaves, 2020), which we investigated within this project.

Given our goal of understanding nuances of the association between cannabis use and cognition, as an exploratory analysis, we assessed for unique effects of lifetime heaviest frequency ever used within cannabis users, excluding non-users. There may be factors specific to cannabis users that could influence cognitive outcomes or patterns of cannabis use (Harvey et al., 2007; Pope et al., 1997); however, this has yet to be explored in the longitudinal literature using dimensional measures of cannabis use.

**Hypotheses given the current state of the literature**

Based on the above-summarized literature, we hypothesized that greater overall cannabis exposure, higher lifetime heaviest frequencies, and an earlier age of cannabis initiation would be associated with poorer neurocognitive outcomes. Between the cross-

sectional and longitudinal literature of adolescent and young adult research, deficits most consistently arose in the domain of verbal learning and memory with more modest evidence for impaired decision-making, processing speed, and cognitive inhibition. There is mixed evidence or uncertainty regarding temporal sequencing of deficits, suggesting possible reverse causation, for the domains of verbal attention and working memory, visuospatial attention and working memory, and general cognitive abilities.

While the importance of covarying for relevant factors is evident, the exact role that our confounding variables of pre-exposure IQ, socioeconomic status, alcohol and nicotine use, education, and recent cannabis use will play in the relationship between our cannabis variables and each of our cognitive outcomes. However, broadly, we hypothesized that our confounders would likely attenuate effect sizes, if not wholly moderate, some of the effects between cannabis use and cognitive outcomes.

Several neurobiological differences suggest sex-specific effects may emerge with cannabis use, which is broadly supported within the human and animal literature. The exact pattern of such effects is unclear given the paucity of research for cannabis use on cognition. As such, we anticipate finding sex-specific effects; however, it is unclear the exact pattern that may emerge regarding if males or females may be at a greater risk for deficits. Sex-specific deficits may also be domain specific (Savulich et al., 2021). Prior research has been inconsistent regarding how abstinence from cannabis impacts the relationship between cannabis use and cognition, and as such, we do not have a specific hypothesis regarding the implications of the length of abstinence. As stated above, our investigation for effects unique to cannabis users was exploratory, and, as such, we do not have a specific hypothesis for results.

# Methods

## Sample

Participants were same-sex twins drawn from the Enrichment Study (ES) of the Minnesota Twin Family Study. See Keyes et al. (2009) and Wilson et al. (2019) for a detailed overview of inclusion/exclusion criteria and study design. Intake was conducted at age 11, and subsequent follow-up assessments were administered at ages 14, 17, and 24. Assessments at each study wave included a comprehensive, multimodal battery of clinical interviews, questionnaires, and cognitive assessments conducted by trained assessors. Information was also collected from biological and stepparents across assessments.

Of the original 998 twins recruited at the age-11 intake, 81% (n = 809) participated in the most recent age-24 follow-up in some capacity. Twin participation at the age-24 assessment was not uniform across all neurocognitive measures due to various logistic factors, such as time constraints during interviewing or impractical travel distances to participate in-person that necessitated phone interviews (n = 111). Eight individuals who reported a history of cannabis exposure on their age-11 intake questionnaires were excluded.

The final sample size consisted of 801 twins, and task-dependent sample sizes ranged from 666 to 794. Sample sizes for models will be presented in tables detailing initial model statistics. Approximately 60% of participants were monozygotic twins, and 55% were female, with a mean age of 24.43 (SD: 0.91) at the most recent follow-up assessment. Twins were asked to refrain from all substance use for 24-hours before their age-24 follow-up; however, participants were not excluded if they reported use during

this period. Sixty-four participants reported cannabis use in the 24-hours preceding their age-24 follow-up assessment, and recent use was subsequently explored in follow-up analyses as a covariate of interest.

**Substance use**

Substance use was assessed at ages 11, 14, and 17 using a Computerized Substance Use (CSU; McGue et al., 2014) questionnaire and a revised version of the drug supplement from the Diagnostic Interview for Children and Adolescents - Revised (DICA-R; Reich, 2000; Welner et al., 1987). A modified version of the Substance Abuse Module (SAM; Robins et al., 1987) from the Composite International Diagnostic Interview (CIDI; Robins et al., 1988) was used to assess substance use at ages 17 and 24. The CSU, DICA, and the expanded version of the SAM assess for information, such as the number of intoxications, frequency (past 12 months) and quantity of use (since last assessment), heaviest frequency, and age of initiation of substance use.

***Cannabis use***

Six variables were used to capture cannabis use behaviors. Two of these variables (frequency of cannabis use (past 12 months) and the number of uses (since last assessment)) were integrated across follow-up assessment waves (i.e., 14, 17, and 24) to form a single cumulative measure of cannabis exposure across adolescence to young adulthood (cannabis index). Combining measures and collapsing across adolescence to young adulthood, we encompassed exposure more thoroughly than a single measure that narrowly focuses on a brief window of time (e.g., six months to a year). The validity of the methods used to derive the cannabis index (described below) were supported by comparable studies that explored implications of common substance use behaviors

(Harper et al., 2021; Malone et al., 2021; Schaefer et al., 2021; Wilson et al., 2017). The other three variables (lifetime heaviest frequency, age of initiation, past 24-hour use, time since last use) were examined individually. Our primary cannabis variables of interest were the cannabis index, lifetime heaviest frequency, and age of initiation. Past 24-hour use (recent use) and time since last use (length of abstinence) were used in subsequent follow-up analyses as covariates.

*Cannabis index.* To obtain our cannabis index, which characterized cumulative cannabis exposure from adolescence to young adulthood, separate cannabis indices were first calculated for each follow-up wave (i.e., 14, 17, and 24) by averaging two items: (1) frequency of use in the past 12 months, and (2) number of times used since last assessment. Due to skew and spareness, we transformed responses of frequency and number of uses into ordinal measures before averaging these two items, with six categories per item. For frequency of use in the past 12 months, categories included: 0 (no use), 1 (<1x/month), 2 (1-3x/month), 3 (1-4x/week), 4 (every day or nearly every day), or 5 (>1x/day). For number of uses since last assessment, categories included: 0 (no use), 1 (1-4 uses), 2 (5-30 uses), 3 (31-100 uses), 4 (101-400 uses), or 5 (>400 uses or "too many to count"). After we obtained individual indices for each follow-up assessment wave, we then computed our cannabis index by averaging each of the separate indices into a single composite measure to summarize overall exposure from adolescence to young adulthood. We did not include the age-11 intake when computing the cannabis index as we had purposefully excluded individuals who had used cannabis before their intake assessment and, as such, age-11 cannabis use was zero for all participants.

*Lifetime heaviest frequency.* Participants were asked to think about their period of heaviest use either in their lifetime (age 17) or since their last assessment (asked at age 24) and report the frequency of their cannabis use during that period of heaviest use. To obtain a measure of heaviest frequency ever used over a participant's lifetime (i.e., from birth to age 24), we took the max value reported at either their age-17 or age-24 evaluation. Like procedures used for our cannabis index, we transformed the lifetime heaviest frequency variable into an ordinal measure containing six categories to reduce skew and spareness of responses. Categories included: 0 (no use), 1 (<1/year), 2 (>1x/year to 2-3x/month), 3 (1-2x/week to nearly every day), 4 (1-2x/day), 5 (≥3x/day).

*Age of initiation.* For our purposes, age of initiation was defined as the first exposure to cannabis regardless of the amount used. To obtain this value, we asked participants how old they were when they first tried marijuana at each assessment wave. We used the age of initiation reported at the earliest assessment wave as this provided the most proximal report of cannabis use behaviors to when use occurred and would likely reduce the impact of retrospective recall error.

*Other cannabis covariates.* A binary measure was used to evaluate for recent cannabis use to characterize if the person had (coded as 1) or had not (coded as 0) used cannabis in the 24-hours preceding their age-24 evaluation. To account for the length of abstinence, at their age-24 assessment, we assessed for the length of time since the participants had last used cannabis. Categories to characterize the length of abstinence included: 1 (within the last 2 weeks), 2 (2 weeks to <1 month), 3 (1 month to <6 months), 4, (6 months to <1 year), 5 (within the last year but don't know exactly when), and 6 (1 year or more ago).

***Other substance use***

As other substance use has been found to influence or attenuate the relationship between cannabis use and cognitive outcomes (Gonzalez et al., 2017; Ross et al., 2020), indices summarizing alcohol and nicotine use assessed at the age-24 follow-up were also computed. Calculations mimicked the above-described procedures for creating the cannabis indices and followed the methodology used in previous investigations (Harper et al., 2021; Malone et al., 2021; Wilson et al., 2017). Using indices summarizing alcohol and nicotine exposure at the age-24 follow-up allowed us to capture proximal use, likely during participants' heaviest use period, providing a more substantial control for alcohol and nicotine behaviors than if individual variables were used.

*Alcohol index.* The alcohol index calculated at the age-24 follow-up consisted of four items: (1) number of drinks typically consumed per occasion since the last assessment (0 = none to 6 = 30+), (2) frequency of drinking since the last assessment (0 = never to 5 = 2+ times per day), (3) maximum drinks consumed in a 24-hour period since last assessment (0 = none to 6 = 30+), and (4) number of times intoxicated in lifetime (0 = never to 6 = 150+ times). Similar to the cannabis indices, we transformed responses into ordinal measures, with six to seven categories per item due to skew and sparseness; items were averaged to form a single index of alcohol use at age-24.

*Nicotine index.* The nicotine index at the age-24 follow-up consisted of two items: (1) number of days in a typical month used tobacco in the past 12 months (0 = none to 2 = 15-30 days per month) and (2) quantity of tobacco used in a typical day in the past 12 months (0 = none to 3 = 20+). The quantity of tobacco used in a typical day was the sum of four individual items on the number of cigarettes, cigars, and pipes smoked and the

number of chews used. As with the other substance indices, we transformed responses into ordinal measures, with three to four categories per item, and items were averaged to form a single index of nicotine use at age-24.

**Neurocognitive battery**

Neurocognitive measures included test of (1) *verbal learning and memory:* Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996); (2) *processing speed*: Wechsler Adult Intelligence Scale-III Processing Speed Index, Digit Symbol-Coding, Symbol Search (WAIS-III; Wechsler, 1997); (3) *verbal attention and working memory*: RAVLT Trial 1 (Schmidt, 1996), WAIS-III Longest Digit Span Forward/Backward (Wechsler, 1997); (4) *visuospatial attention and working memory*: Longest Spatial Span Forward/Backward (Wechsler, 1997); (5) *decision-making*: Iowa Gambling Task (IGT; Bechara et al., 1994); (6) *cognitive inhibition*: Go/No-Go Task (Roche, Garavan, Foxe, & O'Mara, 2005); (7) *general cognitive ability*: Wechsler Adult Intelligence Scale-Revised (WAIS-R) Prorated Full Scale IQ (FSIQ), Block Design, Vocabulary (Wechsler, 1981). These measures are summarized in Table 3 along with variables obtained from each measure. Please see the general study characteristics section for full task descriptions.

**Additional covariates**

***Age-11 intelligence quotient (IQ)***

Pre-exposure IQ was assessed at intake (age 11) utilizing the revised Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1981). Pre-exposure IQ was derived from performance on the block design, picture completion, vocabulary, and information subtests of the WISC-R and estimated following WISC-R prorated scoring procedures for IQ.

### *Socioeconomic status (SES)*

A single composite measure of parental socioeconomic status was derived from information provided by twins' parents and stepparents at intake. The parental socioeconomic status variable reflected the mean of four standardized scores, including highest parent occupational status, mother's and father's highest degree, and household income.

### *Years of education*

Education for each participant was defined as the number of academic school years of formal education successfully completed at the time of their age-24 assessment.

## Statistical Analysis

### *Preliminary analyses: attrition and multicollinearity*

Because ES participants were followed over an extended period, attrition from the sample is to be expected. As such, we examined for differences between our sample of age-24 participants (n = 801) and age-24 non-participants (n=189) on relevant intake variables (sex, age, zygosity, socioeconomic status, pre-exposure IQ). As there was minimal to no substance use at intake in either the participant or non-participant group, we examined differences in cannabis use between age-24 participants and non-participants at their first follow-up assessment (age 14) as this provided the closest approximation in terms of sample to individuals who participated at the intake assessment (participants: n = 772, non-participants: n=158). Cluster robust group comparisons using a sandwich estimator for the standard errors were conducted in R using coef_test from the "clubSandwich" package with a Satterthwaite approximation (Pustejovsky, 2017). A chi-square test was conducted in R using the "stats" package to examine attrition bias for sex

(R Core Team, 2020). We ran zero-order correlations between our primary cannabis use variables and covariates. We expected that our covariates would be significantly correlated with our cannabis use variables as covariates were chosen based on previous literature demonstrating a relationship with cannabis use behaviors. Because of this correlation, including these covariates in our subsequent analyses could impact standard errors through collinearity. Generalized variance-inflation factors, adapted for linear mixed models using the corvif function in R (Zuur et al., 2009), were calculated for our predictor variables to examine concerns for collinearity.

***Associations between cannabis use and cognitive performance***

Linear mixed models (LMMs) were conducted in R using lmer from the "lme4" package (Bates et al., 2015) with denominator degrees of freedom adjusted by Kenward-Roger approximation from the lmerTest package (Kuznetsova et al., 2017). Random intercepts were included at the twin-pair level to account for within-pair correlations. All models included participant age, sex, and zygosity as covariates. Initial LMMs evaluated the relationship between each of the above-described age-24 cognitive outcomes and our primary cannabis use variables of interest: cannabis index, heaviest frequency, and age of initiation. Note that the no-go error rate and ambiguous decision-making measures were square-root transformed before LMM analyses to correct for positive skew.

***Exploration of relevant covariates***

Subsequent analyses explored for factors influencing the observed associations between our cannabis use variables and cognition and rule out other alternative explanations for significant effects. These analyses allowed us to examine the robustness of the relationships between cannabis and cognition and explore if findings were uniquely

associated with cannabis use above other confounds. Zero-order correlations were first conducted between our primary covariates and cognitive outcomes to demonstrate relevance for our covariate analyses. Planned follow-up analyses then investigated possible confounding of pre-exposure IQ and parental SES (step 1), then other common substance use (i.e., alcohol and nicotine use; step 2), years of education (step 3), and finally recent cannabis use (step 4) by including them as covariates in iterative LMMs. Given changes in the pattern of findings when including these variables as covariates, they were carried forward to all subsequent analyses reported in this study.

***Sex-specific effects of cannabis use on neurocognitive performance***

Males and females may be differentially susceptible to adverse effects associated with cannabis exposure for several neurobiological reasons. We first assessed for sex differences in neurocognitive performance using cluster-robust group comparisons to assess if males and females performed differently on our cognitive outcomes. LMMs were then conducted with a cannabis use variable by sex interaction term included. For variables that demonstrated significant effects, LMMs were run in males and females separately to examine the pattern of effects in each sex. Significant findings in either males or females were carried forward through follow-up analyses.

***Isolating impact of age cannabis of initiation from other cannabis use behaviors***

It can be challenging to disentangle the impact of age of cannabis initiation from effects related to quantities or frequencies of cannabis use as individuals who begin using earlier tend to report larger quantities and higher frequencies of cannabis use. In particular, early-onset cannabis users typically escalate to greater cannabis use later in life (Pacheco-Colón et al., 2021). It may be that heavier patterns of cannabis use are more

relevant than the age at which initial exposure occurred, so we attempted to disentangling these variables. Isolating the role of age of initiation was approached in two ways. First, significant effects demonstrated in our previous analyses between the age of initiation and cognitive performance were re-run with the cannabis index from the most recent assessment (age-24 cannabis index) as a covariate, accounting for both quantity and frequency of use and more proximal exposure during peak substance use periods. Second, if another of our cannabis variables of interest (i.e., cannabis index, lifetime heaviest frequency) demonstrated similar findings to our age of initiation variable, LMMs were conducted with both variables included to investigate if one variable would rise above the other to predict findings.

***The role of abstinence on cannabis use and cognitive outcome associations***

Whether or not deficits associated with cannabis use resolve over time have significant functional and policy implications. We assessed the role of abstinence from cannabis in two ways. First, LMMs were run exploring the relationship between our measure of the length of abstinence from cannabis use and any of our cognitive variables that demonstrated significant relationships with our primary cannabis use variables. Second, cluster-robust group comparisons were conducted comparing the cognitive performance of individuals with less than a month of abstinence from cannabis (n = 173) and those with at least one year of abstinence (n = 222) to compare performance at the extremes of abstinence length to see if differences emerged.

***Unique relationships within cannabis users***

We focused a set of LMM analyses specifically on lifetime heaviest frequency in cannabis users to examine for unique relationships within cannabis users that may be

obscured when including individuals with extremely minimal to no exposure. Analyses explored relationships between our lifetime heaviest frequency variable and our cognitive outcomes in a subsample excluding individuals that had used less than five times in their lifetime, which was consistent with several prior studies definitions for characterizing non-users (Epstein et al., 2015; Hanson et al., 2010; Lamers et al., 2006; Medina et al., 2007; Padula et al., 2007; Solowij et al., 2012; Tapert et al., 2007; Winward et al., 2014).

## Results

Descriptive statistics for demographic and substance use variables are presented in Table 1. Cannabis use across assessments and demographic breakdown broadly mimicked national patterns, such that cannabis use increased with age, and males used more heavily than females (Johnston et al., 2021). Males also used more alcohol and nicotine than females at their age-24 assessment, which is consistent with expectations based on national patterns. Cannabis exposure was prevalent in our sample, with 29% of participants endorsing some use by their age-17 assessment and 63% endorsing use by their age-24 assessment.

### Preliminary analyses

Age-24 assessment participants and non-participants did not significantly differ in age or zygosity (*ps* > 0.47). Age-24 non-participants were more likely to be male ($\chi^2$ (1) = 11.57, $p < 0.01$), have a lower parental socioeconomic status (Estimate [SE] = 0.38 [0.08], $t = 4.92$, $p < 0.01$), and lower pre-exposure IQ scores (Estimate [SE] = 6.18 [1.36], $t = 4.56$, $p < 0.01$). However, the overall distribution for pre-exposure IQ for age-24 participants was still normally distributed, encompassing the lower tail of the distribution (*range* = 64 to 150; *lower quartile mean* = 87.26). The sample mean and

standard deviation ($M$ = 104.04, $SD$ = 12.75) were similar to a typical distribution for standard scores (e.g., mean of 100, standard deviation of 15; see Figure S2 for distribution of pre-exposure IQ scores for age-24 participants). Further, we observed no significant associations between cannabis use (either cannabis index scores or age of initiation) at the age-14 assessment wave and contributing data to the most recent age-24 follow-up ($ps > 0.11$). As expected, at least one of our three cannabis use variables was significantly correlated with each of our covariates ($ps < 0.05$; see Table 4 for correlations between primary cannabis variable and covariates), except participant age. The cannabis index and lifetime heaviest frequency were strongly correlated ($r = 0.85$, $p < 0.01$) and were not examined in joint models to avoid collinearity. Otherwise, all GVIF values were below 2 for our primary cannabis use variables, below conservative cut-offs of 2.5 for GVIF values (Kock & Lynn, 2012; Petker et al., 2019).

**Associations between cannabis use and cognitive performance**

We assessed the relationship between our three primary cannabis use measures of interest and young adult cognitive outcomes. Performance measure descriptive statistics can be found in Table 2, and statistics for initial linear mixed model effects of our cannabis variables and cognitive outcomes (discussed in this section) are summarized in Table 5.

*Verbal learning and memory.* No significant effects were demonstrated between our three cannabis variables and total learning, short-delay recall, and long-delay recall scores ($ps \geq 0.11$).

*Processing speed.* Age of cannabis initiation was significantly associated with all three of our processing speed variables, including the processing speed index (Estimates

(SE) = 0.95 (0.23), $t$ = 4.30, $p$ < 0.01), digit symbol-coding (Estimates (SE) = 0.18 (0.04), $t$ = 4.09, $p$ < 0.01), and symbol search (Estimates (SE) = 0.17 (0.04), $t$ = 3.74, $p$ < 0.01), such that an earlier age of initiation predicted worse performance in all cases. Higher cannabis index scores were also associated with poorer performance on digit symbol-coding (Estimates (SE) = -0.28 (0.11), $t$ = -2.56, $p$ = 0.01) and lower processing speed index scores; however, this later finding just missed significance (Estimates (SE) = -1.05 (0.55), $t$ = -1.91, $p$ = 0.06). A significant association was not found between our cannabis index and symbol search performance ($p$ = 0.34), and lifetime heaviest frequency did not predict performance on any of our measures of processing speed ($ps \geq$ 0.14).

*Verbal attention and working memory.* Consistent with prior research, differences in the relationship between our verbal attention measures and cannabis use appeared task dependent. Specifically, all three cannabis use variables evidenced a significant relationship with our initial list-learning task (RAVLT trial 1), such that higher cannabis index scores and lifetime heaviest frequency, and an earlier age of onset were associated with recalling fewer words on an the first trial of a list-learning task (*cannabis index*: Estimates (SE) = -0.18 (0.07), $t$ = -2.57, $p$ = 0.01; *lifetime heaviest frequency*: Estimates (SE) = -0.09 (0.04), $t$ = -2.31, $p$ = 0.02; *age of initiation*: Estimates (SE) = 0.06 (0.03), $t$ = 2.08, $p$ = 0.04). In contrast, higher cannabis index scores and lifetime heaviest frequency, but not age of initiation ($p$ = 0.40), predicted better performance on longest digit span forward (*cannabis index*: Estimates (SE) = 0.11 (0.05), $t$ = 2.18, $p$ = 0.03; *lifetime heaviest frequency*: Estimates (SE) = 0.06 (0.03), $t$ = 2.32, $p$ = 0.02). No

significant relationships were demonstrated between our cannabis use variables and longest digit span backward (*ps* $\geq$ 0.34)

*Visuospatial attention and working memory.* Several significant associations were demonstrated between our visuospatial attention and working memory variables and cannabis use measures. Higher cannabis index scores and lifetime heaviest frequency, and an earlier age of initiation all predicted poorer performance on our visuospatial attention and working memory measure (longest spatial span forward: [*cannabis index*: Estimates (SE) = -0.09 (0.05), *t* = -1.97, *p* = 0.05; *age of initiation*: Estimates (SE) = 0.07 (0.02), *t* = 3.59, *p* < 0.01]; longest spatial span backwards: [*cannabis index*: Estimates (SE) = -0.13 (0.05), *t* = -2.43, *p* = 0.02; *lifetime heaviest frequency*: Estimates (SE) = -0.07 (0.03), *t* = -2.29, *p* = 0.02; *age of initiation*: Estimates (SE) = 0.05 (0.02), *t* = 2.28, *p* = 0.02]). The only exception was that the relationship between lifetime heaviest frequency and longest spatial span forward did not reach significance, though it demonstrated a similar pattern of findings (Estimates (SE) = -0.03 (0.03), *t* = -1.26, *p* = 0.21).

*Decision-making.* Our cannabis use variables were also highly associated with decision-making performance, such that higher cannabis index scores and lifetime heaviest frequency, and an earlier age of initiation all significantly predicted poorer performance on our three decision-making variables (DM overall: [*cannabis index*: Estimates (SE) = -3.16 (1.47), *t* = -2.15, *p* = 0.03; *lifetime heaviest frequency*: Estimates (SE) = -2.60 (0.80), *t* = -3.27, *p* < 0.01; *age of initiation*: Estimates (SE) = 1.58 (0.61), *t* = 2.58, *p* = 0.01]; DM ambiguity: [*lifetime heaviest frequency*: Estimates (SE) = -0.05 (0.02), *t* = -2.23, *p* = 0.03; *age of initiation*: Estimates (SE) = 0.05 (0.02), *t* = 2.37, *p* =

0.02]; DM risk: [*cannabis index*: Estimates (SE) = -2.40 (1.16), $t$ = -2.07, $p$ = 0.04; *lifetime heaviest frequency*: Estimates (SE) = -2.05 (0.63), $t$ = -3.25, $p < 0.01$; *age of initiation*: Estimates (SE) = 1.07 (0.48), $t$ = 2.23, $p$ = 0.03]). The only relationship that did not reach significance was between our cannabis index and decision-making under ambiguity, but it showed a similar pattern of effects (Estimates (SE) = -0.07 (0.04), $t$ = -1.61, $p$ = 0.11).

*Cognitive inhibition.* Only age of initiation was significantly associated with performance on our measure of cognitive inhibition (*d-prime:* Estimates (SE) = 0.05 (0.02), $t$ = 3.07, $p < 0.01$; *no-go error rate*: Estimates (SE) = -0.08 (0.03), $t$ = -3.16, $p < 0.01$), with poorer overall ability to inhibit responses and higher error rates occurring with an earlier age of initiation. Associations between our cannabis index and lifetime heaviest frequency variables and our measures of cognitive inhibition did not reach significance ($p \geq 0.08$).

*General cognitive ability.* Of our cannabis use variables, the strongest predictor of general cognitive ability scores was age of cannabis initiation. Cannabis users reporting an earlier age of initiation had lower prorated FSIQ scores (Estimates (SE) = 1.45 (0.27), $t$ = 5.48, $p < 0.01$), and poorer performance on block design (Estimates (SE) = 0.22 (0.05), $t$ = 4.71, $p < 0.01$) and vocabulary tasks (Estimates (SE) = 0.17 (0.04), $t$ = 4.67, $p < 0.01$). Higher cannabis index scores were also related to poorer performance on block design (Estimates (SE) = -0.23 (0.12), $t$ = -1.95, $p$ = 0.05) and the relationship with lower prorated FSIQ scores just missed significance (Estimates (SE) = -1.29 (0.68), $t$ = -1.91, $p$ = 0.06). However, our cannabis index was not related to vocabulary performance ($p$ =

0.16) and all associations with lifetime heaviest frequency were not significant (*ps* ≥ 0.39).

*Summary.* Several significant associations were evidenced in initial LMMs between our cannabis use variables and cognition, particularly with age of initiation. Specifically, an earlier age of initiation predicted poorer performance across all tasks, except for RAVLT (total learning, short- and long-delay recall) and digit span measures. Both greater cannabis index scores and higher lifetime heaviest frequencies were associated with RAVLT trial 1, longest spatial span backward and overall and risky decision-making. Greater cannabis index scores were also significantly related to worse digit-symbol coding and block design performance, and higher lifetime heaviest frequencies predicted poorer decision-making under ambiguity. Better performance with greater cannabis use was demonstrated on only one task (longest digit span forward). No other associations suggested better performance in cannabis users.

**Covariate analyses**

Zero-order correlations are presented in Table 6 to assess relationship between our primary covariates and cognitive outcomes. Of note, higher pre-exposure IQ, SES, and education significantly predicted better performance on almost all cognitive tasks. Four sets of iterative linear mixed models were conducted for each cannabis use variable by cognitive measure combination to explore the robustness of associations to covariates. Covariates included pre-exposure IQ and SES (*step 1)*, other common substance use (alcohol/nicotine; *step 2*), years of education (*step 3)*, and recent cannabis use (*step 4*). Covariates were carried forward to subsequent models, such that step 4 included all covariates. Table 7 presents statistics for cannabis effects on cognitive outcomes

following each iterative step (e.g., 1 through 4) and are organized into sections by cognitive domain. Each section will be summarized below with references to the corresponding section of Table 7.

*Verbal learning and memory (Table 7 section A).* There was little evidence of deficits on total learning, short-delay recall, or long-delay recall measures with greater cannabis index scores, lifetime heaviest frequency, or an earlier age of initiation. Results showed a positive relationship between the cannabis index and short-delay recall; however, this was only significant after inclusion of recent cannabis use, which negatively predicted short-delay recall performance (Estimates (SE) = -0.64 [0.29], $t$ = -2.23, $p$ = 0.03). No other associations were significant.

*Processing speed (Table 7 section B).* An earlier age of initiation continued to predict poorer scores on digit symbol-coding, symbol search, and the processing speed index after accounting for pre-exposure IQ/SES (step 1) and alcohol/nicotine use (step 2). These associations were attenuated after accounting for education ($ps \geq 0.06$; step 3) with little change after covarying for recent cannabis use, although the relationship with symbol search performance hovered near significance (Estimates (SE) = 0.09 (0.05), $t$ = 1.77, $p$ = 0.08). The association between higher cannabis index scores and lower digit-symbol coding scores followed a similar pattern remaining significant after accounting for pre-exposure IQ, SES, alcohol, and nicotine but were significantly diminished after accounting for education ($p$ = 0.42) and recent cannabis use ($p$ = 0.83). No significant relationships were demonstrated between the cannabis index and symbol search or processing speed index scores, except that the cannabis index predicted processing speed index scores after covarying for pre-exposure IQ/SES (step 1). However, this association

was not significant in any subsequent steps and was significantly attenuated after the inclusion of education and recent cannabis use (*ps* ≥ 0.42). Lifetime heaviest frequency was associated with digit-symbol coding only after accounting for pre-exposure IQ/SES, but this association was no longer significant in successive steps (e.g., steps 2, 3, or 4); otherwise, consistent with initial models, lifetime heaviest frequency did not significantly predict performance on symbol search or lower scores on the processing speed index (ps ≥ 0.18).

*Verbal attention and working memory (Table 7 section C).* Greater cannabis index scores and lifetime heaviest frequency continued to be associated with learning fewer words on the first trial of the RAVLT after accounting for pre-exposure IQ/SES and alcohol and nicotine use *(ps* < 0.03*)*. However, they were drastically attenuated when including education (ps ≥ 0.20) and recent cannabis use (ps ≥ 0.44). The relationship between an earlier age of initiation and trial one on the RAVLT did not survive the inclusion of pre-exposure IQ and SES (p = 0.54), which did not change significantly in subsequent steps (ps ≥ 0.63).

The relationships between better longest digit span forward scores and greater cannabis index scores and higher lifetime heaviest frequency remained after covarying for pre-exposure IQ and SES (step 1) but were attenuated after including alcohol and nicotine use (ps ≥ 0.29) and continued to not be significant in subsequent steps. Consistent with initial models, our primary cannabis variables of interest were not significantly associated with longest digit span backward scores, nor did age of initiation predict longest digit span forward performance throughout any steps of the covariate analyses (ps ≥ 0.14).

*Visuospatial attention and working memory (Table 7 section D).* Regardless of covariates, the relationship between an earlier age of initiation and lower spatial span forward scores remained significant (Estimates (SE) = 0.05 (0.02), $t = 2.19$, $p = 0.03$). However, this was the only relationship found to uniquely predict spatial span scores independent of covariates. The association between age of initiation and longest spatial span backward was drastically diminished with the inclusion of pre-exposure IQ/SES ($p = 0.35$), which was reduced further with our other covariates (ps ≥ 0.51). Higher cannabis index scores continued to significantly predict longest spatial span forward and backward scores until we covaried for education (ps ≥ 0.11) and attenuated further with recent cannabis use (ps ≥ 0.23). The association between lifetime heaviest frequency and longest spatial span backward demonstrated a similar pattern, such that the relationship was attenuated with the inclusion of education ($p = 0.09$) and reduced further with the addition of recent cannabis use ($p = 0.27$). The relationship between longest spatial span forward and lifetime heaviest frequency remained non-significant and the final model was not close to significance ($p = 0.37$).

*Decision-making (Table 7 section E).* Independent of all covariates, higher lifetime heaviest frequencies significantly predicted making fewer advantageous and more disadvantageous choices on a gambling task overall (across 100 trials; Estimates (SE) = -2.60 (1.05), $t = -2.47$, $p = 0.01$), under ambiguity (first 40 trials; Estimates (SE) = -0.08 (0.03), $t = -2.39$, $p = 0.02$), and under risk (last 60 trials; Estimates (SE) = -1.69 (0.82), $t = -2.05$, $p = 0.04$). Earlier age of initiation was also associated with poorer decision-making under ambiguity regardless of covariates (Estimates (SE) = 0.04 (0.02), $t = 1.96$, $p = 0.05$). However, including pre-exposure IQ and SES drastically attenuated the

relationship between age of initiation and overall decision-making ($p = 0.15$) and decision-making under risk ($p = 0.35$), which were further diminished in subsequent steps with the inclusion of our other covariates (ps ≥ 0.21). Higher cannabis index scores predicted poorer scores for overall decision-making and decision-making under risk until alcohol and nicotine use were covaried (ps ≥ 0.10), and inclusion of other confounders reduced effects further (ps ≥ 0.22). Models examining the association between the cannabis index and decision-making under ambiguity were significant but only for steps 2 and 3 and were not significant when all confounders were addressed (step 4, $p = 0.22$).

*Cognitive inhibition (Table 7 section F).* Age of initiation was associated with both d-prime and no-go error rate scores in initial models, but these findings were attenuated with the inclusion of alcohol and nicotine use (*ps* ≥ 0.08) and were further diminished when covarying for all of our other variables (*ps* ≥ 0.13). All models with our cannabis index and lifetime heaviest frequency remained non-significant and were drastically reduced by step 4 (*ps* ≥ 0.68).

*General cognitive ability (Table 7 section G).* Independent of covariates, an earlier age of initiation was significantly associated with prorated FSIQ scores (Estimates (SE) = 0.47 (0.23), $t = 2.03$, $p = 0.04$) and block design performance (Estimates (SE) = 0.09 (0.05), $t = 2.10$, $p = 0.04$). The relationship between higher cannabis index scores and block design also survived adjustment for confounds (Estimates (SE) = -0.26 (0.13), $t = -2.00$, $p = 0.05$). The association between the cannabis index and prorated FSIQ became larger, reaching significance, after including pre-exposure IQ and SES; however, after covarying for education, the association was significantly attenuated ($p = 0.27$). The relationship between higher cannabis index scores and poorer vocabulary performance

did not survive the inclusion of alcohol and nicotine use ($p = 0.36$). Similarly, the relationship between age of initiation and vocabulary was diminished after covarying for alcohol and nicotine use ($p = 0.08$) and dropped further when controlling for other confounders ($ps \geq 0.40$). Consistent with initial models, lifetime heaviest frequency did not significantly predict performance on block design, vocabulary, or prorated FSIQ scores.

*Summary.* Notable alterations occurred in some of the relationships found between our cannabis variables and cognitive outcomes following the inclusion of our covariates. Typically, the addition of subsequent covariates attenuated estimates of the association between cannabis use and cognition. Despite this, our cannabis use variables continued to uniquely predict specific cognitive outcomes independent of confounders. Higher cannabis index scores were related to worse block design performance. Higher lifetime heaviest frequencies continued to predict poorer decision-making performance (overall, ambiguous, risky), and an earlier age of cannabis initiation remained associated with worse longest spatial span forward performance, poorer decision-making under ambiguity, and lower prorated FSIQ and block design scores. Only one association was found that suggested cannabis use was related to better performance. Specifically, higher cannabis index scores predicted recalling more words after a short delay, but only after recent cannabis use was included in the model.

**Sex-specific effects**

Cluster-robust group comparisons between males and females on neurocognitive performance are presented in Table 8. Females demonstrated higher mean scores on total learning, long-delay recall, processing speed index, digit symbol-coding, RAVLT trial 1,

d-prime, and lower no-go error rates than males. Group means were significantly higher for decision-making under ambiguity, prorated FSIQ, and block design for males compared to females. Statistically significant sex differences were not found for short-delay recall, symbol search, longest digit span forward/backward, longest spatial span forward/backward, overall decision-making, decision-making under risk, and vocabulary scores.

Table 9 presents results for all sex-interaction effects with our cannabis variables on cognitive outcomes. All analyses included the covariates explored above. Sex interaction effects with each of our cannabis variables were significant for symbol search (*cannabis index:* Estimates (SE) = 0.45 (0.13), $t = 2.11$, $p = 0.04$; *heaviest frequency:* Estimates (SE) = 0.25 (0.12), $t = 2.13$, $p = 0.03$; *age of initiation:* Estimates (SE) = -0.19 (0.08), $t = -2.19$, $p = 0.03$).

Both of the sex-specific interaction effects for lifetime heaviest frequency on overall decision-making (Estimates (SE) = 3.00 (1.57), $t = 1.91$, $p = 0.06$) and decision-making under risk (Estimates (SE) = 2.29 (1.23), $t = 1.85$, $p = 0.06$) just barely missed significance thresholds. Given our a priori hypothesis of potential sex-differences and that a similar pattern of sex-specific interactions was found for both overall decision-making and decision-making under risk, we explored the trending sex-specific effect for decision-making in males and females separately despite the interactions term not quite meeting significance thresholds.

Analyses of significant findings conducted separately in males and females are presented in Table 10. When exploring the sex-specific interactions on symbol search performance, males consistently demonstrated worse performance with cannabis use,

although only the relationship between an earlier age of initiation and poorer symbol search performance reached significance in males (Estimates (SE) = -0.15 (0.08), $t$ = 2.02, $p$ = 0.04). Conversely, females demonstrated no significant effects with symbol search performance and, at times, even a slight pattern of better performance with higher cannabis index scores and lifetime heaviest frequency, though none of these relationships came close to reaching significance (*ps* > 0.31). For overall decision-making and decision-making under risk, males demonstrated significant and negative effects with greater lifetime heaviest frequencies (*DM overall:* Estimates (SE) = -4.07 (1.56), $t$ = -2.61, $p$ = 0.01; *DM risk*: Estimates (SE) = -2.73 (1.20), $t$ = -2.27, $p$ = 0.02). Females demonstrated a similar pattern of findings as males, but the relationships did not reach significance nor were they close to significance (*ps* > 0.31). Overall, males demonstrated significant deficits on a processing speed task with an earlier age of initiation and weaker decision-making performance with higher lifetime heaviest frequencies, but females did not.

**Isolating the impact of age of cannabis initiation**

Individuals who demonstrate earlier ages of initiation also tend to report greater quantities and frequencies of use, making disentangling the impact of age of onset challenging as they are often correlated. Age of initiation linear mixed models that demonstrated unique associations, independent of covariates, were re-run with the age-24 cannabis index included as a covariate. The age-24 cannabis index was chosen as a covariate as it is an index of both frequency and quantity of use likely during the period of heaviest cannabis use and accounts for more proximal exposure as individuals who used earlier were more like to report use at the most recent assessment. All previously

demonstrated effects remained significant (see Table 11 for age of initiation estimates on cognitive outcomes with age-24 cannabis index included as a covariate) and estimates for the association with age of initiation remained practically unchanged. Further, the age-24 cannabis index did not significantly predict performance on prorated FSIQ, block design, symbol search, longest spatial span forward, or decision-making under ambiguity.

When significant findings for a particular cognitive measure were demonstrated with both our age of initiation measure and another of our primary cannabis use measures (i.e., cannabis index, lifetime heaviest frequency), we re-ran models including both variables (see Table 12 for cannabis effects when both primary cannabis variables were included in the same model). This occurred for performance on block design and decision-making under ambiguity. When age of initiation and our cannabis index were both included in our model to examine the association with block design performance, the cannabis index just missed significance (Estimates (SE) = -0.30 (0.15), $t$ = -1.94, $p$ = 0.05), while the age of initiation effect size was fully attenuated (Estimates (SE) = 0.05 (0.05), $t$ = 1.10, $p$ = 0.27), suggesting that the cannabis index predominantly is driving the relationship with block design. For the relationship between decision-making in ambiguous situations and age of initiation and lifetime heaviest frequency, when both were entered into the same model, neither variable remained significant. That being said, the effect for age of initiation was larger and the model was closer to significance (Estimates (SE) = 0.04 (0.02), $t$ = 1.74, $p$ = 0.08) than the effect for lifetime heaviest frequency (Estimates (SE) = 0.05 (0.04), $t$ = -1.23, $p$ = 0.22).

In summary, these findings suggest that age of initiation was the prevailing predictor of performance for prorated FSIQ, longest spatial span forward, and symbol

search performance (in males) above proximal quantity and frequency of use. However, cumulative cannabis exposure appears to be a more prominent contributor to performance on block design than age of initiation. The relationship with decision-making under ambiguity remains somewhat unclear given that neither age of initiation nor lifetime heaviest frequency rose above the other as significant predictors. It may be that both factors contribute to deficits in this area to varying degrees.

**Length of abstinence**

Using linear mixed models, the impact of length of abstinence from cannabis use was examined for cognitive outcomes that demonstrated previously significant effects with at least one of our primary cannabis use variables. Length of abstinence was not significantly related to short-delay recall, symbol search, longest spatial span forward, decision-making (overall, ambiguous, risky), block design, or prorated FSIQ (see Table 13 for length of abstinence estimates).

We also utilized another approach to examine the relationship between length of abstinence and cognition to maximize the possibility of seeing significant differences in cognitive performance by contrasting extremes in abstinence length. To do this, utilizing cluster robust group comparisons, individuals with <1 month of abstinence from cannabis (n = 173) were compared with individuals with ≥ 1 year of abstinence (n = 222). However, even when comparing extremes, these two groups did not perform significantly differently on cognitive measures (*ps* > 0.06; see Table 14 for group comparison models). As length of abstinence was not significantly related to our cognitive measure, nor did group differences emerge between extremes of abstinence length, it appears findings are unchanged by length of abstinence from cannabis.

**Relationships unique to cannabis users**

We explored the relationship between our heaviest frequency ever used variable in a sample cannabis users only (see Table 15 for lifetime heaviest frequency effects on cognitive outcomes in cannabis users only). Cannabis users demonstrated a significant and negative association with longest digit span backward performance (Estimates (SE) = -0.13 (0.06), $t$ = -2.31, $p$ = 0.02), even when relevant covariates were accounted for. This pattern of findings was not evidenced in the full sample. The slight opposite pattern was found in the full sample, such that cannabis users appeared to perform better overall than individuals with less or no cannabis use, suggesting that these effects may be unique to cannabis users only. No other significant relationships were demonstrated between heaviest frequency and cognition in our subsample of cannabis users.

**Summary of findings**

| | | | *Primary covariate analyses* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **CU*sex** | **Initial** | **Step 1** | **Step 2** | **Step 3** | **Step 4** | **Isolate** | **Abst.** | **CUs** |
| **Vb. Learning/Memory** | | | | | | | | | |
| *RAVLT Total Learning* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| *RAVLT Short-Delay Recall* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | ↑ | | N | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| *RAVLT Long-Delay Recall* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| **Processing Speed** | | | | | | | | | |
| *Processing Speed Index* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | ↓ | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | n.s. | n.s. | | | |
| *Digit Symbol-Coding* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | ↓ | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | n.s. | n.s. | | | |
| *Symbol Search* | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cannabis index | W<M | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | W<M | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | W<M* | ↑ | ↑ | ↑ | n.s. | n.s. | ↑[a] | N | |
| **Vb. Attention/WM** | | | | | | | | | |
| *RAVLT Trial 1* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | n.s. | n.s. | n.s. | n.s. | | | |
| *Longest DS Forward* | | | | | | | | | |
| Cannabis index | n.s. | ↑ | ↑ | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | ↑ | ↑ | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| *Longest DS Backward* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | ↓ |
| Age of initiation | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| **Vis. Attention/WM** | | | | | | | | | |
| *Longest SS Forward* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | N | |
| *Longest SS Backward* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | ↓ | ↓ | ↓ | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | n.s. | n.s. | n.s. | n.s. | | | |
| **Decision-Making** | | | | | | | | | |
| *DM Overall* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | W<M* | ↓ | ↓ | ↓ | ↓ | ↓ | | N | n.s. |
| Age of initiation | n.s. | ↑ | n.s. | n.s. | n.s. | n.s. | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *DM Ambiguity* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | ↓ | ↓ | n.s. | | | |
| Heaviest frequency | n.s. | ↓ | ↓ | ↓ | ↓ | ↓ | ~ | N | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | ↑ | ↑ | ~ | N | |
| *DM Risk* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | W<M* | ↓ | ↓ | ↓ | ↓ | ↓ | | N | n.s. |
| Age of initiation | n.s. | ↑ | n.s. | n.s. | n.s. | n.s. | | | |
| **Cognitive Inhibition** | | | | | | | | | |
| *D-prime* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | n.s. | n.s. | n.s. | | | |
| *No-go Error Rate* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↓ | ↓ | n.s. | n.s. | n.s. | | | |
| **General Cog. Ability** | | | | | | | | | |
| *Prorated FSIQ* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | ↓ | ↓ | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | N | |
| *Block design* | | | | | | | | | |
| Cannabis index | n.s. | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | N | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | ↑ | ↑ | ↑ | n.s. | N | |
| *Vocabulary* | | | | | | | | | |
| Cannabis index | n.s. | n.s. | ↓ | n.s. | n.s. | n.s. | | | |
| Heaviest frequency | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | | n.s. |
| Age of initiation | n.s. | ↑ | ↑ | n.s. | n.s. | n.s. | | | |

*Note:* ↓ = negative association; ↑= positive association; n.s. = not significant; W<M = effect size greater in males than females; W<M* = significant and larger effect size in males than females. N = no group differences between individuals with <1 month abstinence and those with at least a year abstinence. ~ Indicates neither lifetime heaviest frequency nor age of initiation rose above the other to predict decision-making under ambiguity

[a]Analysis conducted in males only

Primary covariate analyses: step 1: pre-exposure IQ/SES; step 2: alcohol/nicotine use; step 3: education; step 4: recent cannabis use

*Abbreviations:* CU*sex, cannabis variable x sex interaction; Initial, initial models without other covariates; isolate, isolating age of initiation effect from amount of use; Abst., abstinence group comparisons; CUs, analyses conducted in cannabis users only.

**Figure 2.** Summary of the findings for each cannabis use variable and cognitive measure.

## Discussion

The current study assessed unique associations between nonacute cannabis use across adolescence and young adulthood and young adult cognitive outcomes, independent of confounding factors. Before discussing findings, there are strengths worth highlighting from the current project to provide context for the interpretation of results. First, research was conducted in a large population-based sample that recently transitioned to young adulthood and demonstrated a range of cannabis use behaviors from normative use levels consistent with the US more broadly to more severe use patterns. This is notable for a few reasons. First, we increased the likelihood of detecting more subtle effects while also making findings more generalizable to a broader population. Second, encompassing several types of cannabis use behaviors and documenting those behaviors on dimensional scales, as opposed to discrete groups, allowed for a broader understanding of the impact of cannabis use, teasing apart what behaviors may be associated with the most detrimental outcomes. Dimensional measures have also been found to be more reliable and valid than discrete group comparisons (Markon et al., 2011), which are predominantly used in cannabis research. This sample design also included a large proportion of females, allowing us to explore novel sex-specific interactions in a longitudinal sample. THC content has increased within recreational cannabis products, and, as such, studies conducted in previous decades may no longer be as applicable to individuals using today's higher potency cannabis products. The current study sample came of age during this period of increased potency and was likely exposed to cannabis strains with high THC levels. Thus, the current project results have increased relevance and can more confidently be generalized to the larger population. Another

primary strength of the current study is its longitudinal design. We were able to assess for pre-exposure cognitive ability, better addressing temporal sequencing of findings. Further, assessments included extensive interviewing at multiple points that covered relevant familial, environmental, and contextual factors and used common, psychometrically sound neuropsychological tests to more easily compare findings to previous research. Multiple assessments throughout adolescence and young adulthood likely reduced error due to retrospective reporting. Additionally, the holistic approach to interviewing allowed us to explore alternative explanations that other studies could not accommodate. The strengths of this study enabled the current research to replicate previous work while also extending and filling gaps in the research base.

A general summary of the findings is presented above in Figure 2. Overall, consistent with cross-sectional literature (Grant et al., 2003; Lovell et al., 2020; Schreiner & Dunn, 2012; Scott et al., 2018), in initial analyses, significant associations were found between nonacute cannabis use and impairments in neurocognitive performance, including deficits in processing speed, visuospatial attention and working, verbal attention, decision-making, cognitive inhibition, and general cognitive abilities, as well as some evidence for better performance with cannabis use on a digit span task. As expected, our study also highlights the importance of controlling for relevant confounding variables as some of these associations did not survive subsequent covariate analyses to uniquely predict cognitive performance. However, patterns of significant results did emerge independent of confounders with deficits evidenced in decision-making, general cognitive abilities, processing speed, and visuospatial attention, predominantly with higher lifetime heaviest frequencies of use and an earlier age of

initiation and sex-specific effects suggesting cannabis use conveys greater risk in males for specific deficits.

One of the most robust findings from this study that emerged was that cannabis use uniquely predicted deficits in decision-making above confounders. Higher lifetime heaviest frequencies were consistently associated with making fewer advantageous choices and more disadvantageous choices overall (over all 100 trials), under ambiguity (first 40 trials), and under risk (last 60 trials) on a gambling task. An earlier age of onset also predicted poorer decision-making under ambiguity. Of particular interest, our measure of overall decision-making and decision-making under risk demonstrated sex-specific effects, such that heavier lifetime frequency significantly predicted worse decision-making in males but not females. Our findings for deficits in decision-making converge with several studies in the cross-sectional literature (Becker et al., 2014; Crane, Schuster, & Gonzalez, 2013; Gonzalez et al., 2012; Solowij et al., 2012; Verdejo-García et al., 2007) and a large meta-analysis (Lovell et al., 2020) along with a longitudinal study examining decision-making performance in males (Castellanos-Ryan et al., 2017). Our findings contrast with two recent longitudinal studies that did not find an association between cannabis and decision-making. However, these studies covered shorter follow-up periods (e.g., roughly age 14 to 19) than the current project and did not examine sex-specific effects (Pacheco-Colón et al., 2021, Wendel et al., 2021), which may have limited their ability to detect significant effects.

However, our findings of decision-making deficits with cannabis use across adolescence and young adulthood follow logically from other research areas, particularly given sex-specific effects during the adolescent and young adult periods. Specifically,

research has demonstrated that adolescence is associated with significant restructuring in the brain, particularly in the prefrontal cortex (Gogtay et al., 2004), which subsumes functions such as decision-making. Further, males undergo a protracted course of neurodevelopment compared to females, such that gray matter volume in the prefrontal cortex has been found to peak one to two years earlier in females than males (Giedd et al., 1999), and total brain size peaked at 10.5 years in females and 14.5 in males (Lenroot et al., 2007). CB1 sites are also densely populated in areas such as the prefrontal cortex (Atkinson & Abbott, 2018). Because of males' protracted developmental trajectory compared to females, it has been hypothesized that males may be at greater risk for developing cannabis-related cognitive deficits for more extended periods during adolescence and into young adulthood, especially as they tend to use more heavily and earlier (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013), which would be consistent with our findings. Sex-specific effects for decision-making have been noted in prior research as well (Crane, Schuster, & Gonzalez, 2013). Additionally, our results may converge most closely with findings from Castellanos-Ryan and colleagues' (2017) investigation, as their study included males exclusively.

Maturational differences in males and females may also account for the sex-specific effects of age of initiation we found on a processing speed task. Specifically, in our study, males, but not females, performed poorly on a symbol search task with an earlier age of cannabis initiation, and a similar pattern of effects was demonstrated for lifetime heaviest frequency and cannabis index; however, the relationship did not reach significance for heaviest frequency or our cannabis index when examined in males and females separately. Imaging studies suggest sex differences in the age at which males and

females reach peak white matter volumes, with females peaking earlier than males (Ladouceur et al., 2012). Males also demonstrate ongoing maturation of white matter into adulthood, whereas females' maturation ends earlier in adolescence. White matter growth is associated with faster and more efficient responding on cognitive tasks (Simmonds et al., 2014), as such disruption of growth processes may impact speed. Given this, much like with decision-making, adolescence may pose a particularly vulnerable period for males for deficits in processing speed due to their protracted neurodevelopmental path compared to females. Individual cross-sectional studies have found evidence for similar patterns of sex-specific effects to the current projects (King et al., 2011; Lisdahl & Price, 2012; Pope & Yurgelun-Todd, 1196). The current work partially confers with a large meta-analysis conducted on studies of adolescent and young adult cannabis users, which found small effect sizes for differences in processing speed between a large sample of cannabis users and comparison participants but failed to find a relationship with age of onset (Scott et al., 2018). The current project only found significant effects for age of onset once sex-specific interactions were accounted for, which was not a focus within the meta-analysis conducted by Scott and colleagues (2018) and may account for discrepant findings. Longitudinal studies that have noted exploring for sex-specific effects did not find patterns to suggest differences in results between males and females (Fried et al., 2005; Jacobus et al., 2015); however, neither examined sex-specific effects for age of initiation.

Prior research examining the phenotypic relationship between general cognitive abilities and nonacute cannabis use generally find significant associations (Boccio & Beaver, 2017; Fried et al., 2005; Meier et al., 2012; Morin et al., 2019; Ross et al., 2020).

Indeed, a recent meta-analysis of longitudinal studies of IQ found cannabis use predicted declines in IQ (Power et al., 2021). The current project results generally cohere with these findings in that we found greater cumulative cannabis use across adolescence and young adulthood predicted worse block design performance, and an earlier age of cannabis initiation was associated with lower prorated FSIQ scores. Age of initiation predicted block design performance as well; however, cumulative cannabis use appeared to be predominantly driving this relationship as opposed to age of initiation. Our results also suggested that the relationship between cannabis use and lower vocabulary scores appeared to be due to confounding factors, which converges with prior research (Castellanos-Ryan et al., 2017; Jackson et al., 2016; Schaefer et al., 2021). However, our significant findings between cumulative cannabis use and block design performance contrast with a recent twin study from our group that did not find a significant association between cumulative cannabis use and block design performance (Schaefer et al., 2021). Methodological differences may account for this discrepancy, as Schaefer et al. (2021) examined cumulative cannabis use separately during adolescence and young adulthood. Combined cumulative use across adolescence and young adulthood may be more critical for predicting block design performance than either developmental period independent of the other. Supporting this rationale, in a slightly older sample followed for only three years, cannabis users did not perform significantly worse on a block design task than controls (Jacobus et al., 2015). In contrast, when adolescents were followed over 14 years into young adulthood, Infante and colleagues (2020) found that greater mean levels of percent days of cannabis use across time were associated with poorer performance on block design. Etiological explorations of deficits in cannabis users using cotwin control

analyses generally did not find evidence for a causal influence of cannabis on general cognitive abilities (Jackson et al., 2021; Meier et al., 2018; Ross et al., 2020; Schaefer et al., 2021), although only one of these studies explored the role of age of initiation as a continuous measure (Ross et al., 2020). Taken together, cumulative use across both adolescence and young adulthood and age of initiation warrant additional exploration.

Our results suggest a persistent relationship between an earlier age of initiation and worse visuospatial attention. However, relatively few longitudinal studies have assessed for visuospatial attention deficits, and cross-sectional studies are inconsistent (Becker et al., 2014; Harvey et al., 2007; Pope et al., 1997; Schuster et al., 2015). That being said, similar to current findings, in a large twin study, Meier et al. (2018) found a phenotypic relationship between poorer visuospatial attention and both cannabis dependence and cannabis frequency, although results from their cotwin analyses suggest deficits in visuospatial attention may represent a premorbid liability. Conversely, when using discrete group comparisons, both Wendell et al. (2021) and Fried et al. (2005) did not find differences. It may be that continuous measures are needed to detect significant effects for visuospatial attention.

Research is also mixed regarding visuospatial working memory deficits. Some longitudinal studies have found significant effects (Becker et al., 2018; Meier et al., 2018), while others have not (Ross et al., 2020; Wendel et al., 2021). It appears that several factors may impact or confer risk for visuospatial working memory deficits. In the current project, the relationships between lifetime heaviest frequency and cumulative cannabis use and visuospatial working memory tended to follow a similar pattern such that the effects were diminished with the inclusion of pre-exposure IQ, SES, alcohol and

nicotine use, and education into the models but were more fully attenuated after accounting for recent cannabis use. Supporting the complexity of the relationship with visuospatial working memory, Morin et al. (2019) found evidence to suggest visuospatial working memory deficits were a common vulnerability for both later alcohol and cannabis use, and cannabis use may impact later spatial working memory performance. Additionally, previous literature suggests that visuospatial working memory is impacted by acute exposure to THC (D'Souza et al., 2008; Bourque & Potvin, 2021), which would be consistent with the drop in effects we saw in our covariate analyses. Taken together, while we did not find evidence for a unique nonacute cannabis-related association above and beyond covariates, it could be that inconsistencies seen in the literature are related to these interactive and shared effects of pre-existing liability, current substance use, and nonacute cannabis effects.

Prior literature suggests an inconsistent relationship between verbal attention and cannabis use that at least in part appears to be task-dependent, with studies finding significant results when using a list-learning task, whereas studies that use a digit span task typically do not (Becker et al., 2014; Hanson et al., 2014; Price et al.,2015; Pujol et al., 2014; Schaefer et al., 2021; Takagi et al., 2011). Our results mimicked task-dependent results in our initial analyses, such that our cannabis measures predicted learning fewer words on the first trial of a list-learning task when confounds were not accounted for, but impairments were not seen on a digit span task. Differences in results based on task could also be compounded by inconsistent control of confounding variables in the literature. In a previous twin study from our group using an overlapping sample to the current project, associations between trial one initial learning on the RAVLT were no longer significant

once propensity to use alcohol was covaried, which included factors such as parental occupation and participant-specific academic factors. Similarly, in our study, pre-exposure IQ/SES, education, and other substance use appeared to play significant roles in attenuating the relationships between our cannabis variables and trial one performance. Indeed, research indicates a strong relationship between education and RAVLT initial learning performance (Bolla-Wilson & Bleecker, 1986), and a powerful impact of education has been found for tasks with high-attention demand, such as list-learning tasks (Le Carret et al., 2003). As such, while cannabis does not appear to uniquely predict trail one performance, it may cohere with other factors to confer risk for poorer initial list-learning performance. For instance, a twin study from our group found evidence that cumulative cannabis use during adolescence has potentially deleterious effects on adolescent academic functioning and socioeconomic outcomes (Schaefer et al., 2021). It may be that cannabis has an indirect impact on RAVLT trial one performance, such that cannabis use impacts academic and SES outcomes, which may influence initial learning performance on list-learning tasks. Supporting this, prior studies finding significant effects with list-learning tasks often did not control for confounds such as SES, education, or other substance use (Jacobus et al., 2015; Pope & Yurgelun-Todd, 1996; Hanson et al., 2010; Pujol et al., 2011; Takagi et al., 2011) and results no longer reached significance when confounders were consistently accounted for (Medina et al., 2007). Compared to the complex relationship with verbal attention, even in initial models of the full sample, there was little evidence for an association between nonacute cannabis use and verbal working memory. This finding coheres fairly closely with much of the longitudinal literature exploring verbal working memory in adolescence and young adults

who also found little evidence for an association with cannabis use (Becker et al., 2018; Castellanos-Ryan et al., 2017; Ellingson et al., 2021; Infante et al., 2019; Ross et al., 2020; Schaefer et al., 2021; Tait et al., 2011).

Even in initial models without covariates, little evidence was found for a relationship between cannabis use and cognitive inhibition. The only significant associations demonstrated in initial analyses were between an earlier age of cannabis initiation and poorer ability to inhibit responses and an increased error rate; however, these relationships were attenuated with the inclusion of pre-exposure IQ/SES and alcohol and nicotine use. These findings cohere with a recent meta-analysis of 13 studies that did not find evidence for a significant association between cannabis use and cognitive inhibition measures, such as the one we used in the present study (e.g., Go/No-Go tasks; Figueiredo et al., 2020). However, our results contrast partially with two recent longitudinal studies. Mahedy et al. (2021) found that early, regular cannabis users compared to non-users performed more poorly on a response inhibition task. Similarly, Infante et al. (2020) noted that greater mean levels of percent days of cannabis use across adolescence to young adulthood were associated with a measure of cognitive inhibition. Inconsistencies between these studies and the current project may be due to methodological differences in the choice of included covariates as a measure of tobacco use was not included in one study (Infante et al., 2020), and alcohol use was characterized as a "whole drink" before the age of 13 in the other (Mahedy et al., 2021), which may have underestimated the role of alcohol use given their most recent assessment was around the age of 24 when alcohol use typically peaks (Johnston et al., 2021). Supporting the hypothesis that inconsistencies may be due to confounding factors,

cross-sectional studies with significant findings for cognitive inhibition often did not covary for other substance use and/or socioeconomic status (Clark et al., 2009; Gruber et al., 2013; Lamers et al., 2006). Studies that adjusted for these did not find unique cannabis-related effects (Gonzalez et al., 2012; Hooper et al., 2014; Tapert et al., 2007). Indeed, in a sample of school children, Morin et al. (2019) concluded that common vulnerability effects were detected for cognition inhibition and alcohol and cannabis use and, in a twin study, Ross and colleagues (2020) found evidence to suggest the association between age of initiation and a common executive functioning composite that accounted for all variance contributed by inhibition was likely due to premorbid liability. Together with our current results, the pattern of findings within the literature suggests more support for confounding, particularly from other substance use, than a unique, direct cannabis-related association.

Contrary to expectations, even in initial models, our measures of cannabis use did not demonstrate associations with worse verbal learning or memory performance. This finding was somewhat confusing given that the relationship between cannabis use and poorer verbal learning and memory is one of the more consistent findings established in the literature (Grant et al., 2003; Lovell et al., 2020; Pacheco-Colón et al., 2021; Scott et al., 2018). However, our findings cohere with a previous project from our group that did not find an association between total learning, short-delay recall, or long-delay recall and cumulative cannabis use (Malone et al., 2021). Our findings may also converge with Scott et al.'s (2018) meta-analysis that reported non-significant effects between neurocognitive performance and cannabis use once the analyses were limited to studies with at least 72 hours of abstinence. The authors concluded that associations between

cannabis and cognition might be better explained by the residual impact of acute cannabis intoxication or withdrawal effects. Fried et al. (2005) also found significant group differences between current cannabis users and controls in immediate/delayed recall performance but not in former cannabis users, suggesting findings may not be attributable to nonacute cannabis use. Our results would support this hypothesis as a significant and negative relationship emerged between our covariate of recent cannabis use and verbal memory scores. A puzzling aspect of our results was that once the relationship with recent cannabis use was covaried, a positive association was demonstrated between short-delay recall and higher cannabis index scores. But a direct benefit of greater cumulative cannabis use on verbal learning and memory seems unlikely, particularly given the well-documented adverse impacts of cannabis intoxication on verbal memory performance (Broyd et al., 2016; Cuttler et al., 2021; Ragnathan et al., 2017). This finding could be due to chance seeing as a pattern of significant findings did not emerge as the association only reached significance with the inclusion of recent cannabis use, nor were relationships significant for any of our other cannabis use variables across the steps of our analyses. Another explanation could be confounding by an unaccounted for third variable. For instance, better memory performance has been linked to more openness to experience (Chapman et al., 2017; Simon et al., 2020). Openness to experience has also been associated with substance use (Phillips et al., 2017; Terracciano et al., 2008). It may be that openness predicts both higher levels of cannabis use and better short-delay recall performance. In either case, this association did not appear to be a direct nor robust association with nonacute cannabis use.

Part of our assessment of nonacute cannabis use and cognition was to examine the impact of length of abstinence from cannabis, which has been under-explored in longitudinal studies and often demonstrates inconsistent findings across the extant literature. Overall, our analyses found little evidence that deficits changed with prolonged abstinence of at least a year. Results could reflect cannabis-related alterations occurring in the brain that may be carried forward regardless of later cannabis use. Alternatively, this may suggest that associations index some pre-existing liability that predates cannabis exposure and thus would be present regardless of cannabis initiation. Given that our significant associations survived covarying for several common confounders that could index risk for cannabis use and cognitive deficits, the latter hypothesis seems less likely to fully explain the relationships demonstrated in this study. However, while findings appear robust, we cannot account for all confounding factors, such as shared familial and environmental liability, and thus cannot speak to the exact etiology of the cognitive deficits associated with cannabis use.

As part of an exploratory analysis, we found an association between verbal working memory on a digit span task and lifetime heaviest frequency that was only seen in cannabis users but not when comparing across users and non-users. The relationship with verbal attention was nearly significant as well. Comparatively in the full sample, a slight trend was seen in the opposite direction when examining effects, though this did not survive covariate analyses. If these findings are to be taken at face value, the fact that significant results do not often emerge in the literature for digit span performance is unsurprising as studies typically compare "users" to "non-users." However, as these

findings were part of an exploratory analysis, it is as of yet unclear what the nature of these findings are or if they would be replicated in a separate sample.

**Limitations of the current work**

The current study is not without limitations. As stated above, this study accounted for numerous relevant factors; however, it cannot control for all risk factors, both measured and unmeasured, such as familial risk factors. As such, the question of causality cannot fully be addressed. Given this, it will be essential to investigate the current findings using genetically informative designs, such as the cotwin control designs, to better disentangle shared familial and environmental factors from possible causal influences of cannabis exposure.

Another important consideration for this study is the risk for Type I error. It can be challenging to balance the risks of a Type I and Type II error, particularly as one of the strengths of this study was how comprehensive it was with its neurocognitive battery and its exploration of various measures of cannabis behaviors and alternative explanations. The statistical comparisons in this study were not corrected for multiple comparisons as many of the findings demonstrated would not be interpreted as significant with more rigorous thresholding. This may have increased our risk for Type I error; however, given the importance of these findings, we felt this was necessary to provide a full view of the data and more easily compare with prior research. To balance this, we provided statistics for cannabis effects where relevant in the narrative text and additional statistics in our tables so that readers may weigh the various considerations related to Type I and Type II errors when interpreting findings.

Additionally, while large and population-based, our study sample is modeled after the population in Minnesota at the time of the intake assessment. Due to this, our sample is predominantly white, and minority groups are generally under-represented, which is a limiting factor in the generalizability of findings, particularly given evidence of differences in rates of cannabis use behaviors in various racial/ethnic populations (Wu et al., 2016). Attrition in our sample could also be a source of bias that may limit the generalizability of findings given that non-participants tended to be male and have lower pre-exposure IQ scores and parental socioeconomic status. However, this would seem less probable as our cannabis use behaviors did not appear to be significantly impacted by attrition. Further, pre-exposure IQ scores for individuals who participated in our most recent assessment appeared normally distributed with adequate representation of scores from the lower tail of the distribution and a mean/standard deviation close to that of a typical standard score distribution. If attrition bias were present, it would seem unlikely for our findings to drastically change as to no longer be significant. Rather, given that males were more likely to not participate in the most recent assessment and several of our findings were specific to males, it would seem more likely that effects may be underestimated and some of the effects that just missed significance would have met significance thresholds.

**Conclusions**

The results from this longitudinal study suggest that cannabis use during adolescence and young adulthood is associated with deficits in neurocognitive performance above and beyond common confounding factors. Findings demonstrated an association between an earlier age of initiation and lower prorated FSIQ scores and

poorer visuospatial attention and decision-making performance under ambiguity. Higher lifetime heaviest frequencies of cannabis use predicted lower decision-making scores overall, under ambiguity, and under risk; however, sex-specific effects were evidenced such that only males demonstrated significantly worse performance on overall decision-making and decision-making under risk with higher lifetime heaviest frequencies of use. A similar pattern was seen for processing speed, such that an earlier age of initiation predicted symbol search performance but only in males. Cumulative cannabis use across adolescence and young adulthood also predicted lower block design performance. Verbal working memory deficits were uniquely evidenced by cannabis users with higher lifetime heaviest frequencies and cognitive performance did not differ based on length of abstinence from cannabis. When findings are taken together, patterns of earlier onset of use and heavier peak frequencies appear to be most relevant for predicting poorer cognitive outcomes, suggesting that more diffuse moderate levels of cannabis use, mainly occurring later into young adulthood, may be associated with fewer long-term adverse outcomes.

While we cannot fully speak to whether these associations represent exposure-related effects of cannabis use, our results demonstrate overall good coherence with previous literature, strengthening confidence in our results. Future work could extend these findings by exploring effects in larger longitudinal samples with more frequent follow-ups, such as those conducted in the Adolescent Brain and Cognitive Development (ABCD) project, or in robust casually informative cotwin control designs to speak more directly to potential exposure-related effects of cannabis. This information can be used to focus efforts on delaying and reducing the severity of cannabis use during vulnerable

periods, such as adolescence, particularly in males, and assist in informing health policies. Future work may also benefit from exploring the clinical and functional implications of the cognitive deficits demonstrated in this study.

## Study 2. The Effects of Cannabis Use Behaviors Across Adolescence on Young Adult Cognitive Outcomes: A Cotwin Control Study


### Abstract

**Background.** Research suggests that there is an association between nonacute cannabis use and impaired cognitive performance. However, the etiology of cognitive deficits in adolescent and young adult cannabis users remains largely unclear as other factors that may increase the risk for cannabis use, such as familial liabilities, may confound causal interpretations. We examined casual associations between nonacute cannabis use during adolescence and young adulthood and young adult neurocognitive outcomes in a sample of twins using a cotwin control design to separate familial liability from cannabis exposure-related effects.

**Methods.** A large population-based sample of twins (*N* =801; 55% female) was followed from age 11 to 24. Dimensional measures of cannabis and other substance use were obtained across four assessments waves (age 11, 14, 17, 24). Cognitive outcomes were assessed at the most recent assessment (age 24), with pre-exposure cognitive ability assessed at intake (age 11). Linear mixed models assessed individual-level associations between cannabis and cognition. Cotwin control analyses were conducted to tease apart risk conferred by genetic and environmental factors from potential cannabis exposure-related effects on cognition.

**Results.** Individual-level associations for the full neurocognitive battery were presented in our previous report. In the present study, associations that survived multiple comparison adjustments indicated deficits in visuospatial attention with greater lifetime heaviest frequencies of cannabis use and lower estimated intelligence scores with an

earlier age of onset. Sex-specific effects in decision-making and processing speed performance were observed, such that males demonstrated significant decision-making deficits with greater lifetime heaviest frequencies and poorer processing speed scores with an earlier age of initiation, but females did not. Cotwin control results suggest that deficits in decision-making, estimated intelligence, visuospatial attention, and processing speed reflect pre-existing liability toward substance. However, evidence was also consistent with a causal influence of an earlier age of cannabis initiation on general intelligence in both males and females and an exposure-related effect of greater lifetime heaviest frequency on decision-making but only in males. Results suggested that differences in length of abstinence did not significantly impact these findings, nor did they predict cognitive performance

**Conclusions.** Evidence suggests a bidirectional association between cannabis use and neurocognition, such that cognitive deficits may represent premorbid characteristics of the familial predisposition to use cannabis and may also be adversely impacted by later cannabis exposure with specific risk for exposure-related consequences in males. Results have potentially important implications for health policy decisions and intervention efforts, emphasizing reducing and delaying cannabis use.

## Introduction

In the last few decades, perceptions regarding the risk of cannabis use have decreased, accompanied by an increase in the legalization of use at the state level (Berke & Gould, 2020; Johnston et al., 2021). With shifts toward greater acceptance, understanding the long-term implications of cannabis use is imperative. This is particularly true for cannabis use occurring during adolescence and young adulthood, given these are critical periods of neural development (Sturman & Moghaddam, 2011) and may be sensitive to exogenous assault from exposure to cannabis (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013). Animal research supports this vulnerability hypothesis for youth (Atkinson and Abbott, 2018), and cannabis exposure in adolescence, particularly high-potency cannabis, has been associated with poorer mental health or psychosocial outcomes (Hines et al., 2020).

Several meta-analytic studies of the cross-sectional research have supported the assertion that at the phenotypic level nonacute cannabis use is associated with impairments in neurocognitive performance with the most significant evidence for learning and memory and more modest evidence for decision-making, attention, processing speed, and global cognition (Figeiredo et al., 2020; Grant et al., 2003; Lovell et al., 2020; Schreiner & Dunn, 2012; Scott et al., 2018). These associations are often assumed to represent neurotoxic effects of exposure. However, the exact nature of the relationship between cannabis and cognition has yet to be fully discerned as speaking to causality remains a challenge. Cross-sectional research studies are unable to speak to the etiology of cognitive deficits or temporal sequencing of associations. A primary difficulty

is that lower neurocognitive ability may predispose an individual to later substance use (Morin et al., 2019; Ridenour et al., 2009), and controlling for pre-exposure cognitive abilities has been found to attenuate relationships between nonacute cannabis use during adolescence and later cognitive performance (Meier et al., 2018).

Longitudinal studies with pre-and post-initiation measures of cognitive ability can better speak to the temporal sequencing of the relationship with cannabis. However, evidence that cannabis use was associated with declines in neurocognition has been characterized as inconsistent (Meier et al., 2018; Power et al., 2020; see Study 1 summary). Moreover, critics have pointed out that the association between cannabis and cognition may arise due to pre-existing vulnerabilities, such as low socioeconomic status, rather than cannabis adversely impacting cognition (Daly, 2013; Rogeberg, 2013). Indeed, it can be challenging to account for all predisposing familial and environmental factors that may confer risk toward substance use and cognitive deficits. Studies that disentangle possible causal exposure-related effects from confounding, such as twin studies, are needed to better address shared unmeasured confounding factors.

In response to concerns related to potential confounding, Jackson et al. (2016) examined the link between declines in intelligence from ages 9-12 to 17-20 and cannabis use in two large samples of twins. Study results showed declines in intelligence scores (e.g., vocabulary/information from the Wechsler Abbreviated Scale of Intelligence) of cannabis users compared to nonusers; however, differences were not found between twins discordant for cannabis use, suggesting the associations were not due to causal effects of cannabis. In a twin sample followed to age 18, Meier and colleagues (2018) found that cannabis-dependent adolescents had lower IQ scores in childhood before

cannabis initiation than non-dependent adolescents but found little evidence that cannabis use was associated with declines in IQ. Adolescents who used cannabis also demonstrated poorer executive functioning at age 18 than those that did not use cannabis, but most of these associations were not evident within twin pairs (i.e., not consistent with a causal effect of cannabis); however, they did find that twins who used cannabis more frequently in the 12 months before their age 18 assessment performed worse than their less frequently using cotwin on a spatial span task of working memory (Meier et al., 2018). Similarly, Ross et al. (2020) found evidence for a possible causal exposure-related effect of frequency of use (past six months) at age 17 on executive functioning performance. However, the authors cautioned against over-interpreting this relationship as evidence of a causal impact of cannabis on cognition as this was the only significant association suggestive of an exposure-related effect out of their analyses. Ross et al. (2020) also noted that most associations between cannabis use and intelligence and executive functioning were accounted for by other substance use, and associations between age of initiation and intelligence and executive functioning appeared to be due primarily to familial confounding. In two combined twin cohorts that followed twins into their mid-and late-20s, Schaefer et al. (2021), much like the other twin studies, found an association between cumulative cannabis use and vocabulary, but this association again appeared to be due to shared familial and environmental confounding as opposed to an exposure-related effect. In another twin study focused on a list-learning task from our group, propensity to use alcohol was found to account for the relationship between cumulative cannabis use and initial and overall learning, and no associations were found with memory (Malone et al., 2021).

These studies are informative, but twin studies in adolescents and young adults are still rare and relatively narrow in the cognitive domains they address. In this study, a longitudinal sample of twins extending from adolescence into young adulthood was assessed on a comprehensive battery of neurocognitive assessments. Unique phenotypic associations between nonacute cannabis use and cognition, independent of common confounders, were described in our previous study (see study 1). Results of that project found deficits in general cognitive abilities and visuospatial attention, along with sex-specific effects for decision-making and processing, such that males demonstrated significant impairments with cannabis use, but females did not. These associations rose above confounding factors in our previous analyses. Conversely, robust associations, independent of confounds, were not demonstrated for verbal learning and memory, visuospatial or verbal working memory, or cognitive inhibition. Consistent with the literature (Broyd et al., 2016; Scott et al., 2018), associations most typically were found with greater heaviest frequencies of use and earlier ages of cannabis initiation, with less evidence for more moderate cannabis use behaviors. Deficits did not appear to resolve with an abstinence period of at least a year. Within an exploratory analysis, our previous project found a negative association between verbal working memory and lifetime heaviest frequency that was unique to cannabis users only.

The current project extends findings from our previous report by exploring the etiology of the unique relationships between nonacute cannabis use and cognition by capitalizing on our reared-together twins' genetic and environmentally informative nature, which more stringently controls for shared familial and environmental influences. To the best of our knowledge, the relationship between decision-making and processing speed

and nonacute cannabis use has not yet been the focus of a twin study in adolescents and young adults, nor have sex-specific effects been demonstrated. The prospective design of the sample enabled cannabis use to be characterized from multiple time points across adolescence and control for cognitive ability measured pre-initiation of cannabis. The cotwin control design is unable to account for all confounding factors unshared by twins. We were well situated to address potentially nonshared variables such as pre-exposure cognitive abilities, years of education, alcohol and nicotine use, recent cannabis use, and recency of last cannabis use, as assessment waves included extensive interviewing regarding psychosocial and environmental factors.

## Methods

### Sample

Participants were same-sex twins from the Enrichment Study (ES), a component of the Minnesota Twin Family Study (MTFS) at the Minnesota Center for Twin and Family Research (MCTFR). Participants were identified from Minnesota birth records. The ES sample is a population-based, longitudinal study of reared-together twins followed from intake at age 11 and subsequently at age 14, 17, and 24; a detailed overview of the ES sample and study design, including inclusion/exclusion criteria, are described in Keyes et al. (2009) and Wilson et al., (2019). Assessments at each study wave included a comprehensive, multimodal battery of clinical interviews, questionnaires, and cognitive assessments conducted by trained assessors. Information was also collected from biological and stepparents across assessments.

Of the original 998 twins recruited for the ES sample at the age-11 intake, 81% (n = 809) participated in the most recent age-24 follow-up in some capacity. Twin

participation at the age-24 assessment was not uniform across all cognitive assessments due to logistic factors, such as time constraints during interviewing or impractical travel distances to participate in-person that necessitated phone interviews (n = 111). Eight individuals were excluded due to reporting cannabis exposure before their age-11 intake assessment. See previous report for further description of the sample characteristics and attrition across study duration.

The final sample contained 801 individuals (age: mean [SD] = 24.43 [0.91] years; 439 women), with 481 monozygotic (233 complete pairs) and 320 dizygotic (153 complete pairs) twins. Twins were asked to refrain from all substance use for 24-hours before their age-24 assessment but were not excluded if they reported recent use. Sixty-four participants reported cannabis use in the 24-hours preceding their age-24 follow-up assessment.

**Substance use**

Substance use was assessed at ages 11, 14, and 17 using a Computerized Substance Use (CSU; McGue et al., 2014) questionnaire and a revised version of the drug supplement from the Diagnostic Interview for Children and Adolescents-R (DICA-R; Reich, 2000; Welner et al., 1987). A modified version of the Substance Abuse Module (SAM; Robins et al., 1987) from the Composite International Diagnostic Interview (CIDI; Robins et al., 1988) was utilized to assess substance use at ages 17 and 24. The CSU, DICA, and the expanded version of the SAM assess for information, such as the number of intoxications, frequency and quantity of use, heaviest periods of use, and age of initiation of substance use.

***Cannabis use***

Cannabis was measured with six variables, including frequency of use (past 12 months), number of uses (since last assessment), heaviest frequency (lifetime), age of initiation, recent use (past-24 hours), and length of abstinence (time since last use). Frequency of use (12 months) and number of uses (since the last assessment) were combined across follow-up waves to form a cumulative measure of cannabis (cannabis index). Description of the cannabis index computation is presented below; the validity of the methods used to derive the cannabis index was supported by comparable studies that explored implications of common substance use behaviors (Harper et al., 2018; Malone et al., 2021; Schaefer et al., 2021; Wilson et al., 2018). Our primary cannabis variables of interest were the cannabis index, lifetime heaviest frequency, and age of initiation.

*Cannabis index.* The cannabis index characterized cumulative cannabis exposure from adolescence to young adulthood. To compute this measure, separate indices were first calculated for each follow-up wave (i.e., 14, 17, and 24) by averaging two items: (1) frequency of use (past 12 months), and (2) number of times used (since last assessment). For frequency of use in the past 12 months, categories included: 0 (no use), 1 (<1x/month), 2 (1-3x/month), 3 (1-4x/week), 4 (every day or nearly every day), or 5 (>1x/day). For number of uses since last assessment, categories included: 0 (no use), 1 (1-4 uses), 2 (5-30 uses), 3 (31-100 uses), 4 (101-400 uses), or 5 (>400 uses or "too many to count"). Because responses to these questions tended to be sparse and positively skewed, they were transformed into 6-point ordinal scales using methods developed at the MCTFR before averaging them. We derived a single index by averaging these scores across follow-up assessment waves (i.e., age 14, 17, and 24). We did not include age-11 when computing the cannabis index as individuals who had used cannabis before their

intake assessment were excluded and, as such, age-11 cannabis use was zero for all participants.

*Lifetime heaviest frequency.* Participants were asked to think about the period when they were using cannabis the most, either in their lifetime (asked at age 17) or since their last assessment (asked at age 24), heaviest frequency was not assessed at the earlier assessment waves. Participants were then asked to report the frequency of their cannabis use during the time of their heaviest use. We used the max value reported at either their age-17 or age-24 evaluation to assess for heaviest frequency ever used in the participant's lifetime. Mimicking procedures for the cannabis index, we transformed lifetime heaviest frequency into an ordinal measure containing six categories to reduce skew and spareness of responses. Categories included: 0 (no use), 1 (<1/year), 2 (>1x/year to 2 to 3x/month), 3 (1 to 2x/week to nearly every day), 4 (1 to 2x/day), 5 (≥3x/day).

*Age of initiation.* Age of initiation was defined as the first exposure to cannabis regardless of the amount used. To obtain this value, we asked participants how old they were when they first tried cannabis at each assessment wave. The age reported at the earliest assessment was used, as this was the report most proximal to when use occurred, likely reducing measurement error due to retrospective reporting over more extended periods.

*Other cannabis covariates.* At the age-24 follow-up, participants were asked if they had used cannabis in the 24 hours before their assessment. Responses were coded as either a yes (1) or no (0) answer. Participants were also asked when they had last used cannabis. Categories to characterize time since last used included: 1 (within last 2

weeks), 2 (2 weeks to <1 month), 3 (1 month to <6 months), 4, (6 months to <1 year), 5 (within the last year but don't know exactly when), and 6 (1 year or more ago).

***Other substance use***

Two composite measures were calculated to approximate alcohol (age-24 alcohol index) and nicotine (age-24 nicotine index) exposure during emerging adulthood (17-25 years), likely during peak substance use (Johnston et al., 2021). Computation was similar to those used to calculate the cannabis indices and followed methods used in several other studies from our group that have examined implications of common substance use behaviors (Harper et al., 2018; Malone et al., 2021; Schaefer et al., 2021; Wilson et al., 2018).

The alcohol index was calculated by taking the average of four dimensional alcohol use items assessed at the age-24 follow-up: (1) number of drinks typically consumed per occasion since the last assessment (0 = none to 6 = 30+), (2) frequency of drinking since the last assessment (0 = never to 5 = two+ times per day), (3) maximum drinks consumed in a 24-hour period since last assessment (0 = none to 6 = 30+), and (4) number of times intoxicated in lifetime (0 = never to 6 = 150+ times). The nicotine index was derived by taking the average of two items: (1) number of days in a typical month used tobacco in the past 12 months (0 = none to 2 = 15 to 30 days per month), and (2) number times used tobacco in a typical day in the past 12 months (0 = none to 3 = 20+). The number of times used tobacco in a typical day was the sum of four individual items on the number of cigarettes, cigars, and pipes smoked, and the number of chews used.

**Neurocognitive battery**

This report focused on a subset of the neurocognitive battery used in our previous report that demonstrated robust, unique effects with our cannabis measures (see study 1 for complete list). Neurocognitive measures included test of (1) processing speed: Wechsler Adult Intelligence Scale-III (WAIS-III) Symbol Search (Wechsler, 1997); (2) verbal working memory: WAIS-III Longest Digit Span Backward (Wechsler, 1997); (3) visuospatial attention: Longest Spatial Span Forward (Wechsler, 1997); (4) decision-making: Iowa Gambling Task (IGT; Bechara et al., 1994); (5) general cognitive ability: Wechsler Adult Intelligence Scale-Revised (WAIS-R) Prorated Full Scale IQ (FSIQ), Block Design (Wechsler, 1981). Measures for the full neurocognitive battery examined in our previous study and the subset focused on in the current project are summarized in Table 3 along with variables obtained from each measure. See general study characteristics section for full task descriptions.

**Additional covariates**

***Age-11 intelligence quotient (IQ)***

Pre-exposure IQ, assessed at intake, was derived from performance on the block design, picture completion, vocabulary, and information subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) and estimated following WISC-R prorated scoring procedures for IQ (Wechsler, 1981).

***Years of education***

Education for each participant was defined as the number of academic school years of formal education successfully completed at the time of their age-24 assessment.

**Statistical Analysis**

Cotwin control (CTC) analyses rely both on the similarities and differences between twins. The degree to which our cannabis measures of interest are similar or dissimilar can impact our ability to detect either a causal exposure-related effect of cannabis or a pre-existing liability toward use. To illustrate similarities, correlations were conducted between twins in a twin pair for our measures of cannabis use using intra-class correlations for MZ and DZ twins separately. Additionally, we examined the distribution of absolute twin difference scores (|TwinA – TwinB|), providing descriptive statistics of within-pair differences to characterize twin differences in cannabis use behaviors in our sample.

Both individual-level and CTC analyses used linear mixed models (LMMs) to examine effects. LMMs were conducted in R using lmer from the lme4 package (Bates et al., 2015) with denominator degrees of freedom adjusted by Kenward-Roger approximation from the lmerTest package (Kuznetsova et al., 2017). Random intercepts were included at the twin-pair level to account for within-pair correlations. All analyses included covariates for age, sex, and zygosity as appropriate.

Unique, robust associations between our cannabis use and cognitive variables demonstrated in our previous report were carried forward to this project to assess for evidence of causal effects of exposure (see study 1 for detailed exploration of phenotypic associations). While our previous study reported the phenotypic associations between our cannabis and cognitive variables, individual-level associations were assessed in this project and summarized below for baseline comparison to subsequent CTC analyses. Given sex-specific effects evidenced in our previous project for decision-making and processing speed, associations for these measures were also assessed in males and

females. A false discovery rate (FDR) procedure adjusting for multiple comparisons was applied (Storey, 2003; Storey & Tibshirani, 2003) at $q < 0.05$ (Storey et al., 2018). Associations that survived FDR adjustment were assessed in the CTC analyses. For investigations of sex-specific effects, non-significant findings in females were also carried forward to CTC analyses for exploratory purposes and a better understanding of sex-related influences.

CTC analyses assessed for possible causal exposure and shared familial and environmental risk effects by using reared-together twins to control for both measured and unmeasured familial confounding more stringently. For CTC analyses, cognitive outcomes are compared between members of a twin pair. For example, if a twin used cannabis more than their cotwin, the cognitive outcome of the lesser-using twin provides a close approximation of the expected outcome for their heavier-or earlier-using cotwin had they used cannabis less or began using at a later age (unobserved counterfactual; Rutter, 2007).

Our cannabis use variables (e.g., cannabis index, lifetime heaviest frequency, age of initiation) were each split into two orthogonal components: (1) the between-pair effect, or twin-pair mean score, and (2) the within-pair effect, or each twin's deviation from their respective twin-pair mean (Begg & Parides, 2003). The between-pair effect, or what is shared within a twin-pair, primarily reflects both measured and unmeasured pre-existing genetic and shared environmental vulnerability influencing both cannabis use and cognitive performance. The within-pair effect, or what differs within a twin pair, reflects nonshared environmental effects of cannabis exposure unconfounded by familial risk factors influencing use.

Given this parameterization, a significant between-pair effect in the CTC model would suggest that the association between cannabis use and a neuropsychological outcome is most consistent with shared genetic or environmental confounding. On the other hand, a significant within-pair effect would be more compatible with a causal cannabis exposure-related effect on cognitive performance. As the CTC relies on the similarity between twins, only complete twin pairs were be used for this method. We compared the magnitude of within-pair effects between MZ and DZ twin pairs with a within-pair by zygosity interaction term in our CTC models. Statistically commensurate MZ and DZ within-pair effects would be consistent with an exposure-related effect of cannabis (McGue et al., 2010)

While the CTC can control for measured and unmeasured shared genetic and environmental factors, it cannot fully control for factors unshared by twins. As such, for associations that demonstrated significant within-pair effects, CTC models were conducted to include pre-exposure IQ, years of education, alcohol use, nicotine use, and recent cannabis use. These are variables that may differ between twins and are relevant for cannabis use and cognitive outcomes. These variables were represented as each twin's deviation from their twin-pair mean. Cannabis users who begin using earlier often use more heavily, and relationships with age of onset may be better accounted for by frequency of use (Castellanos-Ryan et al., 2017). Thus, for any within-pair effects found for age of onset, models exploring unshared confounds also included a covariate for twin differences in the age-24 cannabis index to account for both proximal quantity and frequency of use during peak substance use periods (Johnston et al., 2021).

Length of time since last use may mediate the relationship between cannabis and cognition (Scott et al., 2018; Schreiner & Dunn, 2012). Twin differences in length of abstinence from cannabis were included as a covariate in a final set of cotwin models to assess if recency of last use predicted neurocognitive performance or attenuated previously demonstrated significant within-pair effects.

## Results

### Preliminary analyses

Twin correlations for our exposure variables are presented in Table 16. Descriptive statistics for demographic and substance use variables are presented in Table 1 and neurocognitive descriptive statistics are in Table 2. All within-pair twin correlations were higher in MZ relative to DZ twins, consistent with influences of additive genetic factors. All correlations were less than 1, which also suggests influences from environmental factors not shared by twins. For complete twin pairs, absolute twin differences (|TwinA – TwinB|) in our cannabis index ranged from 0 to 3.25 (M = 0.45, SD = 0.56). Thirty-three percent of twins were concordant (e.g., had the same index score) for the cannabis index (n = 254, 160 MZ/94 DZ), and the rest were discordant (n = 518, 306 MZ/212 DZ). Our cannabis index collapses ordinal measures of the number of uses and frequency of use (past 12 months), so a difference of 1 between twins would be equivalent with one twin using <1x/month and the other using 1-3x/month, or one twin using 1-4x/week and the other using every day or nearly every day. Another possibility is that one twin reported 1-4 uses since their last assessment and the other reported 5-30, or one reported 31-100 uses and the other reported 101 to 400 uses. Absolute twin differences for lifetime heaviest frequency ranged from 0 to 5 (M = 1.05, SD = 1.19).

Forty-two percent of twins were concordant for lifetime heaviest frequency (n = 322, 226 MZ/96 DZ) and the rest were discordant (n = 450, 240 MZ/210 DZ). Absolute twin differences in age of initiation ranged from 0 to 8 years (M = 1.75, SD = 1.68). Twenty-three percent of twins were concordant for age of initiation (n = 98, 68 MZ/ 30 DZ) with the remaining discordant (n = 314, 184 MZ/ 130 DZ).

**Individual-level associations**

Table 17 presents individual-level associations, including sex-specific effects. Associations demonstrated with decision-making under ambiguity, block design, and digit span did not survive FDR adjustment ($q > 0.05$). All other significant associations survived multiple comparison adjustments. A summary is provided below.

Diminished longest spatial span forward and prorated FSIQ scores were associated with an earlier age of cannabis initiation ($p < 0.01$). Sex-specific effects were demonstrated for overall decision-making ($p < 0.01$; the total number of advantageous minus disadvantageous choices across 100 trials) and decision-making under risk ($p < 0.01$; last 60 trials), such that males, but not females ($p \geq 0.12$) demonstrated significant impairments with greater lifetime heaviest frequencies of use. Males also demonstrated lower symbol search scores with an earlier age of cannabis initiation ($p < 0.01$), but the relationship was not significant in females ($p \geq 0.15$).

**Cotwin control analyses**

CTC models, including within-and between-pair estimates are presented in Table 18. Lifetime heaviest frequency within-pair estimates were significant for both measures of decision-making in males (*overall decision-making*: Estimate (SE): -4.87 (2.11), $t = -2.31$, p = 0.02; *decision-making under risk:* Estimate (SE): -4.35 (1.58), $t = -2.75$, $p =$

0.01), which are consistent with a causal effect of cannabis; however, the between-pair effect was also significant for overall decision-making (Estimate (SE): -3.50 (1.50), $t$ = -2.34, $p$ = 0.02) and was nearly significant for decision-making under risk (Estimate (SE): -2.27 (1.18), $t$ = -1.93, $p$ = 0.06). Similar findings were demonstrated in the full sample (e.g., males and females) for the association between age of initiation and prorated FSIQ, such that both the between- and within-pair effects for age of initiation were significant (*between-pair:* Estimate (SE): -2.52 (0.45), $t$ = 5.59, $p < 0.01$); *within-pair:* Estimate (SE): 1.00 (0.41), $t$ = 2.45, $p$ = 0.02). These findings suggest that the associations seen with decision-making (in males) and prorated FSIQ may, at least in part, reflect pre-existing liability, in addition to adverse consequences of greater lifetime heaviest frequencies of cannabis use. Consistent with expectations for a within-pair effect (McGue et al., 2010), within-pair by zygosity interaction terms were not significant ($ps \geq 0.32$).

In contrast to their male counterparts, females demonstrated a significant negative between-pair effect of lifetime heaviest frequency, but not a within-pair effect, on decision-making. Females demonstrated a slight positive lifetime heaviest frequency within-pair effect for overall decision-making and decision-making under risk; however, these did not come close to significance ($p \geq 0.30$). Contrasting signs of the between- and within-pair effects in females likely contribute to the lack of a significant association seen at the phenotypic level. Overall, this pattern suggests that decision-making deficits may index some pre-existing liability toward cannabis use in females.

The age of onset between-pair effects, but not within-pair effects ($ps \geq 0.38$), were significant for both processing speed in males and visuospatial attention in the full sample. These results are consistent with familial risk, as opposed to a causal influence of

cannabis use. Neither the between- nor within-pair effect were significant for the relationship between age of initiation and symbol search performance in females; however, the between-pair effect was larger. A larger sample may be necessary to tease apart findings given previous literature's overall small effect sizes (Scott et al., 2018).

**Unshared confounding**

The CTC models can control for both measured and unmeasured genetic and familial factors shared by twins that may confound the relationship between cannabis and cognition; however, CTC analyses cannot account for possible confounding by factors not shared by twins that might influence cannabis use and cognition. We attempted to account for primary factors that may confound within-pair effects of cannabis on cognition, such as differences in pre-exposure IQ, education, alcohol and nicotine use, and recent cannabis use. For significant age of onset within-pair effects, we also covaried for the age-24 cannabis index to better isolate the impact of age of initiation from heavy frequencies and quantities of cannabis use.

Independent of unshared confounding factors, the significant within-pair effect of lifetime heaviest frequency held for decision-making under risk in males (see right-hand column of Table 19 for adjusted within-pair estimates for decision-making variables), which is not consistent with unshared confounding. Conversely, unshared confounding appeared to attenuate somewhat the within-pair effect of lifetime heaviest frequency on overall decision-making performance in males, though it remained close to significance (Estimate [SE] = -4.60 (2.61), $t$ = -1.76, $p$ = 0.08). The age of onset within-pair effect on prorated FSIQ in the full sample remained significant and thus does not appear to reflect confounding of unshared measured characteristics and is not better accounted for by

differences in proximal frequency and quantity of cannabis use (see right-hand column of Table 20 for adjusted within-pair estimates for FSIQ).

The impact of differences in length of abstinence was also explored for significant within-pair effects that remained after covarying for other confounders. Within-pair estimates for length of abstinence were not significantly related to scores for either decision-making under risk or prorated FSIQ (*ps* ≥ 0.68; see Table 21 for decision-making within-pair estimate and Table 22 for FSIQ within-pair estimates after covarying for abstinence length). Additionally, cannabis use within-pair estimates remained significant. This pattern suggests that differences in length of abstinence did not mediate the relationship between exposure-related effects of cannabis, nor did it predict neurocognitive performance.

## Discussion

As a follow-up to our previous study, we assessed the causal association between cannabis use and neurocognitive performance in a large sample of twins assessed from adolescence to young adulthood. Our prior investigation examined the robustness of the association between cannabis use and cognition, independent of potential confounds. Results of that report that survived adjustment for multiple comparisons in the present study indicated persistent deficits in estimated intelligence and visuospatial attention. Sex-specific effects were found, such that males performed significantly worse on overall and risky decision-making and processing speed measures with higher lifetime heaviest frequencies, but females did not. Consistent with previous research, impairments were seen with heavier patterns of use (Fried et al., 2005; Meier et al., 2012; Scott et al., 2018) and an earlier age of onset (Broyd et al., 2018). Using a quasi-experimental cotwin

control design, the present study expands on these results providing important and novel information regarding the nature of the association between cannabis use and cognition in adolescence and young adulthood.

Associations found between lifetime heaviest frequency ever used and decision-making concurs with previous literature (Becker et al., 2014; Castellanos-Ryan et al., 2017; Gonzalez et al., 2012; Grant et al., 2012; Lovell et al., 2019; Solowij et al., 2002), as do our sex-specific effects suggesting significant deficits in males, but not females (Crane, Schuster, & Gonzalez, 2013). Within the current study, cotwin control analyses demonstrated a significant within-pair effect of cannabis on decision-making under risk, with a between-pair effect that approached but just missed significance in males. The reverse pattern was demonstrated for the relationship with overall decision-making. While individual-level effects were not significant, females did demonstrate a significant between-pair effect for both overall decision-making and decision-making under risk, with no evidence of a negative within-pair effect. Taken together, these suggest a complex relationship between greater lifetime heaviest frequency of use and decision-making such that deficits may index both a pre-existing liability toward cannabis use in both males and females but only a causal exposure-related effect of cannabis in males.

Brain regions that subsume functioning related to decision-making, such as the prefrontal cortex (Funahashi, 2017), are known to be rich in cannabinoid receptor type 1 (CB1) binding sites, where cannabis' main psychoactive ingredient Δ-9-tetrahydrocannabinol (THC) binds in the brain. Prefrontal cortical regions undergo critical maturational processes during adolescence and young adulthood (Tau & Peterson, 2010), and disruption of these processes have been theorized to account for some of the

poor cognitive outcomes related to cannabis exposure (Atkinson and Abbott, 2018). Our findings, that suggest a possible causal influence of cannabis on decision-making, would support this hypothesis. Imaging studies converge on this as well. Cousijin et al. (2012) found brain activation differences in core brain regions associated with decision-making in young adult heavy cannabis users compared to controls. Additionally, brain activation differences in prefrontal cortex regions between cannabis users and controls were linked to poorer performance on a decision-making task in cannabis users (Vaidya et al., 2012). Consistent with the present study findings, a prior functional magnetic resonance imaging study found that chronic young adult cannabis users performed more poorly at the end of a gambling task compared to controls, but differences were not seen between groups during the initial strategy development phase (Wesley et al., 2011). In that same study, brain activation differences were found alongside performance differences in brain regions such as the frontal cortex. The authors posit that cannabis users are less sensitive to negative feedback during strategy development than controls (Wesley et al., 2011). Taken a step further, our study demonstrated evidence consistent with an adverse impact of cannabis exposure in males but not females. As reviewed in our previous report, research has posited that protracted neurodevelopmental trajectories in prefrontal brain regions may make adolescent and young adult males more vulnerable to cannabis-related neural disruptions than females, particularly given that males tend to use more heavily and earlier than females (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013). The findings in the current study support the theory that sex-specific differences in neurodevelopmental trajectories may place adolescent and young adult males at heightened risk for cognitive deficits following cannabis exposure compared to their female counterparts. It will be

important for future studies to explore this sex-specific effect in cannabis users who did not use in adolescence or young adulthood to further explore this hypothesis.

Associations between an earlier age of onset and estimated intelligence are consistent with longitudinal studies that found associations with or declines in IQ with cannabis use (Boccio & Beaver, 2017; Infante et al., 2019; Meier et al., 2012; Powers et al., 2020) and phenotypic analyses within other twin studies (Jackson et al., 2016; Meier et al., 2018; Ross et al., 2020; Schaefer et al., 2021). Our findings from the cotwin control analyses are in partial accordance with other twin studies, such that we found evidence for potential shared familial and environmental confounding (e.g., significant between-pair effect) and the relationship between cumulative cannabis use and block design did not appear to be robust, which was also demonstrated in other twin analyses (Jackson et al., 2016; Meier et al., 2018; Ross et al., 2020; Schaefer et al., 2021). However, our findings contrast in that we also found evidence to suggest a possible adverse causal influence of an earlier age of cannabis on prorated FSIQ (e.g., significant within-pair effect), independent of shared familial risk, measured unshared confounding, and severity of cannabis use. This discordance may be for several reasons. First, most of the other twin analyses did not explore the implications of age of initiation as a continuous measure, instead focusing on measures of cumulative cannabis use, frequency of use, or cannabis dependence/cannabis use disorder (Jackson et al., 2016; Meier et al., 2018; Schaefer et al., 2021). Ross et al. (2020) assessed the causal impact of age of initiation but only found evidence for significant between-pair effects with measures of intelligence. Discrepancies with this study may be attributable to methodological differences as age of initiation was defined somewhat differently, such that Ross et al.

(2020) used the youngest age of initiation reported across all assessments as well as assigned non-cannabis users an age a year above the highest age reported in the sample (i.e., age 30). Conversely, in the present study, we took an individual's first report of age of initiation as it was the most proximal report to when cannabis use occurred to reduce measurement error from retrospective report, and we focused on individuals who had previous cannabis exposure. It will be necessary for future research to examine this relationship further; however, if an exposure-related effect of an earlier age of onset is replicated in future research, this finding has public health ramifications as it may represent a widespread disruption in neurodevelopmental processes (e.g., synaptic pruning, dendritic plasticity) and influences on the endocannabinoid systems subserving neurotransmitter processes for ongoing maturational rearrangement in the brain.

Literature on whether neurocognitive deficits related to cannabis persist despite abstinence has been mixed (Castellanos-Ryan et al., 2017; Lovell et al., 2020; Scott et al., 2018). For both our lifetime heaviest frequency and age of onset within-pair effects on decision-making (in males) and general estimated intelligence scores, evidence did not suggest that results were impacted by differences in the recency of last cannabis use. Nor did we find evidence that differences in length of time since last cannabis use was associated with improvements in neurocognitive performance. Some of the inconsistencies in prior literature may, at least in part, be due to methodological differences. For instance, a recent 14-year longitudinal study did not find evidence that recency of last cannabis use predicted neuropsychological performance, nor did it mediate the association between block design performance over time and cannabis use (Infante et al., 2020). Conversely, in an early longitudinal study by Fried and colleagues

(2005), current, heavy cannabis users had lower mean IQ scores compared to controls, but no differences were found in former cannabis users (at least three months abstinence); however, this investigation covered a shorter period (8 years), ended earlier in young adulthood, and relied on groups comparisons as opposed to dimensional measures of use, all of which may have limited ability to detect significant group differences. Our results converge with a recent meta-analysis of imaging studies that found alterations in prefrontal regions involved with executive functioning in adolescent cannabis users compared to controls, and group differences were also noted between an abstinent group of cannabis users (~25 days) and nonusers (Blest-Hopley et al., 2019). Taken together, these suggest that possible adverse consequences related to cannabis use may not resolve even with prolonged abstinence; however, longitudinal studies are needed that extend beyond the developmental period of young adulthood to assess if deficits are enduring once neuromaturation stabilizes.

Meta-analyses of the relationship between nonacute cannabis use and neurocognition have repeatedly demonstrated small to, at best, moderate effect sizes (Grant et al., 2003; Schreiner & Dunn, 2012; Scott et al., 2018; Lovell et al., 2020). Our results are generally in line with these findings. It is worthwhile to consider the clinical significance of such effects given their magnitude. Given the complexity of the relationships demonstrated (e.g., evidence for causal relationships in addition to pre-existing liability), it is challenging to say how the unique impact specific to cannabis exposure affects functional outcomes, which we did not speak to here. Additionally, cannabis use does not occur in a vacuum. Many of the factors that we controlled for as possible confounders (e.g., education, alcohol use, nicotine use) share overlapping

variance and co-occur with cannabis use, the combination of which may compound adverse effects. Understanding how these effects play out in an individual's day-to-day life will be necessary to better grasp the implications of cannabis use during adolescence and young adulthood. The landmark Adolescent Brain Cognitive Development study will hopefully help address some of these questions with a longitudinal dataset of 10,0000 children that includes more frequent and intensive interviewing, assessment, and neuroimaging (https://abcdstudy.org).

As noted above, in addition to within-pair effects, we also observed cannabis effects in the cotwin control analysis that are likely not due directly to cannabis exposure but rather index vulnerability to use cannabis (between-pair effect). This was found for both decision-making and estimated intelligence for both males and females. Evidence was also demonstrated for a pre-existing liability for visuospatial attention and processing speed, though the between-pair effect was weaker and did not reach significance for processing speed in females. While decision-making and processing speed have not previously been a focus of twin studies in adolescents and young adults, our other findings generally cohere with twin studies on visuospatial attention and intelligence (Jackson et al., 2016; Meier et al., 2018; Ross et al., 2020; Schaefer et al., 2021). Shared familial and environmental risk factors that influence cannabis use also appear to impact all of the neurocognitive measures related to cannabis use. Thus, neurocognitive deficits would likely be observed before cannabis exposure and may subsequently contribute to risky actions, such as cannabis use. Indeed, studies have found that deficits in neurocognitive performance predict later increases in cannabis use in adolescents (Morin et al., 2019), and as cannabis use is related to other externalizing problems (Iacono et al.,

2008), individuals with these predispositions are at risk for other adverse outcomes, such as cannabis use disorders or dependence (Butterworth et al., 2014). Meier et al. (2018) found that lower IQ scores in childhood predicted later cannabis dependence at age 18. In conjunction with previous research, this study demonstrates the complexity of the relationship between nonacute cannabis use and cognition, particularly in adolescence to young adulthood when maturational processes are ongoing, which likely contributes to the inconsistencies found in the overall extant literature. But this also highlights the importance of continued focus on the implications of cannabis exposure on the adolescent and young adult brain.

While the relationship between verbal working memory and lifetime heaviest frequency did not survive statistical adjustment, it does highlight the possibility that unique relationships could be demonstrated within cannabis users that are potentially masked by nonusers or those who use very minimally. Indeed, there is some evidence to suggest that individuals who use only minimally may demonstrate an unexpected relationship between cannabis and cognition, such that they perform better than individuals with no exposure to cannabis (Wendel et al., 2021). It may be worthwhile to explore this avenue further as the relationship between cannabis use and cognition appears to be nuanced.

**Strengths**

A primary strength of the present investigation is the twin sample, which increases our ability to draw inferences regarding the etiology of cannabis-related cognitive deficits beyond what is possible in cross-sectional studies or studies with unrelated individuals. Another strength is that this research was conducted in a large

population-based sample of males and females that more recently transitioned to young adulthood. Follow-up assessments covered both critical maturational periods of brain development and captured a spectrum of cannabis use behaviors ranging from normative to more severe use behaviors, which is essential for generalizing findings to broader populations. Their transition to young adulthood also coincided with increases in cannabis potency in the medicinal and recreational market (Chandra et al., 2019), making the current findings more relevant to users who now use products with higher THC content. Additionally, by using detailed gold-standard interviewing measures, we were able to avoid relying solely upon discrete group comparisons and instead used dimensional measures of cannabis, which have been suggested as a better representation of substance use (Iacono et al., 2008; Krueger et al., 2002; Infante et al., 2019) and have been shown to have greater validity and reliability than discrete measures (Markon et al., 2011). Participants also completed extensive neuropsychological testing covering a wide array of cognitive domains, some of which had yet to be explored using a CTC design. The strengths of this study enabled the current research to replicate previous work while also extending and filling gaps in the research base.

**Limitations**

While the CTC design allows for greater confidence in interpretations regarding the etiology of cognitive deficits, it is not without its limitations. First, the CTC model cannot entirely rule out the possibility of confounding and establish that an association represents a direct causal effect of cannabis on cognition. We attempted to control for several common confounding factors that may differ between twins and that have been noted in the literature as relevant; however, we are limited to those variables that we have

measured. This leaves open the possibility that there may be other unshared confounders that we have not explored, and thus results do not necessarily imply a direct neurotoxic effect of cannabis. Another limitation is that measurement error in our exposure variables is more likely to attenuate estimates of within-pair effects compared to individual-level estimates. This could lead to underestimates of effects and misattribution of findings. However, we employed robust interviewing processes with well-validated assessment measures across multiple time points, which likely reduced bias related to error that is introduced when individuals are required to recall information over long periods retrospectively, sometimes over decades.

Additionally, while large and population-based, our study sample is modeled after the population in Minnesota at the time of the intake assessment. Due to this, our sample is predominantly white, and minority groups are generally under-represented, which is a limiting factor in terms of the generalizability of findings. Lack of attention to cultural variation risks potentially incomplete or inaccurate conclusions when applied to a broader context of individuals (Apicella & Barrett, 2016). Future work would benefit from recruiting more diverse samples with appropriate representation of minority groups to improve generalizability.

A final consideration for the current study is that we could not ascertain fine-grained details regarding cannabis use behaviors, such as the potency of products used, route of consumption, or cannabis metabolite levels. A recent investigation comparing methods of characterizing cannabis use (e.g., self-report vs. urinary metabolite measurements) found that 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH), a cannabis metabolite, predicted poorer learning and memory performance in a sample of

adolescent and young adults, but self-report measures did not (Wade et al., 2021). It may be more informative moving forward to obtain objective measures of cannabis use, such as measuring metabolites, to better index cannabis exposure and patterns of use that may be influenced by person-specific factors.

### Conclusions

Results of the current project suggest pre-existing deficits in neurocognitive performance may index risk toward both greater lifetime heavier frequencies and earlier initiation of cannabis use during adolescence and young adulthood, which may in turn adversely impact estimated intelligence scores and, in males specifically, decision-making performance. These findings have important implications for prevention efforts. Prevention campaigns may focus on delaying and reducing cannabis use and targeting efforts toward individuals with a predisposition toward cannabis use, particularly those who may be at high risk for exposure-related neurocognitive insults (e.g., males). The information documented here could be used to inform health policies surrounding legalization, given the push at the state level for access both medicinally and recreationally to cannabis. Clinical correlation of these findings to functional outcomes may also help inform treatment planning.

## General Conclusion

Adolescence and young adulthood are critical periods for neuromaturation and neuronal restructuring and are often periods of peak substance use (Johnston et al., 2021). Exposure to substances, such as cannabis, during these time frames, may disrupt brain developmental processes and produce harmful and potentially lasting effects that would otherwise not be seen if maturation was completed. Broadly, cross-sectional research has

found relationships between nonacute cannabis use and neurocognitive performance in adolescents and young adults across cognitive domains (Scott et al., 2018); however, the exact nature of these relationships remains elusive. Cross-sectional studies tended to rely on small sample sizes and were unable to determine the temporal sequencing or causality of associations. Meta-analytic and longitudinal studies have attempted to address some of these issues, but the extant literature has produced inconsistent findings and has highlighted questions regarding the robustness of unique cannabis-related impacts on cognition above confounding factors along with other limitations in the literature (Grant et al., 2003; Power et al., 2020; Scott et al., 2018). Longitudinal studies with pre-and post-cannabis initiation measures of cognitive ability can better speak to temporal sequencing of associations. However, they cannot stringently control unmeasured confounds, such as shared familial and environmental liability toward cannabis use. As such, longitudinal studies could not fully disentangle possible causal influences of cannabis exposure from the effects of pre-existing liability factors on cognitive performance. Twin studies are well suited to address questions of causality; however, twin studies on nonacute cannabis use and cognition in adolescents and young adults are still rare and tend to focus on a narrow set of cognitive domains.

To address limitations and gaps in the literature, this dissertation was designed to assess the nature of associations found between nonacute cannabis use and neurocognitive performance and understand the implications of cannabis exposure on the developing brain. To do this, we used a large longitudinal sample of male and female twins followed at multiple time points across adolescence and into young adulthood with extensive interviewing and assessment protocols. As iterated in Study 1 and Study 2,

using this type of design conferred several strengths to the current project, including 1) use of several dimensional measures characterizing cannabis use across adolescence and young adulthood from multiple time points, 2) assessment of pre-cannabis exposure general cognitive ability, 3) roughly equal number of males and females allowed for the exploration of sex-specific effects, and 4) extensive interviewing allowed us to control for several relevant confounding factors and neurocognitive assessments covered a wide variety of cognitive domains.

Across the two studies, consistent with previous literature, nonacute cannabis use was associated with deficits in neurocognitive functioning. Evidence suggested that many of these relationships were not robust or unique to nonacute cannabis use, independent of confounding variables. Study 1 also highlighted that many of the inconsistencies seen in the literature might be due to methodological differences, such as suboptimal control of confounding variables or differences in neurocognitive task selection. However, beyond other factors, heavier and early cannabis use was related to persistent deficits in decision-making, processing speed, visuospatial attention, and general cognitive abilities. We also found evidence for sex-specific effects, such that males performed more poorly than females on decision-making and processing speed tasks with cannabis use. Converging on conclusions from Study 1 to explore the etiology of the most robust relationships, Study 2 found evidence that deficits in neurocognitive performance both indexed pre-existing familial or environmental liability toward cannabis use but may in turn also be adversely impacted by heavy and early cannabis use, specifically for estimated IQ and, in males, decision-making performance. Taken together, these findings have significant implications for health policy. Legalization has been a common topic at the state level

given an uptick in the acceptance of use and desire to explore the potential medicinal effects of cannabis. It will be necessary for findings such as these to be considered when informing specific policy guidelines.

The overall study focus of these projects should be considered when interpreting findings and considered in the context of relevant factors. For instance, the purpose of this dissertation was to examine associations unique to cannabis use above and beyond other potential confounding factors, such as other substance use. However, it is important to note that psychoactive substances are associated with some level of risk, and cannabis use does not occur in a vacuum. It would seem plausible that even when nonacute cannabis use is not a unique predictor of a cognitive outcome, that use may contribute to or compound deleterious outcomes. This project does not address factors such as co-occurring substance use beyond statistically controlling for differences in common substance use (alcohol/nicotine). Co-occurrence of cannabis with other substances, such as alcohol or nicotine, is common (Richter, 2019), and co-occurrence of these substances may have an additive effect on adverse outcomes. For instance, the use of alcohol, nicotine, or cannabis substantially increases the risk of becoming dependent on one of the other substances and can interfere with attempts to quit or reduce the use of the other substance (Kristman-Valente et al., 2017; Rabin & George, 2015). It will be necessary for future research to consider the potential interaction effects of co-occurring substance use on cognitive outcomes moving forward. Another important direction for future research will be the consideration of the measurement of cannabis. One of the biggest challenges when comparing across studies is that cannabis metrics are often defined differently, such as how to characterize discrete groups (e.g., "user" versus "nonuser") or when reporting

on frequency or quantity of use units of measurement may vary. Additionally, the potency of THC ratio to other cannabinoids, such as cannabidiol (CBD), can significantly impact the pharmacokinetic implications of a particular cannabis plant (Hložek et al., 2017), and may also lead to differences in outcomes. Understanding how these factors interact to either reduce or exacerbate adverse outcomes associated with cannabis use will be essential.

The results of this dissertation provide important and novel contributions to the field regarding the nature of the association between nonacute cannabis use and cognitive functioning during periods of key neuromaturation. Findings collectively suggest a complex relationship such that deficits in neurocognition represent a combination of pre-existing shared familial and environmental risk, unshared confounding contributions, and causal exposure-related effects of cannabis. These results could guide decisions regarding cannabis legalization policies and intervention efforts aimed at reducing and delaying cannabis use beyond critical neuromaturation periods

## Tables

**Table 1.** Sample descriptive statistics and substance use variables.

| | **Male (N = 362)** | | **Female (N = 439)** | | **Total (N = 801)** | |
|---|---|---|---|---|---|---|
| Variables | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| Age[a] | 24.36 (0.81) | 22.63 - 27.95 | 24.50 (0.97) | 22.66 - 28.08 | 24.43 (0.91) | 22.63 - 28.08 |
| Monozygotic (%) | N = 215 (59%) | - | N = 266 (61%) | - | N = 481 (60%) | - |
| Age-24 Years of education | 14.46 (1.71) | 10.00 - 18.00 | 14.99 (1.76) | 8.00 - 20.00 | 14.75 (1.75) | 8.00 - 20.00 |
| Age-11 Socioeconomic status | 0.14 (0.79) | -2.40 - 1.50 | 0.02 (0.72) | -1.73 - 1.50 | 0.07 (0.75) | -2.40 - 1.50 |
| *Cannabis variables* | | | | | | |
| Cannabis index | 0.94 (1.01) | 0.00 - 4.75 | 0.61 (0.88) | 0.00 - 4.50 | 0.76 (0.96) | 0.00 - 4.75 |
| Age-11 cannabis index[b] | - | - | - | - | - | - |
| Quantity | - | - | - | - | - | - |
| Frequency | - | - | - | - | - | - |
| Age-14 cannabis index | 0.09 (0.37) | 0.00 – 2.50 | 0.12 (0.53) | 0.00 - 4.50 | 0.11 (0.47) | 0.00 - 4.50 |
| Quantity | 0.12 (0.50) | 0.00 - 5.00 | 0.12 (0.56) | 0.00 - 5.00 | 0.12 (0.53) | 0.00 - 5.00 |
| Frequency | 0.07 (0.38) | 0.00 - 4.00 | 0.11 (0.54) | 0.00 - 4.00 | 0.09 (0.48) | 0.00 - 4.00 |
| Age-17 cannabis index | 0.74 (1.24) | 0.00 - 5.00 | 0.50 (1.08) | 0.00 - 5.00 | 0.61 (1.16) | 0.00 - 5.00 |
| Quantity | 0.80 (1.38) | 0.00 - 5.00 | 0.56 (1.21) | 0.00 - 5.00 | 0.67 (1.30) | 0.00 - 5.00 |
| Frequency | 0.66 (1.16) | 0.00 - 5.00 | 0.41 (0.91) | 0.00 - 5.00 | 0.53 (1.04) | 0.00 - 5.00 |
| Age-24 cannabis index | 1.81 (1.69) | 0.00 - 5.00 | 1.12 (1.38) | 0.00 - 5.00 | 1.43 (1.57) | 0.00 - 5.00 |
| Quantity | 2.12 (1.94) | 0.00 - 5.00 | 1.33 (1.64) | 0.00 - 5.00 | 1.69 (1.83) | 0.00 - 5.00 |
| Frequency | 1.43 (1.57) | 0.00 - 5.00 | 0.91 (1.21) | 0.00 - 5.00 | 1.16 (1.41) | 0.00 - 5.00 |
| Lifetime heaviest frequency | 2.10 (1.79) | 0.00 – 5.00 | 1.41 (1.62) | 0.00 – 5.00 | 1.72 (1.72) | 0.00 – 5.00 |
| Age of initiation | 16.93 (2.41) | 11.00 - 25.00 | 17.52 (2.92) | 12.00 - 25.00 | 17.22 (2.69) | 11.00 - 25.00 |
| Length of abstinence | 3.46 (2.19) | 1.00 – 6.00 | 4.12 (2.07) | 1.00 – 6.00 | 3.78 (2.16) | 1.00 – 6.00 |
| Recent cannabis use[c] (%) | N = 40 (11%) | - | N = 24 (5%) | - | N = 64 (8%) | - |
| *Other substance use variables* | | | | | | |
| Age-24 alcohol index | 3.11 (1.03) | 0.00 – 5.67 | 2.48 (0.95) | 0.00 – 5.75 | 2.76 (1.04) | 0.00 – 5.75 |
| Drinks per occasion | 1.81 (0.94) | 0.00 – 5.00 | 1.45 (0.79) | 0.00 – 6.00 | 1.61 (0.88) | 0.00 – 6.00 |
| Frequency | 2.98 (0.90) | 0.00 – 5.00 | 2.68 (0.83) | 0.00 – 5.00 | 2.81 (0.88) | 0.00 – 5.00 |
| Max drinks in 24-hrs | 3.95 (1.31) | 0.00 – 6.00 | 3.03 (1.19) | 0.00 – 6.00 | 3.45 (1.33) | 0.00 – 6.00 |
| # of intoxications | 3.69 (1.96) | 0.00 – 6.00 | 2.76 (1.92) | 0.00 – 6.00 | 3.18 (1.99) | 0.00 – 6.00 |
| Age-24 nicotine index | 1.02 (0.84) | 0.00 – 2.50 | 0.44 (0.68) | 0.00 – 2.50 | 0.70 (0.81) | 0.00 – 2.50 |
| Quantity | 1.02 (0.92) | 0.00 – 3.00 | 0.41 (0.66) | 0.00 – 3.00 | 0.69 (0.84) | 0.00 – 3.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cigarettes | 0.90 (1.20) | 0.00 – 4.00 | 0.50 (0.97) | 0.00 – 4.00 | 0.68 (1.09) | 0.00 – 4.00 |
| Cigars | 0.36 (0.51) | 0.00 – 3.00 | 0.09 (0.29) | 0.00 – 1.00 | 0.21 (0.43) | 0.00 – 3.00 |
| Pipe | 0.09 (0.36) | 0.00 – 4.00 | 0.02 (0.13) | 0.00 – 1.00 | 0.05 (0.26) | 0.00 – 4.00 |
| Snuff | 0.42 (0.73) | 0.00 – 3.00 | 0.02 (0.16) | 0.00 – 2.00 | 0.20 (0.54) | 0.00 – 3.00 |
| Frequency | 1.03 (0.83) | 0.00 – 2.00 | 0.50 (0.75) | 0.00 – 2.00 | 0.75 (0.83) | 0.00 – 2.00 |

*Notes.* Transformed values are presented for ordinal cannabis variables.

[a]Age of participant at most recent age-24 assessment

[b]Individuals who had reported use prior to their age 24 assessment were excluded and cannabis use was 0 for all participants at intake

[c]Used in 24-hours preceding age-24 assessment

**Table 2**. Descriptive performance statistics for neurocognitive measures.

| | Male (N = 362) | | Female (N = 439) | | Total (N = 801) | |
|---|---|---|---|---|---|---|
| Cognitive Measure | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| **Age-11 Cognitive Measure** | | | | | | |
| Pre-exposure IQ[a] | 105.77 (12.96) | 64.00 – 146.00 | 102.69 (12.45) | 69.00 – 150.00 | 104.09 (12.77) | 64.00 – 150.00 |
| **Age-24 Cognitive Measures** | | | | | | |
| *Vb. Learning/Memory* | | | | | | |
| Total Learning[b] | 44.81 (9.10) | 15.00 – 71.00 | 48.93 (8.52) | 27.00 – 69.00 | 47.12 (9.01) | 15.00 – 71.00 |
| Short-delay Recall[b] | -1.72 (1.75) | -9.00 – 2.00 | -1.67 (1.86) | -9.00 – 6.00 | -1.69 (1.81) | -9.00 – 6.00 |
| Long-delay Recall[b] | -2.26 (1.95) | -8.00 – 2.00 | -1.91 (1.73) | -7.00 – 4.00 | -2.06 (1.83) | -8.00 – 4.00 |
| *Processing Speed* | | | | | | |
| PSI[a] | 103.75 (13.20) | 76.00 – 145.00 | 109.09 (12.78) | 71.00 – 143.00 | 106.74 (13.23) | 71.00 – 145.00 |
| Digit Sym-Cod[c] | 9.84 (2.52) | 4.00 – 17.00 | 11.33 (2.57) | 4.00 – 18.00 | 10.67 (2.65) | 4.00 – 18.00 |
| Symbol Search[c] | 11.61 (2.65) | 6.00 – 19.00 | 12.00 (2.60) | 5.00 – 19.00 | 11.83 (2.62) | 5.00 – 19.00 |
| *Vb. Attention/WM* | | | | | | |
| RAVLT Trial 1[b] | 5.67 (1.69) | 0.00 – 13.00 | 6.25 (1.66) | 2.00 – 11.00 | 6.00 (1.70) | 0.00 – 13.00 |
| Longest DSF[b] | 6.93 (1.18) | 4.00 – 9.00 | 6.76 (1.22) | 4.00 – 9.00 | 6.83 (1.12) | 4.00 – 9.00 |
| Longest DSB[b] | 4.91 (1.26) | 2.00 – 8.00 | 4.93 (1.23) | 2.00 – 8.00 | 4.92 (1.24) | 2.00 – 8.00 |
| *Vis. Attention/WM* | | | | | | |
| Longest SSF[b] | 6.48 (1.20) | 2.00 – 9.00 | 6.42 (1.01) | 3.00 – 9.00 | 6.45 (1.10) | 2.00 – 9.00 |
| Longest SSB[b] | 6.33 (1.21) | 2.00 – 9.00 | 6.27 (1.26) | 2.00 – 9.00 | 6.30 (1.24) | 2.00 – 9.00 |
| *Decision-Making* | | | | | | |
| DM Overall[b] | 6.18 (35.22) | -80.00 – 100.00 | 2.30 (33.70) | -96.00 – 100.00 | 4.00 (34.40) | -96.00 – 100.00 |
| DM Ambiguity[d] | 6.09 (1.12) | 3.00 – 9.00 | 5.95 (0.92) | 2.24 – 9.00 | 6.00 (1.02) | 2.24 – 9.00 |
| DM Risk[b] | 8.80 (27.26) | -50.00 – 60.00 | 7.42 (26.98) | -60.00 – 60.00 | 8.02 (27.09) | -60.00 – 60.00 |
| *Cognitive Inhibition* | | | | | | |
| D-prime[b] | 3.41 (0.90) | 0.24 – 5.57 | 3.63 (0.80) | 0.54 – 5.57 | 3.53 (0.85) | 0.24 – 5.57 |
| No-go Error Rate[d,e] | 3.63 (1.61) | 0.00 – 8.66 | 3.28 (1.36) | 0.00 – 8.55 | 3.43 (1.49) | 0.00 – 8.66 |
| *General Cog Ability* | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Prorated FSIQ[a] | 109.04 (15.73) | 76.00 – 151.00 | 104.66 (16.75) | 70.00 – 151.00 | 106.59 (16.44) | 70.00 – 151.00 |
| Block Design[c] | 12.91 (2.71) | 6.00 – 19.00 | 12.14 (2.77) | 5.00 – 19.00 | 12.48 (2.77) | 5.00 – 19.00 |
| Vocabulary[c] | 9.72 (2.13) | 5.00 – 19.00 | 12.14 (2.77) | 5.00 – 19.00 | 12.48 (2.77) | 5.00 – 19.00 |

*Abbreviations:* IQ, intelligence quotient; Vb., verbal; PSI, processing speed index, Digit Symb-Cod, digit symbol-coding; WM, working memory; RAVLT, Rey Auditory Verbal Learning Test; DSF, digit span forward; DSB, digit span backwards; Vis., visuospatial; SSF, spatial span forward; SSB, spatial span backwards; DM, decision-making; FSIQ, full scale intelligence quotient.

[a]Standard score: mean of 100, standard deviation of 15

[b]Raw score

[c]Scaled score: mean of 10, standard deviation of 3

[d]Square-root transformed

[e]Higher values = more errors

**Table 3.** Neurocognitive battery.

| Domain | Measure | Variables | References |
|---|---|---|---|
| Verbal learning & memory | Rey Auditory Learning Test (RAVLT): learn a list of 15 words across 5 trials and recall list after short- and long-delay recall | *Total learning*: total # of words repeated back across 5 learning trials<br><br>*Short-delay recall:* # of words recalled after short delay minus # of words learned on last learning trial<br><br>*Long-delay recall:* # of words recalled after 30-minute delay minus # of words learned on last learning trial | Schmidt, 1996 |
| Processing speed | Digit Symbol-Coding: match symbols to numbers using reference key as quickly as possible<br><br>Symbol Search: visually scan row of symbols, mark matching symbol to target symbol or "no" box if no match is found<br><br>Processing Speed Index (PSI) | Derived scaled score following standard administration and scoring procedures; reflects # of correctly paired symbols completed in 120 sec<br>Derived scaled score following standard administration and scoring procedures; reflects # of accurately marked symbols/"no" boxes less any errors completed in 120 secs<br>Derived standard score following standard scoring procedures based on digit symbol-coding and symbol search scores | Wechsler, 1999<br><br>Wechsler, 1999 |
| Verbal attention & working memory | Digit Span: repeat back a string of digits either in the forward or backwards order | *Longest digit span forward:* max # of digits correctly repeated in the original presentation order<br><br>*Longest digit span backward:* max # of digits correctly repeated in the backwards order | |
| | RAVLT Trial 1: learn a list of 15 words | Total # of accurately repeated words after initial presentation of word list | Schmidt, 1996 |

| | | | |
|---|---|---|---|
| Visuospatial attention & working memory | Spatial Span: click on irregularly spaced blocks in the same or backwards order that they initially lit up on the screen | *Longest spatial span forward:* max # correctly identified squares in the original presentation order<br><br>*Longest spatial span backward:* max # correctly identified squares selected in the backwards order | Wechsler, 1997; E-Prime version 2.0, Schneider et al., 2002 |
| Decision-making | Iowa Gambling Task (IGT): select cards from 4 decks of cards to maximize winnings using feedback about winning/losing money | *Overall decision-making:* # of advantageous deck selections minus # of disadvantageous deck selections across all 5 blocks (100 trials)<br>*Decision-making under ambiguity:* # of advantageous deck selections minus # of disadvantageous deck selections across the first 2 blocks (40 trials)<br><br>*Decision-making under risk:* # of advantageous deck selections minus # of disadvantageous deck selections across the last 3 blocks (60 trials) | Bechara et al., 1994; Almy et al., 2019; E-Prime version 2.0, Schneider et al., 2002 |
| Cognitive inhibition | Go/No-Go Task: press button when the stimulus presented (e.g., letters) followed a different stimulus ("go" trial) and withhold response when stimulus was preceded by an identical stimulus ("no-go" trials) | *D-prime:* z-transformed hit rate minus the z-transformed false-alarm rate<br><br>*No-go error rate:* frequency of responding to no-go trials | Garavan et al., 2005; Wickens, 2002 |
| General cognitive ability | Block Design: duplicate a presented patten using 2, 4, or 9 identical red/white blocks | Derived scaled score reflects # correct based on standard administration and scoring procedures | Wechsler, 1981 |
| | Vocabulary: define a word that is presented both orally and visually | Derived scaled score reflects # correct based on standard administration and scoring procedures | |
| | Prorated Full Scale IQ (FSIQ) | Derived standard score following standard prorating scoring procedures based on block design and vocabulary scores | |

*Notes.* Description of all age-24 cognitive outcomes and their derived variables.

**Table 4.** Zero order correlations between cannabis variables and covariates.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Cannabis index | 1 | | | | | | | | | | | | | |
| 2. Lifetime heaviest frequency | 0.85** | 1 | | | | | | | | | | | | |
| 3. Age of initiation | -0.53** | -0.42** | 1 | | | | | | | | | | | |
| 4. Sex[a] | -0.17** | -0.20** | 0.11* | 1 | | | | | | | | | | |
| 5. Age | 0.02 | 0.00 | 0.07 | 0.08* | 1 | | | | | | | | | |
| 6. Zygosity | -0.05 | -0.03 | 0.12** | 0.02 | 0.03 | 1 | | | | | | | | |
| 7. Pre-exposure IQ | 0.04 | 0.04 | 0.23** | -0.12** | 0.05 | 0.00 | 1 | | | | | | | |
| 8. Socioeconomic status | -0.01 | 0.04 | 0.18** | -0.08* | -0.03 | -0.03 | 0.28** | 1 | | | | | | |
| 9. Age-24 Alcohol index | 0.46** | 0.54** | -0.22** | -0.30** | -0.01 | 0.01 | 0.08* | 0.01 | 1 | | | | | |
| 10. Age-24 Nicotine index | 0.49** | 0.52** | -0.36** | -0.36** | -0.01 | -0.04 | -0.03 | -0.06 | 0.52** | 1 | | | | |
| 11. Education | -0.30** | -0.25** | 0.37** | 0.15** | 0.09* | 0.00 | 0.27** | 0.39** | -0.13** | -0.31** | 1 | | | |
| 12. Recent cannabis use[b] | 0.49** | 0.46** | -0.18** | -0.10**[c] | 0.04 | -0.02 | 0.03 | -0.01 | 0.22** | 0.25** | -0.17** | 1 | | |
| 13. Length of abstinence | -0.51** | -0.57** | 0.16** | 0.15** | 0.06 | -0.02 | 0.00 | -0.06 | -0.20** | -0.22** | 0.14** | -0.44** | 1 | |
| 14. Age-24 Cannabis index | 0.87** | 0.92** | -0.29** | -0.22** | -0.01 | -0.02 | 0.09* | 0.07* | 0.50** | 0.47** | -0.23** | 0.58** | -0.69** | 1 |

*Notes.* Correlations between our primary cannabis use variables and covariate variables.
*significant at the 0.05 level; **significant at the 0.01 level
[a]Sex = Females (1), Males (0); [b]Recent cannabis use (past 24-hours) = Yes (1), No (0); [c]phi-coefficient for two dichotomous variables

**Table 5.** Linear mixed models of the association between cannabis use and cognitive outcomes.

| | Cannabis index | | | | Lifetime heaviest frequency | | | | Age of initiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognitive measures | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value |
| *Vb. Learning/Memory* | | | | | | | | | | | | |
| Total Learning | 690 | -0.50 (0.37) | -1.34 | 0.18 | 690 | -0.11 (0.20) | -0.53 | 0.60 | 459 | 0.26 (0.16) | 1.62 | 0.11 |
| Short-delay Recall | 690 | 0.03 (0.07) | 0.39 | 0.69 | 690 | 0.00 (0.04) | 0.12 | 0.91 | 459 | 0.00 (0.03) | 0.06 | 0.95 |
| Long-delay Recall | 689 | 0.02 (0.08) | 0.21 | 0.84 | 689 | 0.01 (0.04) | 0.24 | 0.81 | 459 | 0.02 (0.03) | 0.66 | 0.51 |
| *Processing Speed* | | | | | | | | | | | | |
| PSI | 688 | -1.05 (0.55) | -1.91 | 0.06 | 688 | -0.24 (0.29) | -0.81 | 0.42 | 458 | **0.95 (0.22)** | **4.30** | **<0.01** |
| Digit Sym-Cod | 688 | **-0.28 (0.11)** | **-2.56** | **0.01** | 688 | -0.09 (0.06) | -1.48 | 0.14 | 458 | **0.18 (0.04)** | **4.09** | **<0.01** |
| Symbol Search | 688 | -0.11 (0.11) | -0.96 | 0.34 | 688 | 0.00 (0.06) | -0.05 | 0.96 | 458 | **0.17 (0.04)** | **3.74** | **<0.01** |
| *Vb. Attention/WM* | | | | | | | | | | | | |
| RAVLT Trial 1 | 690 | **-0.18 (0.07)** | **-2.57** | **0.01** | 690 | **-0.09 (0.04)** | **-2.31** | **0.02** | 459 | **0.06 (0.03)** | **2.08** | **0.04** |
| Longest DSF | 689 | **0.11 (0.05)** | **2.18** | **0.03** | 689 | **0.06 (0.03)** | **2.32** | **0.02** | 458 | 0.02 (0.02) | 0.84 | 0.40 |
| Longest DSB | 683 | 0.05 (0.05) | 0.95 | 0.34 | 683 | 0.02 (0.03) | 0.85 | 0.39 | 454 | 0.01 (0.02) | 0.63 | 0.53 |
| *Vis. Attention/WM* | | | | | | | | | | | | |
| Longest SSF | 667 | **-0.09 (0.05)** | **-1.97** | **0.05** | 667 | -0.03 (0.03) | -1.26 | 0.21 | 442 | **0.07 (0.02)** | **3.59** | **<0.01** |
| Longest SSB | 666 | **-0.13 (0.05)** | **-2.43** | **0.02** | 666 | **-0.07 (0.03)** | **-2.29** | **0.02** | 441 | **0.05 (0.02)** | **2.28** | **0.02** |
| *Decision-Making* | | | | | | | | | | | | |
| DM Overall | 672 | **-3.16 (1.47)** | **-2.15** | **0.03** | 672 | **-2.60 (0.80)** | **-3.27** | **<0.01** | 445 | **1.58 (0.61)** | **2.58** | **0.01** |
| DM Ambiguity[a] | 672 | -0.07 (0.04) | -1.61 | 0.11 | 672 | **-0.05 (0.02)** | **-2.23** | **0.03** | 445 | **0.05 (0.02)** | **2.37** | **0.02** |
| DM Risk | 672 | **-2.40 (1.16)** | **-2.07** | **0.04** | 672 | **-2.05 (0.63)** | **-3.25** | **<0.01** | 445 | **1.07 (0.48)** | **2.23** | **0.03** |
| *Cognitive Inhibition* | | | | | | | | | | | | |
| D-prime | 679 | -0.06 (0.04) | -1.74 | 0.08 | 679 | -0.03 (0.02) | -1.54 | 0.12 | 453 | **0.05 (0.02)** | **3.07** | **<0.01** |
| No-go Error Rate[a,b] | 679 | 0.04 (0.06) | 0.60 | 0.55 | 679 | 0.02 (0.03) | 0.58 | 0.57 | 453 | **-0.08 (0.03)** | **-3.16** | **<0.01** |
| *General Cognitive Ability* | | | | | | | | | | | | |
| Prorated FSIQ | 685 | -1.29 (0.68) | -1.91 | 0.06 | 685 | -0.09 (0.35) | -0.25 | 0.80 | 454 | **1.45 (0.27)** | **5.48** | **<0.01** |
| Block Design | 686 | **-0.23 (0.12)** | **-1.95** | **0.05** | 686 | -0.05 (0.06) | -0.87 | 0.39 | 455 | **0.22 (0.05)** | **4.71** | **<0.01** |
| Vocabulary | 794 | -0.13 (0.09) | -1.42 | 0.16 | 794 | 0.00 (0.05) | -0.01 | 0.99 | 510 | **0.17 (0.04)** | **4.67** | **<0.01** |

*Notes.* All linear mixed models include covariates for age, sex, and zygosity and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.

*Abbreviations:* Vb., verbal; PSI, processing speed index, Digit Symb-Cod, digit symbol-coding; WM, working memory; RAVLT, Rey Auditory Verbal Learning Test; SS, scaled score; DSF, digit span forward; DSB, digit span backwards; Vis., visuospatial; SSF, spatial span forward; SSB, spatial span backwards; DM, decision-making; FSIQ, full scale intelligence quotient

[a]Values were square-root transformed prior to analyses

[b]Higher values = more errors

**Table 6.** Zero order correlations between primary covariates and cognitive outcomes.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1.Pre-exposure IQ | 1 | | | | | | | | | |
| 2.SES | 0.28** | 1 | | | | | | | | |
| 3.Age-24 Alcohol index | 0.08* | 0.01 | 1 | | | | | | | |
| 4.Age-24 Nicotine index | -0.03 | -0.06 | 0.52** | 1 | | | | | | |
| 5.Education | 0.27** | 0.39** | -0.13** | -0.31** | 1 | | | | | |
| 6.Recent use[a] | 0.03 | -0.01 | 0.22** | 0.25** | -0.17** | 1 | | | | |
| 7. Total learning | 0.27** | 0.16** | -0.07 | -0.16** | 0.27** | -0.09* | 1 | | | |
| 8.Short-delay recall | 0.10** | 0.03 | -0.05 | -0.04 | 0.04 | -0.05 | 0.12** | 1 | | |
| 9.Long-delay recall | 0.06 | -0.01 | -0.08* | -0.10** | 0.04 | 0.00 | 0.19** | 0.70** | 1 | |
| 10.Processing speed index | 0.28** | 0.13** | -0.03 | -0.22** | 0.27** | -0.09* | 0.34** | 0.11** | 0.10* | 1 |
| 11.Digit symbol-coding | 0.20** | 0.15** | -0.08* | -0.27** | 0.32** | -0.09* | 0.32** | 0.09* | 0.07 | 0.88** |
| 12.Symbol Search | 0.29** | 0.09* | 0.03 | -0.12** | 0.16** | -0.07 | 0.27** | 0.10* | 0.09* | 0.88** |
| 13.RAVLT Trial 1 | 0.27** | 0.16** | -0.06 | -0.14** | 0.27** | -0.09* | 0.72** | 0.09* | 0.17** | 0.26** |
| 14.Longest DS forward | 0.19** | 0.22** | 0.14** | 0.07 | 0.14** | 0.03 | 0.15** | -0.04 | -0.12** | 0.15** |
| 15.Longest DS backward | 0.23** | 0.18** | 0.03 | -0.04 | 0.13** | 0.03 | 0.29** | 0.05 | 0.05 | 0.21** |
| 16.Longest SS forward | 0.19** | 0.12** | 0.04 | -0.04 | 0.17** | -0.05 | 0.23** | 0.09* | 0.06 | 0.31** |
| 17.Longest SS backward | 0.19** | 0.11** | 0.01 | -0.07 | 0.22** | -0.09* | 0.26** | 0.03 | 0.03 | 0.30** |
| 18.DM overall | 0.20** | 0.17** | -0.02 | -0.06 | 0.18** | -0.09* | 0.18** | 0.05 | 0.03 | 0.07 |
| 19.DM risk | 0.23** | 0.18** | -0.06 | -0.10** | 0.21** | -0.07 | 0.22** | 0.07 | 0.06 | 0.08* |
| 20.DM ambiguity[b] | 0.04 | 0.07 | 0.05 | 0.04 | 0.04 | -0.10* | 0.01 | -0.02 | -0.05 | 0.02 |
| 21.D_prime | 0.12** | 0.13** | -0.04 | -0.20** | 0.26** | -0.04 | 0.24** | 0.05 | 0.07 | 0.43** |
| 22.No-go error rate[b,c] | -0.16** | -0.15** | 0.03 | 0.16** | -0.25** | 0.00 | -0.22** | -0.06 | -0.05 | -0.41** |
| 23.Prorated FSIQ | 0.68** | 0.35** | -0.02 | -0.08* | 0.34** | -0.00 | 0.34** | 0.13** | 0.10** | 0.36** |
| 24.Block design | 0.53** | 0.19** | 0.01 | -0.05 | 0.18** | -0.01 | 0.20** | 0.11** | 0.08* | 0.40** |
| 25.Vocabulary | 0.60** | 0.37** | -0.04 | -0.11** | 0.40** | -0.02 | 0.37** | 0.11** | 0.09* | 0.21** |

*Notes.* Correlations between our primary covariates and cognitive outcomes. Correlation Table continued on next page.

*significant at the 0.05 level; **significant at the 0.01 level

[a]Recent cannabis use (past 24-hours) = Yes (1), No (0); [b] Square-root transformed; [c]Higher scores = more errors

*Abbreviations:* IQ, intelligence quotient; SES, socioeconomic status; RAVLT, Rey Auditory Learning Task; DS, digit span; SS, spatial span; DM, decision-making; FSIQ, full scale intelligence quotient

**Table 6.** Zero order correlations between primary covariates and cognitive outcomes (continued)

| | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11.Digit symbol-coding | 1 | | | | | | | | | | | | | | |
| 12.Symbol Search | 0.54** | 1 | | | | | | | | | | | | | |
| 13.RAVLT Trial 1 | 0.26** | 0.19** | 1 | | | | | | | | | | | | |
| 14.Longest DS forward | 0.13** | 0.14** | 0.16** | 1 | | | | | | | | | | | |
| 15.Longest DS backward | 0.21** | 0.16** | 0.26** | 0.38** | 1 | | | | | | | | | | |
| 16.Longest SS forward | 0.26** | 0.28** | 0.17** | 0.10** | 0.18** | 1 | | | | | | | | | |
| 17.Longest SS backward | 0.27** | 0.26** | 0.17** | 0.12** | 0.20** | 0.26** | 1 | | | | | | | | |
| 18.DM overall | 0.04 | 0.09* | 0.13** | 0.10* | 0.17** | 0.10* | 0.04 | 1 | | | | | | | |
| 19.DM risk | 0.06 | 0.08* | 0.15** | 0.12** | 0.19** | 0.11** | 0.08* | 0.95** | 1 | | | | | | |
| 20.DM ambiguity[b] | -0.02 | 0.05 | 0.02 | 0.02 | 0.04 | 0.04 | -0.05 | 0.71** | 0.45** | 1 | | | | | |
| 21.D-prime | 0.44** | 0.33** | 0.16** | 0.15** | 0.23** | 0.18** | 0.24** | 0.15** | 0.17** | 0.04 | 1 | | | | |
| 22.No-go error rate[b,c] | -0.42** | -0.30** | -0.15** | -0.18** | -0.27** | -0.17** | -0.21** | -0.15** | -0.18** | -0.03 | -0.88** | 1 | | | |
| 23.Prorated FSIQ | 0.28** | 0.36** | 0.29** | 0.21** | 0.32** | 0.25** | 0.29** | 0.26** | 0.29** | 0.07 | 0.21** | -0.23** | 1 | | |
| 24.Block design | 0.30** | 0.40** | 0.16** | 0.12** | 0.24** | 0.29** | 0.33** | 0.16** | 0.18** | 0.04 | 0.16** | -0.15** | 0.81** | 1 | |
| 25.Vocabulary | 0.17** | 0.20** | 0.33** | 0.23** | 0.29** | 0.15** | 0.16** | 0.26** | 0.29** | 0.09* | 0.19** | -0.22** | 0.81** | 0.34** | 1 |

*Notes.* Correlations between our primary covariates and cognitive outcomes
*significant at the 0.05 level; **significant at the 0.01 level
[a]Recent cannabis use (past 24-hours) = Yes (1), No (0); [b] Square-root transformed; [c]Higher scores = more errors
*Abbreviations:* IQ, intelligence quotient; SES, socioeconomic status; RAVLT, Rey Auditory Learning Task; DS, digit span; SS, spatial span; DM, decision-making; FSIQ, full scale intelligence quotient

**Table 7.** Associations between cannabis use and cognitive outcomes adjusted for covariates.

| | | **Cannabis index** | | | | **Lifetime heaviest frequency** | | | | **Age of initiation** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Estimates $_{(SE)}$ | t | p | | Estimates $_{(SE)}$ | t | p | | Estimates $_{(SE)}$ | t | p |
| ***Section A*** | Step | | | | Step | | | | Step | | | |
| RAVLT Total Learning | 1 | -0.49 (0.35) | -1.37 | 0.17 | 1 | -0.16 (0.19) | -0.82 | 0.42 | 1 | 0.05 (0.16) | 0.30 | 0.77 |
| | 2 | -0.43 (0.41) | -1.06 | 0.29 | 2 | -0.10 (0.23) | -0.42 | 0.67 | 2 | 0.05 (0.16) | 0.33 | 0.74 |
| | 3 | 0.02 (0.42) | 0.04 | 0.97 | 3 | 0.13 (0.24) | 0.56 | 0.58 | 3 | -0.06 (0.17) | -0.36 | 0.72 |
| | 4 | 0.30 (0.46) | 0.65 | 0.52 | 4 | 0.28 (0.25) | 1.10 | 0.27 | 4 | -0.08 (0.17) | -0.50 | 0.62 |
| RAVLT Short-Delay Recall | 1 | 0.03 (0.07) | 0.43 | 0.67 | 1 | 0.00 (0.04) | 0.04 | 0.97 | 1 | -0.01 (0.03) | -0.29 | 0.77 |
| | 2 | 0.12 (0.09) | 1.37 | 0.17 | 2 | 0.06 (0.05) | 1.10 | 0.27 | 2 | -0.03 (0.03) | -0.94 | 0.35 |
| | 3 | 0.15 (0.09) | 1.59 | 0.11 | 3 | 0.06 (0.05) | 1.18 | 0.24 | 3 | -0.04 (0.04) | -1.13 | 0.26 |
| | 4 | **0.24 (0.10)** | **2.36** | **0.02** | 4 | 0.10 (0.06) | 1.80 | 0.07 | 4 | -0.05 (0.04) | -1.30 | 0.20 |
| RAVLT Long-Delay Recall | 1 | 0.02 (0.08) | 0.23 | 0.82 | 1 | 0.01 (0.04) | 0.20 | 0.84 | 1 | 0.01 (0.03) | 0.34 | 0.74 |
| | 2 | 0.14 (0.09) | 1.54 | 0.13 | 2 | 0.09 (0.05) | 1.71 | 0.09 | 2 | -0.01 (0.04) | -0.42 | 0.67 |
| | 3 | 0.17 (0.09) | 1.87 | 0.06 | 3 | 0.10 (0.05) | 1.88 | 0.06 | 3 | 0.03 (0.04) | -0.79 | 0.43 |
| | 4 | 0.18 (0.10) | 1.82 | 0.07 | 4 | 0.10 (0.06) | 1.81 | 0.07 | 4 | -0.03 (0.04) | -0.77 | 0.44 |
| ***Section B*** | Step | | | | Step | | | | Step | | | |
| Processing Speed Index | 1 | **-1.15 (0.52)** | **-2.21** | **0.03** | 1 | -0.37 (0.28) | -1.33 | 0.18 | 1 | **0.64 (0.22)** | **2.94** | **<0.01** |
| | 2 | -1.11 (0.59) | -1.90 | 0.06 | 2 | -0.35 (0.33) | -1.07 | 0.28 | 2 | **0.55 (0.23)** | **2.43** | **0.02** |
| | 3 | -0.49 (0.61) | -0.81 | 0.42 | 3 | -0.06 (0.34) | -0.19 | 0.85 | 3 | 0.42 (0.23) | 1.79 | 0.07 |
| | 4 | -0.11 (0.65) | -0.17 | 0.87 | 4 | 0.14 (0.35) | 0.38 | 0.70 | 4 | 0.39 (0.23) | 1.66 | 0.10 |
| Digit Symbol-Coding | 1 | **-0.29 (0.10)** | **-2.76** | **0.01** | 1 | **-0.11 (0.06)** | **-2.01** | **0.05** | 1 | **0.12 (0.04)** | **2.81** | **0.01** |
| | 2 | **-0.24 (0.12)** | **-2.03** | **0.04** | 2 | -0.09 (0.07) | -1.27 | 0.20 | 2 | **0.09 (0.04)** | **2.05** | **0.04** |
| | 3 | -0.10 (0.12) | -0.80 | 0.42 | 3 | -0.02 (0.07) | -0.32 | 0.75 | 3 | 0.06 (0.05) | 1.37 | 0.17 |
| | 4 | -0.03 (0.13) | -0.21 | 0.83 | 4 | 0.01 (0.07) | 0.20 | 0.84 | 4 | 0.06 (0.05) | 1.25 | 0.21 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Symbol Search | 1 | -0.13 (0.11) | -1.21 | 0.23 | 1 | -0.02 (0.06) | -0.40 | 0.69 | 1 | **0.11 (0.04)** | **2.46** | **0.01** |
| | 2 | -0.16 (0.12) | -1.31 | 0.19 | 2 | -0.04 (0.07) | -0.57 | 0.57 | 2 | **0.11 (0.05)** | **2.24** | **0.03** |
| | 3 | -0.10 (0.13) | -0.75 | 0.45 | 3 | 0.00 (0.07) | -0.07 | 0.95 | 3 | 0.09 (0.05) | 1.88 | 0.06 |
| | 4 | -0.04 (0.14) | -0.28 | 0.78 | 4 | 0.03 (0.07) | 0.38 | 0.70 | 4 | 0.09 (0.05) | 1.77 | 0.08 |
| ***Section C*** | Step | | | | Step | | | | Step | | | |
| RAVLT Trial 1 | 1 | **-0.18 (0.07)** | **-2.70** | **0.01** | 1 | **-0.09 (0.04)** | **-2.59** | **0.01** | 1 | 0.02 (0.03) | 0.61 | 0.54 |
| | 2 | **-0.18 (0.08)** | **-2.29** | **0.02** | 2 | **-0.10 (0.04)** | **-2.21** | **0.03** | 2 | 0.01 (0.03) | 0.35 | 0.73 |
| | 3 | -0.09 (0.08) | -1.18 | 0.24 | 3 | -0.06 (0.05) | -1.29 | 0.20 | 3 | -0.01 (0.03) | -0.32 | 0.75 |
| | 4 | -0.05 (0.09) | -0.59 | 0.56 | 4 | -0.04 (0.05) | -0.78 | 0.44 | 4 | -0.02 (0.03) | -0.48 | 0.63 |
| Longest DS Forward | 1 | **0.11 (0.05)** | **2.16** | **0.03** | 1 | **0.06 (0.03)** | **2.11** | **0.04** | 1 | -0.01 (0.02) | -0.33 | 0.74 |
| | 2 | 0.06 (0.06) | 1.07 | 0.29 | 2 | 0.03 (0.03) | 0.80 | 0.43 | 2 | 0.00 (0.02) | -0.05 | 0.96 |
| | 3 | 0.10 (0.06) | 1.70 | 0.09 | 3 | 0.04 (0.03) | 1.34 | 0.18 | 3 | -0.01 (0.02) | -0.37 | 0.71 |
| | 4 | 0.10 (0.06) | 1.49 | 0.14 | 4 | 0.04 (0.04) | 1.13 | 0.26 | 4 | -0.01 (0.02) | -0.33 | 0.74 |
| Longest DS Backward | 1 | 0.05 (0.05) | 0.97 | 0.33 | 1 | 0.02 (0.03) | 0.55 | 0.58 | 1 | -0.02 (0.02) | -0.84 | 0.40 |
| | 2 | 0.07 (0.06) | 1.13 | 0.26 | 2 | 0.02 (0.03) | 0.64 | 0.53 | 2 | -0.01 (0.02) | -0.62 | 0.54 |
| | 3 | 0.09 (0.06) | 1.46 | 0.14 | 3 | 0.03 (0.04) | 0.86 | 0.39 | 3 | -0.02 (0.02) | -1.00 | 0.32 |
| | 4 | 0.08 (0.07) | 1.13 | 0.26 | 4 | 0.02 (0.04) | 0.52 | 0.61 | 4 | -0.02 (0.02) | -0.94 | 0.35 |
| ***Section D*** | Step | | | | Step | | | | Step | | | |
| Longest SS Forward | 1 | **-0.09 (0.05)** | **-2.06** | **0.04** | 1 | -0.04 (0.02) | -1.52 | 0.13 | 1 | **0.05 (0.02)** | **2.52** | **0.01** |
| | 2 | **-0.12 (0.05)** | **-2.35** | **0.02** | 2 | -0.06 (0.03) | -1.89 | 0.06 | 2 | **0.06 (0.02)** | **2.78** | **0.01** |
| | 3 | -0.09 (0.06) | -1.62 | 0.11 | 3 | -0.04 (0.03) | -1.30 | 0.20 | 3 | **0.05 (0.02)** | **2.31** | **0.02** |
| | 4 | -0.07 (0.06) | -1.20 | 0.23 | 4 | -0.03 (0.03) | -0.89 | 0.37 | 4 | **0.05 (0.02)** | **2.19** | **0.03** |
| Longest SS Backward | 1 | **-0.13 (0.05)** | **-2.48** | **0.01** | 1 | **-0.07 (0.03)** | **-2.57** | **0.01** | 1 | 0.02 (0.02) | 0.94 | 0.35 |
| | 2 | **-0.14 (0.06)** | **-2.28** | **0.02** | 2 | **-0.09 (0.03)** | **-2.50** | **0.01** | 2 | 0.02 (0.02) | 0.67 | 0.51 |
| | 3 | -0.08 (0.06) | -1.31 | 0.19 | 3 | -0.06 (0.04) | -1.72 | 0.09 | 3 | 0.00 (0.03) | -0.05 | 0.96 |
| | 4 | -0.04 (0.07) | -0.58 | 0.56 | 4 | -0.04 (0.04) | -1.11 | 0.27 | 4 | -0.01 (0.03) | -0.21 | 0.83 |
| ***Section E*** | Step | | | | Step | | | | Step | | | |
| DM Overall | 1 | **-3.15 (1.43)** | **-2.20** | **0.03** | 1 | **-2.75 (0.78)** | **-3.54** | **<0.01** | 1 | 0.91 (0.63) | 1.46 | 0.15 |
| | 2 | -2.77 (1.66) | -1.67 | 0.10 | 2 | **-3.14 (0.96)** | **-3.29** | **<0.01** | 2 | 0.83 (0.66) | 1.25 | 0.21 |
| | 3 | -2.12 (1.74) | -1.22 | 0.22 | 3 | **-2.83 (0.98)** | **-2.87** | **<0.01** | 3 | 0.59 (0.69) | 0.85 | 0.40 |
| | 4 | -1.21 (1.90) | -0.63 | 0.53 | 4 | **-2.60 (1.05)** | **-2.47** | **0.01** | 4 | 0.50 (0.69) | 0.73 | 0.47 |
| DM Ambiguity | 1 | -0.07 (0.04) | -1.60 | 0.11 | 1 | **-0.05 (0.02)** | **-2.30** | **0.02** | 1 | **0.04 (0.02)** | **2.07** | **0.04** |
| | 2 | **-0.11 (0.05)** | **-2.28** | **0.02** | 2 | **-0.10 (0.03)** | **-3.34** | **<0.01** | 2 | **0.05 (0.02)** | **2.48** | **0.01** |
| | 3 | **-0.11 (0.05)** | **-2.18** | **0.03** | 3 | **-0.09 (0.03)** | **-3.16** | **<0.01** | 3 | **0.05 (0.02)** | **2.39** | **0.02** |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 4 | -0.07 (0.06) | -1.23 | 0.22 | 4 | **-0.08 (0.03)** | **-2.39** | **0.02** | 4 | **0.04 (0.02)** | **1.96** | **0.05** |
| DM Risk | 1 | **-2.39 (1.12)** | **-2.13** | **0.03** | 1 | **-2.16 (0.61)** | **-3.56** | **<0.01** | 1 | 0.46 (0.49) | 0.94 | 0.35 |
| | 2 | -1.42 (1.30) | -1.09 | 0.28 | 2 | **-2.02 (0.75)** | **-2.70** | **0.01** | 2 | 0.23 (0.51) | 0.46 | 0.65 |
| | 3 | -0.75 (1.36) | -0.55 | 0.58 | 3 | **-1.73 (0.77)** | **-2.24** | **0.03** | 3 | -0.01 (0.53) | -0.02 | 0.98 |
| | 4 | -0.31 (1.49) | -0.21 | 0.84 | 4 | **-1.69 (0.82)** | **-2.05** | **0.04** | 4 | -0.05 (0.54) | -0.10 | 0.92 |
| ***Section F*** | Step | | | | Step | | | | Step | | | |
| D-prime | 1 | -0.07 (0.04) | -1.88 | 0.06 | 1 | -0.03 (0.02) | -1.75 | 0.08 | 1 | **0.04 (0.02)** | **2.23** | **0.03** |
| | 2 | -0.04 (0.04) | -1.00 | 0.32 | 2 | -0.02 (0.02) | -0.94 | 0.35 | 2 | 0.02 (0.02) | 1.45 | 0.15 |
| | 3 | -0.01 (0.04) | -0.19 | 0.85 | 3 | -0.01 (0.02) | -0.25 | 0.80 | 3 | 0.02 (0.02) | 1.10 | 0.27 |
| | 4 | -0.02 (0.05) | -0.38 | 0.71 | 4 | -0.01 (0.03) | -0.41 | 0.68 | 4 | 0.02 (0.02) | 1.31 | 0.26 |
| No-go Error Rate[a,b] | 1 | 0.04 (0.06) | 0.71 | 0.48 | 1 | 0.02 (0.03) | 0.73 | 0.46 | 1 | **-0.06 (0.03)** | **-2.33** | **0.02** |
| | 2 | 0.01 (0.07) | 0.19 | 0.85 | 2 | 0.01 (0.04) | 0.29 | 0.78 | 2 | -0.05 (0.03) | -1.78 | 0.08 |
| | 3 | -0.05 (0.07) | -0.66 | 0.51 | 3 | -0.02 (0.04) | -0.40 | 0.69 | 3 | -0.04 (0.03) | -1.47 | 0.14 |
| | 4 | -0.03 (0.08) | -0.38 | 0.70 | 4 | -0.01 (0.04) | -0.14 | 0.89 | 4 | -0.05 (0.03) | -1.53 | 0.13 |
| ***Section G*** | Step | | | | Step | | | | Step | | | |
| Prorated FSIQ | 1 | **-1.60 (0.50)** | **-3.21** | **<0.01** | 1 | -0.45 (0.27) | -1.64 | 0.10 | 1 | **0.70 (0.21)** | **3.29** | **<0.01** |
| | 2 | **-1.33 (0.58)** | **-2.30** | **0.02** | 2 | -0.11 (0.33) | -0.34 | 0.73 | 2 | **0.64 (0.23)** | **2.83** | **<0.01** |
| | 3 | -0.65 (0.59) | -1.10 | 0.27 | 3 | 0.23 (0.33) | 0.68 | 0.50 | 3 | **0.46 (0.23)** | **2.00** | **0.05** |
| | 4 | -0.83 (0.64) | -1.30 | 0.19 | 4 | 0.22 (0.36) | 0.62 | 0.54 | 4 | **0.47 (0.23)** | **2.03** | **0.04** |
| Block Design | 1 | **-0.27 (0.10)** | **-2.73** | **0.01** | 1 | -0.08 (0.05) | -1.53 | 0.13 | 1 | **0.11 (0.04)** | **2.65** | **0.01** |
| | 2 | **-0.27 (0.12)** | **-2.31** | **0.02** | 2 | -0.6 (0.07) | -0.89 | 0.37 | 2 | **0.10 (0.04)** | **2.33** | **0.02** |
| | 3 | **-0.24 (0.12)** | **-2.03** | **0.04** | 3 | -0.05 (0.07) | -0.68 | 0.50 | 3 | **0.10 (0.05)** | **2.13** | **0.03** |
| | 4 | **-0.26 (0.13)** | **-2.00** | **0.05** | 4 | -0.04 (0.07) | -0.56 | 0.58 | 4 | **0.09 (0.05)** | **2.10** | **0.04** |
| Vocabulary | 1 | **-0.16 (0.07)** | **-2.19** | **0.03** | 1 | -0.04 (0.04) | -1.11 | 0.27 | 1 | **0.08 (0.03)** | **2.37** | **0.02** |
| | 2 | -0.07 (0.08) | -0.91 | 0.36 | 2 | 0.03 (0.05) | 0.55 | 0.58 | 2 | 0.06 (0.03) | 1.74 | 0.08 |
| | 3 | 0.04 (0.08) | 0.49 | 0.62 | 3 | 0.08 (0.05) | 1.78 | 0.08 | 3 | 0.03 (0.03) | 0.80 | 0.42 |
| | 4 | 0.02 (0.09) | 0.27 | 0.78 | 4 | 0.08 (0.05) | 1.67 | 0.10 | 4 | 0.03 (0.03) | 0.84 | 0.40 |

*Notes.* All linear mixed models include covariates for age, sex, and zygosity and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded. Step 1 = Pre-exposure IQ/SES, Step 2 = alcohol/nicotine age-24 indices, Step 3 = education, Step 4 = recent cannabis use. Each step includes covariates from each of the preceding steps.

*Abbreviations:* RAVLT, Rey Auditory Verbal Learning Test; DS, digit span; SS, spatial span; DM, decision-making; FSIQ, full scale intelligence quotient

[a]Values were square-root transformed prior to analyses

[b]Higher values = more errors

**Table 8.** Group comparisons between males and females for cognitive outcomes.

| | **Male (N = 362)** | **Female (N = 439)** | **Cluster-robust group comparisons** | | |
|---|---|---|---|---|---|
| Cognitive measures | Mean (SD) | Mean (SD) | Estimate (SE) | t-statistic | p-value |
| *Vb. Learning/Memory* | | | | | |
| Total Learning[a] | 44.81 (9.10) | 48.93 (8.52) | **3.97 (0.81)** | **4.92** | **<0.01** |
| Short-delay Recall[a] | -1.72 (1.75) | -1.67 (1.86) | 0.05 (0.15) | 0.35 | 0.72 |
| Long-delay Recall[a] | -2.26 (1.95) | -1.91 (1.73) | **0.35 (0.15)** | **2.28** | **0.02** |
| *Processing Speed* | | | | | |
| PSI[b] | 103.75 (13.20) | 109.09 (12.78) | **5.26 (1,24)** | **4.24** | **<0.01** |
| Digit Sym-Cod[c] | 9.84 (2.52) | 11.33 (2.57) | **1.46 (0.24)** | **6.19** | **<0.01** |
| Symbol Search[c] | 11.61 (2.65) | 12.00 (2.60) | 0.39 (0.25) | 1.58 | 0.11 |
| *Vb. Attention/WM* | | | | | |
| RAVLT Trial 1[a] | 5.67 (1.69) | 6.25 (1.66) | **0.55 (0.14)** | **3.81** | **<0.01** |
| Longest DSF[a] | 6.93 (1.18) | 6.76 (1.22) | -0.19 (0.11) | -1.76 | 0.08 |
| Longest DSB[a] | 4.91 (1.26) | 4.93 (1.23) | 0.01 (0.11) | 0.11 | 0.92 |
| *Vis. Attention/WM* | | | | | |
| Longest SSF[a] | 6.48 (1.20) | 6.42 (1.01) | -0.06 (0.09) | -0.62 | 0.53 |
| Longest SSB[a] | 6.33 (1.21) | 6.27 (1.26) | -0.07 (0.11) | -0.61 | 0.54 |
| *Decision-Making* | | | | | |
| DM Overall[a] | 6.18 (35.22) | 2.30 (33.70) | -3.94 (2.97) | -1.33 | 0.19 |
| DM Ambiguity[a,d] | 6.09 (1.12) | 5.92 (0.92) | **-0.18 (0.08)** | **-2.10** | **0.04** |
| DM Risk[a] | 8.80 (27.26) | 7.42 (26.98) | -1.41 (2.34) | -0.61 | 0.55 |
| *Cognitive Inhibition* | | | | | |
| D-prime[a] | 3.41 (0.90) | 3.63 (0.80) | **0.21 (0.08)** | **2.68** | **0.01** |
| No-go Error Rate[a,d,e] | 3.63 (1.61) | 3.28 (1.36) | **-0.33 (0.14)** | **-2.37** | **0.02** |
| *General Cognitive Ability* | | | | | |
| Prorated FSIQ[b] | 109.04 (15.73) | 104.66 (16.75) | **-4.42 (1.58)** | **-2.80** | **0.01** |
| Block Design[c] | 12.91 (2.71) | 12.14 (2.77) | **-0.77 (0.25)** | **-3.02** | **<0.01** |
| Vocabulary[c] | 9.72 (2.13) | 9.42 (2.34) | -0.33 (0.20) | -1.70 | 0.09 |

*Notes.* Cluster-robust sandwich estimator provided standard errors of parameter estimates, given that individual twins are nested within pairs (families). All models control for age and zygosity. Significant effects (alpha = 0.05) are bolded.

*Abbreviations:* Vb., verbal; PSI, processing speed index, Digit Symb-Cod, digit symbol-coding; WM, working memory; RAVLT, Rey Auditory Verbal Learning Test; SS, scaled score; DSF, digit span forward; DSB, digit span backwards; Vis., visuospatial; SSF, spatial span forward; SSB, spatial span backwards; DM, decision-making; FSIQ, full scale intelligence quotient

[a]Raw score; [b]Standard score: mean of 100, standard deviation of 15; [c]Scaled score: mean of 10, standard deviation of 3; [d]Values were square-root transformed prior to analyses; [e]Higher values = more errors.

**Table 9.** Sex-specific interaction effects of primary cannabis variables on cognitive outcomes.

| | Cannabis index | | | | Lifetime heaviest frequency | | | | Age of initiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cognitive measures | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value |
| *Vb. Learning/Memory* | | | | | | | | | | | | |
| Total Learning | 676 | 0.43 (0.72) | 0.61 | 0.55 | 676 | 0.54 (0.39) | 1.40 | 0.16 | 451 | 0.15 (0.31) | 0.49 | 0.63 |
| Short-delay Recall | 676 | 0.00 (0.15) | -0.02 | 0.98 | 676 | 0.06 (0.08) | 0.71 | 0.48 | 451 | -0.06 (0.07) | -0.96 | 0.33 |
| Long-delay Recall | 675 | 0.09 (0.16) | 0.58 | 0.57 | 675 | 0.05 (0.09) | 0.64 | 0.52 | 451 | -0.03 (0.07) | -0.47 | 0.64 |
| *Processing Speed* | | | | | | | | | | | | |
| PSI | 675 | 1.74 (1.04) | 1.67 | 0.10 | 675 | 0.65 (0.55) | 1.19 | 0.24 | 451 | -0.71 (0.43) | -1.66 | 0.10 |
| Digit Sym-Cod | 675 | 0.16 (0.21) | 0.76 | 0.45 | 675 | -0.02 (0.11) | -0.15 | 0.88 | 451 | -0.05 (0.08) | -0.59 | 0.56 |
| Symbol Search | 675 | **0.45 (0.22)** | **2.11** | **0.04** | 675 | **0.25 (0.12)** | **2.13** | **0.03** | 451 | **-0.19 (0.08)** | **-2.19** | **0.03** |
| *Vb. Attention/WM* | | | | | | | | | | | | |
| RAVLT Trial 1 | 676 | 0.05 (0.14) | 0.40 | 0.69 | 676 | 0.04 (0.07) | 0.55 | 0.58 | 451 | -0.02 (0.06) | -0.25 | 0.80 |
| Longest DSF | 676 | 0.07 (0.10) | 0.66 | 0.51 | 676 | 0.07 (0.05) | 1.30 | 0.19 | 451 | -0.03 (0.04) | -0.62 | 0.54 |
| Longest DSB | 670 | 0.20 (0.11) | 1.87 | 0.07 | 670 | 0.06 (0.06) | 1.08 | 0.28 | 447 | -0.01 (0.04) | -0.32 | 0.75 |
| *Vis. Attention/WM* | | | | | | | | | | | | |
| Longest SSF | 653 | 0.03 (0.09) | 0.29 | 0.78 | 653 | 0.05 (0.05) | 0.93 | 0.36 | 433 | -0.01 (0.04) | -0.33 | 0.74 |
| Longest SSB | 652 | -0.01 (0.11) | -0.09 | 0.93 | 652 | 0.02 (0.06) | 0.30 | 0.76 | 433 | -0.03 (0.05) | -0.67 | 0.50 |
| *Decision-Making* | | | | | | | | | | | | |
| DM Overall | 658 | 3.30 (2.93) | 1.13 | 0.26 | 658 | 3.00 (1.57) | 1.91 | 0.06 | 437 | -1.07 (1.23) | -0.87 | 0.38 |
| DM Ambiguity[a] | 658 | 0.08 (0.09) | 0.93 | 0.35 | 658 | 0.06 (0.05) | 1.37 | 0.17 | 437 | -0.03 (0.04) | -0.81 | 0.42 |
| DM Risk | 658 | 2.40 (2.29) | 1.05 | 0.30 | 658 | 2.29 (1.23) | 1.85 | 0.06 | 437 | -0.52 (0.95) | -0.54 | 0.59 |
| *Cognitive Inhibition* | | | | | | | | | | | | |
| D-prime | 665 | 0.05 (0.07) | 0.75 | 0.45 | 665 | 0.00 (0.04) | -0.06 | 0.96 | 445 | -0.04 (0.03) | -1.25 | 0.21 |
| No-go Error Rate[a,b] | 665 | 0.01 (0.13) | 0.08 | 0.93 | 665 | 0.05 (0.07) | 0.77 | 0.44 | 445 | 0.07 (0.05) | 1.40 | 0.16 |
| *General Cognitive Ability* | | | | | | | | | | | | |
| Prorated FSIQ | 673 | -0.08 (1.00) | -0.08 | 0.93 | 673 | 0.47 (0.54) | 0.87 | 0.39 | 448 | 0.22 (0.42) | 0.54 | 0.59 |
| Block Design | 674 | 0.05 (0.20) | 0.24 | 0.81 | 674 | 0.14 (0.11) | 1.24 | 0.22 | 449 | -0.04 (0.08) | -0.54 | 0.59 |
| Vocabulary | 782 | -0.12 (0.14) | -0.89 | 0.37 | 782 | -0.02 (0.07) | -0.28 | 0.78 | 504 | 0.08 (0.06) | 1.31 | 0.19 |

*Notes.* Females were coded as 1 and males were coded as 0 in analyses of sex-interaction effects. All models included covariates for age, sex, zygosity, pre-exposure IQ, SES, education, alcohol/nicotine use, recent cannabis use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.

*Abbreviations*: Vb., verbal; PSI, processing speed index, Digit Symb-Cod, digit symbol-coding; WM, working memory; RAVLT, Rey Auditory Verbal Learning Test; SS, scaled score; DSF, digit span forward; DSB, digit span backwards; Vis., visuospatial; SSF, spatial span forward; SSB, spatial span backwards; DM, decision-making; FSIQ, full scale intelligence quotient.
[a]Values were square-root transformed prior to analyses; [b]Higher values = more errors.

**Table 10.** Associations between cannabis variables and neurocognitive outcomes separated by sex.

| | | **Females** | | | | **Males** | | |
|---|---|---|---|---|---|---|---|---|
| Cognitive measures | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value |
| *Symbol Search* | | | | | | | | |
| Cannabis index | 375 | 0.14 (0.20) | 0.70 | 0.48 | 300 | -0.25 (0.19) | -1.32 | 0.19 |
| Lifetime heaviest frequency | 375 | 0.11 (0.11) | 1.02 | 0.31 | 300 | -0.09 (0.10) | -0.84 | 0.40 |
| Age of initiation | 230 | 0.03 (0.07) | 0.51 | 0.60 | 221 | **0.15 (0.08)** | **2.02** | **0.04** |
| *DM Overall* | | | | | | | | |
| Lifetime heaviest frequency | 367 | -1.48 (1.45) | -1.02 | 0.31 | 291 | **-4.07 (1.56)** | **-2.61** | **0.01** |
| *DM Risk* | | | | | | | | |
| Lifetime heaviest frequency | 367 | -1.09 (1.15) | -0.95 | 0.35 | 291 | **-2.73 (1.20)** | **-2.27** | **0.02** |

*Notes.* All models included covariates for age, zygosity, pre-exposure IQ, SES, education, alcohol/nicotine use, recent cannabis use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.
*Abbreviations*: DM, decision-making

**Table 11.** Associations between age of initiation and neurocognitive outcomes covarying for age-24 cannabis index (frequency/quantity).

| | **Age of initiation** | | | **Age-24 Cannabis index** | | |
|---|---|---|---|---|---|---|
| Cognitive measures | Estimates (SE) | t | p | Estimates (SE) | t | p |
| Prorated FSIQ | **0.48 (0.23)** | **2.07** | **0.04** | 0.23 (0.49) | 0.47 | 0.64 |
| Block Design | **0.09 (0.05)** | **2.00** | **0.05** | -0.04 (0.10) | -0.47 | 0.64 |
| Symbol Search[a] | **0.15 (0.08)** | **1.96** | **0.05** | -0.04 (0.14) | -0.27 | 0.79 |
| Longest SS Forward | **0.05 (0.02)** | **2.02** | **0.04** | -0.04 (0.05) | -0.84 | 0.40 |
| DM Ambiguity[b] | **0.04 (0.02)** | **1.96** | **0.05** | -0.07 (0.02) | -1.41 | 0.16 |

*Notes.* All models included covariates for age, sex, zygosity, pre-exposure IQ, SES, education, alcohol/nicotine use, recent cannabis use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.
*Abbreviations*: FSIQ, full scale intelligence quotient; SS, spatial span; DM, decision-making.
[a]Analysis conducted in males only; [b] Values were square-root transformed prior to analyses.

**Table 12.** Associations between age of initiation and neurocognitive outcomes covarying for the cannabis index or lifetime heaviest frequency.

| | **Age of initiation** | | | **Cannabis index** | | | **Lifetime heaviest frequency** | | |
|---|---|---|---|---|---|---|---|---|---|
| Cognitive measures | Estimates (SE) | t | p | Estimates (SE) | t | p | Estimates (SE) | t | p |
| Block Design | 0.05 (0.05) | 1.10 | 0.27 | -0.30 (0.15) | -1.94 | 0.05 | | | |
| DM Ambiguity[a] | 0.04 (0.02) | 1.74 | 0.08 | | | | -0.05 (0.04) | -1.23 | 0.22 |

*Notes.* All models included covariates for age, sex, zygosity, pre-exposure IQ, SES, education, alcohol/nicotine use, recent cannabis use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded. The p-value for the effect of cannabis index on block design appears significant, but this is due to rounding.
*Abbreviations*: DM, decision-making
[a]Values were square-root transformed prior to analyses

**Table 13.** Associations between length of abstinence and neurocognitive outcomes.

| | Length of abstinence | | |
|---|---|---|---|
| Cognitive measures | Estimates $_{(SE)}$ | t | p |
| Prorated FSIQ | 0.03 (0.26) | 0.10 | 0.92 |
| Block Design | 0.06 (0.05) | 1.10 | 0.27 |
| Symbol Search | 0.07 (0.06) | 1.35 | 0.18 |
| Longest SS Forward | 0.02 (0.03) | 0.92 | 0.36 |
| Short-Delay Recall | 0.04 (0.04) | 1.05 | 0.30 |
| DM Overall | 0.90 (0.78) | 1.15 | 0.25 |
| DM Ambiguity[a] | 0.04 (0.02) | 1.48 | 0.14 |
| DM Risk | 0.39 (0.61) | 0.64 | 0.53 |

*Notes:* All models included covariates for age, sex, zygosity, pre-exposure IQ, SES, education, and alcohol/nicotine use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.
*Abbreviations:* FSIQ, full scale intelligence quotient; SS, spatial span; DM, decision-making
[a]Values were square-root transformed prior to analyses

**Table 14.** Group differences between individuals with less than a month of abstinence compared to those with at least a year of abstinence from cannabis.

| | **< 1 month abstinence** (n = 173) | **≥ 1 year abstinence** (n = 222) | **Cluster-robust group comparisons** | | |
|---|---|---|---|---|---|
| Cognitive measures | Mean (SD) | Mean (SD) | Estimates $_{(SE)}$ | t | p |
| Prorated FSIQ[a] | 106.63 (15.19) | 107.39 (16.80) | -1.78 (1.87) | -0.95 | 0.34 |
| Block Design[b] | 12.32 (2.60) | 12.75 (2.84) | -0.60 (0.31) | -1.91 | 0.06 |
| Symbol Search[b] | 11.59 (2.48) | 12.11 (2.78) | -0.43 (0.29) | -1.47 | 0.14 |
| Longest SS Forward[c] | 6.42 (1.21) | 6.53 (1.13) | -0.12 (0.14) | -0.89 | 0.37 |
| Short-Delay Recall[c] | -1.75 (1.66) | -1.46 (1.93) | -0.25 (0.21) | -1.21 | 0.23 |
| DM Overall[c] | -0.92 (32.08) | 4.89 (35.91) | -6.17 (4.07) | -1.52 | 0.13 |
| DM Ambiguity[c,d] | 5.93 (1.05) | 6.06 (1.08) | -0.17 (0.12) | -1.43 | 0.16 |
| DM Risk[c] | 3.85 (24.52) | 7.98 (27.45) | -4.00 (3.15) | -1.27 | 0.21 |

*Notes:* Cluster-robust sandwich estimator provided standard errors of parameter estimates, given that individual twins are nested within pairs (families). All models control for age, sex, and zygosity. Individuals with less than a month of abstinence from cannabis were coded as 1 and individuals with at least a year of abstinence were coded as 0.

*Abbreviations:* FSIQ, full scale intelligence quotient; SS, spatial span; DM, decision-making

[a]Standard score: mean of 100, standard deviation of 15; [b]Scaled score: mean of 10, standard deviation of 3; [c]Raw score; [d]Values were square-root transformed prior to analyses

**Table 15.** Associations between lifetime heaviest frequency and cognitive measures in cannabis users only.

| | | Lifetime heaviest frequency | | |
|---|---|---|---|---|
| Cognitive measures | N | Estimates (SE) | t-statistics | p-value |
| *Vb. Learning/Memory* | | | | |
| Total Learning | 325 | -0.21 (0.37) | -0.57 | 0.57 |
| Short-delay Recall | 325 | 0.05 (0.08) | 0.65 | 0.52 |
| Long-delay Recall | 325 | 0.03 (0.08) | 0.42 | 0.68 |
| *Processing Speed* | | | | |
| PSI | 325 | -0.18 (0.52) | -0.34 | 0.73 |
| Digit Sym-Cod | 325 | -0.05 (0.11) | -0.51 | 0.61 |
| Symbol Search | 325 | -0.01 (0.11) | -0.14 | 0.89 |
| *Vb. Attention/WM* | | | | |
| RAVLT Trial 1 | 325 | -0.08 (0.08) | -0.99 | 0.32 |
| Longest DSF | 325 | -0.10 (0.05) | -1.83 | 0.07 |
| Longest DSB | 322 | **-0.13 (0.06)** | **-2.31** | **0.02** |
| *Vis. Attention/WM* | | | | |
| Longest SSF | 313 | -0.01 (0.05) | -0.16 | 0.88 |
| Longest SSB | 313 | -0.01 (0.06) | -0.18 | 0.86 |
| *Decision-Making* | | | | |
| DM Overall | 316 | -0.41 (1.54) | -0.27 | 0.79 |
| DM Ambiguity[a] | 316 | 0.05 (0.05) | 0.94 | 0.35 |
| DM Risk | 316 | -1.10 (1.22) | -0.90 | 0.37 |
| *Cognitive Inhibition* | | | | |
| D-prime | 321 | -0.01 (0.04) | -0.38 | 0.70 |
| No-go Error Rate[a,b] | 321 | 0.00 (0.06) | 0.07 | 0.95 |
| *General Cog Ability* | | | | |
| Prorated FSIQ | 324 | -0.17 (0.53) | -0.33 | 0.74 |
| Block Design | 324 | -0.09 (0.10) | -0.85 | 0.40 |
| Vocabulary | 359 | 0.04 (0.07) | 0.56 | 0.58 |

*Notes.* All models included covariates for age, sex, zygosity, pre-exposure IQ, SES, education, alcohol/nicotine use, recent cannabis use and a random intercept at the twin-pair level. Significant effects (alpha = 0.05) are bolded.

*Abbreviations*: Vb., verbal; PSI, processing speed index, Digit Symb-Cod, digit symbol-coding; WM, working memory; RAVLT, Rey Auditory Verbal Learning Test; SS, scaled score; DSF, digit span forward; DSB, digit span backwards; Vis., visuospatial; SSF, spatial span forward; SSB, spatial span backwards; DM, decision-making; FSIQ, full scale intelligence quotient.

[a]Values were square-root transformed prior to analyses; [b]Higher values = more errors.

**Table 16.** Twin correlations for cannabis variables

| | | Twin correlations by zygosity | |
|---|---|---|---|
| | Full | MZ | DZ |
| Cannabis index | 0.72 | 0.81 | 0.62 |
| Lifetime heaviest frequency | 0.58 | 0.72 | 0.38 |
| Age of initiation | 0.55 | 0.60 | 0.45 |

*Notes.* Correlations between twin pairs for the full sample and then split by zygosity. Correlations are displayed as Pearson's r.

**Table 17.** Individual-level analyses between cannabis use and cognition.

| | | Individual-level analyses | | | |
|---|---|---|---|---|---|
| | | N | Estimates $_{(SE)}$ | t-statistics | p-value |
| **Cannabis index** | | | | | |
| *General Cognitive Ability* | | | | | |
| Block Design | | 686 | -0.23 (0.12) | -1.95 | 0.05 |
| **Lifetime heaviest frequency** | | | | | |
| *Decision-Making* | | | | | |
| DM Overall | | 672 | **-2.60 (0.80)** | **-3.27** | **<0.01** |
| | Females | 378 | -1.67 (1.10) | -1.47 | 0.14 |
| | Males | 294 | **-3.84 (1.67)** | **-3.29** | **<0.01** |
| DM Ambiguity[a] | | 672 | -0.05 (0.02) | -2.23 | 0.03 |
| DM Risk | | 672 | **-2.05 (0.63)** | **-3.25** | **<0.01** |
| | Females | 378 | -1.38 (0.88) | -1.58 | 0.12 |
| | Males | 294 | **-2.95 (0.91)** | **-3.25** | **<0.01** |
| **Age of initiation** | | | | | |
| *Processing Speed* | | | | | |
| Symbol Search | | 458 | **0.17 (0.04)** | **3.74** | **<0.01** |
| | Females | 234 | 0.09 (0.06) | 1.45 | 0.15 |
| | Males | 224 | **0.28 (0.07)** | **4.02** | **<0.01** |
| *Visuospatial Attention* | | | | | |
| Longest SS Forward | | 442 | **0.07 (0.02)** | **3.59** | **<0.01** |
| *Decision-Making* | | | | | |
| DM Ambiguity[a] | | 445 | 0.05 (0.02) | 2.37 | 0.02 |
| *General Cognitive Ability* | | | | | |
| Prorated FSIQ | | 454 | **1.45 (0.27)** | **5.48** | **<0.01** |
| **Lifetime heaviest frequency (CU only)** | | | | | |
| *Verbal Attention/WM* | | | | | |
| Longest DS Backward | | 326 | -0.12 (0.05) | -2.44 | 0.02 |

*Notes.* All models included covariates for age, sex, zygosity and a random intercept at the twin-pair level. Bold denotes tests significant at the false discovery rate (FDR) of $q < 0.05$.
*Abbreviations:* DM, decision-making; SS, spatial span; FSIQ, full scale intelligence quotient; WM, working memory; DS, digit span.
[a]Value was square-root transformed prior to analyses

**Table 18.** Associations between cannabis use and neurocognitive outcomes using cotwin control analyses.

| | | **Individual-level models** | | | **Cotwin control analyses** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Between-pair estimate** | | | | **Within-pair estimate** | | |
| | N | Estimates (SE) | t-statistics | p-value | N | Estimates (SE) | t-statistics | p-value | Estimates (SE) | t-statistics | p-value |
| **Lifetime heaviest frequency** | | | | | | | | | | | |
| *Decision-Making* | | | | | | | | | | | |
| DM Overall | 672 | **-2.60 (0.80)** | **-3.27** | **<0.01** | 652 | **-3.18 (0.97)** | **-3.28** | **<0.01** | -1.38 (1.52) | -0.91 | 0.36 |
| Females | 378 | -1.67 (1.10) | -1.47 | 0.14 | 373 | **-3.10 (1.28)** | **-2.43** | **0.02** | 2.25 (2.17) | 1.04 | 0.30 |
| Males | 294 | **-3.84 (1.17)** | **-3.29** | **<0.01** | 279 | **-3.50 (1.50)** | **-2.34** | **0.02** | **-4.87 (2.11)** | **-2.31** | **0.02** |
| DM Risk | 672 | **-2.05 (0.63)** | **-3.25** | **<0.01** | 652 | **-2.39 (0.77)** | **-3.10** | **<0.01** | -1.36 (1.19) | -1.15 | 0.25 |
| Females | 378 | -1.38 (0.88) | -1.58 | 0.12 | 373 | **-2.61 (1.03)** | **-2.54** | **0.01** | 1.77 (1.73) | 1.02 | 0.31 |
| Males | 294 | **-2.95 (0.91)** | **-3.25** | **<0.01** | 279 | -2.27 (1.18) | -1.93 | 0.06 | **-4.35 (1.58)** | **-2.75** | **0.01** |
| **Age of initiation** | | | | | | | | | | | |
| *Processing Speed* | | | | | | | | | | | |
| Symbol Search | 458 | **0.17 (0.04)** | **3.74** | **<0.01** | 371 | **0.23 (0.07)** | **3.34** | **<0.01** | 0.03 (0.09) | 0.40 | 0.69 |
| Females | 234 | 0.09 (0.06) | 1.45 | 0.15 | 183 | 0.12 (0.09) | 1.29 | 0.20 | -0.04 (0.13) | -0.28 | 0.78 |
| Males | 224 | **0.28 (0.07)** | **4.02** | **<0.01** | 188 | **0.34 (0.10)** | **3.50** | **<0.01** | 0.11 (0.12) | 0.88 | 0.38 |
| *Visuospatial Attention* | | | | | | | | | | | |
| Longest SS Forward | 442 | **0.07 (0.02)** | **3.59** | **<0.01** | 357 | **0.10 (0.03)** | **3.83** | **<0.01** | 0.00 (0.05) | 0.05 | 0.96 |
| *General Cognitive Ability* | | | | | | | | | | | |
| Prorated FSIQ | 454 | **1.45 (0.27)** | **5.48** | **<0.01** | 366 | **2.52 (0.45)** | **5.59** | **<0.01** | **1.00 (0.41)** | **2.45** | **0.02** |

*Notes.* Significant effects are in bold. All models included covariates for age, sex, zygosity and a random intercept at the twin-pair level. All individual-level models survived multiple comparison adjustment at the false discovery rate (FDR) of $q < 0.05$.
*Abbreviations*: DM, decision-making; SS, spatial span; FSIQ, full scale intelligence quotient.

**Table 19.** Within-pair associations between lifetime heaviest frequency and decision-making with and without covariate adjustment.

| **Lifetime heaviest frequency (males)** | **Cotwin control analyses** | | | | | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | | | **Covariates, adjusted** | | |
| Cognitive measures | Estimates (SE) | t-statistics | p-value | Estimates (SE) | t-statistics | p-value |
| *Decision-Making* | | | | | | |
| DM Overall | **-4.87 (2.11)** | **-2.31** | **0.02** | -4.60 (2.61) | -1.76 | 0.08 |
| DM Risky | **-4.35 (1.58)** | **-2.75** | **0.01** | **-4.99 (2.49)** | **-2.00** | **0.05** |

*Notes.* Significant effects are in bold. Adjusted models included twin difference scores for pre-exposure IQ, education, age-24 alcohol and nicotine indices, and recent cannabis use. All models included covariates for age, sex, zygosity and a random intercept at the twin-pair level.
*Abbreviations*: DM, decision-making.

**Table 20.** Within-pair associations between age of initiation and decision-making with and without covariate adjustment.

| **Age of initiation** | **Cotwin control analyses** | | | | | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | | | **Covariates, adjusted** | | |
| Cognitive measures | Estimates (SE) | t-statistics | p-value | Estimates (SE) | t-statistics | p-value |
| *General Cognitive Ability* | | | | | | |
| Prorated FSIQ | **1.00 (0.41)** | **2.45** | **0.02** | **0.83 (0.39)** | **2.11** | **0.04** |

*Notes.* Significant effects are in bold. Adjusted models included twin difference scores for pre-exposure IQ, education, age-24 alcohol and nicotine indices, and recent cannabis use. All models included covariates for age, sex, zygosity and a random intercept at the twin-pair level.
*Abbreviations*: FSIQ, full scale intelligence quotient.

**Table 21.** Within-pair associations for lifetime heaviest frequency and length of abstinence on decision-making under risk.

| | Cotwin control analyses | | | | | |
|---|---|---|---|---|---|---|
| | **Lifetime heaviest frequency within-pair effect** | | | **Length of abstinence within-pair effect** | | |
| | Estimates (SE) | t-statistics | p-value | Estimates (SE) | t-statistics | p-value |
| *Decision-Making* | | | | | | |
| DM Risk | **-5.83 (2.53)** | **-2.31** | **0.02** | -0.05 (1.45) | -0.04 | 0.97 |

*Notes.* Significant effects are in bold. All models included covariates for age, sex, zygosity and twin difference scores for pre-exposure IQ, education, age-24 alcohol and nicotine indices, and recent cannabis use. Models also included a random intercept at the twin-pair level
*Abbreviations*: DM, decision-making.

**Table 22.** Within-pair associations for age of initiation and length of abstinence on prorated FSIQ.

| | Cotwin control analyses | | | | | |
|---|---|---|---|---|---|---|
| | **Age of initiation within-pair effect** | | | **Length of abstinence within-pair effect** | | |
| | Estimates (SE) | t-statistics | p-value | Estimates (SE) | t-statistics | p-value |
| *General Cognitive Ability* | | | | | | |
| Prorated FSIQ | **0.79 (0.40)** | **1.98** | **0.05** | -0.20 (0.48) | -0.41 | 0.68 |

*Notes.* Significant effects are in bold. All models included covariates for age, sex, zygosity and twin difference scores for pre-exposure IQ, education, age-24 alcohol and nicotine indices, and recent cannabis use. Models also included a random intercept at the twin-pair level
*Abbreviations*: FSIQ, full scale intelligence quotient.

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# Appendix

## Supplemental Figures

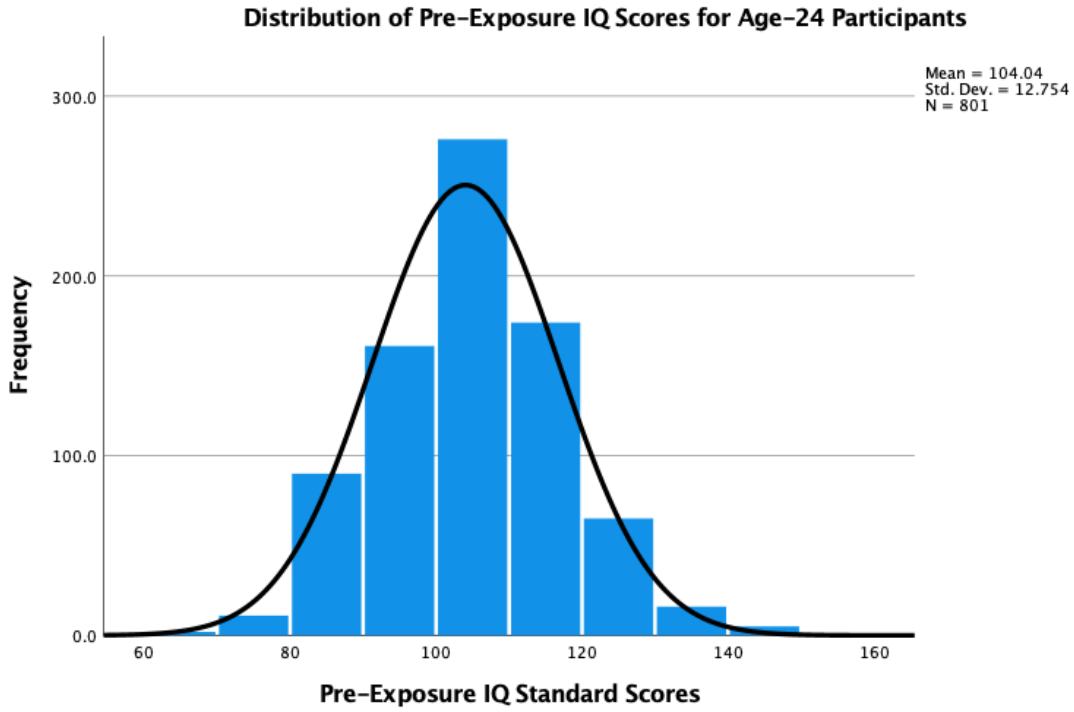


**Figure S1.** Histogram depicting pre-exposure IQ distribution for individuals who participated in the age-24 assessment and were included in the current study sample.