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Sex differences in the association between cumulative use of cannabis and cognitive function in middle age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Abstract

Background: Cannabis use may impair cognitive function differently in men and women, due to sex-specific differences in neurobiological mechanisms and environmental risk factors.

Objective: Assess sex differences in the association between cumulative exposure to cannabis and cognitive performance in middle age.

Methods: We studied participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, including Black and White men and women 18-30 years old at baseline followed over 30 years. Our cross-sectional analysis of cognitive function scores at Year 30 was stratified by sex. We computed categories of cumulative exposure in "cannabis-years" (1 cannabis-year=365 days of use) from self-reported use every 2 to 5 years over 30 years. At Years 25 and 30, we assessed cognitive function with the Rey Auditory Verbal Learning Test (verbal memory), the Digital Symbol Substitution Test (processing speed), and the Stroop Interference Test (executive function). At Year 30, additional measures included Category and Letter Fluency Test (verbal ability) and the Montreal Cognitive Assessment (global cognition). We computed standardized scores for each cognitive test and applied multivariable adjusted linear regression models for self-reported cumulative cannabis use, excluding participants who used cannabis within 24 hours. In a secondary analysis, we examined the association between changes in current cannabis use and changes in cognitive function between Years 25 and 30.

Results: By Year 30, 1,352 men and 1,793 women had measures of cognitive function; 87% (N=1,171) men and 84% (N=1,502) women reported ever cannabis use. Men had a mean cumulative use of 2.57 cannabis-years and women 1.29 cannabis-years. Self-reported cumulative cannabis use was associated with worse verbal memory in men (e.g., -0.49 standardized units (SU) for ≥5 cannabis-years of exposure; 95%CI: -0.76 to -0.23), but not in women (SU 0.02 95%CI: -0.26 to 0.29). Other measures of cognitive function were not

associated with cannabis. Changes in current cannabis use between Years 25 and 30 were not associated with cognitive function in men or women.

Conclusions: Self-reported cumulative cannabis exposure was associated with worse verbal memory in men but not in women. Researchers should consider stratified analyses by sex when testing the association between cannabis and cognition.

Introduction

Cannabis is the most widely used illicit drug.[1] In the U.S., adult men are more likely to have used cannabis in the past month than women (12.5 % of men over 18; 7.4 % of women over 18)[2], but the gap in use prevalence is narrowing.[3] Men and women may differ in the sensitivity to cannabis and its effects on cognition,[4-7] perhaps due to neurobiological factors. Preclinical animal studies describe sex-specific characteristics of the endocannabinoid system and pharmacokinetics of THC metabolization but these have been insufficiently replicated in human studies.[4] In human brain imaging studies, some brain markers differed between men and women as a result of cannabis use, suggesting sex differences in susceptibility to the potential neurotoxic effect of cannabis.[8,9] Environmental factors like social stigma of cannabis use might also affect men and women differentially.[10]

Cannabis use has been associated with impaired cognitive functions.[11] In chronic cannabis users, impairments in cognitive function have most consistently been reported in episodic memory, notably in learning and recall based on verbal memory tests.[12,13,14,15] We previously tested the association between three measures of cognitive function in the Coronary Artery Risk Development in Young Adult (CARDIA) study over 25 years[16] and found a significant association between self-reported cumulative cannabis use and verbal memory.

New data from Year 30 allows us to expand our analyses to other domains of cognitive function, to study changes in cognitive function over time, and to revisit our main analyses. A fresh look is necessary because evidence suggesting a sex interaction on the measure of associations between cannabis use and cognitive function is increasing.

Prior studies that explored sex-differences in the association between chronic cannabis use and episodic memory suffered certain limitations. Some included participants who had only used cannabis for a short time and restricted participation to adolescents.[17,18,19] These reported no interaction by sex on measures of episodic memory but could not have captured differences that manifest only after prolonged exposure. Interpreting sex differences during adolescence is difficult because cognitive systems develop at different rates according to sex and unevenly between individuals.[20]

Other studies with null findings included participants with longer cannabis use duration but included few women or studied small cohorts.[21,22] The few small studies that reported sex differences in the association between chronic cannabis use and memory functions had conflicting results.[23-28] For example, a study of 69 cannabis users reported that cannabis use was more consistently associated with worse verbal memory in women than in men while two recent studies that compared cannabis users to non-users found cannabis use was associated with worse episodic memory in men but not in women. Other cognitive function domains, such as psychomotor speed and decision-making, were reported to be more strongly impaired in men than in women.[22,28]

We thus set out to determine if the associations between cannabis use and 6 measures of cognitive function differed by sex in a large community-based cohort that followed participants over 30 years and assessed cannabis use repeatedly. To our knowledge, the CARDIA study is the largest cohort of middle-aged adults to include an almost equal number of women and men and to collect data on cannabis use. Because verbal memory and cannabis exposure were associated at Year 25[16] and because the literature suggested an association between cannabis exposure and brain markers of the hippocampus,[14] we predefined delayed recall score from the Rey Auditory Verbal Learning Test (RAVLT) as our main outcome. We performed a secondary analysis to estimate the association between changes in categories of current cannabis use over 5 years and changes in three cognitive function scores over the same period.

Methods

Study Design and Sample

We used data from the Coronary Artery Risk Development in Young Adults Study, a population-based cohort of 5115 adults aged 18 to 30 years at baseline and followed up for 30 years. A detailed description of the cohort has been published.[16] All participants gave

informed consent before entering the study and at each visit, and the institutional review boards at each site granted approval for the study.

Cannabis Exposure: Current and Cumulative

Current cannabis use was assessed at each in-person CARDIA visit (at baseline and after 2,5,7,10,15,20,25, and 30 years of follow-up) with the following survey question: “During the last 30 days, on how many days did you use marijuana?” Direct self-reported cumulative exposure was assessed with the question: “About how many times in your lifetime have you used marijuana?” Current and lifetime use were used to compute cannabis-years: one year of exposure was equivalent to 365 days of cannabis use (see Supplementary Material for details). Current use at each visit (the number of days of cannabis was used in the month before each visit) was assumed to indicate the average number of days of use the months before and after each visit. The total number of days the participant used cannabis over follow-up was summed to estimate self-reported cumulative cannabis use. Whenever direct self-reported lifetime use was higher than the computed estimates, the estimate was adjusted upwards. At the Year 30 visit, acute cannabis use was assessed with the following survey question: “Did you use marijuana in the last 24 hours?”[29] As previously, participants were classed into existing categories of self-reported cumulative:[29] never use; 1 day to <0.5 cannabis-years; 0.5 to <2.0 cannabis-years; 2.0 to <5.0 cannabis-years; and 5.0 or more cannabis-years.

Cognitive outcome measures:

Trained and certified CARDIA technicians administered a battery of cognitive function tests at Year 25 and 30 to assess cognitive function (CF). At Year 25, participants took the RAVLT, the Digit Symbol Substitution Test (DSST) and the Stroop Test. RAVLT measures verbal learning and episodic memory;[30] delayed (10 minutes) free recall score was the main outcome. The DSST tests processing speed and attention.[31] The Stroop Test measures executive function.[32] Higher scores on the RAVLT and DSST correspond to better cognitive

performance; higher scores on the Stroop Test reflect worse cognitive performance. The inverse (0 minus actual score) of the Stroop was used to interpret lower scores as worse cognitive function.

At Year 30, the same tests were repeated and three were added: the category fluency test; the letter fluency test; and the Montreal Cognitive Assessment (MoCA). The category and letter fluency tests measure verbal fluency.[33] The category fluency test provides information about semantic memory; letter fluency also assesses executive function.[33] The MoCA detects mild cognitive impairment, assessing attention, executive function, memory, language, visuospatial skills, calculations, and orientation.[34] Each measure was standardized by subtracting the mean and dividing the remainder by the within-CARDIA standard deviation to ensure absolute and relative differences in these standardized measures were comparable ("z-score").[35]

Covariables:

We estimated self-reported cumulative exposure to tobacco cigarettes in pack-years and self-reported cumulative alcohol consumption in drink-years. Men who reported 5 or more drinks on a single occasion and women who reported 4 or more were categorized as having acute heavy exposure to alcohol (bingeing); we estimated cumulative bingeing episodes. We estimated cumulative exposures to cocaine (including crack, powder, free base, and other forms), amphetamines (speed, uppers, methamphetamines), and heroin. Education level (in years) was the participant's highest educational grade by Year 30. Current marital status was assessed at each visit. We measured physical activity with the CARDIA physical activity history questionnaire at each visit. Cardiovascular risk factor measurements included blood pressure, blood cholesterol, blood triglycerides, body mass index (BMI), and diagnosis of diabetes mellitus; these were collected at each CARDIA examination. Depression was measured on the Center for Epidemiologic Studies Depression scale (CES-D) every five years, starting at the Year 5 visit. We analyzed data on antipsychotic or stimulant medication use and measures of socioeconomic hardship (defined a sustained exposure to low income)

in sensitivity analyses.[36] At Year 2, the mirror star tracing test elicited reactive blood pressure, but other studies have suggested it can be used as a measure of executive function,[16,37] so we used it to adjust for baseline cognitive function. We used information on history of stroke as reported by participants and assessed by hospital chart review to exclude participants from some analyses (see Supplementary Material for more details on covariables).

Statistical analysis

Cross-sectional analysis

We first performed a cross-sectional analysis based on Year 30 data to assess the associations between self-reported cumulative cannabis use (categorized as described above) and CF. Given the robust literature on CF impairment in acute cannabis intoxication state[6,38] we excluded from the main analysis participants who reported using cannabis in the 24 hours prior to their visit (N=169). As predefined, we then tested for sex differences in the relationship between cannabis use and CF. Since interaction by sex was significant, we stratified all models by sex. We used descriptive statistics to separately assess participants' characteristics in women and men. We described unadjusted associations between self-reported cumulative cannabis use and each CF measure before and after standardization. We used linear regression to assess independent associations between categories of years of exposure to cannabis and CF outcomes. To fully explore and test potential nonlinear associations, we also modeled cannabis use flexibly as restricted cubic splines.

We tested three models in sequence. The first was unadjusted. The second model controlled for the covariables age, race, study center, and years of education. The third also controlled for covariables that could be associated with cannabis and cognition: cigarette smoking (current, cumulative, age started smoking); alcohol (current, cumulative and binge drinking), cocaine, amphetamines, and heroin (current and cumulative); physical activity; cardiovascular risk factors, including BMI, blood pressure, blood lipids, diabetes mellitus; current depression; and marital status at the Year 30 visit.[39] We used restricted cubic splines

with three knots at the quartiles of their distributions to flexibly model age, years of education, drink-years of alcohol, binge-drinking episodes, tobacco pack-years, physical activity, BMI, blood pressure and blood lipids. We modeled blood pressure, blood lipids and physical activity as cumulative measure (see Supplementary Material). We used inverse probability of censoring weights (IPCW) to minimize potential bias from informative censoring.

Changes in midlife cognitive function by changes in current cannabis use category

Since our measures of self-reported current and cumulative cannabis use are inherently closely collinear, we tested the association between current cannabis exposure and cumulative exposure separately. We estimated the 5-year change in the three cognitive test results scores obtained at Year 25 and Year 30 (RAVLT, DSST, Stroop) for the five possible combinations of cannabis use at these time points (never users, past users (any use before Year 25 and no current use at Year 25 or 30), recent quitters at Year 30 (current use at Year 25 and no current use at Year 30), recent restarters at Year 30 (any use before Year 25, no current use at Year 25 and current use at Year 30), continuous users over 5 years (current use at Year 25 and at Year 30). We then used linear regression models to assess the associations between changes in categories of current cannabis use and the changes in midlife CF over these 5 years. In multivariable adjusted linear regression models, we adjusted for the same covariables we already described, measuring covariables at Year 25. To consider variations in participants' initial cognitive performance and cannabis use up to Year 25, we adjusted for CF scores and self-reported cumulative cannabis use at Year 25.[40] We also performed logistic regression analyses to examine the associations between the categories of current cannabis use and the odds of a cognitive decline (defined as a lower CF of -0.1 SD or more from the mean change between Year 25 and Year 30, see Supplementary Material).

Sensitivity analyses

We performed the following sensitivity analyses: (1) excluding current cannabis users (past month use), since duration of abstinence may influence the association between cannabis

use and CF[41,42]; (2) including all participants with use in the past 24 hours, to test our results on the full spectrum of cannabis use; (3) excluding participants with a history of stroke or transient ischemic attack (TIA), since both are associated with cognitive impairment[43]; (4) testing the interaction and stratifying by race; (5) adjusting for the mirror star tracing test at Year 2 to address potential reverse causation; (6) removing marital status as covariable, as marital status might be a collider on the association between cannabis use and CF according to a previous study[44]; (7) adjusting for socioeconomic hardship, since a study from the same cohort found that sustained exposure to low income was associated with worse CF[36]; (8) excluding participants who reported using antipsychotic medications or stimulant drugs at any of the CARDIA exams, since symptoms of psychosis and ADHD are associated with cannabis use and cognitive impairment[45,46]; (9) testing the association between self-reported cumulative cannabis use and measures of immediate memory and learning (RAVLT). Statistical significance tests were 2-tailed; alpha level was set at 0.05 for RAVLT (primary outcome based on prior literature) and 0.008 for other CF measures (secondary outcomes), correcting for multiple testing with Bonferroni-correction (6 CF domains). STATA 16 was used for all analyses (StataCorp LP, College Station, TX).

Results

Demographics. Of the 3,357 participants assessed at the Year 30 visit, 3,145 (94%) had data on CF: 1,352 men and 1,793 women. Of these, 87% (N=1,171) of men and 84% (N=1,502) of women reported ever using cannabis use; 18% of men (249) and 11% of women (198) reported using cannabis within the last 30 days; and 8% of men (102) and 4% of women (67) reporting use within the last 24 hours. Men had more mean cannabis-years than women and were also more likely to be heavy users (Table 1). In both sexes, self-reported cumulative exposure to cannabis was strongly associated with participant characteristics (Table 1).

Interaction by sex. In a joint model that included men and women, sex significantly interacted with the association between cumulative categorical cannabis use and verbal

memory (p-value=0.04) after participants with cannabis use in the last 24 hours had been excluded. No other interaction between CF and sex reached significance (DSST = 0.2; Stroop = 0.47; MoCA = 0.78; Letter Fluency = 0.49; Category Fluency = 0.83). We stratified all results by sex, and present CF by sex and self-reported cumulative cannabis use category (Table 2).

Cumulative cannabis use, cross-sectional analysis. In unadjusted analyses and after excluding participants who had used cannabis within the last 24 hours, categories of self-reported cumulative exposure to cannabis were associated with worse performance on RAVLT and DSST in men and women (Table 3). In MoCA this association was evident only in men. In fully adjusted analyses, categories of self-reported cumulative exposure to cannabis remained associated with worse verbal memory (RAVLT) in men (e.g., -0.49 standardized units for ≥5 cannabis-years of exposure; 95%CI: -0.76 to -0.23; p-value across categories= 0.006) but not in women (0.02 standardized units for ≥5 cannabis-years of exposure; 95%CI: -0.26 to 0.29; p-value across categories = 0.4). Before correcting for multiple testing, we noted a significant positive association between cannabis use and letter fluency in men (p-value across categories 0.02). In the sex-stratified analysis, no other CF domain was significantly associated with categories of self-reported cumulative cannabis exposure in either men or women (Table 3 and Figure 1). When we modeled self-reported cumulative cannabis exposure flexibly with restricted cubic splines, we also found a dose-related, nonlinear association in men (e.g., RAVLT -0.02 standardized units for each 1 cannabis year; 95%CI: -0.04 to -0.004) but not in women (-0.00; 95%CI: -0.02 to 0.02)**.**

Current cannabis use, changes in midlife cognitive function. We found no association between changes in categories of current cannabis use and changes in midlife CF between Year 25 and Year 30 even after extensively adjusting for covariables at Year 25 (see Table 4 and Figure 2). Stopping or starting cannabis between these visits was not associated with the odds of greater cognitive decline (see Appendix Figure 4 and Table 16).

Sensitivity analyses. (1) When we excluded current users (use within the last 30 days), we found categories of self-reported cumulative exposure were still associated with worse verbal memory in men but not in women; this association was weaker, likely due to loss of power (p-value across categories in men = 0.05; see Appendix Table 1 and Appendix Figure 1). (2) When we included all participants (use in the last 24 hours, see characteristics in Appendix Table 2) results were unchanged (see Appendix Table 3 and Appendix Figure 2). (3) When we excluded participants with a history of stroke or TIA, results were similar (p-value across categories for men = 0.008, see Appendix Table 4). (4) There was no significant interaction by race (p-value = 0.59). When we stratified by sex and race, our main findings remained unchanged (see Appendix Figure 3). (5) When we adjusted for the mirror star tracing test at Year 2, the p-value across categories was no longer significant (p=0.08) but point estimates were similar (e.g., -0.38 standardized units for ≥5 cannabis-years of exposure in men; 95%CI: -0.66 to -0.09), suggesting that the drop in significance was caused by loss of power (see Appendix Table 5). (6) Removing marital status as a covariable did not change our main results (see Appendix Table 6). (7) When we included socioeconomic hardship as a covariable in the main multivariable adjusted model, our results remained similar (see Appendix Table 7). (8) When we excluded participants with current or previous exposure to antipsychotics or stimulant drugs, results remained unchanged (see Appendix Table 8 and Table 9). (9) Other measures of the RAVLT (immediate memory, learning) were not associated with self-reported cumulative cannabis use (see Appendix Table 10). After we adjusted for measures of verbal learning (Total Encoding), delayed recall was still associated with self-reported cumulative exposure to cannabis in men (p-value = 0.005).

Discussion

Self-reported cumulative cannabis use was associated with worse verbal memory in men but not in women. In this cohort of 3,145 middle-aged adults followed over 30 years, men with light and heavy self-reported cumulative cannabis use had significantly worse delayed recall than men who had never used cannabis. Self-reported cumulative cannabis use was not associated with verbal memory function in women. Other CFs were not associated with self-reported cumulative cannabis use in participants in aggregate or after we stratified by sex. Changes in current cannabis use between Year 25 and Year 30 exam were not associated with changes in verbal memory over 5 years.

In our study, sex moderated the association between cannabis use and measures of memory in participants with a mean age of 55 years. With exception of one, the 10 studies that previously examined sex differences in the association between cannabis and measures of memory had included participants with mean ages between 12.7 – 21 years.[18,19,21,22,24-28] Since adolescents exhibit sexual dimorphism in neurodevelopment, in this age group it is hard to disentangle sex differences in cannabis effects from normal sex differences during neurodevelopment.[8,47] Our results are consistent with two small (31 and 22 female cannabis users) cross-sectional studies on young adults that used a single assessment to evaluate self-reported cannabis use. These studies found men but not women cannabis users performed worse on measures of verbal memory than same-sex non-users.[26,27]

The underlying mechanism of the sex differences we identified is probably multi-factorial. It is possible women resist potential neurotoxicity of cannabis longer than men, owing to their greater cognitive reserve in verbal memory.[48] The women in our cohort had significantly higher initial verbal memory scores than the men. Strikingly, except for one study,[28] studies that had reported women performed worse in measures of memory had relied on spatial memory tests[19,25] while studies that reported men were more affected had used verbal memory tests.[27] Cannabis use might exacerbate existing differences in memory function,[49] a hypothesis supported by a recently published exploratory data-driven analysis of a

community sample of 1204 participants. This study found reduced hippocampal volume was a “male-dominated” brain factor in cannabis use disorder.[50] Our results showed a positive association between cannabis use and letter fluency in men before we corrected for multiple testing. Deficits in fluent lexical access do not appear to explain impairment in delayed recall.[51]

Another possible explanation is that cannabis may aggravate sex differences in age-related cognitive decline.[52] Associations between cardiovascular risk factors and midlife cognitive decline have been reported, and midlife cardiovascular risk factors are more common in middle-aged men than women.[35,53] The observed sex differences in memory function could reflect men’s higher cardiovascular risk factors, but we extensively adjusted for cardiovascular risk factors and so far, cannabis use has not been associated with increased risk of cardiovascular conditions.[29] While there are sex differences in age-related cognitive decline, a recent multicohort study found decline in memory performances was similar in middle-aged and older men and women.[54]

Sex-specific characteristics of the endocannabinoid system might also explain the differences. Animal studies revealed that the endocannabinoid system has sex-specific characteristics, including differences between female and male vulnerability to the neurotoxic effect of cannabis,[55] CB1 receptor density,[56] CB1 receptor desensitization,[57] and metabolization of THC.[58] For example, some studies found the male hippocampus was more vulnerable to the disruptive effect of cannabis on neurogenesis and neuroplasticity, which would explain spatial memory impairments.[55,56] Other studies suggested that observed higher sensitivity to cannabinoid effects in female rats might be due to preferential metabolization of THC in an active metabolite and higher CB1 receptor desensitization in females.[4] However, these neurobiological sex differences have not been conclusively replicated in humans.[59-63] More human studies are needed before we can explain the neurobiological mechanisms that may cause sex-specific differences in cannabis effects. Finally, a study found that men reported using cannabis more frequently and in higher quantities than women.[64] We did not assess frequency and modality of daily use or THC concentration in our cohort. Previous

longitudinal studies[15,65] have reported dose-response associations between cannabis use and memory, which could partly explain the lack of association between cannabis and memory in women, but we found no association between cannabis use and verbal memory even in women with heavy long-term use (> 5 cannabis-years).

In our study, men who used cannabis heavily over a long time scored about 0.5 SD worse on verbal memory than men who had never used cannabis. While this finding aligns with the literature,[66] its clinical significance is unclear. Since this 0.5 standard deviation is within the norm of possible variation in cognition, it does not necessarily indicate impairment but may still be associated with worse psychosocial and academic outcomes.[66]

To assess the association between current level of cannabis use or recent changes in cannabis use and measures of CF, we measured the 5-year (Year 25 to Year 30) change in test scores of RAVLT, Stroop and DSST. Changes in categories of current cannabis use between Year 25 and Year 30 were not associated with changes in midlife CF, suggesting that current cannabis use was not associated with cognition. Likewise, a recent large prospective cohort study of 1037 adults followed over 42 years found learning and memory problems in long-term cannabis users that were not explained by recent cannabis use.[15]

Our study has several limitations. The CARDIA study was designed to examine the factors that contribute to developing cardiovascular disease. While it is the largest study in the U.S. to collect information on cannabis use over 30 years, substance use and its potential adverse effects on cognition were not CARDIA's primary focus. We thus constructed the main variables of this study or included later in course of the study, limiting the precision of our estimates. For example, we constructed a cannabis exposure measurement from self-reported information collected periodically over 30 years; these assessments of self-reported cannabis use were up to 5 years apart. We extrapolated self-reported past month cannabis use up to a 5-year period, assuming an invariant use of cannabis, as has been done previously. [16,29,67-69] Cannabis years are thus an approximation of true cumulative cannabis use. We used similar methods of extrapolation to construct cumulative use of other

substances. Since we had to rely on self-reports, we could not test the association between cognitive function and THC concentration, which might have varied between participants and over the years.

We lacked data on age of initiation of cannabis use; a cross-sectional study on 69 young adults suggested that sex mediated the relationship between age of onset of cannabis use and subsequent neuropsychological differences in chronic cannabis users.[28] Women's better performance in measures of memory may thus be a result of later onset of cannabis use, but the single study's finding was not replicated in any of the studies on sex differences.

We were also limited by the fact cognitive function tests were added at Year 25, leaving us with no formal baseline measure of memory and thus no way to comment on the direction of the association between cannabis use and cognition. To assess the probability of "reverse causation," we did adjust analyses for the mirror star tracing test, a proxy measure of cognitive function assessed early in CARDIA (Year 2), and found it did not alter point estimates. Assessing delayed recall after a short period (10 minutes) instead of the more usual longer period (20 – 45 minutes), may have limited our ability to compare our results to those of previous studies that used longer delays.

Finally, although our dataset enabled us to extensively control for potential confounders known to vary in incidence by sex (history of stroke, tobacco and illicit drug use, depressive disorder), there may still be other variables we could not control for that may explain sex differences, e.g., gonadal hormones[4], stereotype threat,[6] or subjective effects of cannabis.[64]

In our large cohort study followed participants over 30 years and represented the broad spectrum of cannabis use typical of the general population, we found that self-reported cumulative cannabis exposure was associated with worse verbal memory in men, but not in women. Changes in categories of current cannabis use in 5 years at middle-age were not associated with changes in midlife CF over the same period. Researchers should consider stratifying analyses by sex when testing the association between cannabis and cognition.

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CARDIA Data Availability Statement:
CARDIA data are available upon reasonable request from the CARDIA Coordinating Center. CARDIA investigators are eager to collaborate with investigators interested in using CARDIA data. Please see the CARDIA website (https://www.cardia.dopm.uab.edu) for publications policies and for a list of CARDIA investigators. CARDIA data are also publicly available on the NIH-supported BioLINCC and dbGaP platforms.

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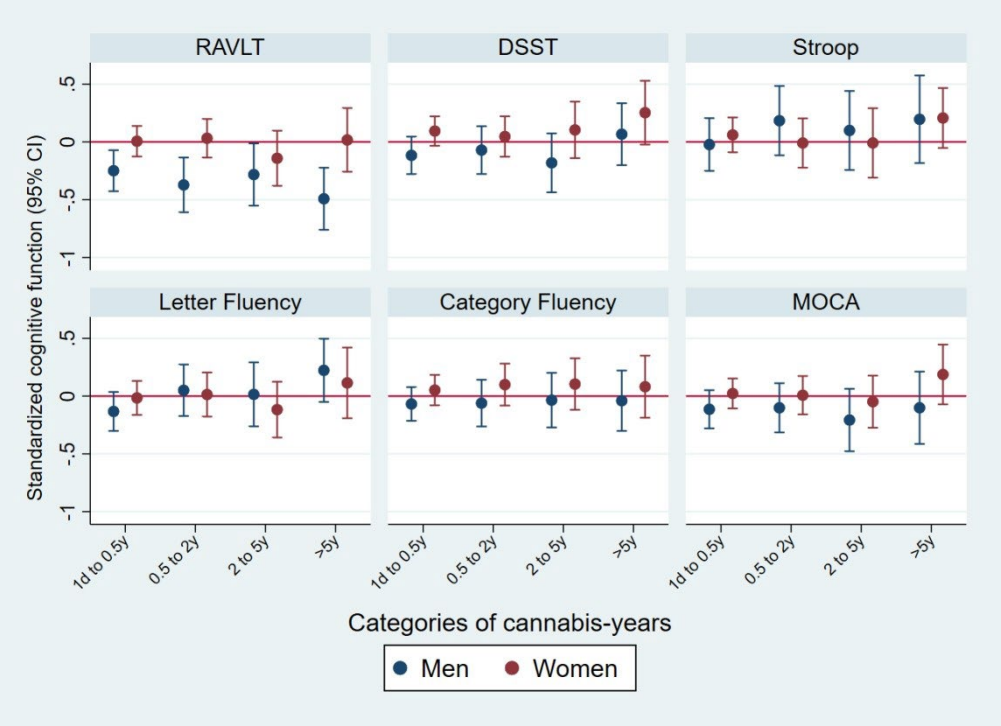
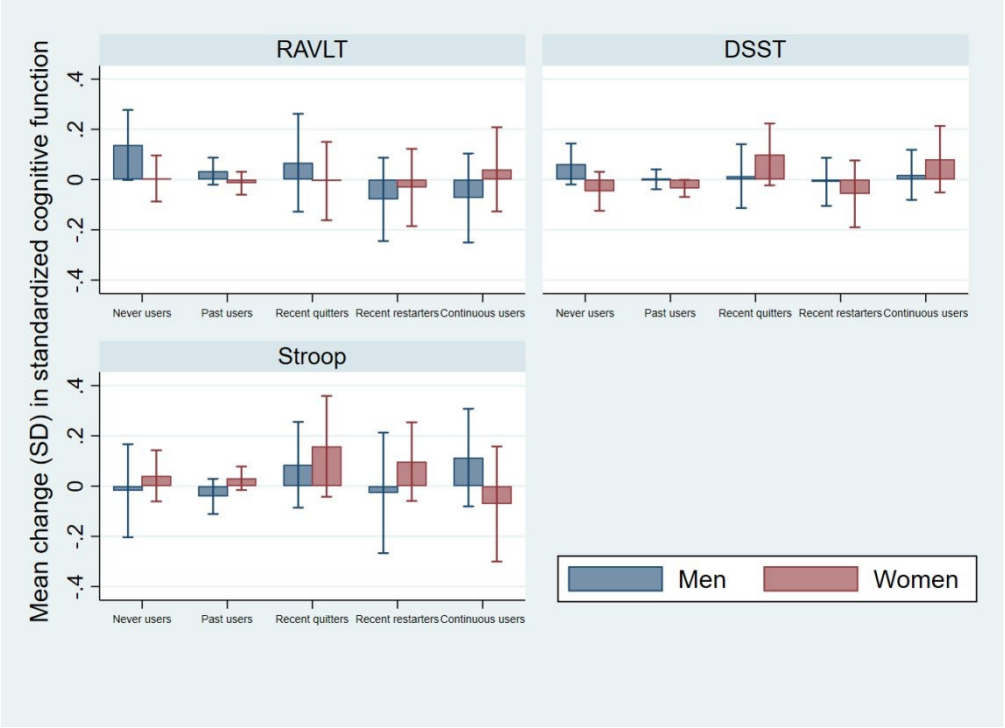
Figure Titles and Legends

Figure 1: Adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in 'cannabis-years'. 2974 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit).
Results stratified by sex.



CARDIA = Coronary Artery Risk Development in Young Adults study
Self-reported cumulative exposure to cannabis joints in cannabis-years; 1-cannabis-year of exposure = 365 days of cannabis use (1 year x 365 days/y). Cannabis users within the 24 hours prior of the Year 30 visit excluded (N=169). Model results adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age started smoking), alcohol (current, cumulative, binge), illicit drug use, cardiovascular risk factors, physical activity, depression, marital status and compared with never users (baseline). All test results standardized: a 1-unit negative deviation indicates a standard deviation worse CF than the mean. We used the inverse of the Stroop score so we could interpret worse CF with negative standardized scores for all six CF tests. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test; MOCA - Montreal cognitive assessment

Figure 2: Multivariable adjusted 5-year change in midlife cognitive function by categories of current cannabis use between Year 25 and Year 30 exams.



Never users: Never used cannabis; **Past users:** Any use before Year 25 visit and no current use at Year 25 or Year 30 visits; **Recent quitters:** Current use at Year 25 visit and no current use at Year 30 visit. **Recent restarters:** Any use before Year 25 visit. No current use at Year 25 visit and current use at Year 30 visit. **Continuous users:** Current use at Year 25 and at Year 30 visit.

Results from multivariable linear regression models, adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age started smoking), alcohol (current, cumulative, binge), illicit drug use, cardiovascular risk factors, physical activity, depression, marital status, cannabis use and cognitive function scores at Year 25. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test

Table 1: Characteristics of 2974 CARDIA participants with cognitive function test results at Year 30 excluding participants with cannabis use in the 24 hours prior to the study visit. Characteristics stratified by sex.

Variable	Men					Women					p-value[b]	
	Never user	Ever Cannabis Use[a]				Never users		Ever Cannabis Use[a]				
		1 day to <0.5 cannabis years	0.5 to < 2 cannabis years	2 to < 5 cannabis years	> 5 cannabis years		1 day to <0.5 cannabis years	0.5 to < 2 cannabis years	2 to < 5 cannabis years	> 5 cannabis years		
N (%)	181 (14)	478 (39)	362 (29)	112 (9)	116 (9)	291 (17)	929 (54)	340 (20)	91 (5)	74 (4)		
Demographics												
Age, mean (SD)	54.7 (3.9)	55.0 (3.5)	55.6 (3.3)	55.0 (3.6)	55.1 (3.7)	54.6 (3.8)	55.1 (3.6)	55.7 (3.4)	55.4 (3.4)	54.8 (3.5)	0.04	0.001
Race, N (Col. %)[c]											0.01	< 0.001
- Black	74 (41)	192 (40)	160 (44)	64(57)	58(50)	177 (61)	453 (49)	130 (38)	53(58)	41(55)		
- White	107 (59)	286 (60)	202 (56)	48(43)	58(50)	114 (39)	477 (51)	210 (62)	38(42)	33(45)		
Education, mean (SD)	16.4 (2.7)	16.3 (2.6)	15.4 (2.5)	14.7 (2.4)	14.5 (2.7)	15.9 (2.6)	16.2 (2.5)	15.8 (2.5)	15.1 (2.4)	14.8 (2.3)	< 0.001	< 0.01
Study center, N (Col. %) do you need this detail>											< 0.001	< 0.01
- Birmingham, AL	78 (43)	128 (27)	76 (21)	20 (18)	20 (17)	133 (46)	180 (19)	45 (13)	13 (14)	8 (11)		
- Chicago, IL	48 (27)	105 (22)	83 (23)	27 (24)	19 (16)	67 (23)	202 (22)	77 (23)	20 (22)	13 (18)		
- Minneapolis, MI	31 (17)	96 (20)	112 (31)	35 (31)	47 (41)	59 (20)	215 (23)	100 (29)	25 (27)	26 (35)		
- Oakland, CA	24 (13)	149 (31)	91 (26)	30 (27)	30 (26)	32 (11)	333 (36)	118 (35)	33 (36)	27 (36)		
Substance use exposure												
Cannabis use category, N (Col. %)[d]											< 0.01	< 0.01
- No current use	181 (100)	466 (97)	330 (88)	84 (75)	42 (36)	291 (100)	919 (99)	301 (89)	53 (58)	31 (42)		
- 1 to 10 days per month	0 (0)	12 (3)	29 (10)	19 (17)	51 (44)	0 (0)	11(1)	39 (11)	36 (40)	24 (32)		
- 11 to 29 days per month	0 (0)	0 (0)	3 (2)	8 (7)	17 (15)	0 (0)	0 (0)	0 (0)	2 (2)	12 (16)		
- 30 days per month (everyday)	0 (0)	0 (0)	0 (0)	1 13)	6 (5)	0 (0)	0 (0)	0 (0)	0 (0)	7 (9)		

Cumulative cannabis exposure, cannabis-years[a], mean (SD)	0 (0)	0.1 (0.1)	1.4 (0.5)	3.2 (0.9)	10.4 (4.5)	0 (0)	0.1 (0.1)	1.2 (0.5)	3.2 (0.9)	10.4 (4.8)	< 0.001	< 0.001
Tobacco smoking, N (Col. %) - Never smoker - Former smoker - Current smoker	161 (89) 15 (8) 5 (3)	325 (68) 111 (23) 42 (9)	116 (32) 175 (48) 71 (20)	33(29) 44(39) 35(31)	29(25) 50(43) 37(32)	246 (85) 40 (14) 5 (2)	550 (59) 287 (31) 92 (10)	90 (26) 190 (56) 60 (18)	16(18) 52(57) 23(27)	5 (7) 40(54) 29(39)	< 0.001	< 0.01
Age started smoking among ever tobacco smokers, mean (SD)	26.1 (11.5)	22.4 (9.8)	19.7 (7.1)	19.1 (7.3)	18.2 (5.3)	25.4 (10.4)	19.7 (17.1)	17.4 (4.6)	19.7 (8.7)	19.4 (7.3)	< 0.001	< 0.01
Cumulative tobacco exposure among ever smokers, mean (SD), pack-years[e]	1.1 (6.3)	3.6 (9.9)	9.5 (13.4)	9.4 (11.4)	11.8 (14.5)	1.1 (5.1)	3.8 (8.2)	8.4 (11.1)	8.9 (11.1)	11.7 (12.0)	< 0.001	< 0.01
Alcohol use - Cumulative alcohol use among ever drinkers, mean (SD), drink-years[f]	10.2 (17.0)	20.2 (23.3)	34.8 (38.6)	46.1 (50.1)	54.5 (53.0)	3.6 (8.4)	11.2 (15.2)	17.4 (18.8)	19.2 (19.0)	32.1 (31.1)	< 0.001	< 0.01
Binge drinking days, cumulative use, N (Col.%)[g] - never reported bingeing - ≤250 days - > 250 days	120 (66) 32(18) 29(16)	186 (39) 145 (30) 147 (31)	79(22) 91(25) 192 (53)	14(13) 24(21) 74(66)	7 (6) 32(28) 77(66)	259 (89) 26 (9) 6 (2)	561 (60) 252 (27) 116 (12)	126 (37) 120 (35) 94 (28)	39(43) 24(26) 28(31)	18(24) 20(27) 36(49)	< 0.001	< 0.01
Illicit drug use Current use[h] Cocaine, crack, speed or methamphetamine, N (Col. %)	0 (0)	1 (0)	11 (3)	4 (4)	11 (9)	1 (0)	5 (1)	9 (3)	5 (5)	6 (8)	< 0.001	< 0.01
Heroin, N (Col. %)	0 (0)	1 (0)	4 (1)	1 (1)	2 (2)	0 (0)	1 (0)	0 (0)	0 (0)	1 (1)	0.2	0.4
Physical activity Physical activity score, mean (SD)[i]	335.2 (268.8)	393.7 (290.7)	390.2 (308.0)	344.3 (279.9)	359.4 (252.9)	228.4 (227.6)	276.9 (231.6)	313.9 (267.1)	227.6 (204.7)	288.2 (238.0)	0.1	< 0.01

Anthropomorphic variable												
BMI, mean (SD)[j]	31.3 (6.2)	29.8 (6.4)	29.9 (6.1)	29.8 (5.6)	28.5 (5.0)	32.4 (8.5)	31.0 (8.0)	29.7 (7.7)	31.6 (7.8)	31.0 (6.3)	< 0.01	< 0.01
Cardiovascular risk factors												
Systolic blood pressure, mean (SD), mmHg	121.5 (14.8)	121.5 (14.9)	122.6 (14.7)	122.9 (16.5)	125.6 (15.8)	120.2 (18.5)	119.3 (17.5)	117.5 (16.8)	121.9 (19.2)	124.1 (17.8)	0.1	0.01
Diastolic blood pressure, mean (SD), mmHg	75.0 (11.4)	74.4 (10.8)	74.6 (10.5)	76.0 (11.5)	76.4 (10.8)	73.4 (11.4)	73.2 (11.2)	71.9 (10.4)	74.9 (12.5)	77.3 (12.1)	0.3	< 0.01
LDL-Cholesterol, mean (SD), mg/dl	111.1 (36.2)	110.1 (33.5)	110.7 (33.0)	104.4 (32.2)	100.6 (32.7)	112.7 (33.3)	111.4 (32.6)	112.8 (34.2)	112.1 (32.7)	109.6 (31.9)	0.02	0.9
HDL-Cholesterol, mean (SD), mg/dl	48.5 (12.1)	52.4 (15.4)	51.5 (14.6)	51.3 (14.6)	53.9 (16.6)	64.2 (17.0)	66.1 (18.3)	67.6 (21.9)	66.7 (25.2)	66.9 (20.5)	0.02	0.3
Triglycerides, mean (SD), mg/dl	118.9 (64.7)	116.6 (93.0)	130.2 (183.7)	119.4 (79.3)	121.0 (86.1)	92.8 (50.2)	95.4 (60.7)	101.1 (59.2)	103.1 (50.2)	91.4 (35.5)	0.5	< 0.01
Diabetes mellitus, N (%)	26 (14)	73 (15)	53 (15)	14 (13)	16 (14)	39 (13)	126 (14)	53 (16)	14 (15)	8 (11)	0.9	0.4
Psychological variables												
Depression, current CES-D >=16/30, N (%)[k]	10 (6)	45 (9)	45 (12)	27 (23)	27 (23)	44 (15)	129 (14)	61 (18)	18 (20)	16 (22)	< 0.001	0.1
Socioeconomical variable												
Currently married, N (%)	118 (65)	296 (62)	207 (57)	45 (40)	54 (47)	160 (55)	476 (51)	156 (46)	39 (43)	18 (24)	< 0.01	< 0.01

BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults study; Col. % = column percentage; LDL = low density lipoprotein (LDL); HDL = high-density lipoprotein; n = number of participants; SD = standard deviation

[a]Self-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y). Cannabis users within the 24 hours prior of the Year 30 visit excluded (N=169).

[b]P-values are from Kruskal-Wallis rank test for age, years of education, pack-years, drink-years, age started smoking, triglycerides, BMI and physical activity and from a $\chi 2$ test for race, study site, current smoking status, CES-D, cannabis use categories, cumulative binge drinking categories, illicit drug use categories, and marital status.

[c]By design, the CARDIA study sampled self-identified white men, white women, black men and black women in roughly equal numbers for participation in the study.

[d]Categories based on the answer to the question: “During the last 30 days, on how many days did you use marijuana?”

[e]Self-reported cumulative exposure to cigarettes in pack-years: 1 pack-year of exposure = 7300 cigarettes (1 year × 365 days/y × 1 pack/d × 20 cigarettes/pack).

[f]Cumulative alcohol use in drink-years: 1 drink-year is the total amount of ethanol consumed by a person who had 1 alcoholic drink per day for 1 year (1 drink-year = 17.24 ml of ethanol/drink x 1 drink/d x 365 days/y = 6292.6 ml of ethanol).

[g]Binge drinking days, defined as ≥5 drinks per day. If bingeing were to be constant over 25 years in one individual, 250 binge drinking days would correspond to 10 days of bingeing each year for 25 years.

[h]Current use, defined as any use within the last 30 days. We computed the number of days on the illicit drug over the study duration based on current exposure at each visit, which we replaced with lifetime exposure when the latter was higher. Cocaine included all forms of cocaine, like crack, powder, free base; amphetamines included speed, uppers, and methamphetamines.

[i]Physical activity, measured with the CARDIA Physical Activity History questionnaire, which queries the amount of time per week spent performing 13 categories of leisure, occupational, and household

physical activities over the past 12 months.
[j]Calculated as weight in kilograms divided by height in meters squared.
[k]Self-reported depression was measured every five years, starting at the Year 5 visit, on the Center for Epidemiologic Studies Depression scale (CES-D).18 A score of ≥16 was the cut-off for both sexes, indicating clinically significant depressive symptoms.

Table 2: Distribution of cognitive function at Year 30 and cumulative exposure to cannabis in 'cannabis-years'[a] among 2974 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit). Results stratified by sex.

Variable	Men					Women					p-value[b]	
	Never users	Ever Cannabis Use				Never users		Ever Cannabis Use				
		1 day to <0.5 cannabis years	0.5 to < 2 cannabis years	2 to < 5 cannabis years	> 5 cannabis years		1 day to <0.5 cannabis years	0.5 to < 2 cannabis years	2 to < 5 cannabis years	> 5 cannabis years		
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)												
- N	181	478	362	112	116	291	929	340	91	74		
- Raw mean (SD)	8.4 (3.6)	7.7 (3.3)	7.3 (3.4)	7.4 (3.4)	6.8 (3.4)	9.1 (3.3)	9.4 (3.3)	9.3 (3.2)	8.1 (3.3)	8.5 (3.7)	<0.001	0.002
- Standardized mean[c]	0.27	0.06	-0.06	-0.05	-0.26	-0.0	0.07	0.04	-0.35	-0.32		
Digit Symbol Substitution Test (DSST)												
- N	177	474	362	112	116	288	927	346	98	127		
- Raw mean (SD)	65.8(15.4)	64.4(16.4)	61.8(15.9)	57.7(17.4)	60.1(16.0)	68.4(17.0)	72.5(16.7)	70.8(16.6)	68.9(16.8)	68.9(15.7)	<0.001	0.002
- Standardized mean	0.19	0.10	-0.05	-0.30	-0.13	-0.15	0.09	-0.02	-0.11	-0.17		
Stroop Interference Test[d]												
- N	180	467	362	112	116	290	922	345	97	127		
- Raw mean (SD)	-23.3(15.5)	-23.1(13.2)	-22.7(10.8)	-25.0(14.0)	-24.1(13.7)	-23.9(11.3)	-22.1(10.6)	-22.4(11.1)	-25.0(13.1)	-22.4(8.5)	0.263	0.04
- Standardized mean	0.00	0.02	0.05	-0.18	-0.02	-0.10	0.05	0.02	-0.17	-0.07		
Letter Fluency Test												
- N	179	476	362	112	116	291	925	346	98	125		
- Raw mean (SD)	40.6 (12.7)	39.8 (13.7)	40.8 (15.1)	37.6 (14.5)	39.2 (12.2)	40.5 (14.8)	42.2 (15.0)	42.7 (12.7)	38.5 (12.3)	41.6 (15.5)	0.25	0.06
- Standardized mean	0.03	-0.03	0.05	-0.11	0.016	-0.10	0.02	0.06	-0.21	0.08		

Category Fluency Test												
- N	180	477	369	126	195	291	927	347	98	126		
- Raw mean (SD)	20.0 (5.0)	20.4 (6.4)	20.2 (8.1)	19.9 (5.7)	19.1 (6.3)	19.4 (5.2)	20.5 (5.9)	20.9 (5.8)	19.6 (5.1)	19.9 (5.6)	0.424	0.008
- Standardized mean	-0.02	0.04	0.02	-0.03	-0.11	-0.16	0.03	0.11	-0.16	-0.06		
MOCA Test												
- N	180	472	366	125	195	288	924	346	98	126		
- Raw mean (SD)	24.2 (4.1)	23.7 (3.9)	23.5 (4.0)	22.2 (4.9)	22.7 (4.2)	23.7 (4.1)	24.2 (3.7)	24.3 (4.0)	23.0 (4.0)	23.5 (3.9)	<0.001	0.01
- Standardized mean	0.18	0.07	0.00	-0.26	-0.20	-0.07	0.06	0.06	-0.27	-0.21		

CARDIA = Coronary Artery Risk Development in Young Adults study; MOCA = Montreal Cognitive Assessment; N = number of participants; SD = standard deviation.

[a]Self-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y). Cannabis users within the 24 hours prior of the Year 30 visit excluded (N=169).

[b]P-values are from 1-way analyses of variance. All P-values two sided.

[c] Each CF measure was standardized by subtracting the mean and then dividing the score by the within-CARDIA sex-specific standard deviation.

[d]We used the inverse of the Stroop score so we could interpret worse CF with negative standardized scores for all six CF tests.

Table 3: Unadjusted and adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in 'cannabis-years'[a]. 2974 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit). Results stratified by sex.

Cognitive Function Measure - Self-reported cumulative exposure in cannabis-years[b]	Standardized difference in each CF measures (95% CI)[c]					
	Men			Women		
	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW[d]	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW[d]
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1248	1248	1222	1722	1722	1683
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.20 (-0.37 to -0.03)	-0.19 (-0.34 to -0.03)	-0.25 (-0.43 to -0.07)	0.08 (-0.05 to 0.21)	-0.01 (-0.13 to 0.11)	0.01 (-0.13 to -0.14)
- 0.5 to < 2 cannabis years	-0.32 (-0.50 to -0.14)	-0.21 (-0.38 to -0.05)	-0.37 (-0.61 to -0.14)	0.06 (-0.09 to 0.22)	-0.06 (-0.20 to 0.08)	0.03 (-0.14 to 0.20)
- 2 to < 5 cannabis years	-0.31 (-0.54 to -0.07)	-0.07 (-0.29 to 0.15)	-0.28 (-0.55 to -0.01)	-0.31 (-0.54 to -0.07)	-0.22 (-0.43 to -0.01)	-0.13 (-0.38 to 0.10)
- > 5 cannabis years	-0.48 (-0.71 to -0.24)	-0.25 (-0.47 to -0.04)	-0.49 (-0.76 to -0.23)	-0.19 (-0.44 to 0.07)	-0.12 (-0.35 to 0.11)	0.02 (-0.26 to 0.29)
P-value for trend[e]	< 0.001	0.05	0.006	0.002	0.18	0.59
Digit Symbol Substitution Test (DSST)						
- Number of participants	1233	1233	1208	1718	1718	1678
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.09 (-0.2 to 0.08)	-0.12 (-0.26 to 0.03)	-0.12 (-0.28 to 0.04)	0.24 (0.11 to 0.37)	0.07 (-0.05 to 0.19)	0.09 (-0.03 to 0.22)
- 0.5 to < 2 cannabis years	-0.24 (-0.42 to -0.07)	-0.14 (-0.29 to 0.01)	-0.07 (-0.28 to 0.14)	0.14 (-0.02 to 0.29)	-0.05 (-0.19 to 0.09)	0.05 (-0.13 to 0.22)
- 2 to < 5 cannabis years	-0.49 (-0.73 to -0.26)	-0.24 (-0.44 to -0.04)	-0.18 (-0.44 to 0.07)	0.03 (-0.20 to 0.26)	-0.02 (-0.19 to 0.23)	0.10 (0.14 to 0.35)
- > 5 cannabis years	-0.35 (-0.58 to -0.11)	-0.10 (-0.30 to 0.10)	0.07 (-0.20 to 0.33)	0.03 (-0.22 to 0.28)	-0.02 (-0.25 to 0.21)	0.25 (-0.02 to 0.53)
P-value for trend	< 0.001	0.19	0.16	0.002	0.24	0.29

Stroop Interference Test						
- Number of participants	1226	1226	1201	1713	1713	1673
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	0.02 (-0.15 to 0.18)	-0.02 (-0.18 to 0.14)	-0.02 (-0.25 to 0.21)	0.16 (0.03 to 0.27)	0.04 (-0.09 to 0.17)	0.06 (-0.09 to 0.21)
- 0.5 to < 2 cannabis years	0.05 (-0.13 to 0.23)	0.11 (-0.06 to 0.28)	0.18 (-0.12 to 0.48)	0.14 (-0.02 to 0.27)	-0.01 (-0.17 to 0.14)	-0.01 (-0.22 to 0.21)
- 2 to < 5 cannabis years	-0.13 (-0.36 to 0.11)	0.04 (-0.19 to 0.27)	0.11 (-0.24 to 0.44)	-0.10 (-0.31 to 0.12)	-0.10 (-0.32 to 0.13)	-0.01 (-0.31 to 0.29)
- > 5 cannabis years	-0.06 (-0.29 to 0.17)	0.10 (-0.12 to 0.33)	0.20 (-0.18 to 0.57)	0.13 (-0.12 to 0.35)	0.12 (-0.11 to 0.37)	0.21 (-0.05 to 0.47)
P-value for trend	0.52	0.33	0.38	0.04	0.48	0.33
Letter Fluency Test						
- Number of participants	1244	1244	1220	1719	1713	1680
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.05 (-0.23 to 0.12)	-0.07 (-0.23 to 0.08)	-0.13 (-0.30 to 0.04)	0.12 (-0.14 to 0.25)	0.01 (-0.12 to 0.14)	-0.02 (-0.16 to 0.13)
- 0.5 to < 2 cannabis years	0.02 (-0.16 to 0.19)	0.12 (-0.04 to 0.29)	0.05 (-0.17 to 0.27)	0.15 (-0.01 to 0.31)	0.02 (-0.13 to 0.17)	0.02 (-0.18 to 0.21)
- 2 to < 5 cannabis years	-0.22 (-0.45 to 0.17)	0.01 (-0.20 to 0.23)	0.02 (-0.26 to 0.29)	-0.14 (-0.37 to 0.10)	-0.12 (-0.34 to 0.11)	-0.11 (-0.36 to 0.13)
- > 5 cannabis years	-0.10 (-0.33 to 0.13)	0.15 (-0.06 to 0.37)	0.22 (-0.05 to 0.50)	0.08 (-0.18 to 0.34)	0.08 (-0.16 to 0.33)	0.12 (-0.19 to 0.42)
P-value for trend	0.24	0.02	0.02	0.06	0.69	0.51
Category Fluency Test						
- Number of participants	1246	1246	1221	1722	1719	1683
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	0.06 (-0.11 to 0.23)	0.04 (-0.12 to 0.20)	-0.07 (-0.21 to 0.08)	0.18 (0.05 to 0.30)	0.06 (-0.06 to 0.18)	0.05 (-0.08 to 0.18)
- 0.5 to < 2 cannabis years	0.03 (-0.14 to 0.21)	0.11 (-0.06 to 0.28)	-0.06 (-0.26 to 0.14)	0.25 (0.10 to 0.39)	0.10 (-0.05 to 0.24)	0.10 (-0.08 to 0.28)
- 2 to < 5 cannabis years	-0.01 (-0.25 to 0.22)	0.17 (-0.06 to 0.39)	-0.04 (-0.27 to 0.20)	0.03 (-0.19 to 0.25)	0.06 (-0.15 to 0.28)	0.10 (-0.12 to 0.33)
- > 5 cannabis years	-0.13 (-0.37 to 0.10)	0.02 (-0.20 to 0.25)	-0.04 (-0.30 to 0.22)	0.08 (-0.16 to 0.32)	0.09 (-0.14 to 0.33)	0.08 (-0.19 to 0.35)
P-value for trend	0.42	0.48	0.92	0.008	0.76	0.86
MOCA Test						
- Number of participants	1237	1237	1212	1715	1715	1678
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.11 (-0.28 to 0.06)	-0.12 (-0.26 to 0.02)	-0.12 (-0.28 to 0.05)	0.13 (-0.01 to 0.25)	0.27 (-0.08 to 0.14)	0.02 (-0.11 to 0.15)
- 0.5 to < 2 cannabis years	-0.17 (-0.35 to 0.01)	-0.04 (-0.19 to 0.11)	-0.10 (-0.32 to 0.11)	0.14 (-0.02 to 0.28)	0.01 (-0.13 to 0.14)	0.00 (-0.16 to 0.17)
- 2 to < 5 cannabis years	-0.47 (-0.71 to -0.24)	-0.18 (-0.38 to 0.01)	-0.21 (-0.48 to 0.06)	-0.19 (-0.42 to 0.04)	-0.06 (-0.25 to 0.13)	-0.05 (-0.27 to 0.18)
- > 5 cannabis years	-0.36 (-0.60 to -0.13)	-0.08 (-0.28 to 0.12)	-0.10 (-0.41 to 0.21)	-0.05 (-0.30 to 0.20)	0.08 (-0.13 to 0.29)	0.18 (-0.07 to 0.45)
P-value for trend	< 0.001	0.24	0.57	0.01	0.82	0.51

CARDIA = Coronary Artery Risk Development in Young Adults study, MOCA = Montreal Cognitive Assessment

[a]Self-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y). Cannabis users within the 24 hours prior of the Year 30 visit excluded (N=169).
[b]Years of cannabis exposure was modeled as a 5-level categorical predictor.
[c]Linear regression models determined the association between CF scores and self-reported cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.
[d]Analyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring
[e]Tests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT and 0.008 for other CF measures to correct for multiple testing (6 cognitive function domains).

Table 4. Multivariable adjusted 5-year change in midlife cognitive function by categories of current cannabis use between Year 25 and Year 30 exams. 2786 CARDIA participants with measures of cognitive function at Year 25 and 30 exams.

Test results across categories of current cannabis exposure[a]	**Men**					**Women**					**p-value**[b]	
	Never users	Past users	Recent quitters	Recent restarters	Continuous users	Never users	Past users	Recent quitters	Recent restarters	Continuous users		
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)	0.14 (-0.01 to 0.28)	0.03 (-0.02 to 0.09)	0.07 (-0.13 to 0.26)	-0.08 (-0.24 to 0.09)	-0.07 (-0.25 to 0.10)	0.00 (-0.09 to 0.10)	-0.01 (-0.06 to 0.03)	-0.01 (-0.16 to 0.15)	-0.03 (-0.19 to 0.12)	0.04 (-0.13 to 0.21)	0.32	0.96
Digit Symbol Substitution Test (DSST)	0.06 (-0.02 to 0.14)	0.00 (-0.04 to 0.04)	0.01 (-0.11 to 0.14)	-0.01 (-0.10 to 0.09)	0.02 (-0.08 to 0.12)	-0.05 (-0.12 to 0.03)	-0.04 (-0.07 to -0.00)	0.10 (-0.02 to 0.22)	-0.06 (-0.19 to 0.08)	0.08 (-0.05 to 0.21)	0.75	0.13
Stroop Interference Test	-0.02 (-0.20 to 0.17)	-0.04 (-0.11 to 0.03)	0.08 (-0.09 to 0.33)	-0.03 (-0.27 to 0.21)	0.11 (-0.08 to 0.31)	0.04 (-0.06 to 0.14)	0.03 (-0.02 to 0.08)	0.16 (-0.04 to 0.36)	0.10 (-0.06 to 0.25)	-0.07 (-0.30 to 0.16)	0.57	0.54

[a]**Never users:** Never used cannabis; **Past users:** Any use before Year 25 visit and no current use at Year 25 or Year 30 visits; **Recent quitters:** Current use at Year 25 visit and no current use at Year 30 visit. **Recent restarters:** Any use before Year 25 visit. No current use at Year 25 visit and current use at Year 30 visit. **Continuous users:** Current use at Year 25 and at Year 30 visit.
Results from multivariable linear regression models, adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age starting smoking), alcohol, illicit drug use, BMI, cardiovascular risk factors, physical activity, depression, marital status, cannabis use and cognitive function scores at Year 25. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test

[b] Tests of statistical significance were 2-tailed, with an alpha level set at 0.05