Title: Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Authors: Auer R, Vittinghoff E, Yaffe K, Künzi A, Kertesz SG, Levine DA, Albanese E, Whitmer RA, Jacobs DR Jr, Sidney S, Glymour MM, Pletcher MJ

Journal: JAMA internal medicine

Year: 2016 Mar

Volume: 176

Issue: 3

Pages: 352-61

DOI: 10.1001/jamainternmed.2015.7841

Original Investigation

Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Reto Auer, MD, MAS; Eric Vittinghoff, PhD, MPH; Kristine Yaffe, MD; Arnaud Künzi, BA; Stefan G. Kertesz, MD, MSc; Deborah A. Levine, MD, MPH; Emiliano Albanese, MD, PhD, MPH; Rachel A. Whitmer, PhD; David R. Jacobs Jr, PhD; Stephen Sidney, MD; M. Maria Glymour, ScD, MS; Mark J. Pletcher, MD, MPH

Invited Commentary page 362

Supplemental content at jamainternalmedicine.com

IMPORTANCE Marijuana use is increasingly common in the United States. It is unclear whether it has long-term effects on memory and other domains of cognitive function.

OBJECTIVE To study the association between cumulative lifetime exposure to marijuana use and cognitive performance in middle age.

DESIGN, SETTING, AND PARTICIPANTS We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort of 5115 black and white men and women aged 18 to 30 years at baseline from March 25, 1985, to June 7, 1986 (year 0), and followed up over 25 years from June 7, 1986, to August 31, 2011, to estimate cumulative years of exposure to marijuana (1 year = 365 days of marijuana use) using repeated measures and to assess associations with cognitive function at year 25. Linear regression was used to adjust for demographic factors, cardiovascular risk factors, tobacco smoking, use of alcohol and illicit drugs, physical activity, depression, and results of the mirror star tracing test (a measure of cognitive function) at year 2. Data analysis was conducted from June 7, 1986, to August 31, 2011.

MAIN OUTCOMES AND MEASURES Three domains of cognitive function were assessed at year 25 using the Rey Auditory Verbal Learning Test (verbal memory), the Digit Symbol Substitution Test (processing speed), and the Stroop Interference Test (executive function).

RESULTS Among 3385 participants with cognitive function measurements at the year 25 visit, 2852 (84.3%) reported past marijuana use, but only 392 (11.6%) continued to use marijuana into middle age. Current use of marijuana was associated with worse verbal memory and processing speed; cumulative lifetime exposure was associated with worse performance in all 3 domains of cognitive function. After excluding current users and adjusting for potential confounders, cumulative lifetime exposure to marijuana remained significantly associated with worse verbal memory. For each 5 years of past exposure, verbal memory was 0.13 standardized units lower (95% CI, −0.24 to −0.02; $P = .02$), corresponding to a mean of 1 of 2 participants remembering 1 word fewer from a list of 15 words for every 5 years of use. After adjustment, we found no associations with lower executive function (−0.03 [95% CI, −0.12 to 0.07]; $P = .56$) or processing speed (−0.04 [95% CI, −0.16 to 0.08]; $P = .51$).

CONCLUSIONS AND RELEVANCE Past exposure to marijuana is associated with worse verbal memory but does not appear to affect other domains of cognitive function.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Reto Auer, MD, MAS, Department of Ambulatory Care and Community Medicine, University of Lausanne, Rue du Bugnon 44. 1011 Lausanne, Switzerland (reto.auer@hospvd.ch).

JAMA Intern Med. 2016;176(3):352-361. doi:10.1001/jamainternmed.2015.7841
Published online February 1, 2016.

Marijuana use is common among adolescents and young adults. Data from the United States in 2012 indicate that among students in the 12th grade (aged 17-18 years), 37% had used marijuana within the last year, 23% within the last 30 days, and 6.5% daily.[1] If marijuana has significant long-term adverse effects, use early in life may have important public health consequences. Long-term effects from marijuana use, however, can be difficult to detect.

Impaired cognitive function is an acute effect of marijuana use,[2] and there is increasing evidence that such effects may persist later in life.[3-5] Heavy, long-term use of marijuana has been associated with cognitive impairment, particularly in learning and remembering new information.[3,6] Evidence from population-based studies, however, is scarce, and it remains unclear whether there are long-term effects from low-intensity or occasional marijuana use earlier in life[3] and whether the magnitude and persistence of impairment depends on the duration of cannabis use or the age of exposure.[4,5]

With 25 years of repeated measurements of marijuana exposure starting in early adulthood, the Coronary Artery Risk Development in Young Adults (CARDIA) study provides an opportunity to assess the long-term effects of marijuana exposure among community-based adults. In year 25, CARDIA measured cognitive performance using standardized tests of verbal memory, processing speed, and executive function. We used these measurements to study the association between cumulative years of exposure to marijuana use and cognitive performance in middle age among CARDIA participants with marijuana exposures typical of the communities in which they live.

Methods

Study Design and Sample

The CARDIA study is a population-based epidemiologic study of 5115 adults aged 18 to 30 years at baseline; these adults were followed up from June 7, 1986, to August 31, 2011.[7] Participants were recruited from March 25, 1985, to June 7, 1986, by random selection of telephone numbers from designated census tracts in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and by random selection from the membership list of a health care plan in Oakland, California. The sampling scheme was designed to achieve a balance at each of the 4 sites by race (self-identified as black, not Hispanic or white, not Hispanic), sex, educational level (high school degree or less or more than high school), and age (18-24 years or 25-30 years). All participants provided written informed consent, with institutional review board approval at each field center (University of Alabama at Birmingham, Northwestern University, University of Minnesota, and Kaiser Permanente).

Marijuana Exposure: Current and Cumulative

Current marijuana use was assessed at each in-person CARDIA visit (at baseline and after 2, 5, 7, 10, 15, 20, and 25 years of follow-up) using the following survey question: "During the last 30 days, on how many days did you use marijuana?" Direct self-reported lifetime exposure was assessed using the question, "About how many times in your lifetime have you used marijuana?" We used current and lifetime use to compute marijuana-years, with 1 year of exposure equivalent to 365 days of marijuana use (eAppendix 1 in the Supplement).[8] We assumed that current use at each visit (ie, the number of days of using marijuana during the month before each visit) reflected the average number of days of use during the months before and after each visit. We estimated the cumulative lifetime use by adding the total number of days using marijuana during follow-up. We adjusted our estimate upward whenever directly self-reported lifetime use was higher than our computed estimates.[8]

Outcome Measure

Cognitive function was assessed by trained and certified CARDIA technicians who administered a battery of 3 cognitive tests at the year 25 visit.[9] The Rey Auditory Verbal Learning Test (RAVLT) mainly assesses verbal memory through the ability to memorize and retrieve lists of 15 words. The RAVLT yields 3 separate scores; in the main analyses we used the delayed (25 minutes) free recall score only (and used the other 2 in sensitivity analyses [eAppendix 1 in the Supplement]).[10] The Digit Symbol Substitution Test assesses visual motor speed, executive function, sustained attention, and working memory; we refer to this domain as *processing speed*.[11] The Stroop Interference Test evaluates the ability to view complex visual stimuli and to respond to 1 stimulus dimension while suppressing the response to another dimension; we refer to this domain as *executive function*.[12,13] The resulting interference score provides a measure of how much additional executive processing is needed to respond to an incongruent trial; thus, a higher interference score indicates worse performance on the task. The inverse of this score was used in the present analyses such that increasing scores indicate better performance. Each measure was standardized by dividing the score by the within-CARDIA standard deviation and subtracting the mean such that absolute and relative differences in these standardized measures are comparable.

Other Covariates

Cigarette smoking behavior was evaluated during each in-person CARDIA visit and at yearly contacts via the telephone between CARDIA visits. These data were used to estimate cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to smoking 1 pack of cigarettes per day for 1 year.[8,14] 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 per day (eAppendix 1 in the Supplement).[15] We estimated total lifetime episodes of acute heavy exposure to alcohol (bingeing), defined as reporting 5 or more drinks on 1 occasion. We estimated total number of lifetime exposures to cocaine (including other forms of cocaine, such as crack, powder, or freebase), amphetamines (speed, uppers, or methamphetamines), and heroin (eAppendix 1 in the Supplement).[16,17] Educational level was measured as the maximum educational grade attained for each participant across reports at each visit. Physical activity was measured with the CARDIA Physical

Activity History questionnaire, which queries the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities during the past 12 months.[18] Self-reported depression was measured every 5 years starting at the year 5 visit using the Center for Epidemiologic Studies Depression scale.[19] We used cardiovascular risk factor measurements, including blood pressure, blood cholesterol levels (total, low-density lipoprotein, and high-density lipoprotein cholesterol, as well as triglyceride levels), fasting glucose level, and body mass index, and calculated cumulative exposures to these measurements and for physical activity and depression (area under the curve for continuous measurements [eAppendix 1 in the Supplement]).[20] The number of years using antidepressant medication was computed by adding the number of years reporting the use of 1 or more antidepressant medication (eAppendix 1 in the Supplement). Self-reported schizophrenia was based on self-reported mental disease, reasons for hospitalizations, and reasons for taking a psychoactive medication (eAppendix 1 in the Supplement). 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.[21,22] 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 number of errors over 3 minutes were recorded. Although initially intended as a stressor to measure blood pressure reactivity and not as a cognitive test,[21,23] some have suggested that the mirror star tracing test measures aspects of executive function.[22,24]

Statistical Analysis

Data analysis was performed from June 7, 1986, to August 31, 2011. We used descriptive statistics to compare participants with different levels of exposure to marijuana at the year 25 visit. We then described unadjusted associations between marijuana use (current and lifetime) and each cognitive function measure, before and after standardization. Current and lifetime marijuana exposure were significantly associated with each other, and their potential effects on cognitive function were difficult to differentiate owing to colinearity and potential interactions in their effects on cognitive function. Given our primary goal of assessing potential effects of cumulative marijuana exposure, we eliminated the obscuring influence of current marijuana use by excluding the few CARDIA participants who were currently using marijuana at the year 25 visit from our primary analyses. We used linear regression to assess independent associations between years of exposure to marijuana and cognitive function outcomes. We estimated a sequence of models: the first model was unadjusted; the second model controlled for the covariates used to achieve a balance of sampling in CARDIA: age, race/ethnicity, sex, study center, and years of education. The third model additionally controlled for covariates potentially associated with both marijuana use and cognition: use of alcohol, cocaine, amphetamines, and heroin; age the participants started smoking cigarettes; cardiovascular risk factors; physical activity; body mass index; depression; and type 2 diabetes mellitus at the year 25 visit. Educational level, drink-years of alcohol, physical activity, and body mass index were flexibly modeled using restricted cubic splines with 3 knots at the quartiles of their distributions. To minimize potential bias due to informative censoring, we used inverse probability of censoring weights (eAppendix 1 in the Supplement).[25] We adjusted for the mirror star tracing test score at year 2 (near baseline) to minimize reverse causation as an explanation for any associations between marijuana use and the year 25 cognitive function scores, and we assessed correlations between mirror star tracing test scores and year 25 cognition and marijuana use to further investigate this potential issue (eAppendix 1 and eAppendix 2 in the Supplement). Schizophrenia and psychotropic medication have been associated with both cognitive impairment and marijuana use and could therefore act as confounders of the association between marijuana use and cognitive function.[26,27] We evaluated the sensitivity of the analyses to inclusion of self-reported schizophrenia (eAppendix 1 in the Supplement) as a covariate in the multivariable adjusted models and by exclusion of participants with self-reported schizophrenia. We also tested the sensitivity of the results by inclusion of psychoactive medications in the main multivariable model. We also tested the association between cumulative years of exposure to marijuana with the components of the RAVLT (eAppendix 2 and the eFigure in the Supplement). Tests of statistical significance were 2-tailed, with $P < .05$ considered significant. All analyses were conducted using STATA, version 13 (StataCorp LP).

Results

Of the 3499 participants reassessed at the year 25 visit, 3385 (96.7%) had data on cognitive function and 3326 (95.1%) had complete data on all 3 cognitive outcomes. Attrition was more common among men, black participants, those with heavy marijuana use, tobacco smokers, and cocaine users (eAppendix 2 in the Supplement). Most participants (2852 [84.3%]) reported having used marijuana before or during the 25 years of follow-up, but most had relatively few cumulative years of exposure (**Table 1**).[8,18,19,28-31] Total years of marijuana exposure was significantly associated with other participant characteristics, including race and sex, educational level, study site, other substance use, physical activity, body mass index, high-density lipoprotein cholesterol and triglyceride levels, and total number of stars completed and errors on the mirror star tracing test, and weakly associated with depressive symptoms and antidepressant medication use (Table 1).

In unadjusted analyses, current marijuana use at the year 25 visit was associated with worse verbal memory (RAVLT) and processing speed (Digit Symbol Substitution Test) (eTable in the Supplement), while lifetime exposure was associated with worse performance on all 3 measures of cognitive function (**Table 2**). In preliminary analyses, we found evidence of a negative interaction between years of marijuana use and current

Table 1. Characteristics of 3385 Participants With Cognitive Function Test Results at the Year 25 Visit

Variable	No Marijuana Use (n = 533)	Ever Marijuana Use, y[a] <0.5 (n = 1505)	0.5-2.0 (n = 800)	2.0-5.0 (n = 236)	>5.0 (n = 311)	*P* Value[b]
Age, mean (SD), y	49.7 (3.9)	50.1 (3.6)	50.7 (3.4)	50.1 (3.6)	49.8 (3.7)	<.01
Race and sex, No. (%)[c]						
Black women	193 (36.2)	475 (31.6)	147 (18.4)	50 (21.2)	71 (22.8)	<.01
Black men	88 (16.5)	189 (12.6)	180 (22.5)	81 (34.3)	95 (30.5)	
White women	130 (24.4)	527 (35.0)	223 (27.9)	47 (19.9)	45 (14.5)	
White men	122 (22.9)	314 (20.9)	250 (31.3)	58 (24.6)	100 (32.2)	
College education at any visit, No. (%)	306 (57.4)	931 (61.9)	405 (50.6)	89 (37.7)	105 (33.8)	<.01
Length of education, median (IQR), y	16 (14-18)	16 (14-18)	15 (12-16)	14 (13-16)	14 (12-16)	<.01
Study center, No. (%)						
Birmingham, AL	240 (45.0)	355 (23.6)	132 (16.5)	45 (19.1)	43 (13.8)	<.01
Chicago, IL	138 (25.9)	344 (22.9)	201 (25.1)	49 (20.8)	48 (15.4)	
Minneapolis, MI	101 (18.9)	347 (23.1)	264 (33.0)	72 (30.5)	113 (36.3)	
Oakland, CA	54 (10.1)	459 (30.5)	203 (25.4)	70 (29.7)	107 (34.4)	
Current marijuana use, days per month, No. (%)[d]						
No current use	533 (100)	1483 (98.5)	743 (92.9)	153 (64.8)	81 (26.0)	<.01
1-10	0	12 (0.8)	23 (2.9)	16 (6.8)	9 (2.9)	
11-29	0	10 (0.7)	34 (4.3)	64 (27.1)	159 (51.1)	
30 (every day)	0	0	0	3 (1.2)	62 (19.9)	
Cigarette smoking, No. (%)						
Never	462 (86.7)	923 (61.3)	219 (27.4)	59 (25.0)	60 (19.3)	<.01
Current	17 (3.2)	162 (10.8)	199 (24.9)	78 (33.1)	124 (39.9)	
Former	54 (10.1)	420 (27.9)	382 (47.8)	99 (41.9)	127 (40.8)	
Age started smoking among ever cigarette smokers, median (IQR), y	22 (17-32)	18 (15-21)	16 (15-19)	17 (15-20)	17 (15-21)	<.01
Pack-years during lifetime among ever cigarette smokers, median (IQR), No.[e]	2 (0-12)	5 (1-13)	9 (2-17)	9 (3-18)	10 (3-21)	<.01
Current alcohol use, No. (%)[f]						
Abstainer	362 (67.9)	682 (45.3)	310 (38.8)	84 (35.6)	92 (29.6)	<.01
Light to moderate	171 (32.1)	802 (53.3)	453 (56.6)	141 (59.7)	189 (60.8)	
Heavy	0	17 (1.1)	36 (4.5)	10 (4.2)	29 (9.3)	
Cumulative drink-years, median (IQR)[g]	8 (3-17)	14 (6-26)	21 (11-37)	24 (11-48)	35 (17-68)	<.01
Binge-drinking days, cumulative use, No. (%)[h]						
Never reported bingeing	432 (81.1)	817 (54.3)	241 (30.1)	57 (24.2)	51 (16.4)	<.01
≤250 d	64 (12.0)	431 (28.6)	260 (32.5)	67 (28.4)	85 (27.3)	
>250 d	37 (6.9)	257 (17.1)	299 (37.4)	112 (47.5)	175 (56.3)	
Current illicit drug use,[i] No. (%)						
Cocaine, crack, speed, or metamphetamine	2 (0.4)	11 (0.7)	26 (3.3)	15 (6.4)	33 (10.6)	<.01
Heroin	0	2 (0.1)	6 (0.8)	2 (0.8)	4 (1.3)	<.01
Cumulative use of cocaine, crack, speed or metamphetamine, No. (%)						
Never reported using	526 (98.7)	1000 (66.4)	202 (25.3)	46 (19.5)	47 (15.1)	<.01
1-25 d	4 (0.8)	338 (22.5)	217 (27.1)	58 (24.6)	63 (20.3)	
>25-250 d	1 (0.2)	132 (8.8)	253 (31.6)	77 (32.6)	109 (35.0)	
>250 d	2 (0.4)	35 (2.3)	128 (16.0)	55 (23.3)	92 (29.6)	
Cumulative use of heroin, No. (%)						
Never reported using	528 (99.1)	1469 (97.6)	695 (86.9)	202 (85.6)	266 (85.5)	<.01
1-25 d	5 (0.9)	29 (1.9)	63 (7.9)	19 (8.1)	21 (6.8)	
≥25 d	0	7 (0.5)	42 (5.3)	15 (6.4)	24 (7.7)	
Physical activity score, median (IQR)[j]	233 (83-409)	267 (136-485)	309 (151-529)	263 (133-475)	322 (171-520)	<.01
BMI, mean (SD)	31.5 (7.3)	30.1 (7.6)	29.8 (6.8)	30.1 (29.1)	29.5 (6.0)	<.01
Cardiovascular risk factors, mean (SD)						

(continued)

Table 1. Characteristics of 3385 Participants With Cognitive Function Test Results at the Year 25 Visit (continued)

Variable	No Marijuana Use (n = 533)	Ever Marijuana Use, y[a] <0.5 (n = 1505)	0.5-2.0 (n = 800)	2.0-5.0 (n = 236)	>5.0 (n = 311)	P Value[b]
Blood pressure, mm Hg						
Systolic	120 (17)	118 (16)	119 (16)	122 (16)	123 (16)	<.01
Diastolic	75 (12)	74 (11)	75 (11)	76 (12)	77 (11)	<.01
Cholesterol level, mg/dL						
LDL	113 (34)	112 (32)	112 (33)	109 (32)	110 (32)	.44
HDL	56 (16)	60 (18)	57 (18)	57 (20)	56 (18)	<.01
Triglycerides	109 (71)	107 (79)	123 (95)	115 (68)	129 (124)	<.01
Type 2 diabetes mellitus, No. (%)	77 (14.4)	204 (13.6)	114 (14.3)	26 (11.0)	33 (10.6)	.41
Psychological variables						
Depression, current CES-D score ≥16/30, No. (%)[k]	72 (13.5)	216 (14.4)	118 (14.8)	47 (19.9)	60 (19.3)	.03
Years of antidepressant medication use, No. (%)[l]						
Never reported using	453 (85.0)	1166 (77.5)	616 (77.0)	180 (76.3)	251 (80.7)	<.01
1-5 y	57 (10.7)	263 (17.5)	138 (17.3)	40 (16.9)	51 (16.4)	
>5 y	22 (4.1)	76 (5.0)	46 (5.8)	16 (6.8)	9 (2.9)	
Self-reported schizophrenia[m]	0	6 (0.4)	5 (0.6)	2 (0.8)	1 (0.3)	.38
Cognitive function at the year 2 visit, mirror star tracing test score,[n] median (IQR)						
No. of stars completed	4 (3-6)	4 (3-7)	4 (2-6)	4 (2-6)	4 (2-6)	<.01
No. of errors	21 (7-48)	23 (8-48)	24 (9-53)	23 (9-49)	27 (12-54)	.03

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Center for Epidemiologic Studies Depression scale; IQR, interquartile range; LDL, low density lipoprotein; HDL, high-density lipoprotein.

SI conversion factors: To convert LDL and HDL to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] Cumulative lifetime exposure to marijuana joints in terms of marijuana-years, with 1 marijuana-year of exposure equivalent to 365 days used marijuana (1 year × 365 days per year).[8,28]

[b] *P* values are from 1-way analyses of variance for age, BMI, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol, and triglyceride levels; from a χ^2 test for race and sex, college education, study center, income, and alcohol use category; and from a Kruskal-Wallis nonparametric test for pack-years, years of education, cigarettes smoked per day, drink-years, binge-drinking days, and physical activity. All *P* values are 2-tailed.

[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.[29]

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

[e] Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 year × 365 days per year × 1 pack per day × 20 cigarettes per pack).[8]

[f] Categories of alcohol consumption were based on the sex-specific weekly maximum drinking limits published by the National Institute on Alcohol Abuse and Alcoholism (for men, ≤14 [women ≤7] standard drinks per week or ≤4 [≤3] drinks per day).[30]

[g] Drink-years in those reporting ever drinking alcohol. A drink-year was defined as 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 per drink × 1 drink per day × 365 days per year = 6292.6 mL of ethanol).

[h] Binge-drinking days were defined as 5 or more drinks per episode. If bingeing were to be constant over 25 years in 1 individual, 250 binge-drinking days would correspond to 10 episodes of bingeing per year over 25 years.

[i] Current use defined as any use within the last 30 days. The number of days using the illicit drug listed over the study duration was computed using current exposure at each visit and replaced by lifetime exposure when the latter was higher. Cocaine included other forms of cocaine such as crack, powder, freebase; amphetamines included speed, uppers, and metamphetamines.

[j] Physical activity measured with the CARDIA Physical Activity History questionnaire, which queries the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.[18]

[k] Self-reported depression was measured every 5 years starting at the year 5 visit by using the CES-D.[19] A score of 16 or higher was used as the cutoff value for both sexes as an indication of clinically significant depressive symptoms.[31]

[l] Antidepressant and mood stabilizing medications recorded at each clinical visit.

[m] Self-reported schizophrenia based on self-reported mental disease, reasons for hospitalizations, and reasons for taking a psychoactive medication.

[n] Mirror star tracing test performed at the year 2 visit to test blood pressure reactivity, which tests cognitive domains similar to the Stroop test; 280 of 3385 participants (8.3%) were missing data on mirror star tracing.

use at the year 25 visit in both unadjusted (*P* < .001) and multivariable-adjusted models (*P* = .03) for the RAVLT, such that past marijuana use appeared to be less important as a predictor of verbal memory among participants who were currently using marijuana (eAppendix 2 in the Supplement). With or without exclusion of current users, lifetime exposure to marijuana was associated with reductions in all 3 measures of cognitive function (Table 2).

In fully adjusted analyses excluding current users, lifetime exposure to marijuana remained significantly associated with worse verbal memory (RAVLT), even after extensive adjustment for other factors associated with marijuana use and mirror star tracing scores at the year 2 visit (**Table 3**). The association was dose dependent, with no evidence of nonlinearity (**Figure**); each additional 5 years of exposure to marijuana was associated with 0.13 lower standardized units in the

Table 2. Association Between Cognitive Function and Exposure to Marijuana Among CARDIA Study Participants at Year 25

	Rey Auditory Verbal Learning-Test			Digit Symbol Substitution Test			Stroop Interference Test[a]		
Marijuana Exposure	No.	Raw Mean (SD)	Standardized Mean	No.	Raw Mean (SD)	Standardized Mean	No.	Raw Mean (SD)	Standardized Mean
All participants	3365	8.3 (3.7)	0.00	3370	69.9 (16)	0.00	3352	−23 (11)	0.00
Overall exposure									
Never	531	8.6 (3.2)	0.09	531	70 (16)	−0.02	528	−23 (12)	−0.07
Past	2443	8.4 (3.2)	0.03	2448	71 (16)	0.04	2436	−22 (11)	0.03
Current	391	7.2 (3.4)	−0.32	391	67 (15)	−0.21	388	−24 (12)	−0.08
P value[b]			<.001			<.001			.03
Current use (last 30 d)[c]									
None	2974	8.5 (3.2)	0.04	2979	70 (16)	0.03	2964	−23 (11)	0.01
1-10 d	226	7.5 (3.5)	−0.24	226	68 (15)	−0.15	224	−23 (11)	−0.05
11 to 29 d	100	7.3 (3.3)	−0.31	101	68 (16)	−0.13	100	−22 (10)	0.02
30 d (daily)	65	6.2 (3.4)	−0.66	64	61 (13)	−0.55	64	−27 (15)	−0.37
P value[b]			<.001			<.001			.02
Lifetime exposure, cumulative[d]									
Never used	531	8.6 (3.2)	0.09	531	70 (16)	−0.02	528	−23 (12)	−0.07
1 d to <0.5 Marijuana-years	1496	8.8 (3.2)	0.14	1498	72 (16)	0.16	1493	−22 (11)	0.06
0.5 to <2 Marijuana-years	792	8.1 (3.2)	−0.08	799	68 (16)	−0.10	791	−23 (11)	0.00
2 to <5 Marijuana-years	236	7.5 (3.3)	−0.24	233	65 (17)	−0.28	234	−23 (10)	−0.05
>5 Marijuana-years	310	6.9 (3.4)	−0.43	309	65 (15)	−0.28	306	−24 (12)	−0.12
P value[b]			<.001			<.001			.01
Lifetime exposure, cumulative, excluding current users[e]									
Never used	531	8.6 (3.2)	0.09	531	70 (16)	−0.02	528	−23 (12)	−0.07
1 d to <0.5 Marijuana-years	1474	8.8 (3.1)	0.15	1476	73 (16)	0.16	1472	−22 (11)	0.06
0.5 to <2 Marijuana-years	735	8.0 (3.2)	−0.08	742	68 (16)	−0.10	734	−23 (10)	0.02
2 to <5 Marijuana-years	153	7.5 (3.3)	−0.24	150	64 (17)	−0.35	151	−24 (11)	−0.10
>5 Marijuana-years	81	6.9 (3.2)	−0.43	80	66 (15)	−0.27	79	−25 (11)	−0.19
P value[b]			<.001			<.001			.02

Abbreviation: CARDIA, Coronary Artery Risk Development in Young Adults.

[a] The inverse of the Stroop score is used in the present analyses to allow interpretation of worse cognitive function with negative standardized scores for all 3 cognitive function tests.

[b] *P* values are from 1-way analyses of variance. All *P* values are 2-tailed.

[c] Current exposure to marijuana assessed through the question, "During the last 30 days, on how many days did you use marijuana?"

[d] Cumulative exposure to marijuana expressed in marijuana-years, with 1 marijuana-year of exposure equivalent to 365 days of marijuana use.

[e] Current marijuana users at the year 25 visit excluded (n=391).

RAVLT (95% CI, -0.24 to -0.02; $P = .02$) (Table 3). In contrast, adjusted models demonstrated no association of cumulative marijuana exposure with processing speed and executive function (Digit Symbol Substitution Test and Stroop Interference Test; Table 3). In multivariable-adjusted analyses, total number of stars completed and errors were not associated with higher marijuana use at the year 2 visit and over 25 years of follow-up (eAppendixes 1 and 2 in the Supplement). Total number of stars completed and errors were associated with cognitive function scores at the year 25 visit in both unadjusted and adjusted analyses (eAppendixes 1 and 2 in the Supplement). In exploratory analyses, the attenuation of the association between marijuana exposure and all 3 measures of cognitive function was seen mostly after adjustment for race and sex strata and educational level. Sensitivity analyses demonstrated no evidence of significant interactions by race or sex ($P > .10$ for all tests).

Our method of identifying participants with a potential diagnosis of schizophrenia through self-reported mental disease, reasons for hospitalizations, and reasons for taking psychoactive medication identified 28 participants in the entire CARDIA cohort of 5115 (0.5%). Of those, 14 of 3385 attended the year 25 visit (0.4%) compared with 14 of 1730 not attending (0.8%) ($P = .07$ for those not attending the year 25 visit). Results were virtually unchanged when including this covariate in the main multivariable-adjusted model and the inverse probability of censoring weights or excluding these participants from the main analyses. Similarly, inclusion of the predictor of antidepressant medication led to similar results.

Table 3. Association Between Cognitive Function and Cumulative Lifetime Exposure to Marijuana in Marijuana-years Among Those Without Recent Use[a]

Cumulative Lifetime Exposure in Marijuana-years[c]	Standardized Difference in Each Cognitive Function Measure (95% CI)[b]			
	Unadjusted Model	Adjusted for Age, Race, Sex, Educational Level, Study Center, and With IPCW[d]	Additionally Adjusted for Substance Use, Depression, and Cardiovascular Risk Factors[e]	Additionally Adjusted for Mirror Star Tracing Test Score at the Year 2 Visit[f]
Rey Auditory Verbal Learning Test				
Never used marijuana	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
1 d to <0.5 Marijuana-years	0.06 (−0.04 to 0.16)	−0.01 (−0.11 to 0.08)	−0.02 (−0.12 to 0.08)	−0.03 (−0.13 to 0.08)
0.5 to <2 Marijuana-years	−0.17 (−0.28 to −0.06)	−0.07 (−0.18 to 0.04)	−0.07 (−0.21 to 0.06)	−0.08 (−0.22 to 0.06)
2 to <5 Marijuana-years	−0.33 (−0.51 to −0.15)	−0.11 (−0.28 to 0.06)	−0.09 (−0.28 to 0.09)	−0.08 (−0.27 to 0.11)
>5 Marijuana-years	−0.52 (−0.75 to −0.29)	−0.27 (−0.49 to −0.05)	−0.31 (−0.54 to −0.07)	−0.25 (−0.50 to −0.01)
P value for trend	<.001	.007	.01	.04
For every 5 marijuana-years	−0.34 (−0.45 to −0.24)	−0.15 (−0.24 to −0.05)	−0.15 (−0.25 to −0.04)	−0.13 (−0.24 to −0.02)
P value	<.001	.002	.005	.02
Digit Symbol Substitution Test				
Never used marijuana	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
1 d to <0.5 Marijuana-years	0.17 (0.07 to 0.27)	0.03 (−0.06 to 0.12)	0.06 (−0.04 to 0.16)	0.06 (−0.04 to 0.16)
0.5 to <2 Marijuana-years	−0.08 (−0.19 to 0.03)	−0.03 (−0.13 to 0.07)	0.07 (−0.06 to 0.19)	0.05 (−0.08 to 0.18)
2 to <5 Marijuana-years	−0.33 (−0.51 to −0.16)	−0.12 (−0.28 to 0.04)	−0.03 (−0.21 to 0.15)	−0.02 (−0.20 to 0.17)
>5 Marijuana-years	−0.25 (−0.48 to −0.02)	−0.04 (−0.24 to 0.15)	0.12 (−0.08 to 0.33)	0.13 (−0.09 to 0.34)
P value for trend	<.001	.26	.57	.45
For every 5 marijuana-years	−0.31 (−0.41 to −0.20)	−0.08 (−0.17 to 0.01)	−0.01 (−0.10 to 0.08)	−0.03 (−0.12 to 0.07)
P value	<.001	.08	.77	.56
Stroop Interference Test[g]				
Never used marijuana	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
1 d to <0.5 Marijuana-years	0.12 (0.02 to 0.22)	0.06 (−0.05 to 0.17)	0.05 (−0.06 to 0.17)	0.05 (−0.07 to 0.17)
0.5 to <2 Marijuana-years	0.09 (−0.02 to 0.20)	0.10 (−0.02 to 0.23)	0.13 (−0.04 to 0.29)	0.11 (−0.06 to 0.27)
2 to <5 Marijuana-years	−0.03 (−0.21 to 0.15)	0.10 (−0.09 to 0.29)	0.08 (−0.13 to 0.29)	0.10 (−0.11 to 0.31)
>5 Marijuana-years	−0.12 (−0.36 to 0.11)	−0.08 (−0.32 to 0.17)	−0.02 (−0.30 to 0.24)	−0.09 (−0.37 to 0.20)
P value for trend	.12	.71	.92	.71
For every 5 marijuana-years	−0.09 (−0.20 to 0.01)	−0.02 (−0.12 to 0.09)	−0.01 (−0.13 to 0.10)	−0.04 (−0.16 to 0.08)
P value	.08	.80	.80	.51

Abbreviation: IPCW, inverse probability of censoring weight.

[a] Cumulative exposure to marijuana expressed in marijuana-years, with 1 marijuana-year of exposure equivalent to 365 days of marijuana use. Current marijuana users within the 30 days prior of the year 25 visit excluded (n=392).

[b] Cumulative exposure to marijuana use. Negative standardized scores indicate worse cognitive function.

[c] Years of marijuana exposure was modeled first as a 5-level categorical predictor and then as a continuous linear predictor, per 5 marijuana-years (separate models).

[d] Adjusted for age, race/ethnicity, sex, study site, and years of education. Analyses weighted by the inverse probability of censoring to address potential bias by informative censoring.

[e] Additionally adjusted for cumulative and current exposure to licit and illicit substances and other covariates.

[f] Additionally adjusted for total number of stars completed and errors made drawing the stars. Participants with missing data on mirror star tracing test excluded (n=280).

[g] The inverse of the Stroop score was used in the present analyses to allow interpretation of worse cognitive function with negative standardized scores for all 3 cognitive function tests.

Discussion

In this large community-based cohort of white and black young adults followed up over 25 years, we found a dose-dependent independent association between cumulative lifetime exposure to marijuana and worsening verbal memory in middle age. For each additional 5 marijuana-years of exposure (1825 days of use), verbal memory was 0.13 standardized units lower after full adjustment than for those who had never used marijuana, corresponding to a mean of 1 of 2 participants remembering 1 word fewer from a list of 15 words for every 5 years of use. We found no significant associations of cumulative exposure with executive function or processing speed.

Our findings are consistent with those of previous studies demonstrating associations between heavy exposure to marijuana and cognitive function, but, to our knowledge, the association with lower levels of marijuana exposure has not previously been demonstrated.[3-5,32,33] In one study, for example, the association with verbal memory was apparent only among those with heavy long-term use of marijuana (n=51),[4] defined as use of marijuana every day or nearly every day for more than 20 years (23.9 years of use), compared with more recent use (10.2 years of use; n=51) or nonusers (n=33). In an-

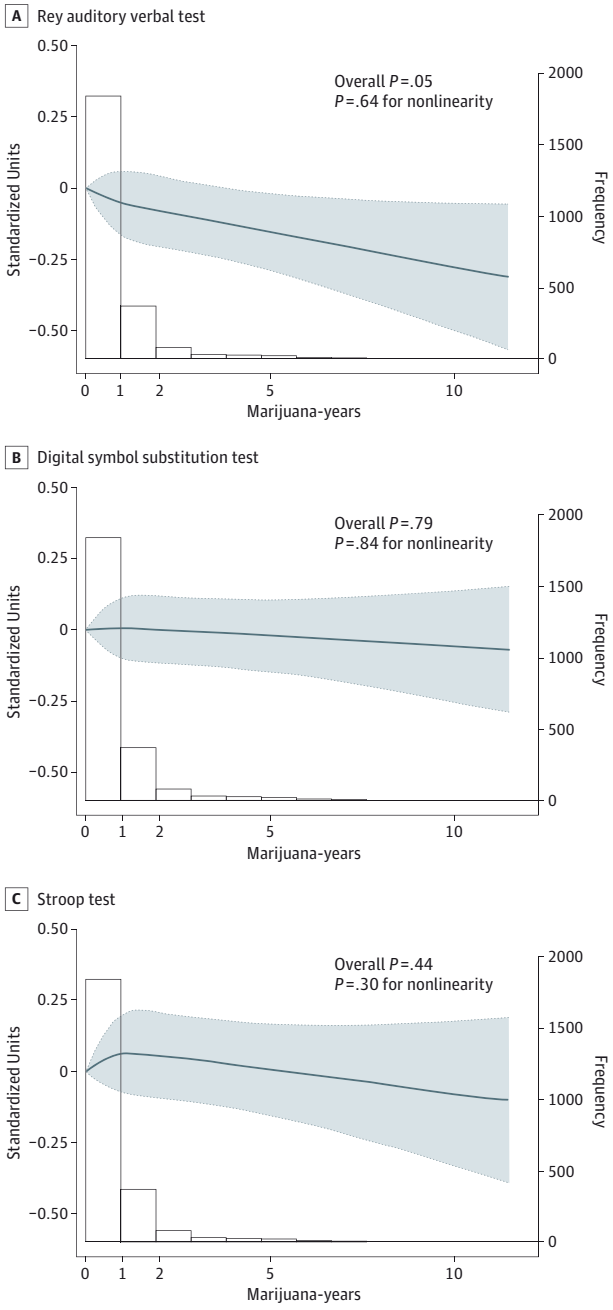
other study, investigators used 38 years of follow-up data from 1037 participants in a birth cohort in New Zealand and found that persistent regular cannabis use (4 days per week or more) was associated with neuropsychological decline, while those who reported nonregular use (508 [50.6%] of the total) showed no decline in IQ or neuropsychological performance.[5] Similarly, a longitudinal study with 10 years of follow-up found evidence of cognitive decline with heavy marijuana use,[33] but those who stopped using marijuana during follow-up did not show a decline in IQ score. In contrast, with more detailed measurement of lifetime marijuana exposure in a larger sample, we were able to detect a negative association at lower levels of cumulative use and among persons with remote past exposure to marijuana.

The extent of association between worse verbal memory and cumulative marijuana use is of uncertain clinical significance. In the context of cognitive decline after stroke, Levine et al[34] used a 0.5-SD cutoff for defining a clinically meaningful decline in global cognition. The point estimate for verbal memory in our study for those with 5 marijuana-years of exposure (0.13 standardized units; 95% CI, −0.24 to −0.02) is of lesser magnitude than the decline found in the study by Levine et al and the confidence interval excludes the 0.5-SD cutoff. However, participants with up to 10 marijuana-years of exposure might have a significant decline in verbal memory given the lower bound of the 95% CI. Similarly, participants with current daily marijuana use in the month before the year 25 visit might have a clinically significant decrease in verbal memory and other measures of cognitive function (eAppendix 2 in the Supplement).

The mechanism by which marijuana exposure might affect verbal memory is unclear but might be explained by the potential effect of tetrahydrocannabinol on the way in which information is processed in the hippocampus.[35] Marijuana use has been associated with functional changes in the activation of brain regions involved in associative learning,[36] particularly in the parahippocampal regions and the dorsolateral prefrontal cortex.[36-38] Some have found suggestions of lower hippocampal and amygdala volumes in those with heavy, long-term use of marijuana (>5 joints daily for >10 years),[39] as well as alterations in the cerebellum, frontal cortex,[36] and medial temporal cortex,[38] although other researchers were unable to confirm these findings.[35,40] Numerous issues related to the methods, such as variation in imaging techniques and in measurement of exposures, dose-threshold effects, and small sample sizes, limit the possibility for drawing significant conclusions on the published findings.[36,38]

Our study has limitations. We constructed a marijuana exposure measurement from self-reported information collected prospectively and periodically over 25 years, but self-report is not always reliable,[41] measurements were infrequent, and age of exposure, especially during adolescence and young adulthood, was not queried. However, even if imprecise, the repeated question over the 25 years was prospectively obtained and allowed us to demonstrate a potential deleterious association, one that is not easily studied without a large, well-characterized cohort with long-term follow-up, such as the CARDIA study. Another limitation is the availability of

Figure. Associations Between Lifetime Exposure to Marijuana and Cognitive Function



Years of marijuana use modeled flexibly and current marijuana users at the year 25 visit excluded (n = 392). Results are adjusted for age, race/ethnicity, sex, study site, educational level, cigarette smoking, alcohol use, illicit drug use, cardiovascular risk factors, depression, mirror star tracing test score at the year 2 visit, and differential likelihood of follow-up (see the Methods section). All test results are standardized, such that a 1-U negative deviation indicates 1-SD worse cognitive function than the mean. Histograms describe the distribution of marijuana-years in participants in the Coronary Artery Risk Development in Young Adults study with any exposure to marijuana by presenting the frequency of participants in each considered interval. The inverse of the Stroop score is used in the present analyses to allow interpretation of worse cognitive function with negative standardized scores for all 3 cognitive function tests. DSST indicates Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test.

cognitive function measurements at only 1 time point, which limits our ability to pinpoint when a change in the outcome might have occurred and associate it in time with a change in exposure. We found no significant change in the measure of association between cumulative marijuana exposure and measures of cognitive function after inclusion of the mirror star tracing tests score measured early in life (year 2 visit). Even with this adjustment, we cannot rule out reverse causation as an explanation for our results.[5] While some have suggested that the mirror star tracing test measures aspects of executive function,[22,24] to our knowledge, no study has compared the cognitive function domains measured in the mirror star tracing test and those measured in the other tests used at the year 25 visit. Factors significantly associated with marijuana use could confound the association between marijuana and cognitive function. The New Zealand study, for example, has been criticized for lack of adequate control of socioeconomic status,[42] even though additional analyses have shown that controlling for socioeconomic status did not attenuate the association between sustained daily marijuana use and worse IQ.[43] In our study, the observed associations were substantially attenuated by control for core demographic variables, including educational level, race, and sex. However, adjustment for a host of additional behavioral, psychosocial, and cardiovascular risk factors available, including self-reported schizophrenia and psychoactive medication, did not further attenuate the estimates.

Conclusions

We found past exposure to marijuana use to be significantly associated with worse verbal memory in middle age. Future studies with multiple assessments of cognition, brain imaging, and other functional outcomes should further explore these associations and their potential clinical and public health implications. In the meantime, with recent changes in legislation and the potential for increasing marijuana use in the United States,[44] continuing to warn potential users about the possible harm from exposure to marijuana seems reasonable.[45]

ARTICLE INFORMATION

Accepted for Publication: November 26, 2015.

Published Online: February 1, 2016. doi:10.1001/jamainternmed.2015.7841.

Author Affiliations: Department of Epidemiology and Biostatistics, University of California–San Francisco (Auer, Vittinghoff, Yaffe, Glymour, Pletcher); Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Auer, Künzi); Department of Psychiatry and Neurology, University of California–San Francisco (Yaffe); Center for Surgical Medical and Acute Care Research, Birmingham Veterans Affairs Medical Center, Birmingham, Alabama (Kertesz); Department of Medicine, University of Alabama at Birmingham School of Medicine (Kertesz); Department of Internal Medicine, University of Michigan Medical School, Ann Arbor (Levine); Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan (Levine); Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor (Levine); Department of Neurology and Stroke Program, University of Michigan, Ann Arbor (Levine); Department of Psychiatry, University of Geneva, Geneva, Switzerland (Albanese); Kaiser Permanente Division of Research, Oakland, California (Whitmer, Sidney); Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis (Jacobs).

Author Contributions: Dr Auer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Auer, Künzi, Whitmer, Jacobs, Sidney, Pletcher.
Acquisition, analysis, or interpretation of data: Auer, Vittinghoff, Yaffe, Kertesz, Levine, Albanese, Jacobs, Glymour, Pletcher.
Drafting of the manuscript: Auer.
Critical revision of the manuscript for important intellectual content: Vittinghoff, Yaffe, Künzi, Kertesz, Levine, Albanese, Whitmer, Jacobs, Sidney, Glymour, Pletcher.
Statistical analysis: Auer, Vittinghoff, Künzi, Albanese, Jacobs, Glymour.
Obtained funding: Yaffe, Jacobs, Sidney.
Administrative, technical, or material support: Yaffe, Levine.
Study supervision: Whitmer, Pletcher.

Conflict of Interest Disclosures: None reported.

Funding/Support: The Coronary Artery Risk Development in Young Adults (CARDIA) study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (grants HHSN268201300025C and HHSN268201300026C), Northwestern University (grant HHSN268201300027C), University of Minnesota (grant HHSN268201300028C), Kaiser Foundation Research Institute (grant HHSN268201300029C), and The Johns Hopkins University School of Medicine (grant HHSN268200900041C). The CARDIA study is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between the NIA and the NHLBI (AG0005).

Role of the Funder/Sponsors: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript. Before submission for publication, the manuscript was reviewed and approved by the CARDIA Publications and Presentations committee.

REFERENCES

1. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future: national results on drug use: 2012 overview: key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan. http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2012.pdf. Published February 2013. Accessed March 21, 2013.

2. Solowij N. *Cannabis and Cognitive Functioning*. New York, NY: Cambridge University Press; 1998.

3. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc*. 2003;9(5):679-689.

4. Solowij N, Stephens RS, Roffman RA, et al; Marijuana Treatment Project Research Group. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287(9):1123-1131.

5. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012;109(40):E2657-E2664.

6. Gonzalez R, Martin EM, Grant I. Marijuana. In: Kalechstein A, van Gorp WG, eds. *Neuropsychology and Substance Use: State-of-the-Art and Future Directions*. New York, NY: Taylor & Francis; 2007:139-170.

7. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41(11):1105-1116.

8. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173-181.

9. Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol*. 2013;73(2):170-179.

10. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test: Adult Version Manual*. San Antonio, TX: The Psychological Corporation; 1987.

11. Wechsler D. *Administration and Scoring Manual for the Wechsler Adult Intelligence Scale–III*. London, England: Psychological Corporation; 2008.

12. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull*. 1991;109(2):163-203.

13. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.

14. Auer R, Vittinghoff E, Kiefe C, et al. Change in physical activity after smoking cessation: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Addiction*. 2014;109(7):1172-1183.

15. Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB. Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Epidemiol*. 2005;161(5):423-433.

16. Kertesz SG, Khodneva Y, Richman J, et al. Trajectories of drug use and mortality outcomes among adults followed over 18 years. *J Gen Intern Med*. 2012;27(7):808-816.

17. Kertesz SG, Pletcher MJ, Safford M, et al. Illicit drug use in young adults and subsequent decline in general health: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Drug Alcohol Depend*. 2007;88(2-3):224-233.

18. Jacobs DR Jr, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of short physical activity history: CARDIA and the Minnesota Heart Health Program. *J Cardiopulm Rehabil Prev*. 1989;9(11):448-459.

19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306.

20. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation*. 2014;129(15):1560-1567.

21. Kasprowicz AL, Manuck SB, Malkoff SB, Krantz DS. Individual differences in behaviorally evoked cardiovascular response: temporal stability and hemodynamic patterning. *Psychophysiology*. 1990;27(6):605-619.

22. Zhu N, Jacobs DR, Meyer KA, et al. Cognitive function in a middle aged cohort is related to higher quality dietary pattern 5 and 25 years earlier: the CARDIA study. *J Nutr Health Aging*. 2015;19(1):33-38.

23. Waldstein SR, Bachen EA, Manuck SB. Active coping and cardiovascular reactivity: a multiplicity of influences. *Psychosom Med*. 1997;59(6):620-625.

24. Gardner RM. The reverse affect test: a new interference task. *Percept Mot Skills*. 1985;60(2):384-386.

25. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561-570.

26. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychol Med*. 2012;42(6):1321-1328.

27. McLoughlin BC, Pushpa-Rajah JA, Gillies D, et al. Cannabis and schizophrenia. *Cochrane Database Syst Rev*. 2014;10:CD004837.

28. Hancox RJ, Poulton R, Ely M, et al. Effects of cannabis on lung function: a population-based cohort study. *Eur Respir J*. 2010;35(1):42-47.

29. Bild DE, Jacobs DR Jr, Sidney S, Haskell WL, Anderssen N, Oberman A. Physical activity in young black and white women: the CARDIA study. *Ann Epidemiol*. 1993;3(6):636-644.

30. National Institute on Alcohol Abuse and Alcoholism. *Helping patients who drink too much: a clinician's guide*. http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm. Updated 2005. Accessed September 25, 2013.

31. Radloff LS, Locke BZ. The community mental health assessment survey and the CES-D scale. In: Weissman MM, Myers JK, Ross CE, eds. *Community Surveys of Psychiatric Disorders*. New Brunswick, NJ: Rutgers University Press; 1986:177-189.

32. Pope HG Jr, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 1996;275(7):521-527.

33. Fried P, Watkinson B, James D, Gray R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. *CMAJ*. 2002;166(7):887-891.

34. Levine DA, Galecki AT, Langa KM, et al. Trajectory of cognitive decline after incident stroke. *JAMA*. 2015;314(1):41-51.

35. Jager G, Ramsey NF. Long-term consequences of adolescent cannabis exposure on the development of cognition, brain structure and function: an overview of animal and human research. *Curr Drug Abuse Rev*. 2008;1(2):114-123.

36. Batalla A, Bhattacharyya S, Yücel M, et al. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. *PLoS One*. 2013;8(2):e55821.

37. Jager G, Van Hell HH, De Win MM, et al. Effects of frequent cannabis use on hippocampal activity during an associative memory task. *Eur Neuropsychopharmacol*. 2007;17(4):289-297.

38. Lorenzetti V, Solowij N, Fornito A, Lubman DI, Yucel M. The association between regular cannabis exposure and alterations of human brain morphology: an updated review of the literature. *Curr Pharm Des*. 2014;20(13):2138-2167.

39. Yücel M, Solowij N, Respondek C, et al. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry*. 2008;65(6):694-701.

40. Tzilos GK, Cintron CB, Wood JB, et al. Lack of hippocampal volume change in long-term heavy cannabis users. *Am J Addict*. 2005;14(1):64-72.

41. van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction*. 2013;108(10):1801-1808.

42. Rogeberg O. Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. *Proc Natl Acad Sci U S A*. 2013;110(11):4251-4254.

43. Moffitt TE, Meier MH, Caspi A, Poulton R. Reply to Rogeberg and Daly: no evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline. *Proc Natl Acad Sci U S A*. 2013;110(11):E980-E982.

44. Pacula RL, Sevigny EL. Natural experiments in a complex and dynamic environment: the need for a measured assessment of the evidence. *J Policy Anal Manage*. 2014;33(1):232-235.

45. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.