

Supplementary Material

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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eMethods

Measurements

Cannabis use

We present below an example of one participant included in the study illustrating the method for computing cannabis-years more fully and how we applied linear imputation (Box 1). This is the same method of imputation used in a previous publication by our research group.¹

Box 1. Example of computing cannabis-years for one participant:

visit	mj30d_	mj30d_imp	domj	life_	yomj_max
0	15	15	300	100 to 499 times	0.82
1	.	15	482	.	1.32
2	20	20	725	100 to 499 times	1.99
3	.	20	968	.	2.65
4	.	4	1017	.	2.79
5	4	4	1066	100 to 499 times	2.92
6	.	4	1115	.	3.05
7	20	20	1358	100 to 499 times	3.72
8	.	20	1601	.	4.39
9	.	20	1844	.	5.05
10	20	20	2087	500 to 1000 times	5.72
11	.	20	2330	.	6.38
12	.	20	2573	.	7.05
13	.	10	2695	.	7.38
14	.	10	2817	.	7.72
15	10	10	2939	500 to 1000 times	8.05
16	.	10	3061	.	8.39
17	.	10	3183	.	8.72
18	.	1	3195	.	8.75
19	.	1	3207	.	8.79
20	1	1	3219	100 to 499 times	8.82

Visit: visit year; mj30d_: Self-reported days of using cannabis during the month before the visit (“During the last 30 days, on how many days did you use cannabis?”), mj30d_imp: imputed mj30d_ variable; domj: computed cumulative days of cannabis use, life_: self-reported lifetime use of cannabis queried at each visit (“About how many times in your lifetime have you used marijuana?”), yomj_max: computed cumulative years of cannabis use (domj/365).

According to example 1, the participant reported having used cannabis 100 to 499 times during the lifetime (categorical variable life_) at the baseline examination (visit 0). This was used to estimate the exposure prior to the first examination (domj at visit 0=300, where domj signifies “days of cannabis”).

At this baseline examination, the participant reported using cannabis 15 days per month (mj30d_). Multiplied by 12.17 months (365/30), we estimated that this participant used cannabis 182 days in the first year after the first exam (15 * 12.17). The number of days of cannabis use in the month before the baseline examination was imputed forward at year 1 (mj30d_imp). At year 2, the participant reported using cannabis 20 days per month; at year 5, he/she reported 4 days per month. These numbers were imputed backwards and forwards; when there were an uneven number of intervals (preventing us from evenly splitting the

imputation based on the prior value as opposed to the post-value), the exposure at the prior interval was favoured arbitrarily. Participants then accrued lifetime days of cannabis use over follow-up. The cumulative number of cannabis-years over lifetime is presented in the last column (yomj_max). For this participant, the cumulative number of cannabis years was 8.82, corresponding to 3,219 estimated days of cannabis use. We found no change in the estimates when using alternate methods for imputing missing values such as using the mean number of days of cannabis use between two examinations with data on this variable.

Cigarette smoking exposure

Detailed cigarette smoking behavior was evaluated during each in-person CARDIA visit by responses to an interviewer-administered questionnaire.² Participants were also asked the number of cigarettes smoked daily at yearly contact over the phone between CARDIA visits. Current smoking was defined as smoking one cigarette or more per day. At baseline, participants were asked the number of years they had smoked in total, the age at which they started smoking regularly (“How old were you when you started smoking cigarettes regularly?”) and years since cessation (“How many years ago did you stop?”), if appropriate. These data were used to estimate cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 year × 365 days/y × 1 pack/d × 20 cigarettes/pack).¹

Alcohol exposure

Alcohol consumption was measured during each CARDIA visits. Participants were asked, “Did you drink any alcoholic beverages in the past year?” and three follow-up questions regarding how many drinks of wine, beer, and liquor they usually consumed per week. Assuming that one drink of beer, wine, or liquor contains 16.7 ml, 17.0 ml, or 19.1 ml of ethanol, respectively (per CARDIA protocol), we estimated total ethanol consumption per week in milliliters of ethanol and divided it by 17.24 ml of ethanol per average drink to estimate the usual number of drinks per week that each participant reported at each visit. We estimated lifetime alcohol consumption in “drink-years,” defining 1 drink-year as the amount of alcohol consumed in 1 year by a person consuming 1 drink/day (365 days/year × 17.24 ml of alcohol/day = 6,293 ml of alcohol). Binge drinking at the Year 20 visit was assessed directly by asking participants: “During the past 30 days, on how many days did you have five or more drinks on the same occasion?” For the other visits, we computed bingeing as follows: At each visit, participants were asked: “In the past month what is the largest number of drinks you had in one day?” At baseline, participants were additionally asked: “How many days in the past month did you have about (number of drinks answered in the previous question) drinks?” We used the number of days participants reported having 5 or more drinks for these visits. For binge drinking events at the Year 7 visit, we used the closest available information about the number of days patients reported having 5 or more drinks if they reported having such a use in one day within the last month at the Year 7 visit.

Other illicit drug exposure

Other illicit substances queried included cocaine (including other forms of cocaine such as crack, powder, free base), amphetamines (speed, uppers, methamphetamines) and heroin.⁵ Participants were asked: “Have you ever used (substance)?”; “During the last 30 days, on how many days did you use (substance)?” and “How many times in your lifetime have you used (substance)?” The number of days on cocaine, crack, speed, methamphetamines and heroin over the study duration was computed using current exposure at each visit and replaced by lifetime exposure when the latter was higher.

Cardiovascular risk factors

Blood pressure was measured on the right arm with a Hawksley random zero sphygmomanometer (WA Baum Company, Copaque, NY) by trained and certified

technicians using standardized methods after the participant had rested for 5 minutes at baseline and Year 7, and at Year 20, a digital blood pressure monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used.

Three measurements were obtained at 1-minute intervals. The average of the second and third measurements was used in analyses. Fasting total cholesterol and triglycerides were measured enzymatically at baseline, Years 7, and 20 by the Northwest Lipid Research Laboratory at the University of Washington (Seattle, WA). For all visits, HDL cholesterol was determined by dextran sulfate –magnesium precipitation on the Abbot Spectrum, and LDL cholesterol was calculated using the Friedewald equation. At each visit, weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We built a cumulative measure of some cardiovascular risk factor (blood cholesterol, blood triglycerides, blood pressure) by calculating the area under the curve from year 0 through year 30.

Physical activity

Physical activity was 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.

Psychosocial measures

Depression, symptoms of psychosis and ADHD have been associated with cannabis use and cognitive impairment⁶ In the main model we adjusted for the self-reported depression using the Center for Epidemiologic Studies Depression scale (CES-D). A score of ≥ 16 was the cut-off for both sexes, indicating clinically significant depressive symptoms.

We tested our results to sensitivity excluding participants having ever used antipsychotic medications (1st, 2nd and 3rd generation) and excluding participants having ever used a treatment for ADHD (methylphenidate, amphetamine, dextroamphetamine, metamphetamine, lisdexamfetamine). Antipsychotics and ADHD treatment were recorded verbatim and coded through a centralized automated system and according to the Iowa Drug Information Services. We used the American Hospital Formulary Services (AHFS) and the Women's Health and Aging Study (WHAS) classifications to classify medications used for depression. We had information on use of these medications at every visit.

Socioeconomic hardship

Income data were collected at Year 30 for 3383 adults of the CARDIA cohort study.

Participants were asked "Which of these categories best describe your total combined family income for the past 12 months? This should include income (before taxes) from all sources, wages, veteran's benefits, help from relatives, rent from properties, and so on". 4 Categories of annual income were created at each visit: Less than \$25,000, \$25,000 to \$49,900, \$50,000 to \$99,900, more than \$100,000. We built a cumulative measure of socioeconomic hardship by calculating the area under the curve from year 0 to 30 from these categories of annual income.

Additional measures of the Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT consisted of 5 presentations of a 15-item word list (List A) with recall, one presentation of a 15-item Interference List (List B) with recall, a Short Delay Free Recall of List A (Trial 6) and a Long Delay Free Recall of list A (Trial 7).⁷ The 15 words were read slowly to the subject, requesting him/her to repeat them after the reading, independently from the order they were said. The same procedure was repeated in steps A2 (i.e., second recall of list A), A3, A4 and A5, pointing out that the subject had to remember all the words, including those said previously. Then a second list of words (List B) was read as a distracter, and the subject was asked to recall these new words. After that, the words of the first list were asked (Trial 6, Recall after Interference), without being exposed, in a task of immediate

recall from episodic memory. Ten minutes after this stage the subject was asked to recall the words of the first list (Trial 7, Delayed Recall) to assess the delayed recall of episodic memory.

The immediate recall after Trial 1 provided the score for **Immediate Recall**, the total words recalled across the five learning trials (A1 to A5) the **Total Encoding**, subtracting the words recalled in Trial V from the words recalled in Trial I (Trial V – I) the **amount learned in five trials**, the score of trial 6 provided the score for **Recall after Interference** and the score of Trial 7 provided the score for **Delayed Recall**.

Mirror star tracing test

At Year 2, the mirror star tracing test was conducted to elicit reactive blood pressure. In the mirror star-tracing test, participants had to trace the outline of a star from a reversed image displayed in a mirror while staying within narrow limits. Study participants were instructed to draw stars as quickly as possible with the fewest possible errors. If they moved out of the limits of the star, an error was scored. Total stars completed and total numbers of errors over three minutes were recorded. Although initially intended as a stressor to measure blood pressure reactivity and not as a cognitive test, some have suggested that the mirror star tracing test measures aspects of executive function.³

Changes in categories of current cannabis use between Year 25 and Year 30

We included participants who completed cognitive testing at both Year 25 and Year 30. We then classified participants according to their pattern of cannabis use in never users, past users (any use before Year 25 and not at Year 25 or 30), recent quitters (any use in past month at Year 25 but not at Year 30), recent restarters (any use in past month before Year 25, no use at Year 25 and any use in past month at Year 30) and continuous users (any use in past month at Year 25 and 30). No participant reported using cannabis for the first time within this five-year period. We did not have measures of acute use at Year 25 visit. To avoid comparing acute users (use in the 24 hours prior to the study visit) at Year 25 visit with non-acute users at Year 30 visit, we did not exclude users at Year 30 visit from this analysis.

Statistical analysis

Inverse probability of censoring weights (IPCWs)

To reduce the potential for informative censoring, we computed IPCWs.⁸ Covariables included in the pooled logistic regression model used to estimate the IPCWs were: fixed covariables: race, sex, study center and education; time-dependent covariables were lagged values of: age, study visits, pack-years of cigarette smoking, current smoking, drink-years of alcohol use, binge drinking events, cumulative exposure to cocaine, crack, amphetamines and heroin. Drink-years of alcohol, binge-drinking episodes, tobacco pack-years, BMI, physical activity and CVRF were all modelled as 3-knot restricted cubic splines.

Changes in midlife cognitive function by categories of cannabis exposure

We used descriptive statistics to compare participants with different cannabis use patterns separately for women and men. We estimated the 5-year change in the three cognitive test results z scores assessed at Year 25 and Year 30, for the five possible combinations of current cannabis use. We performed linear and logistic regression models. Linear regression analyses included an unadjusted, a minimally adjusted (age, race, study center and years of education) and a multivariable adjusted model. In the logistic regression analysis, we defined a lower cognitive function of -0.1 SD or more from the mean change between Year 25 and Year 30 as “cognitive decline”. This was based on two studies. Auer et al. found that for every 5 cannabis-years, verbal memory was 0.15 standardized units lower, and Meier et al. reported a 0.6 SD difference in verbal memory and a 1.0 SD difference in informant-reported memory between never users and persistent cannabis users over 20 years.^{3,9} We then

calculated the odds of developing a 0.1 SD cognitive decline according to current cannabis use category compared to participants that never reported cannabis use. We tested this in unadjusted and adjusted logistic regression models, with covariables measured at Year 25. Models were adjusted to the same covariables as for the cross-sectional analysis. We also tested models with 0.5 SD defined as cut-off.

eResults

Association between changes in cannabis use and changes in midlife CF

2,786 participants had CF scores at Year 25 and at Year 30. We describe participants' characteristics at baseline (see Appendix Table 11). After 5 years of follow-up, RAVLT scores changed by $+0.2 \pm 2.6$ points for men and $+0.1 \pm 2.6$ points for women, DSST scores by -0.2 ± 8.1 points for men and -0.3 ± 10.2 points for women, and Stroop scores -0.3 ± 9.1 points for men and -0.1 ± 9.3 points for women across all categories of cannabis use (see Appendix Table 12 and Table 13). Results of the linear regression models (unadjusted and minimally adjusted) are presented in Appendix Table 14 and 15. The chance of developing a 0.1 SD larger cognitive decline in delayed recall, DSST scores or Stroop scores over 5 years was not associated with changes in cannabis use during the same periods, even after we extensively adjusted for covariables at Year 25 (see Appendix Table 15, Figure 4).

eTables and eFigures

Appendix Table 1: Unadjusted and adjusted association between RAVLT at Year 30 and cumulative exposure to cannabis in 'cannabis-years' ^a. 2698 CARDIA participants (excluding participants with cannabis use in the 30 days 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	1102	1100	1078	1592	1592	1555
- 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)	0.02 (-0.12 to 0.15)
- 0.5 to < 2 cannabis years	-0.30 (-0.48 to -0.12)	-0.19 (-0.37 to -0.02)	-0.33 (-0.57 to -0.09)	0.09 (-0.07 to 0.25)	-0.05 (-0.20 to 0.10)	0.04 (-0.14 to 0.21)
- 2 to < 5 cannabis years	-0.31 (-0.57 to -0.04)	-0.05 (-0.28 to 0.19)	-0.22 (-0.51 to 0.08)	-0.46 (-0.75 to -0.17)	-0.30 (-0.57 to -0.05)	-0.20 (-0.48 to 0.08)
- > 5 cannabis years	-0.45 (-0.79 to -0.12)	-0.12 (-0.46 to 0.19)	-0.36 (-0.69 to -0.03)	-0.27 (-0.65 to 0.10)	-0.19 (-0.52 to 0.15)	0.07 (-0.44 to 0.31)
P-value for trend ^e	0.007	0.12	0.05	0.007	0.13	0.46

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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 with use within the last 30-day excluded (N=447).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and self-reported cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 2: Characteristics of 169 CARDIA participants with cognitive function test results at Year 30 with cannabis use in the 24 hours prior to the study visit). Characteristics stratified by sex.

Variable	Cumulative exposure to cannabis ^a								p-value ^b	
	Men				Women					
	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 (%)	0 (0)	8(8)	14(14)	80 (78)	1(2)	7(10)	6(9)	53 (79)		
Demographics										
Age, median (Q1; Q3)	- (-; -)	55 (51;58)	59 (56;59)	54 (52;57)	50 (50;50)	52 (50;59)	57 (49;60)	56 (51;59)	0.014	0.617
Race, N (Col. %) ^c									0.264	0.369
- Black	- (-; -)	3 (38)	10 (71)	42 (53)	1 (100)	4 (57)	2 (33)	35 (66)		
- White	- (-; -)	5 (63)	4 (29)	38 (48)	0 (0)	3 (43)	4 (67)	18 (34)		
Education, median (Q1; Q3), years	- (-; -)	16 (14;20)	15 (13;16)	14 (12;16)	16 (16;16)	14 (13;16)	14 (11;17)	15 (12;16)	0.114	0.848
Study center, N (Col. %) do you need this detail>									0.566	0.274
- Birmingham, AL	- (-; -)	1 (13)	1 (7)	9 (11)	0 (0)	2 (29)	0 (0)	3 (6)		
- Chicago, IL	- (-; -)	1 (13)	4 (29)	7 (9)	0 (0)	2 (29)	0 (0)	5 (9)		
- Minneapolis, MI	- (-; -)	2 (25)	3 (29)	26 (33)	0 (0)	2 (29)	2 (33)	14 (26)		
- Oakland, CA	- (-; -)	4 (50)	6 (43)	38 (48)	1 (100)	1 (14)	4 (67)	31 (58)		
Substance use exposure									0.003	< 0.001
Cannabis use category, N (Col. %) ^d										
- No current use	- (-; -)	0 (0)	0 (0)	1 (36)	0 (0)	0 (0)	0 (0)	0 (0)		
- 1 to 10 days per month	- (-; -)	5 (63)	5 (36)	9 (44)	0 (0)	7 (100)	1 (17)	5 (9)		
- 11 to 29 days per month	- (-; -)	3 (38)	7 (50)	32 (15)	0 (0)	0 (0)	5 (83)	23 (43)		
- 30 days per month (everyday)	- (-; -)	0 (0)	2 (14)	38 (5)	1 (100)	0 (100)	0 (0)	25 (47)		

Tobacco smoking, N (Col. %)									0.748	0.426
- Never smoker	- (-; -)	3 (38)	2 (14)	24 (30)	1 (100)	2 (29)	1 (17)	9 (17)		
- Former smoker	- (-; -)	3 (38)	6 (43)	29 (36)	0 (0)	4 (57)	3 (50)	25 (47)		
- Current smoker	- (-; -)	2 (25)	6 (43)	29 (34)	0 (0)	1 (14)	2 (33)	19 (36)		
Age started smoking among ever tobacco smokers, median (Q1: Q3)	- (-; -)	17 (15; 19)	16 (13;18)	18 (16; 20)	- (-; -)	18 (15; 31)	16 (16; 20)	17 (15; 23)	0.281	0.777
Cumulative tobacco exposure among ever smokers, median (Q1; Q3), pack-years ^e	- (-; -)	2 (0; 9)	12 (2; 21)	6 (0; 18)	- (-; -)	2 (0; 11)	4 (1; 16)	6 (1; 24)	0.362	0.327
Alcohol use - Cumulative alcohol use among ever drinkers, median (Q1, Q3), drink- years ^f	- (-; -)	29 (5; 15)	38 (16;58)	32 (16;75)	1 (1; 1)	18 (2; 44)	22 (3; 38)	16 (7; 36)	0.451	0.432
Binge drinking days, cumulative use, N (Col.%) ^g									0.857	0.908
- never reported bingeing	- (-; -)	1 (13)	3 (21)	10 (13)	1 (100)	2 (29)	2 (33)	18 (34)		
- ≤ 250 days	- (-; -)	2 (25)	4 (29)	18 (23)	0 (0)	2 (29)	2 (33)	16 (30)		
- > 250 days	- (-; -)	5 (63)	7 (50)	52 (65)	0 (0)	3 (43)	2 (33)	19 (36)		
Illicit drug use Current use ^h Cocaine, crack, speed or methamphetamine, N (Col. %)	- (-; -)	0 (0)	1 (7)	6 (8)	0 (0)	0 (0)	0 (0)	3 (6)	< 0.001	0.842
Heroin, N (Col. %)	- (-; -)	0 (0)	0 (0)	1 (7)	0 (0)	1 (14)	0 (0)	0 (0)	0.2	0.034
Physical activity Physical activity score, median (Q1; Q3) ⁱ	- (-; -)	584 (140; 970)	436 (152; 955)	415 (193; 690)	574 (574; 574)	217 (105; 247)	301 (133;492)	241 (94; 361)	0.870	0.509
Anthropomorphic variable BMI, mean (SD) ^j	- (-; -)	27 (2.6)	26.7 (4.0)	29.8 (5.0)	48.3	32.4 (5.6)	28.6 (5.0)	29.8 (7.2)	0.035	0.06

Cardiovascular risk factors										
Systolic blood pressure, mean (SD), mmHg	- (-; -)	123 (16)	122 (14)	123 (14)	108	118 (10)	119 (8)	123 (17)	0.986	0.709
Diastolic blood pressure, mean (SD), mmHg	- (-; -)	78 (11)	75 (10)	76 (11)	71	74 (8)	73 (13)	75 (13)	0.850	0.949
LDL-Cholesterol, mean (SD), mg/dl	- (-; -)	108 (25)	113 (36)	104 (29)	74	91 (39)	85 (31)	109 (35)	0.575	0.210
HDL-Cholesterol, mean (SD), mg/dl	- (-; -)	48 (11)	59 (16)	52 (13)	54	70 (21)	65 (25)	66 (22)	0.119	0.905
Triglycerides, mean (SD), mg/dl	- (-; -)	126 (68; 138)	75 (62; 92)	118 (82; 157)	52 (52; 52)	99 (86; 104)	156 (66; 357)	86 (60; 114)	0.004	0.143
Diabetes mellitus, N (%)	- (-; -)	1 (13)	2 (14)	11 (14)	0 (0)	1 (14)	3 (50)	4 (8)	0.993	0.024
Psychological variables										
Depression, current CES-D >=16/30, N (%) ^k	- (-; -)	0 (0)	2 (14)	16 (20)	0 (0)	1 (14)	1 (17)	11 (21)	0.337	0.930
Socioeconomical variable										
Currently married, N (%)	- (-; -)	2 (25)	4 (29)	34 (43)	0 (0)	4 (57)	3 (50)	19 (36)	0.381	0.544
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT) at Year 30										
- Raw mean (SD)	- (-; -)	6.1 (3.1)	7.2 (3.0)	6.3 (3.2)	9.0	8.3 (3.5)	6.2 (3.7)	7.5 (3.1)	0.592	0.643
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT) at Year 25										
- Raw mean (SD)	- (-; -)	7.0 (3.5)	6.8 (3.7)	6.2 (3.1)	10.0	8.6 (3.4)	6.2 (2.5)	7.8 (3.3)	0.709	0.500
Digit Symbol Substitution Test (DSST) at Year 30										
- Raw mean (SD)	- (-; -)	67.1(8.8)	60.3(10.4)	61.4(11)	78.0	65.3 (19)	71.7 (12)	67 (17)	0.332	0.816
Digit Symbol Substitution Test (DSST) at Year 25										
- Raw mean (SD)	- (-; -)	70.5 (11)	64.3 (11)	62.2 (11)	78.0	68.7 (15)	74.8 (12)	68.8 (15)	0.168	0.730

Stroop Interference Test at Year 30										
- Raw mean (SD)	- (-; -)	-22.9(7.3)	-31.6(11)	-22.9(12)	-23.0	-25.6 (5)	-16.5 (11)	-25 (11)	0.037	0.331
Stroop Interference at Year 25^l										
- Raw mean (SD)	- (-; -)	-25.0(9.9)	-31.3(17)	-24.6(12)	-23.0	-24.7 (8.2)	-21.3 (6.4)	-24.8 (11)	0.234	0.885
Letter Fluency Test at Year 30										
- Raw mean (SD)	- (-; -)	48.3 (3.0)	47.1 (14)	42.3 (12)	43.0	44.1 (19)	49.7 (12)	45.2 (12)	0.214	0.862
Category Fluency Test at Year 30										
- Raw mean (SD)	- (-; -)	22.4 (5.8)	19.8 (6.1)	20.0 (4.9)	15.0	19.9 (2.9)	19.7 (5.8)	20.0 (4.8)	0.445	0.774
MOCA Test at Year 30										
- Raw mean (SD)	- (-; -)	22.3 (3.0)	23.5 (4.5)	22.9 (3.1)	18.0	23.6 (2.2)	22.7 (3.9)	22.7 (3.7)	0.707	0.556

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; Q1, Q3 = 1st and 3rd quartile (percentiles 25 and 75); SD = standard deviation

^aSelf-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y).

^bP-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 χ^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. P-values are from 1-way analyses of variance for the cognitive functions.

^cBy 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.

^dCategories based on the answer to the question: "During the last 30 days, on how many days did you use marijuana?"

^eSelf-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).

^fCumulative 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 × 1 drink/d × 365 days/y = 6292.6 ml of ethanol).

^gBinge 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.

^hCurrent 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 cumulative exposure when the latter was higher. Cocaine included all forms of cocaine, like crack, powder, free base; amphetamines included speed, uppers, and methamphetamines.

ⁱPhysical 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.

^jCalculated as weight in kilograms divided by height in meters squared.

^kSelf-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.

^lWe used the inverse of the Stroop score so we could interpret worse CF with negative standardized scores for all six CF tests.

Appendix Table 3: Unadjusted and adjusted association between RAVLT at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a. 3145 CARDIA participants (including participants with cannabis use in the 24 hours prior to 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	1350	1350	1320	1789	1786	1749
- 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)	-0.18 (-0.34 to -0.02)	-0.25 (-0.42 to -0.07)	0.08 (-0.05 to 0.21)	-0.01 (-0.13 to 0.11)	0.00 (-0.13 to 0.13)
- 0.5 to < 2 cannabis years	-0.32 (-0.50 to -0.15)	-0.23 (-0.39 to -0.06)	-0.38 (-0.61 to -0.14)	0.06 (-0.10 to 0.21)	-0.06 (-0.21 to 0.08)	0.03 (-0.14 to 0.19)
- 2 to < 5 cannabis years	-0.31 (-0.54 to -0.09)	-0.06 (-0.28 to 0.15)	-0.25 (-0.51 to -0.02)	-0.35 (-0.58 to -0.11)	-0.26 (-0.46 to -0.05)	-0.17 (-0.41 to 0.06)
- > 5 cannabis years	-0.53 (-0.73 to -0.32)	-0.31 (-0.50 to -0.11)	-0.54 (-0.79 to -0.29)	-0.31 (-0.51 to 0.10)	-0.19 (-0.38 to 0.01)	-0.05 (-0.27 to 0.17)
P-value for trend ^e	< 0.001	0.01	< 0.001	< 0.001	0.03	0.37

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 4: Unadjusted and adjusted association between RAVLT at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a. 2912 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit and participants with history of stroke or TIA^b). Results stratified by sex.

Cognitive Function Measure - Self-reported cumulative exposure in cannabis-years ^c	Standardized difference in each CF measures (95% CI) ^d					
	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 ^e	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW ^e
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1225	1225	1200	1695	1692	1658
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.21 (-0.38 to -0.04)	-0.19 (-0.35 to -0.03)	-0.23 (-0.41 to -0.05)	0.09 (-0.04 to 0.23)	-0.00 (-0.11 to 0.13)	0.03 (-0.10 to 0.16)
- 0.5 to < 2 cannabis years	-0.32 (-0.50 to -0.14)	-0.22 (-0.39 to -0.05)	-0.34 (-0.58 to -0.10)	0.10 (-0.05 to 0.26)	-0.03 (-0.17 to 0.12)	0.06 (-0.10 to 0.24)
- 2 to < 5 cannabis years	-0.30 (-0.53 to -0.06)	-0.07 (-0.29 to 0.15)	-0.21 (-0.48 to 0.06)	-0.29 (-0.53 to -0.06)	-0.22 (-0.43 to -0.04)	-0.12 (-0.36 to 0.12)
- > 5 cannabis years	-0.49 (-0.73 to -0.26)	-0.28 (-0.50 to -0.06)	-0.48 (-0.74 to -0.20)	-0.17 (-0.42 to 0.09)	-0.10 (-0.33 to 0.13)	0.04 (-0.23 to 0.32)
P-value for trend ^f	< 0.001	0.04	0.008	<0.01	0.24	0.46

CARDIA = Coronary Artery Risk Development in Young Adults study, TIA = Transient ischemic attack

^aSelf-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).

^bCannabis users with history of Stroke (N=50) or TIA (N=12).

^cYears of cannabis exposure was modeled as a 5-level categorical predictor.

^dLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^eAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^fTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 5: 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 and additionally adjusted for the mirror star tracing test). 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 marital status and mirror star tracing test, with IPCW ^d	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression marital status and mirror star tracing test, with IPCW ^d
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1248	1248	1134	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)	-0.2 (-0.39 to -0.014)	0.08 (-0.05 to 0.21)	-0.01 (-0.13 to 0.11)	-0.14 (-0.09 to 0.17)
- 0.5 to < 2 cannabis years	-0.31 (-0.49 to -0.14)	-0.21 (-0.37 to -0.05)	-0.31 (-0.56 to -0.7)	0.06 (-0.09 to 0.22)	-0.06 (-0.20 to 0.08)	-0.15 (-0.11 to 0.36)
- 2 to < 5 cannabis years	-0.31 (-0.54 to -0.07)	-0.07 (-0.28 to 0.14)	-0.22 (-0.50 to 0.06)	-0.31 (-0.54 to -0.07)	-0.22 (-0.43 to -0.01)	-0.72 (-0.37 to 0.04)
- > 5 cannabis years	-0.48 (-0.71 to -0.24)	-0.25 (-0.47 to -0.04)	-0.38 (-0.66 to -0.09)	-0.19 (-0.44 to 0.07)	-0.12 (-0.35 to 0.11)	0.30 (-0.50 to 1.11)
P-value for trend ^e	< 0.001	0.05	0.08	<0.01	0.20	0.42

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 6: 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, not adjusting for marital status.

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 and depression with IPCW ^d	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, and depression with IPCW ^d
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1248	1248	1225	1722	1722	1688
- 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)	-0.18 (-0.34 to -0.03)	-0.24 (-0.42 to -0.06)	0.08 (-0.05 to 0.21)	-0.01 (-0.13 to 0.11)	0.0 (-0.13 to 0.13)
- 0.5 to < 2 cannabis years	-0.32 (-0.50 to -0.14)	-0.20 (-0.37 to -0.04)	-0.36 (-0.59 to -0.12)	0.06 (-0.09 to 0.22)	-0.06 (-0.20 to 0.08)	0.03 (-0.15 to 0.19)
- 2 to < 5 cannabis years	-0.31 (-0.54 to -0.07)	-0.07 (-0.28 to 0.15)	-0.28 (-0.54 to -0.01)	-0.31 (-0.54 to -0.07)	-0.22 (-0.43 to -0.01)	-0.15 (-0.39 to 0.09)
- > 5 cannabis years	-0.48 (-0.71 to -0.24)	-0.27 (-0.48 to -0.05)	-0.48 (-0.75 to -0.21)	-0.19 (-0.44 to 0.07)	-0.12 (-0.35 to 0.11)	-0.01 (-0.28 to 0.27)
P-value for trend ^e	< 0.001	0.05	0.009	0.002	0.19	0.60

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 7: Unadjusted and adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a. 2866 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit). Results stratified by sex and adjusting for socioeconomic hardship.

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, and socioeconomic hardship	Additionally adjusted for substance use, cardiovascular risk factors, depression, marital status and socioeconomic hardship, with IPCW ^d	Unadjusted model	Adjusted for age, race, education, study center, and socioeconomic hardship	Additionally adjusted for substance use, cardiovascular risk factors, depression, marital status and socioeconomic hardship, with IPCW ^d
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1248	1242	1216	1722	1713	1676
- 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 (-0.35 to -0.03)	-0.26 (-0.44 to -0.08)	0.08 (-0.05 to 0.21)	-0.03 (-0.15 to 0.09)	-0.01 (-0.14 to 0.13)
- 0.5 to < 2 cannabis years	-0.32 (-0.50 to -0.14)	-0.21 (-0.38 to -0.05)	-0.39 (-0.62 to -0.15)	0.06 (-0.09 to 0.22)	-0.06 (-0.21 to 0.08)	0.03 (-0.14 to 0.20)
- 2 to < 5 cannabis years	-0.31 (-0.54 to -0.07)	-0.04 (-0.26 to 0.15)	-0.26 (-0.53 to -0.01)	-0.31 (-0.54 to -0.07)	-0.19 (-0.40 to 0.02)	-0.13 (-0.37 to 0.12)
- > 5 cannabis years	-0.48 (-0.71 to -0.24)	-0.24 (-0.47 to -0.03)	-0.52 (-0.80 to -0.25)	-0.19 (-0.44 to 0.07)	-0.11 (-0.34 to 0.12)	-0.03 (-0.25 to 0.30)
P-value for trend ^e	< 0.001	0.04	0.003	<0.01	0.43	0.68

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 8: Unadjusted and adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a. 2922 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit and participants with history of use of antipsychotic medications^b). Results stratified by sex.

Cognitive Function Measure - Self-reported cumulative exposure in cannabis-years ^c	Standardized difference in each CF measures (95% CI) ^d					
	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 ^e	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1232	1223	1207	1694	1694	1655
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0(Ref)
- 1 day to < 0.5 cannabis years	-0.19 (-0.35 to -0.02)	-0.21 (-0.36 to -0.05)	-0.25 (-0.42 to -0.07)	0.10 (-0.03 to 0.23)	0.01 (-0.11 to 0.13)	0.03 (-0.11 to 0.16)
- 0.5 to < 2 cannabis years	-0.30 (-0.48 to -0.12)	-0.21 (-0.38 to -0.05)	-0.41 (-0.63 to -0.18)	0.09 (-0.06 to 0.25)	-0.03 (-0.18 to 0.11)	0.05 (-0.12 to 0.21)
- 2 to < 5 cannabis years	-0.29 (-0.52 to -0.05)	-0.06 (-0.27 to 0.17)	-0.27 (-0.53 to -0.01)	-0.30 (-0.54 to -0.07)	-0.21 (-0.42 to 0.01)	-0.15 (-0.39 to 0.09)
- > 5 cannabis years	-0.46 (-0.69 to -0.23)	-0.24 (-0.46 to -0.03)	-0.50 (-0.77 to -0.24)	-0.19 (-0.44 to 0.07)	-0.11 (-0.34 to 0.12)	0.01 (-0.28 to 0.28)
P-value for trend ^f	< 0.001	0.07	0.002	0.002	0.18	0.45

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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(1st, 2nd and 3rd generation). 52 participants excluded.

^cYears of cannabis exposure was modeled as a 5-level categorical predictor.

^dLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^eAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^fTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 9: Unadjusted and adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a. 2914 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study visit and participants with history of stimulant drug use^b). Results stratified by sex.

Cognitive Function Measure - Self-reported cumulative exposure in cannabis-years ^c	Standardized difference in each CF measures (95% CI) ^d					
	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 ^e	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Number of participants	1223	1223	1197	1687	1687	1648
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0(Ref)
- 1 day to < 0.5 cannabis years	-0.23 (-0.40 to -0.06)	-0.21 (-0.36 to -0.05)	-0.27 (-0.44 to -0.09)	0.08 (-0.05 to 0.21)	-0.01 (-0.13 to 0.10)	0.01 (-0.13 to 0.14)
- 0.5 to < 2 cannabis years	-0.33 (-0.51 to -0.15)	-0.21 (-0.38 to -0.05)	-0.37 (-0.61 to -0.13)	0.05 (-0.11 to 0.21)	-0.07 (-0.21 to 0.08)	0.04 (-0.13 to 0.21)
- 2 to < 5 cannabis years	-0.31 (-0.55 to -0.08)	-0.07 (-0.29 to 0.14)	-0.28 (-0.55 to -0.01)	-0.31 (-0.55 to -0.07)	-0.22 (-0.44 to -0.01)	-0.14 (-0.38 to 0.11)
- > 5 cannabis years	-0.50 (-0.73 to -0.26)	-0.26 (-0.48 to -0.04)	-0.51 (-0.78 to -0.25)	-0.19 (-0.44 to 0.07)	-0.12 (-0.34 to 0.14)	0.03 (-0.25 to 0.30)
P-value for trend ^f	< 0.001	0.04	0.004	0.002	0.18	0.60

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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).

^bmethylphenidate, amphetamine, dextroamphetamine, metamphetamine, lisdexamfetamine). 60 participants excluded.

^cYears of cannabis exposure was modeled as a 5-level categorical predictor.

^dLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^eAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^fTests of statistical significance were 2-tailed, with an alpha level set at 0.05 for RAVLT.

Appendix Table 10: Unadjusted and adjusted association between measures of immediate memory and learning 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). 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, Immediate Recall						
- Number of participants	1247	1247	1221	1721	1721	1681
- 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)	-0.11 (-0.27 to 0.05)	-0.07 (-0.26 to 0.12)	0.06 (-0.07 to 0.19)	-0.02 (-0.14 to 0.10)	-0.02 (-0.16 to 0.11)
- 0.5 to < 2 cannabis years	-0.23 (-0.40 to -0.05)	-0.15 (-0.32 to 0.03)	-0.04 (-0.28 to 0.21)	0.04 (-0.11 to 0.20)	-0.07 (-0.22 to 0.09)	-0.02 (-0.21 to 0.17)
- 2 to < 5 cannabis years	-0.30 (-0.53 to -0.06)	-0.12 (-0.34 to 0.11)	-0.05 (-0.34 to 0.25)	-0.17 (-0.41 to 0.06)	-0.12 (-0.34 to 0.11)	-0.05 (-0.27 to 0.18)
- > 5 cannabis years	-0.46 (-0.69 to -0.22)	-0.28 (-0.50 to -0.05)	-0.05 (-0.34 to 0.23)	-0.17 (-0.43 to 0.09)	-0.12 (-0.37 to 0.12)	-0.05 (-0.33 to 0.22)
P-value for trend ^e	< 0.001	0.19	0.96	0.09	0.67	0.99
Rey Auditory Verbal Learning-Test, Total Encoding						
- Number of participants	1239	1239	1213	1713	1713	1685
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.15 (-0.32 to 0.02)	-0.15 (-0.30 to 0.00)	-0.14 (-0.31 to 0.02)	0.11 (-0.02 to 0.25)	0.03 (-0.09 to 0.15)	0.06 (-0.07 to 0.19)
- 0.5 to < 2 cannabis years	-0.30 (-0.47 to -0.12)	-0.17 (-0.33 to 0.00)	-0.15 (-0.38 to 0.09)	0.01 (-0.15 to 0.17)	-0.11(-0.25 to 0.04)	-0.03 (-0.21 to 0.14)
- 2 to < 5 cannabis years	-0.33 (-0.56 to -0.09)	-0.07 (-0.28 to 0.14)	-0.05 (-0.33 to 0.23)	-0.36 (-0.59 to -0.12)	-0.25 (-0.45 to -0.04)	-0.17 (-0.40 to 0.07)
- > 5 cannabis years	-0.53 (-0.76 to -0.30)	-0.28 (-0.49 to -0.07)	-0.20 (-0.45 to 0.06)	-0.19 (-0.45 to 0.06)	-0.10 (-0.33 to 0.13)	0.01 (-0.27 to 0.28)
P-value for trend	< 0.001	0.08	0.37	< 0.001	0.01	0.13

Rey Auditory Verbal Learning-Test, Amount learned in five trials						
- Number of participants	1241	1241	1215	1713	1713	1676
- Never used cannabis	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
- 1 day to < 0.5 cannabis years	-0.13 (-0.30 to 0.04)	-0.13 (-0.30 to 0.04)	-0.21 (-0.41 to -0.02)	0.06 (-0.07 to 0.19)	0.04 (-0.09 to 0.18)	0.07 (-0.08 to 0.21)
- 0.5 to < 2 cannabis years	-0.20 (-0.38 to -0.03)	-0.14 (-0.31 to 0.04)	-0.26 (-0.51 to 0.02)	-0.05 (-0.20 to 0.11)	-0.08(-0.24 to 0.08)	-0.04 (-0.24 to 0.16)
- 2 to < 5 cannabis years	-0.18 (-0.41 to 0.06)	-0.03 (-0.27 to 0.20)	-0.16 (-0.46 to 0.13)	-0.09 (-0.32 to 0.15)	-0.03 (-0.27 to 0.21)	0.01 (-0.24 to 0.26)
- > 5 cannabis years	-0.17 (-0.40 to 0.07)	-0.03 (-0.27 to 0.21)	-0.27 (-0.56 to 0.03)	-0.07 (-0.33 to 0.18)	-0.03 (-0.27 to 0.23)	0.04 (-0.25 to 0.32)
P-value for trend	0.27	0.44	0.20	0.30	0.48	0.58

CARDIA = Coronary Artery Risk Development in Young Adults study

^aSelf-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).

^bYears of cannabis exposure was modeled as a 5-level categorical predictor.

^cLinear regression models determined the association between CF scores and cumulative exposure to cannabis use. Negative standardized scores indicate worse CF.

^dAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring.

^eTests of statistical significance were 2-tailed, with an alpha level set at 0.05.

Appendix Table 11: Characteristics of 2786 CARDIA with measures of cognitive function at year 25 and year 30 (including participants with use in 24 hours prior to study visit). Results stratified by sex and categories of current exposure to cannabis.

Variable	Cannabis use categories ^a at year 30 based on cannabis use status between year 25 and year 30									
	Men					Women				
	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)
N	N = 168	N = 759	N = 55	N = 81	N = 135	N = 261	N = 1077	N = 69	N = 79	N = 102
Demographics										
Age, median (Q1; Q3)	55 (51; 58)	56 (53; 58)	56 (52; 58)	56 (53; 58)	55 (52; 58)	55 (52; 58)	56 (53; 58)	55 (52; 58)	55 (52; 58)	56 (52; 58)
Race, N (Col. %) ^b										
- Black	66 (39)	306 (40)	28 (51)	40 (49)	62 (46)	155 (59)	477(44)	42 (61)	43 (54)	57 (56)
- White	102 (61)	453 (60)	27 (49)	41 (51)	73 (54)	106 (41)	600(56)	27 (39)	36 (46)	45 (44)
Education, median (Q1; Q3), years	16 (14; 20)	16 (14; 18)	15 (13; 17)	15 (13; 16)	15 (13; 16)	16 (14; 18)	16 (14;18)	15 (14;16)	15 (13;16)	15 (13; 16)
Study center, N (Col. %)										
- Birmingham, AL	74 (44)	190 (25)	18 (33)	6 (7)	17 (13)	119 (46)	194 (18)	16 (23)	15 (19)	8 (8)
- Chicago, IL	45 (27)	168 (22)	14 (25)	17 (21)	23 (17)	64 (25)	247 (23)	17 (25)	14 (18)	18 (18)
- Minneapolis, MI	28 (17)	200 (26)	9 (16)	30 (37)	44 (33)	50 (19)	284 (26)	13 (19)	20 (25)	29 (28)
- Oakland, CA	21 (13)	201 (26)	14 (25)	28 (35)	51 (38)	28 (11)	352 (33)	23 (33)	30 (38)	47 (46)
Substance use exposure										
Cumulative cannabis use, mean (SD) ^c	0 (0)	1.1 (2.0)	3.5 (4.7)	3.2 (3.3)	12.1 (7.4)	0 (0)	0.6 (1.2)	2.5 (4.34)	3.3 (3.7)	9.9 (7.3)
Cannabis use category, N (Col. %) ^d										
- No current use	168 (100)	759 (100)	55 (100)	0 (0)	0 (0)	261 (100)	1077 (100)	69 (100)	0 (0)	0 (0)

Non-fatal Stroke, N (%)	5 (3)	16 (2)	1 (2)	2 (2)	2 (1)	3 (1)	22 (2)	2 (3)	3 (4)	2 (2)
Non-fatal TIA, N (%)	0 (0)	2 (0)	1 (2)	0 (0)	1 (1)	1 (0)	6 (1)	1 (1)	0 (0)	0 (0)

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; Q1, Q3 = 1st and 3rd quartile (percentiles 25 and 75); SD = standard deviation, TIA = Transient ischemic attack

^aCategories based on the answer to the questions: "During the last 30 days, on how many days did you use marijuana?"

^bBy 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.

^cSelf-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y).

^dCategories based on the answer to the question: "During the last 30 days, on how many days did you use marijuana?"

^eSelf-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).

^fCumulative 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 × 1 drink/d × 365 days/y = 6292.6 ml of ethanol)

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

^hCurrent 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 cumulative exposure when the latter was higher. Cocaine included all forms of cocaine, like crack, powder, free base; amphetamines included speed, uppers, and methamphetamines.

ⁱPhysical 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

^jCalculated as weight in kilograms divided by height in meters squared.

^kSelf-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.

Appendix Table 12: Distribution of cognitive function at Year 25 and cumulative exposure to cannabis in ‘cannabis-years’^a among 2786 CARDIA participants with measures of cognitive function at Year 25 and Year 30 exams (including use in 24 hours prior to study visit). Results stratified by sex and categories of current exposure to cannabis.

Variable	Cannabis use categories ^b at year 25 based on cannabis use status between year 25 and year 30										p-value ^c	
	Men					Women						
	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)		
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)												
- Number of participants	168	759	55	81	135	261	1077	69	79	102	<0.001	<0.001
- Raw mean (SD)	8.4 (3.3)	7.6; (3.1)	7.2 (3.1)	7.0 (3.5)	6.7 (3.4)	9.1 (3.2)	9.4 (3.0)	8.4 (3.0)	8.5 (3.0)	8.1 (3.5)	1	
- Standardized mean ^d	0.27	0.01	-0.09	-0.15	-0.26	-0.04	0.07	-0.23	-0.21	-0.35		
Digit Symbol Substitution Test (DSST)												
- Number of participants	166	753	55	81	136	258	1079	69	77	102	0.03	<0.01
- Raw mean (SD)	68.5 (15.2)	66.4 (15.4)	62.2 (15.1)	63.5 (16.7)	65.5 (14.1)	71.8(15.8)	75.7(15.0)	69.7(14.8)	70.6(15.7)	69.7(16.2)		
- Standardized mean	0.15	0.02	-0.29	-0.16	-0.04	-0.15	0.10	-0.29	-0.23	-0.29		
Stroop Interference Test^e												
- Number of participants	168	747	53	81	131	258	1071	70	78	101	0.56	<0.01
- Raw mean (SD)	-23.3(12.7)	-22.4(10.1)	-23.8(10.5)	-24.1(12.3)	-22.4(10.3)	-22.7(10.3)	-21.6(10.4)	-24.7(12.5)	-25.2(16.0)	-24.3(11.0)		
- Standardized mean	-0.03	0.03	-0.12	-0.12	0.01	-0.03	0.06	0.22	-0.27	-0.19		

CARDIA = Coronary Artery Risk Development in Young Adults study, SD = standard deviation.

^aSelf-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y).

^bCategories based on the answer to the question: “During the last 30 days, on how many days did you use marijuana?”

^cP-values are from 1-way analyses of variance. All P values two sided.

^dEach CF measure was standardized by subtracting the mean and then dividing the score by the within-CARDIA sex-specific standard deviation.

^eWe used the inverse of the Stroop score so we could interpret worse CF with negative standardized scores for all three CF tests.

Appendix Table 13: Distribution of cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’^a among 2786 CARDIA participants with measures of cognitive function at Year 25 and Year 30 exams (including use in 24 hours prior to study visit). Results stratified by sex and categories of current exposure to cannabis.

Variable	Cannabis use categories ^b at year 30 based on cannabis use status between year 25 and year 30										p-value ^c		
	Men					Women							
	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)	Never Users	Past users (any use before year 25 visit and not at visit 25 or 30)	Recent quitters (any use at year 25 and not at year 30)	Recent restarters (Any use before year 25 visit. No use at year 25 and any use at year 30)	Continuous users (any use at year 25 and any use at year 30)			
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)													
- Number of participants	168	759	55	81	135	261	1077	69	79	102	<0.001	<0.001	
- Raw mean (SD)	8.5 (3.5)	7.8; (3.3)	7.4 (3.1)	7.0 (3.7)	6.8 (3.3)	9.3 (3.2)	9.5 (3.3)	8.4 (2.9)	8.3 (3.4)	8.3 (3.4)	1		
- Standardized mean ^d	0.25	0.02	-0.09	-0.21	-0.27	-0.01	0.07	-0.27	-0.30	-0.30			
Digit Symbol Substitution Test (DSST)													
- Number of participants	166	753	55	81	136	258	1079	69	77	102	0.06	<0.01	
- Raw mean (SD)	66.1 (15.4)	63.8 (16.1)	59.7 (16.9)	61.5 (15.6)	63.4 (13.7)	69.0(17.0)	72.9(16.1)	68.6(14.5)	66.9(17.3)	68.6(17.1)			
- Standardized mean	0.15	0.01	-0.25	-0.14	-0.02	-0.15	0.08	-0.17	-0.28	-0.17			
Stroop Interference Test^e													
- Number of participants	168	747	53	81	131	258	1071	70	78	101	0.76	0.02	
- Raw mean (SD)	-23.5(15.8)	-23.0(12.6)	-23.9(10.5)	-23.6(13.4)	-21.8(10.2)	-23.3(11.1)	-21.7(10.4)	-22.4(10.9)	-23.8(12.3)	-24.8(11.8)			
- Standardized mean	-0.04	0.01	-0.07	-0.05	0.09	-0.09	0.05	-0.01	-0.13	-0.23			

CARDIA = Coronary Artery Risk Development in Young Adults study, SD = standard deviation.

^aSelf-reported cumulative exposure to cannabis joints in cannabis-years; 1 cannabis-year of exposure = 365 days of cannabis use (1 year × 365 days/y).

^bCategories based on the answer to the question: “During the last 30 days, on how many days did you use marijuana?”

^cP-values are from 1-way analyses of variance. All P values two sided.

^dEach CF measure was standardized by subtracting the mean and then dividing the score by the within-CARDIA sex-specific standard deviation.

^eWe used the inverse of the Stroop score so we could interpret worse CF with negative standardized scores for all three CF tests.

Appendix Table 14. Unadjusted 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 Year 30 exams

Test results across categories of current exposure to cannabis ^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)	0.00 (-0.11 to 0.12)	0.04 (-0.02 to 0.10)	0.02 (-0.18 to 0.23)	-0.03 (-0.20 to 0.14)	0.02 (-0.11 to 0.15)	0.02 (-0.08 to 0.11)	-0.01 (-0.05 to 0.04)	-0.04 (-0.22 to 0.14)	-0.08 (-0.25 to 0.09)	0.05 (-0.10 to 0.20)	0.94	0.79
Digit Symbol Substitution Test (DSST)	0.01 (-0.07 to 0.08)	0.00 (-0.03 to 0.04)	0.02 (-0.11 to 0.15)	0.05 (-0.06 to 0.15)	0.05 (-0.04 to 0.13)	-0.02 (-0.10 to 0.05)	-0.04 (-0.07 to -0.00)	0.08 (-0.06 to 0.23)	-0.08 (-0.21 to 0.06)	0.08 (-0.04 to 0.20)	0.86	0.17
Stroop Interference Test	0.01 (-0.11 to 0.13)	-0.03 (-0.09 to 0.03)	0.02 (-0.20 to 0.24)	0.06 (-0.11 to 0.24)	0.07 (-0.06 to 0.21)	-0.03 (-0.13 to 0.07)	0.01 (-0.04 to 0.06)	0.23 (0.04 to 0.43)	0.16 (-0.02 to 0.35)	-0.01 (-0.17 to 0.15)	0.64	0.08

^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. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test

^bTests of statistical significance were 2-tailed, with an alpha level set at 0.05

Appendix Table 15. Minimally 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 Year 30 exams

Test results across categories of current exposure to cannabis ^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)	0.07 (-0.05 to 0.19)	0.04 (-0.02 to 0.09)	0.05 (-0.15 to 0.25)	-0.09 (-0.25 to 0.08)	-0.02 (-0.16 to 0.11)	0.05 (-0.05 to 0.14)	-0.02 (-0.06 to 0.03)	-0.02 (-0.20 to 0.16)	-0.06 (-0.23 to 0.10)	0.05 (-0.10 to 0.20)	0.58	0.69
Digit Symbol Substitution Test (DSST)	0.03 (-0.05 to 0.11)	0.00 (-0.03 to 0.04)	0.04 (-0.09 to 0.17)	0.03 (-0.08 to 0.13)	0.03 (-0.05 to 0.11)	-0.01 (-0.09 to 0.07)	-0.04 (-0.08 to -0.00)	0.09 (-0.05 to 0.24)	-0.08 (-0.22 to 0.06)	0.08 (-0.04 to 0.20)	0.91	0.15
Stroop Interference Test	0.03 (-0.10 to 0.15)	-0.03 (-0.09 to 0.03)	0.02 (-0.20 to 0.24)	0.06 (-0.12 to 0.23)	0.07 (-0.07 to 0.20)	-0.01 (-0.11 to 0.10)	0.01 (-0.04 to 0.06)	0.21 (0.02 to 0.40)	0.12 (-0.06 to 0.30)	-0.07 (-0.23 to 0.10)	0.65	0.17

^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 minimally adjusted linear regression models, adjusted for age, race, study site, education. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test

^bTests of statistical significance were 2-tailed, with an alpha level set at 0.05

Appendix Table 16: Unadjusted and adjusted association between cognitive function decline of > 0.1 SD between Year 25 and Year 30 exams and categories of exposure to cannabis at year 25 and year 30 among participants with measures of cognitive function at Year 25 and Year 30 exams (2786 participants, including use in 24 hours prior to study visit). Results stratified by sex.

Test results across categories of current exposure to cannabis ^a	Odds Ratio (95% CI) ^b					
	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 ^c	Unadjusted model	Adjusted for age, race, education, study center	Additionally adjusted for substance use, cardiovascular risk factors, depression and marital status, with IPCW ^c
Rey Auditory Verbal Learning-Test, delayed recall (RAVLT)						
- Never users	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
- Past users	0.99 (0.71 - 1.40)	1.10 (0.77 - 1.56)	1.12 (0.73 - 1.73)	0.91 (0.69 - 1.20)	1.01 (0.75 - 1.36)	0.99 (0.70 - 1.40)
- Recent quitters	1.29 (0.70 - 2.38)	1.34 (0.72 - 2.50)	1.45 (0.68 - 3.10)	1.09 (0.64 - 1.87)	1.11 (0.64 - 1.93)	0.94 (0.50 - 1.77)
- Recent restarters	1.37 (0.80 - 2.33)	1.66 (0.95 - 2.89)	1.71 (0.89 - 3.25)	1.14 (0.69 - 1.90)	1.18 (0.69 - 2.00)	0.94 (0.51 - 1.75)
- Continuous users	1.00 (0.63 - 1.59)	1.18 (0.72 - 1.92)	1.33 (0.71 - 2.49)	1.06 (0.66 - 1.68)	1.15 (0.70 - 1.87)	0.93 (0.52 - 1.67)
P-value for trend ^d	0.63	0.42	0.47	0.75	0.94	0.99
Digit Symbol Substitution Test (DSST)						
- Never users	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
- Past users	1.01 (0.72 - 1.42)	1.13 (0.79 - 1.60)	1.26 (0.83 - 1.92)	1.10 (0.84 - 1.45)	1.22 (0.91 - 1.63)	1.13 (0.81 - 1.59)
- Recent quitters	0.94 (0.50 - 1.74)	0.96 (0.51 - 1.80)	1.09 (0.51 - 2.33)	0.69 (0.40 - 1.21)	0.69 (0.39 - 1.22)	0.59 (0.32 - 1.09)
- Recent restarters	1.02 (0.59 - 1.74)	1.21 (0.68 - 2.11)	1.38 (0.71 - 2.66)	1.29 (0.77 - 2.14)	1.39 (0.82 - 2.38)	1.11 (0.62 - 2.01)
- Continuous users	0.93 (0.58 - 1.47)	1.07 (0.66 - 1.74)	1.30 (0.71 - 2.40)	1.05 (0.66 - 1.67)	1.14 (0.70 - 1.84)	0.99 (0.54 - 1.80)
P-value for trend	0.85	0.93	0.83	0.40	0.17	0.20
Stroop Interference Test						
- Never users	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
- Past users	1.16 (0.82 - 1.65)	1.21 (0.85 - 1.73)	1.12 (0.71 - 1.75)	0.99 (0.75 - 1.30)	1.03 (0.78 - 1.37)	1.13 (0.81 - 1.56)
- Recent quitters	1.09 (0.58 - 2.06)	1.11 (0.58 - 2.12)	0.92 (0.44 - 1.94)	0.73 (0.43 - 1.26)	0.77 (0.44 - 1.32)	0.80 (0.44 - 1.46)
- Recent restarters	1.06 (0.61 - 1.84)	1.11 (0.63 - 1.95)	1.17 (0.58 - 2.35)	0.90 (0.54 - 1.50)	0.96 (0.57 - 1.62)	0.95 (0.52 - 1.76)

- Continuous users	1.08 (0.67 - 1.73)	1.15 (0.70 - 1.88)	1.11 (0.59 – 2.10)	1.15 (0.73 - 1.81)	1.25 (0.78 – 2.01)	1.37 (0.77 – 2.40)
P-value for trend	0.93	0.88	0.96	0.70	0.64	0.51

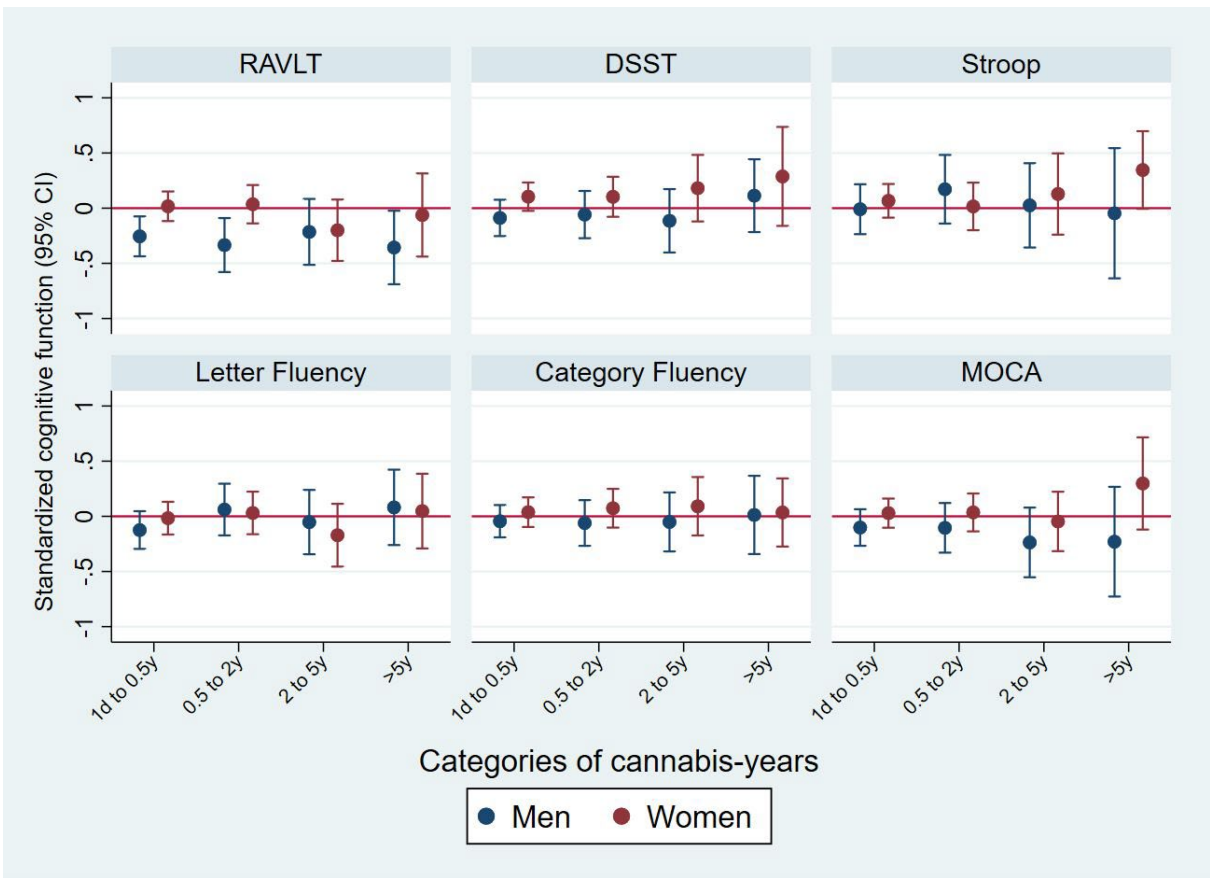
^a**Never users:** Never used cannabis; **Past users:** Any use before Year 25 visit and no current use at Year 25 or Year 30 visits; **Recent quitters:** Current use at Year 25 visit and no current use at Year 30 visit. **Recent restarters:** Any use before Year 25 visit. No current use at Year 25 visit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

^bCognitive decline defined as sex-specific decline > 0.1 standard deviation (SD) from the mean change. Results are shown as odds ratio compared with never users (baseline).

^cAnalyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring

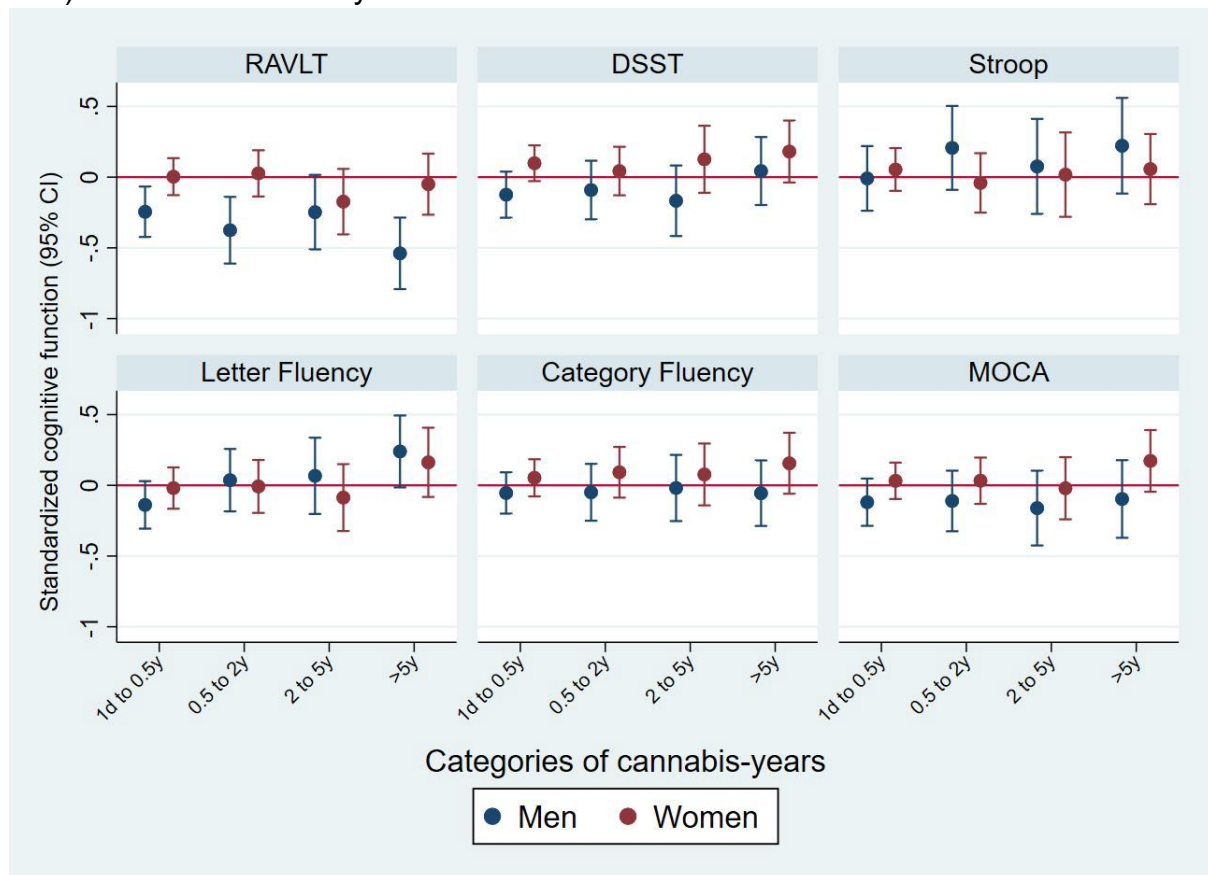
^dTests of statistical significance were 2-tailed, with an alpha level set at 0.05

Appendix Figure 1: Adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’. 2698 CARDIA participants (excluding participants with cannabis use in the 30 days prior to the study visit). Results stratified by sex.



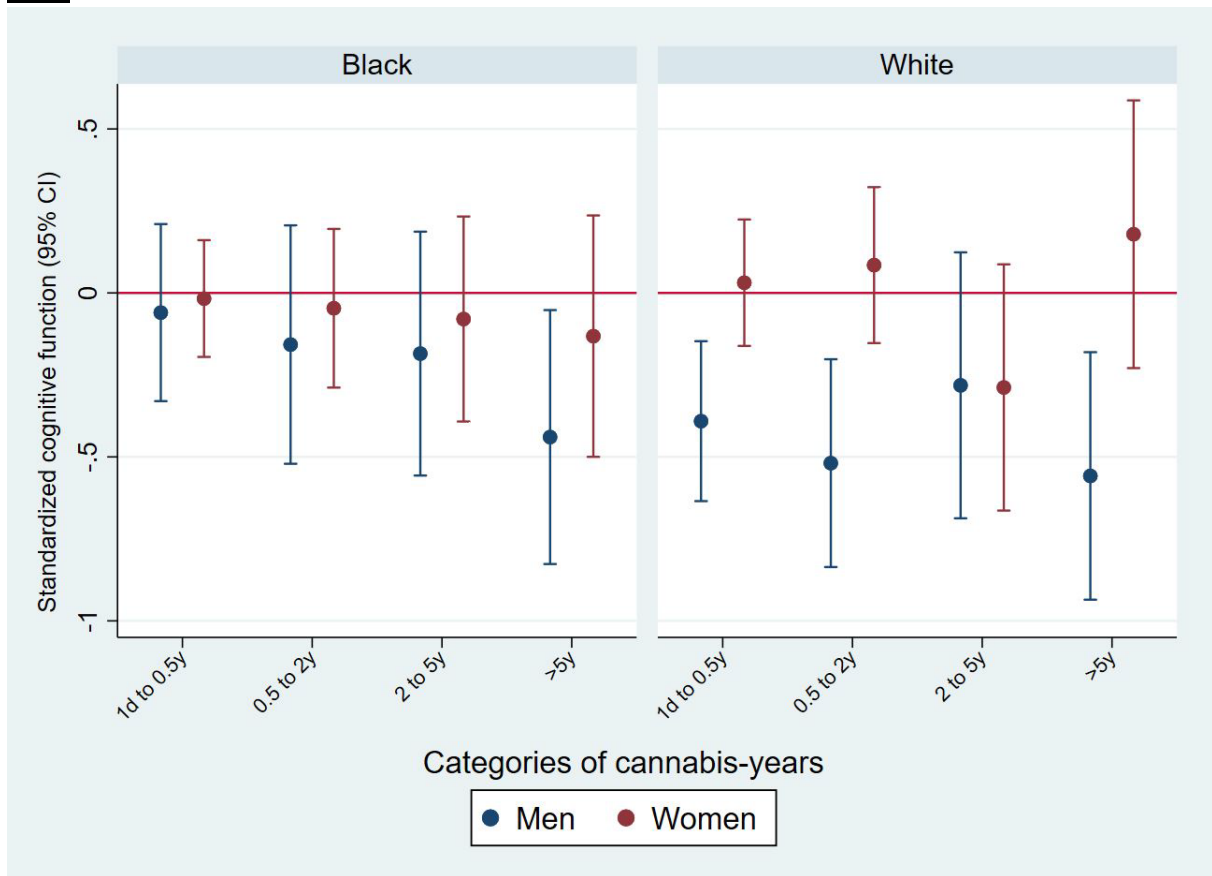
CARDIA = Coronary Artery Risk Development in Young Adults study
 Self-reported cumulative exposure to cannabis joints in cannabis-years; 1-cannabis-year of exposure = 365 days of cannabis use (1 year x 365 days/y). Cannabis users within the last 30 days of the Year 30 visit excluded (N=447). Model results adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age starting smoking), alcohol, 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

Appendix Figure 2: Unadjusted and adjusted association between cognitive function at Year 30 and cumulative exposure to cannabis in ‘cannabis-years’. 3145 CARDIA participants (including participants with cannabis use in the 24 hours prior to study visit). Results stratified by sex.



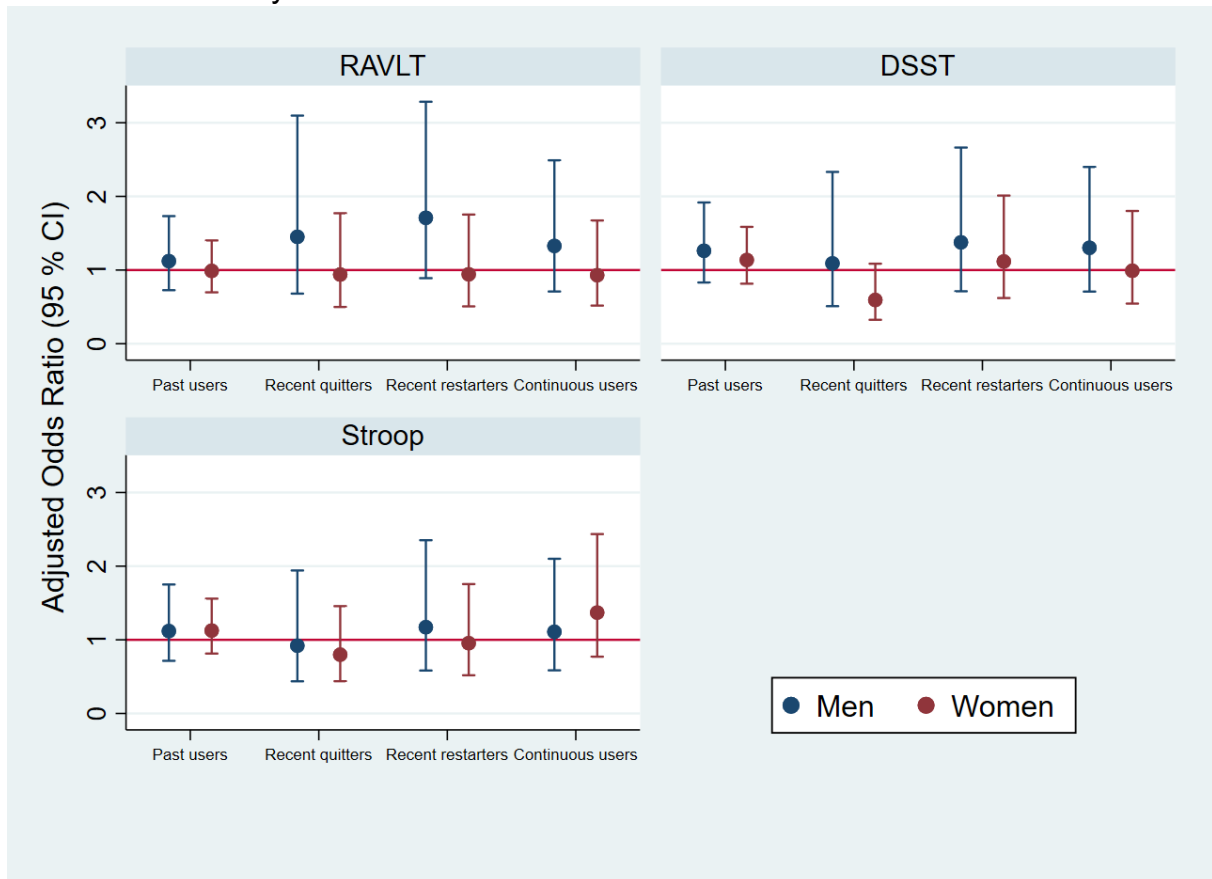
CARDIA = Coronary Artery Risk Development in Young Adults study
 Self-reported cumulative exposure to cannabis joints in cannabis-years; 1-cannabis-year of exposure = 365 days of cannabis use (1 year x 365 days/y). Model results adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age starting smoking), alcohol, 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

Appendix Figure 3: Adjusted association between RAVLT and cumulative exposure to cannabis in ‘cannabis-years’. 2974 CARDIA participants (excluding participants with cannabis use in the 24 hours prior to the study). Results stratified by sex and race.



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, study site, education, cigarette smoking (current, cumulative, age started smoking), alcohol, 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. RAVLT - Rey Auditory Verbal Learning Test

Appendix Figure 4: Adjusted association between cognitive function decline of > 0.1 SD between Year 25 and Year 30 exams and categories of exposure to cannabis at Year 25 and Year 30 among participants with measures of cognitive function at Year 25 and 30 exams (2786 participants, including use in 24 hours prior to study visit). Results stratified by sex.



Accelerated cognitive decline defined as sex-specific decline > 0.1 standard deviation (SD) from the mean change. Model results shown as odds ratio compared with never users (baseline).

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 logistic regression models, adjusted for age, race, study site, education, cigarette smoking (current, cumulative, age starting smoking), alcohol, illicit drug use, cardiovascular risk factors, physical activity, depression, marital status. RAVLT - Rey Auditory Verbal Learning Test; DSST – Digit Symbol Substitution Test

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