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Associations between Current and Cumulative Marijuana Use and Changes in Cognitive Processing Speed and Flexibility for 17-years in HIV-seropositive and HIV-seronegative Men in the Multicenter AIDS Cohort Study

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Abstract

Objective—To determine associations between current and cumulative exposure to marijuana and changes in cognitive processing speed and flexibility.

Methods—We used data from 788 HIV-seropositive (HIV+) and 1,132 HIV-seronegative (HIV-) men in the Multicenter AIDS Cohort Study. Current and cumulative (1 marijuana-use-year = 365 days of use) marijuana exposure were the main predictors. Cognitive processing speed was

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Declaration of interest

The authors declare that there is no conflict of interest.

assessed using the Trail Making Test Part-A (TMTA) and Symbol Digit Modalities Test (SDMT) and cognitive flexibility was assessed with the Trail Making Test Part-B (TMTB). Linear mixed effects models were used to estimate associations between marijuana exposure and cognitive function over a 17-year follow-up period, adjusting for sociodemographic factors, substance use, psychosocial and clinical factors.

Results—Among HIV+ men only, current daily marijuana use compared to none-use, was significantly associated with a greater annual percentage decline on the TMTA (β=−0.41, 95% confidence interval (CI): −0.88, −0.03, p=0.03) and SDMT (β= −0.14, 95% CI: −0.28, −0.01, p=0.04). Further, monthly marijuana use was associated with greater annual percentage decline on the TMTB (β= −0.70, 95% CI: −1.34, −0.05; p=0.03] and SDMT (β= −0.21, 95% CI: −0.40, −0.01, p=0.03). Among the HIV– men only, each 5-marijuana use-years was significantly associated with a 0.17 annual percentage decline on the TMTA only (β= −0.18, 95% CI: −0.36, −0.01; p=0.04).

Conclusion—Our findings suggests that marijuana use, particularly current use, may be associated with worse cognitive processing speed, but the magnitude of the estimates were not clinically meaningful.

1. Introduction

Marijuana is the most frequently used drug of abuse in the United States. Estimates of recent marijuana use in HIV-seropositive (HIV+) individuals have ranged from 14% to 33% (D'Souza et al., 2012; Mimiaga et al., 2013; Okafor, Cook, et al., 2016; Okafor, Zhou, et al., 2016; Sinha et al., 2017), which contrasts with the 2% to 9.5% prevalence estimates in the general United States population (Blanco et al., 2016; Hasin et al., 2015, 2016). Importantly, prevalence of daily or near daily marijuana use has steadily increased in recent years in the general United States population (Hasin et al., 2015) and in HIV+ persons (D'Souza et al., 2012; Okafor, Cook, et al., 2016). Randomized controlled trials and observational studies of HIV+ persons indicate therapeutic benefits of cannabinoids – the active components in marijuana – in reducing pain, nausea, insomnia and improving appetite and mood symptoms (Corless et al., 2009; D'Souza et al., 2012; Furler, Einarson, Millson, Walmsley, & Bendayan, 2004; Ware et al., 2010).

However, marijuana use has been associated with decline in cognitive function (Auer et al., 2016; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Meier et al., 2012; Ranganathan & D'Souza, 2006). Marijuana might influence cognitive function via the actions of tetrahydrocannabidiol (THC) – the main psychoactive cannabinoid in marijuana – on cannabinoid receptor 1(CBR1), located on specific brain regions including the hippocampus, cerebellum, basal ganglia, amygdala and prefrontal cortex (Herkenham et al., 1990; Mackie, 2005; Pertwee, 1997; Westlake, Howlett, Bonner, Matsuda, & Herkenham, 1994), which are involved in cognition (Glass, Dragunow, & Faull, 1997). Therefore, activation of CBR1 by THC in these regions could have effects on cognitive function (Mechoulam & Parker, 2013). Not surprisingly, the associations between marijuana use and cognitive functions has received increased attention.

There is convincing evidence that acute intoxication with marijuana impairs cognitive function in multiple domains including executive functioning, processing speed, attention and working memory—with the most consistent deficits found in learning and memory functions (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crean, Crane, & Mason, 2011; Ranganathan & D'Souza, 2006). However, whether these deficits endure past periods of intoxication (i.e. residual effects), following periods of abstinence, or in the long-term is less clear.

Most cannabinoids, including THC are fat soluble and are easily stored in body fat for prolonged periods of time and are slowly released back into the circulation (Grotenhermen, 2003; Schreiner & Dunn, 2012), a property that potentially supports the hypothesis of residual effects of cannabis on cognitive function. Two meta-analytic studies have synthesized findings of studies assessing residual effects of marijuana use on cognitive function. The first study observed statistically significant negative effects of marijuana use on learning and forgetting domains, of modest effect size (Grant et al., 2003). The second more recent study, found small deficits in multiple domains including forgetting/retrieval, abstraction/executive function, attention, motor skills and verbal/language, but, when the analysis was limited to studies with at least 125 days of abstinence, no significant effect of marijuana on any cognitive domain was observed (Schreiner & Dunn, 2012).

Notwithstanding, majority of the literature on marijuana use and cognitive function have been cross-sectional with modest sample sizes. Furthermore, the literature among HIV+ individuals has been scant. HIV+ individuals are vulnerable to cognitive impairments via direct effects of the virus and indirect effects of comorbid conditions highly prevalent among HIV+ individuals (Clifford & Ances, 2013; Gannon, Khan, & Kolson, 2011; Sanmarti et al., 2014). Cognitive function deficits are common among HIV+ individuals even with highly active antiretroviral therapy (HAART) (Cysique, Maruff, & Brew, 2004; Heaton et al., 2011) and have been associated with medication nonadherence (Hinkin et al., 2002). Thus, any potential negative effects of marijuana on cognitive function may be more pronounced among HIV+ individuals. To date, the relatively small literature on marijuana use and cognitive function in HIV+ individuals have focused on current use (Chang, Cloak, Yakupov, & Ernst, 2006; Cristiani, Pukay-Martin, & Bornstein, 2004; Gonzalez, Schuster, Vassileva, & Martin, 2011; Thames, Mahmood, Burggren, Karimian, & Kuhn, 2015).

With, 29 U.S. states passing laws allowing medical and/or recreational marijuana use, and most state medical marijuana laws listing HIV/AIDS as condition that could benefit from medical marijuana (Fairman, 2016; Wilkinson, Yarnell, Radhakrishnan, Ball, & D'Souza, 2016), there is a need for additional evidence on the impact of marijuana use on cognitive function, including its long-term impact, and the magnitude and clinical importance of any effects. The Multicenter AIDS Cohort Study (MACS) has continuously collected data on marijuana use since its inception in 1984/1985 and evaluated cognitive function for 26 years and thus represents an ideal opportunity to study the long-term effects of marijuana use on cognitive function of HIV+ individuals. The aim of the current study is to evaluate associations between current and cumulative exposure to marijuana and changes in measures of cognitive processing speed and flexibility among HIV+ and HIV-seronegative (HIV–) participants in the MACS. We hypothesized that higher levels of current marijuana use and

greater cumulative marijuana exposure would be associated with worsening cognitive processing speed and flexibility and the magnitude of effects will be greater in HIV+ compared to HIV- men.

2. Methods

2.1. Study Design and Participants

The MACS is an ongoing prospective cohort study of the natural and treated history of HIV infection among Men who have Sex with Men (MSM) in the United States. 6,972 men were enrolled during the history of the study in three waves: 4,954 men in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003 and at 4 centers located in Baltimore/Washington DC, Chicago, Los Angeles, and Pittsburgh. The study design of the MACS has been described previously (Detels et al., 1992; Dudley et al., 1995; Kaslow et al., 1987) and only the design relevant to the current analyses are described here. Participants return every 6 months for physical examinations, HIV testing, laboratory testing, structured clinical interviews, collection of data on cigarette smoking, alcohol use, illicit drug use and cognitive function assessments. The study questionnaires used in the MACS are available at www.aidscohortstudy.org. The institutional review boards at the respective study centers approved the MACS study protocols and all participants provided informed consent. Participants were eligible for the current study if they had two or more cognitive function assessments over the study period (i.e. April 1, 1996 to September 30, 2013). Furthermore, HIV+ individuals were eligible if they initiated highly active antiretroviral therapy (HAART) and reported continuous use for one year. Exclusion criteria for all participants included history of: (1) a learning disorder (via self-report), (2) stroke, (3) seizures, (4) peripheral neuropathy, (5) multiple sclerosis, and (6) head injury with loss of consciousness greater than 1 hour.

2.2. Measurements

2.2.1. Predictor: current and cumulative exposure to marijuana—Marijuana use was assessed at each MACS visit with the following question "*Have you used any pot, marijuana or hash since your last visit*? Among those who responded 'yes', frequency of use was asked with the following question "*How often did you use pot, marijuana or hash since your last visit*?" with the following response options: "daily"; "weekly"; "monthly" and "less often". We categorized participant's current marijuana use status at every visit as none, 'monthly/less often'; 'weekly' or 'daily'. For cumulative exposure to marijuana, we used participant's self-reported frequency of use to compute their average number of days marijuana was used since their last study visit (typically approximately six-months), by assigning weights to each frequency category. For example, if an individual reported using marijuana daily during the last study visit, we calculated his average number of days using marijuana as 30.5 days multiplied by 6 months (183 days). Specifically, the weights assigned to each frequency of use category are as follows: daily use, weight=30.5; weekly use=4.36; monthly use, weight=1; less often, weight=0.33, and none-use, weight=0. This approach of assigning weights to the self-reported frequency of use has been performed in other studies using MACS data. (Hart et al., 2012; Shoptaw et al., 2012) We estimated the cumulative exposure to marijuana use by adding the total number of days marijuana was used during all

follow-up study visits (beginning from when participants were enrolled in the MACS until their last study visit or the end of the study period). The measure was expressed in use-years with 1 marijuana use-year equivalent to using marijuana every day for 1 year. We imputed missing response on marijuana use using predictive mean matching method of imputation which is similar to the regression method except that for each missing value it imputes a value randomly from a set of observed values whose predicted values are closest to the predicted value for the missing value from the simulated regression model (Heitjan & Little, 1991; Schenker & Taylor, 1996).

Outcome: Cognitive Function: Cognitive function was assessed at each study visit. *The Symbol Digit Modalities Tests (SDMT)* (Smith, 1982) requires elements of attention, visuoperceptual processing, working memory and psychomotor speed. We indexed this test to measure cognitive processing speed. Participants were presented with a reference key on a sheet of paper consisting of nine abstract symbols, each paired with a number and participants were asked to scan the reference key and write down the number corresponding to each of the abstract symbol as quickly as possible. The score was calculated as the number of correct pairings of abstract symbols and numbers over a period of 90 seconds, with higher scores indicating better performance.

The *Trail Making Test* (Reitan, 1992) *Part A* (TMTA) which assesses cognitive processing speed consists of 25 circles numbered 1 – 25 which are distributed randomly over a sheet of paper. The participant was asked to use a pencil to connect the numbers in ascending order (i.e. 1–2-3, etc.) as quickly as possible. In the *Trail Making Test* (Reitan, 1992) *Part B* (TMTB) participants were asked to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence (i.e. 1-A, 2-B, 3-C, etc.). Because of the additional set-shifting component, we designate the TMT-B to assess cognitive flexibility. The scores for the TMTA and TMTB were calculated as the time (in seconds) to complete the connections, with higher scores indicating worse performance. The inverse of this score was used in the current analyses, so that higher scores will indicate better performance (in the same direction as the SDMT).

2.2.3. Covariates—*Socio-demographic characteristics* included participant's self-reported age, race/ethnicity status and educational attainment. Study participants were classified according to the MACS study center (Baltimore, MD./Washington DC; Chicago, IL; Pittsburgh, PA; Los Angeles, CA) and MACS cohort status (enrolled prior to or after 2001). *Depressive symptoms* were evaluated at every study visit with the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). Current a*lcohol use* was self-reported at every study visit and categorized. We computed cumulative exposure to alcohol in drink-years with 1 drink-year equivalent to consuming a standard drink of alcohol every day for a year. We calculated the average number of drinks consumed per week for each participant by multiplying the average number of drinking-days per week by the average number of drinks consumed per drinking-day. Alcohol drink-years was computed by adding the total average number of drinks consumed during all follow-up visits (see eAppendix). *Cigarette use* was self-reported at every study visit. We categorized current smoking status at every visit into three groups: (1) never (2) former and (3) current smoker.

Cumulative exposure to cigarettes was computed and defined in pack-years, with one-pack-year of exposure equivalent to 7300 cigarettes (1-year x 365 days/year x 1 pack/day x 20 cigarettes/pack) (Akhtar-Khaleel et al., 2015). *Stimulant/recreational drug use* was self-reported at every study visit. Participants were considered to be users of stimulant drugs if they reported the use of: (1) crack cocaine, (2) other forms of cocaine and (3) methamphetamines and (4) ecstasy. Participants self-reported their frequency of use of poppers (inhaled nitrites – a common class of illicit drug used recreationally among MSM) (Romanelli, Smith, Thornton, & Pomeroy, 2004) using similar response options as for marijuana use, but categorized as any use (yes/no) in the past six months. We used similar approach for marijuana use-years to compute cumulative exposure to stimulants and poppers in use-years. Participants were categorized as having a history of injection drug use (IDU), if they self-reported ever injecting any substance. Hypertension was assessed at every visit and was defined as systolic blood pressure greater than 140 mmHg, or diastolic blood pressure greater than 90 mmHg or diagnosed with hypertension and use of medications. Diabetes status was classified using a combination of HgA1C values ≥6.5 and diagnosed with diabetes and use of medication. Hepatitis C virus (HCV) infection status was categorized as HCV negative if HCV antibody testing was negative. Participants were classified at each MACS study visit as HCV positive if they were found to be in the process of seroconversion, acute infection, chronic infection, clearing (between RNA + and RNA -), or previously HCV positive, but now clear of HCV RNA. HIV-serostatus was assessed using enzyme-linked immunosorbent assay with confirmatory Western blot tests on all participants at each participant's initial study visit and at every semiannual visit thereafter for participants who were initially HIV– to confirm their serostatus. Plasma HIV RNA concentrations were measured using the COBAS Ultrasensitive Amplicor HIV-1 monitor assay for HIV RNA (Roche Molecular Systems, Branchburg, NJ), with a sensitivity of 50 copies of HIV per RNA/mm^3. Standardized flow cytometry was used by each MACS center to quantify CD4+ T-lymphocyte subset levels (Giorgi et al., 1990). Antiretroviral therapy (ART) and ART adherence was self-reported at every study visit. ART was classified as none, nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and non-NRTIs (NNRTIs). Adherence to ART was assessed in the MACS beginning from October 1998 using a scale measuring four levels of adherence, which has been described previously (Kleeberger et al., 2001). ART use prior to October 1998 was considered 100% adherent. We computed cumulative years of each class of ART at each study visit, weighted for self-reported adherence. The weights for the four levels of adherence were 1, 0.975, 0.85, 0.375, 0 for adherence levels of 100%, 95–99%, 75–94% and less than 75%. History of clinical AIDS was determined according to the 1993 CDC definition of AIDS (CDC, 1992).

2.3. Data Analysis

Data analyses was conducted from April 1, 1996, to September 30, 2013. April 1, 1996 was chosen as the baseline because that was when most men in the MACS initiated HAART (Gingo et al., 2013). We used linear mixed effects models to test associations between current (at every visit) and cumulative exposure to marijuana (in marijuana-use-years) and changes in cognitive function measures using SAS PROC MIXED, to account for correlations between repeated cognitive function measures over time, from the same participants. We specified an unstructured covariance matrix for the repeated outcome

measures as this achieved the best model fit (in terms of lower AIC and BICC) compared to other covariance structures (Diggle, Heagerty, Liang, & Zeger, 2002). We used robust standard errors from the robust empirical covariance estimator. Time since baseline (in years) was used as the longitudinal metric for time. Models included both linear and nonlinear (quadratic) time trends. We fit linear mixed effects models over the 17-year follow-up period, using maximum likelihood estimation and allowing for random intercepts and random slopes to account for individual differences in baseline cognitive function and to allow for subject-specific rates of cognitive change. We performed stratified analysis by HIV-serostatus. We modeled each cognitive function outcome separately on current marijuana use, as well as on cumulative exposure to marijuana. The primary coefficients of interest were interactions between current and cumulative marijuana-use-years with time. The model for the HIV- men adjusted for time-stable covariates (race, education, MACS study center, MACS cohort status and history of IDU) and time-varying covariates (age, depressive symptoms, current smoking status, current alcohol use, current popper use, current stimulant use, hepatitis C infection status and hypertension). The models for the HIV + men additionally adjusted for time-stable (history of AIDS) and time-varying HIV-specific parameters (CD4 counts, viral load and ART use status). The models assessing cumulative exposure to marijuana use and cognitive function included time-varying cumulative exposure variables including pack-years of smoking, alcohol drink-years, stimulant and popper use-years. We log transformed test scores from the TMTA and TMTB to approximate a normal distribution. To facilitate interpretation, we transformed the regression coefficients of the TMTA and TMTA models using the formula, 100 (exp $\beta-1$) where β is the regression coefficient (or associated 95% confidence limit for this coefficient). Because the longitudinal metric for time was measured in years, the coefficients can be interpreted as *annual percent change* in test scores across time. We used inverse probabilities of attrition weights (IPAW) (Weuve et al., 2012) to adjust for selective attrition (see eAppendix). Cohen's f^2 effect sizes was calculated to understand the magnitude of the associations between current and cumulative exposure to marijuana use in all models. Cohen's f^2 was calculated using SAS PROC MIXED procedures introduced by Selya et al (2012)(Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012), with $f^2 \geq 0.02$, $f^2 \geq 0.15$, and $f^2 \geq 0.35$ representing small, medium, and large effect sizes, respectively (Cohen, 1988). All statistical analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Statistical tests for significance was defined as $p < 0.05$.

3. Results

3.1. Sample Characteristics

Participants included 1,920 self-identified MSM, 788 (41.0%) of which were HIV+ (Table 1). The men contributed 28,232 of follow-up visits across the 17-year period (10,636 for HIV+ and 17,596 for HIV–), and the median number of visits per participant was 15 [interquartile range (IQR): 6, 22; 13 (IQR=5, 20) for HIV+ and 16 (IQR=7, 22) for HIV- men]. The mean age of the sample at baseline was 43.6 years [(standard deviation (SD) =9.9], majority were non-Hispanic whites (61%) and had completed some college or more (80%). At baseline, 83% self-reported alcohol use; 71% reported ever smoking cigarettes (36% former smokers and 35% current smokers); and 28% reported stimulant use (Table 1).

At baseline,34.7% (n=667) of the sample self-reported marijuana use. Current marijuana use at baseline was significantly associated with younger age, education, MACS study center, all substance use variables, depressive symptoms and hepatitis C positive status.

3.2. Associations between current marijuana use and cognitive processing speed, and flexibility.

In adjusted analysis for the HIV+ men, current daily and monthly marijuana use compared to none-use was significantly associated with a greater decline in the two measures of cognitive processing speed across the 17-year follow-up period. Specifically, the annual percentage change on the TMTA scores was 0.41 percent lower [β=−0.41, 95% confidence interval (CI): −0.88, −0.03; p=0.04] in current daily users compared to nonusers. Similarly, monthly marijuana use compared to none-use was significantly associated with a 0.70 annual percentage decline on the TMTA scores (β= −0.70, 95% CI: −1.34, −0.05; p=0.03). For the SDMT, current monthly (β= −0.21, 95% CI: −0.40, −0.01, p=0.03) and daily marijuana use (β=−0.14, 95% CI: −0.28, −0.01, p=0.04) compared to none-use was significantly associated with a greater annual percentage decline on the SDMT scores over time. No other level of current marijuana use was significantly associated with rate of decline. In contrast, among HIV- men, no level of current marijuana use was significantly associated with changes in any of the cognitive function tests (Table 3). In addition, all effect sizes were very small, falling below Cohen's f^2 criteria for a small effect size (all f^2 <0.02) and were of similar magnitude in both the HIV+ and HIV- men.

3.3. Associations between cumulative marijuana use and cognitive processing speed and flexibility.

Among HIV+ men only, there were no statistically significant association between cumulative marijuana use-years and changes in any cognitive function domain (Table 2). Conversely, in the HIV- men only, each additional 5 marijuana use-years was significantly associated with a decline in TMTA scores by 0.18 percent annually (β= −0.18, 95% CI: −0.36, −0.01; p=0.04; Table 3). Similarly to the findings for current marijuana use, all effect sizes were very small, falling below Cohen's f^2 criteria for a small effect size (all f^2 <0.02) and were similar in the HIV+ and HIV- men.

In exploratory analysis, we tested for interactions between history of AIDS, detectable viral load and CD4 counts by current and cumulative marijuana use but the results were not significant (all ps>0.05). In all models, the most consistent set of covariates that were associated with increased rate of decline across cognitive function tests was advancing age, non-white race and lower education. Supplemental tables 1–4 show the full model estimates stratified by HIV-serostatus. In addition, we conducted a series of sensitivity analyses to assess the impact of multiple imputation on our findings. Specifically, we re-ran all our models without imputing missing marijuana values and compared it to our extant results; and the results for current and cumulative marijuana-use-years remained relatively consistent (results are presented in supplemental tables 5–7).

4. Discussion

In this analysis of HIV+ MSM in the MACS followed for 17-years, we found current monthly and daily marijuana use to be significantly associated with slowed cognitive processing speed, but not cognitive flexibility. Additionally, we found no significant associations between cumulative exposure to marijuana (in marijuana use-years) and changes in cognitive processing speed and flexibility. Among the HIV- MSM, we found no statistically significant association between current marijuana use (for all frequency levels of marijuana use) across all cognitive function measures, although, each additional 5 marijuana-use-years was associated with significant decline in one measure of cognitive processing speed.

4.1. Current marijuana use and cognition

Our findings of significant associations between current monthly and daily marijuana use with slowed cognitive processing speed differ from other studies of HIV+ individuals that found no significant associations (Chang et al., 2006; Cristiani et al., 2004; Lorkiewicz et al., 2017; Thames et al., 2017, 2015). For instance, Thames et al. (2015) in a small cross-sectional study of 89 HIV+ and HIV- subjects found that HIV+ subjects with moderate-to-heavy marijuana use (i.e., 18 −90 times per week in the past year) demonstrated no significant associations with slowed processing speed than none-users (Thames et al., 2015). In a more recent study, Thames et al. (2017) found no significant difference on tasks of processing speed among HIV+ subjects when levels of marijuana use increased over 1.4grams/week (Thames et al., 2017). These studies were cross-sectional with modest sample sizes compared to our study which used cognitive function assessments at multiple time-point from a large sample. However, our study found no significant associations between current marijuana use and decline in cognitive flexibility, which is consistent with other studies of HIV+ individuals that assessed this cognitive domain (Chang et al., 2006; Cristiani et al., 2004).

Our findings of no significant association with current marijuana use and processing speed and flexibility in HIV- men mirror findings from other longitudinal studies of adults conducted in the general population (McKetin, Parasu, Cherbuin, Eramudugolla, & Anstey, 2016; Tait, Mackinnon, & Christensen, 2011). For example, one longitudinal study of 2,404 adults, 22 years of age at baseline followed for 8-years in an Australian cohort found no significant differences in performance on tasks of processing speed in some marijuana using groups versu none-using groups (Tait et al., 2011). Similarly, another longitudinal study of 1,897 adults, mean age at baseline of 42 years followed for nearly 8 years found no significant differences in performance on tasks of cognitive processing speed between weekly or more and less than weekly marijuana use in the past year compared to nonuse (McKetin et al., 2016). In addition, we note that all of the coefficients from our models, were of very small magnitude, falling below Cohen's f^2 criteria for a small effect size suggesting that our findings, likely do not represent clinically meaningful declines in cognitive function.

4.2 Cumulative marijuana use and cognition

Our study is among the first to longitudinally assess the impact of cumulative exposure to marijuana and changes in cognitive function performance for a 17-year follow-up period. Among the HIV- men, our study found cumulative exposure to marijuana was associated with statistically significant decline in one measure of cognitive processing speed (TMTA) and not in the other (SDMT). This is inconsistent with studies in the general population that have found no significant associations with cumulative or chronic marijuana use and decline in cognitive processing speed (Auer et al., 2016; Fried, Watkinson, James, & Gray, 2002; Solowij et al., 2002). For example, in a recent cohort study of 3,385 men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) study, cumulative marijuana use for 25 years was not statistically significantly associated with worse cognitive processing speed (Auer et al., 2016). Although that study assessed cognitive function at a single time-point when participants mean age was ~50 years compared to our study, which had cognitive function assessments at multiple time-points beyond 50 years – when cognitive decline may be more apparent. However, in one study that comprised 1,037 individuals in a New Zealand birth cohort study followed-up for 20 years found that diagnosis with cannabis dependence at 3 or more study waves was associated with widespread declines in cognitive domains including memory, executive function and cognitive processing speed in adulthood (Meier et al., 2012). Nevertheless, this study was among participants in young adulthood (~38 years).

Contrastingly, among HIV+ men in our study, we found no significant association between cumulative marijuana-use-years and rate of decline across all cognitive function measure. One other study that assessed associations of lifetime exposure to marijuana and cognitive function in HIV+ individuals found similar findings. In a cross-sectional analysis of 215 HIV+ adults with substance use disorder, lifetime marijuana use, was defined as the number of years marijuana was used ≥3 times per week. Although they did not assessed cognitive processing speed or flexibility, they authors found no significant association between lifetime marijuana use and worse memory and attention assessed using the Montreal Cognitive Assessment (MoCA) (Lorkiewicz et al., 2017). These findings lend support to the literature on residual effects of marijuana exposure on cognitive function, which suggest that cognitive deficits dissipate following abstinence periods that span 25 days (Gonzalez, 2007; Grant et al., 2003; Schreiner & Dunn, 2012). It is unclear why cumulative exposure to marijuana was significantly associated with slowed processing speed in the HIV- men in our study, but not in the HIV+ men. As noted earlier and similar to our findings for current marijuana use, all of the coefficients for cumulative marijuana-use-years and cognitive function outcomes, were very small, falling below Cohen's f^2 small effect size, indicating that our findings are likely not clinically meaningful.

Further, our study did not find evidence that cognitive function outcome may be worse in HIV+ individuals with disease progression. Our additional analysis found no significant interaction between current and cumulative marijuana-use-years with viral load detectability and CD4 counts. This contrasts with one early study published over 13 years ago that found pronounced memory impairment in subjects with symptomatic HIV infection (Cristiani et al., 2004). One likely explanation is that the men in our sample were medically stable as

nearly all (~85%) were receiving HAART and about half had CD4 counts greater than 500 copies with undetectable viral load at baseline.

4.3. Limitations

Readers should interpret our results in light of some limitations. Marijuana use in this study was obtained via self-report and no biological marker was used to confirm self-reported use. Related to this issue is that our method for calculating cumulative marijuana use may have been imprecise. For example, there is the possibility for significant data loss in average number of days of marijuana use for participants who use marijuana more than weekly but less than daily (e.g., 2–3 times per week). Second, we were not able to account for exposures to marijuana prior to enrollment in the MACS; including data on age of first use. Studies have previously demonstrated that early initiation of marijuana (particularly early adolescent) may confer profound cognitive impairments – via its effect on the developing adolescent brain (Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Lisdahl, Wright, Medina-Kirchner, Maple, & Shollenbarger, 2014; Skalski, Towe, Sikkema, & Meade, 2017). Thirdly, selective attrition was likely a concern in this study as participants who dropped out or died during follow-up performed worse on the cognitive function measures at baseline than those who survived and remained in the study. Participants who reported substance use, including marijuana use, were more likely to drop out or die during follow-up (data not shown), and this trend was greater in HIV+ compared to HIV– participants. We note however, that our analyses employed inverse probability of attrition weights, but this approach may not have completely accounted for these attrition effects, thus our estimates of cognitive decline may have been underestimated. Fourth, our study did not adjust for additional covariates that may confound the associations between marijuana use and cognitive function including psychiatric illness and use of psychotropic medications. Psychiatric illness is prevalent in HIV+ individuals (Lopes et al., 2012; O′Cleirigh, Magidson, Skeer, Mayer, & Safren, 2015) and can interfere with cognitive function (Watkins & Treisman, 2015). This leaves open the possibility that our significant results for current monthly and daily marijuana use and slowed processing speed in HIV+ men may explained by the presence of psychiatric illness and other unmeasured confounds (including use of psychotropic medications). Fifth, our study only focused on two domains of cognitive function (i.e. cognitive processing speed and flexibility). Future investigations of current and the long-term impact of marijuana use on other aspects of cognitive function including executive function, attention and motor functions is warranted. In addition, participants in our study comprised men who have sex with men, majority of whom were non-Hispanic whites with relatively high educational accomplishment and thus our study findings may be less generalizable to other populations (e.g. racial/ethnic minorities or women). Finally, our study did not distinguish between the THC/cannabidiol (CBD) content of the marijuana consumed. There is some evidence that CBD – which does not have psychoactive properties – may confer neuroprotective effects against the negative effects of THC (Englund et al., 2013; Gruber et al., 2016; Morgan, Schafer, Freeman, & Curran, 2010). Notwithstanding, our study has many strengths including among the first studies utilizing a sample size this large, with longitudinal data on marijuana exposure (and many other covariates) and cognitive function assessments for over a 17-year period.

5. Conclusions

In summary, our study found significant associations between some frequency levels of current marijuana use, particularly daily marijuana and slowed processing speed over a 17-year follow-up period, but only among the HIV+ men. We also found no significant association between cumulative marijuana-use-years and declines in any of the cognitive function measure among HIV+ individuals, although the HIV– men demonstrated slowed cognitive processing speed with each 5 cumulative marijuana-use-years. Overall, the magnitude of the effect sizes from all our results did not reach values that indicate clinically meaningful detrimental impacts of current or cumulative exposure to marijuana on cognitive processing speed and cognitive flexibility in the sample. Additional studies are needed to verify this conclusion, including investigations assessing other cognitive domains and in other demographic groups (e.g. women).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of MACS Participants Included in the Study by Marijuana Use at Baseline (N=1920)

Characteristics	Overall		Current marijuana use				*P* value [a]
			Yes (n=667)		No (n=1253)		
	N	%	n	%	n	%	
Age, mean (SD), y	43.6	9.91	41.6	9.99	44.6	9.7	<0.01
Race							0.27
White, non-Hispanic	1170	60.9	399	59.8	771	61.5	
Black, non-Hispanic	493	25.7	185	27.7	308	24.6	
Other	257	13.4	83	12.4	174	13.9	
Education							<0.01
High school diploma or less	386	20.1	144	21.6	242	19.3	
Some college or college degree	954	49.7	368	55.3	586	46.8	
Graduate work or more	578	30.1	154	23.1	424	33.9	
Study center							0.01
Baltimore, MD/Washington DC	480	25.0	143	21.4	337	26.9	
Chicago, IL	374	19.5	146	21.9	228	18.2	
Pittsburgh, PA	489	25.5	161	24.1	328	26.2	
Los Angeles, CA	577	30.1	217	32.5	360	28.7	
Study enrollment							0.82
Pre-2001	1037	54.0	358	53.7	679	54.2	
Post-2001	883	46.0	309	46.3	574	45.8	
Depressive symptoms							0.03
CES-D ≥16	480	25.7	187	28.5	293	24.2	
Current alcohol use							<0.01
None	321	16.7	37	5.5	284	22.7	
1 to 12 drinks/week	1409	73.4	522	78.3	87	70.8	
≥ 13 drinks/wk.	190	9.9	108	16.2	82	6.5	
Smoking status							<0.01
Never	556	29.0	127	19.0	429	34.2	
Former	693	36.1	212	31.8	481	38.4	

Characteristics	Overall		Current marijuana use				*P* value [a]
			Yes (n=667)		No (n=1253)		
	N	%	n	%	n	%	
Current	671	34.9	328	49.2	343	27.4	
Current popper use	433	22.8	231	34.9	202	16.3	<0.01
Current stimulant use	528	28.1	356	53.3	288	22.9	<0.01
Cumulative substance use, median (IQR)							
Cumulative marijuana use-years [b]	0.02 (0, 0.26)		0.42 (0.07, 2.00)		0 (0, 0.02)		<0.01
Cumulative pack-years [c]	2.50 (0, 18.87)		6.13 (0, 22.50)		0.48 (0, 16.19)		<0.01
Cumulative alcohol drink-years [b]	2.96 (0.55, 10.12)		4.49 (1.23, 13.32)		2.03 (0.27, 8.82)		<0.01
Cumulative popper use-years	0 (0, 0.08)		0.01 (0, 0.2)		0 (0, 0.05)		<0.01
Cumulative stimulant use-years	0, (0, 0.01)		0 (0, 0.14)		0 (0, 0)		<0.01
History of IDU	239	12.4	91	13.6	148	11.8	0.24
Hypertension	533	28.9	172	26.8	361	30.0	0.15
Diabetes	103	11.0	29	9.4	74	11.8	0.28
Hepatitis C positive	180	9.5	48	7.3	132	10.6	0.01
HIV-seropositive	788	41.0	290	43.5	498	39.7	0.11
Detectable viral load [d]	385	50.9	149	53.4	236	49.4	0.28
CD4+ T cell count (cells/μL)							
≤ 200	116	15.2	35	12.5	81	16.8	0.16
> 200 – 500	324	42.5	129	46.2	195	40.4	
> 500	322	42.3	115	41.2	207	42.9	
History of AIDS	143	18.1	53	18.3	90	18.1	0.94
ART use							0.91
No HAART	124	15.7	44	15.2	80	16.1	
PI-based HAART	369	46.8	135	46.6	234	47.0	
Non-PI based HAART	295	37.4	111	38.3	184	36.9	
Cognitive tests, median (IQR)							
Trail Making Tests A	23 (18, 29)		22 (17, 28)		23 (18, 30)		0.01
Trail Making Test B	49 (37, 66)		49 (37, 65)		50 (38, 66)		0.26

Characteristics	Overall		Current marijuana use				
			Yes (n=667)		No (n=1253)		*P* value [a]
	N	%	n	%	n	%	
Symbol Digit Modalities	53 (16, 60)		53 (46, 61)		52 (46, 60)		0.10

Note. Abbreviations: MACS, Multicenter AIDS Cohort Study; SD, standard deviation; CES-D, Center for Epidemiologic Studies Depression Scale; wk, week; IQR, interquartile range; IDU, intravenous drug use; AIDS, Acquired Immune Deficiency Syndrome; ART, antiretroviral therapy; PI, protease inhibitors; HAART, highly active antiretroviral therapy.

[a] p values are from 1 way analysis of variance for age, Kruskal-Wallis Test for all cumulative substance use variables and cognitive tests and Chi-square tests for all other variables.

[b] cumulative marijuana use-years computed from frequency of marijuana use across all visits while in the MACS study, with 1 marijuana use-year equivalent to using marijuana every day for 1 year. Similarly, approaches were used for computing cumulative exposure to alcohol and stimulant, with 1 drink year equivalent to consuming 1 standard alcoholic drink every day for 1 year and 1 stimulant use-year equivalent to using stimulants every day for 1 year.

[c] cumulative exposure to cigarettes in pack-years was based on number of cigarettes smoked per day and the number of years smoked and computed across all study visits with 1-pack year exposure equivalent smoking 20 cigarettes per day for 1 year (or 7,305 cigarettes in 1 year).

[d] detectable viral load defined as ≥200 copies/mL

Table 2.

Association of current and cumulative marijuana use and cognitive change over a 17-year period (1996 to 2013) among HIV-positive participants in the MACS (N=788)

	TMT A[1] (Nobs=8,965)	TMT B[1] (Nobs=8,932)	SDMT[2] (Nobs=8,922)
Fixed effects	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Current marijuana use x time[3†]			
None	1 (Reference)	1 (Reference)	1 (Reference)
Monthly or less often	−0.70 (−1.34, −0.05) *	−0.17 (−0.82, 0.48)	−0.21 (−0.40, −0.01) *
Weekly	−0.15 (−0.73, 0.43)	−0.29 (−0.78, 0.21)	−0.15 (−0.39, 0.10)
Daily	−0.41 (−0.88, 0.03) *	−0.03 (−0.49, 0.44)	−0.14 (−0.28, −0.00) *
P value for trend	0.10	0.72	0.14
Cohen f[2]	0.0001	0.0002	0.0002
Cumulative marijuana use[4‡]			
Per 5 marijuana use-years	−0.01 (−0.32, 0.29)	0.14 (−0.15, 0.43)	0.01 (−0.10, 0.11)
Cohen f[2]	0.00001	0.0002	0.00002

Note. Abbreviations: MACS, Multicenter AIDS Cohort Study; SD, standard deviation; CES-D, Center for Epidemiologic Studies Depression Scale; wk, week; IQR, interquartile range; IDU, intravenous drug use; AIDS, Acquired Immune Deficiency Syndrome; ART, antiretroviral therapy; PI, protease inhibitors; HAART, highly active antiretroviral therapy; TMTA, Trail Making Test A; TMTB, Trail Making Test B; SDMT, Symbol Digit Modalities Test; Nobs, Number of observations.

†Models for current marijuana use were adjusted for **time-stable covariates** including race, education, study center, cohort status, history of intravenous drug use, history of AIDS, and **time-varying covariates** including age, depressive symptoms (CESD), smoking status, alcohol use, popper and stimulant use, hepatitis C Infection status, hypertension, viral load, HAART use.

‡Models for cumulative marijuana use were adjusted for the same covariates as in current marijuana use as well as cumulative smoking pack-years, cumulative drink-years, cumulative popper use-years, cumulative methamphetamine use-years and cumulative crack/other cocaine use-years.

1Scores from tests were expressed on a natural logarithmic scale. To facilitate interpretation, we transformed regression coefficients using the formula, 100 (exp β−1) where β is the regression coefficient (or associated 95% confidence limit for this coefficient). Because time was measured in years, the coefficients can be interpreted as *annual percent change* in test scores across time.

2Estimates are in the original test scale

3Defined as marijuana use since last study visit (typically past six-months).

4Cumulative exposure to marijuana expressed as marijuana use-year, with 1 marijuana use-year equivalent to using marijuana every day for 1 year. This model was conducted separately from the model for current marijuana use and was additionally adjusted for cumulative pack-years, drink-years and illicit drug (poppers, methamphetamine and crack/cocaine use-years.

* p=<.05

Table 3.

Association of current and cumulative marijuana use and cognitive change over a 17-year period (1996 to 2013) among HIV-negative participants in the MACS (N=1,132)

	TMT A[1] (Nobs=15,275)	TMT B[1] (Nobs=15,230)	SDMT[2] (Nobs=15,193)
	Coefficient (95% CI)	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Current marijuana use[3†]			
None	1 (Reference)	1 (Reference)	1 (Reference)
Monthly or less often	−0.06 (−0.50, 0.39)	−0.01 (−0.53, 0.51)	−0.03 (−0.24, 0.17)
Weekly	−0.01 (−0.43, 0.41)	−0.15 (−0.65, 0.37)	0.17 (−0.07, 0.40)
Daily	−0.15 (−0.46, 0.15)	−0.29 (−0.60, 0.03)	−0.06 (−0.17, 0.06)
P value for trend	0.79	0.35	0.31
Cohen f[2]	0.00001	0.00001	0.00002
Cumulative marijuana use[4‡]			
Per 5 marijuana use-years	−0.18 (−0.36, −0.01) *	−0.16 (−0.36, 0.04)	−0.02 (−0.11, 0.06)
Cohen f[2]	0.001	0.001	0.0001

Note. Abbreviations: MACS, Multicenter AIDS Cohort Study; SD, standard deviation; CES-D, Center for Epidemiologic Studies Depression Scale; wk, week; IQR, interquartile range; IDU, intravenous drug use; AIDS, Acquired Immune Deficiency Syndrome; ART, antiretroviral therapy; PI, protease inhibitors; HAART, highly active antiretroviral therapy; TMTA, Trail Making Test A; TMTB, Trail Making Test B; SDMT, Symbol Digit Modalities Test; Nobs, Number of observations.

†Models for current marijuana use were adjusted for **time-stable covariates** including race, education, study center, cohort status, history of intravenous drug use and **time-varying covariates** including age, depressive symptoms (CESD), smoking status, alcohol use, popper and stimulant use, hepatitis C Infection status and hypertension.

‡Models for cumulative marijuana use were adjusted for the same covariates as in current marijuana use as well as cumulative smoking pack-years, cumulative drink-years, cumulative popper use-years, cumulative methamphetamine use-years and cumulative crack/other cocaine use-years.

1Scores from tests were expressed on a natural logarithmic scale. To facilitate interpretation, we transformed regression coefficients using the formula, 100 (exp β−1) where β is the regression coefficient (or associated 95% confidence limit for this coefficient). Because time was measured in years, the coefficients can be interpreted as *annual percent change* in test scores across time.

2Estimates are in the original test scale

3Defined as marijuana use since last study visit (typically past six-months).

4Cumulative exposure to marijuana expressed as marijuana use-year, with 1 marijuana use-year equivalent to using marijuana every day for 1 year. This model was conducted separately from the model for current marijuana use and was additionally adjusted for cumulative pack-years, drink-years and illicit drug use-years.

* p=<.05