Data supplement for Meier et al., Long-Term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife, Am J Psychiatry (doi: 10.1176/appi.ajp.2021.21060664)

Table S1. Observational studies of the cognitive and brain health of midlife or older adult cannabis users. Studies were included if the mean age of cannabis users in the sample was 38 years or older. Studies are organized by study design (longitudinal vs. cross-sectional) and date.						
Study	Design	Analysis Sample	Exposure	Outcome	Covariates	Finding
*Auer et al., 2016[1]	Population-based longitudinal study (the Coronary Artery Risk Development in Young Adults Study) of N=5,115 US adults recruited in 1985-86 at age 18-30 years and assessed at baseline and 2, 5, 7, 10, 15, 20, and 25 years later.	N=3,365 had cognitive data at the 25-year assessment. Mean age at 25-year assessment = 50.2 years.	Self-reported past 30-day cannabis use and number of lifetime uses at each assessment were used to estimate cannabis-years, with 1 year=365 days of use. After excluding N=392 current cannabis users: N=531 never used; N=1,474 used 1 to <0.5 cannabis-years; N=735 used 0.5 to <2 cannabis-years; N=153 used 2 to <5 cannabis-years; N=81 used >5 cannabis-years.	At 25-year assessment: Rey Auditory Verbal Learning delayed recall score (memory); Digit Symbol Substitution Test (processing speed); Stroop Interference Test interference score (executive function).	Age, race/ethnicity, sex, educational level, study center, substance use, depression, cardiovascular risk factors, mirror star test performance (executive function) at year 2 assessment.	In covariate-adjusted analyses that excluded current cannabis years, lifetime cannabis use was associated with poorer memory but not poorer processing speed or executive function.
McKetin et al., 2016[2]	Longitudinal cohort study (Personality and Total Health) of 2,530 Australians ages 40-46 years recruited in 2000-01 from the electoral roll and followed-up 4 and 8 years later.	N=1,897 after exclusions for head injury, stroke or transient ischemic attack, epilepsy, English as a second language, psychostimulant use, and missing data on cannabis at	Self-reported past-year cannabis use (no use, <weekly use, weekly or more frequent use) at each wave. Ten percent of the sample (N=576)	Tests administered at each assessment: California Verbal Learning Test (immediate and delayed memory);	Time invariant covariates assessed at wave 1: age, sex, years of education, heaviest past drinking. Time-varying covariates	In unadjusted analyses, cannabis use was associated with worse immediate and delayed recall across all waves but was not associated with processing speed, working memory, or reaction time. In covariate-adjusted

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		all three waves. Approximate age ranges at each wave were 40-46, 44-50, and 48-54.	had used cannabis at any wave, and 2% (N=106) had used cannabis weekly or more frequently.	Symbol Digit Modalities Test (processing speed); Digit Symbols Backwards (working memory); simple and choice reaction time tasks.	assessed at every wave: tobacco smoking, alcohol use; body mass index; depression; Spot the Word score (estimated premorbid verbal ability).	analyses, there was evidence of between-person associations between cannabis use and immediate recall (weekly or more frequent cannabis users had worse immediate recall than non-users), but there was no evidence of within-person associations (when a person's cannabis use increased relative to their typical use, their cognitive test performance was unchanged). Further, there was no evidence that cannabis users showed accelerated decline on any cognitive test.
*Meier et al., 2012[3]	Longitudinal study (Dunedin Multidisciplinary Health and Development Study) of 1,037 babies born in Dunedin, New Zealand and followed up at ages 3,7,9,11,13,15,18, 21, 26, 32, and 38 years.	Of the 1,004 living study members at age 38 years, 964 (96%) participated in the age-38 assessment, and 874 study members with childhood IQ and adulthood IQ data were included in analyses.	Persistence of cannabis dependence following the criteria of the Diagnostic and Statistical Manual of Mental Disorders. Cannabis	Change in intelligence quotient (IQ) from childhood to age 38 years; age-38 tests of executive functions, memory, learning, processing	Sex, childhood IQ, past 24-hour cannabis use, persistent substance dependence (the number of study waves for which study members diagnosed with tobacco, hard-	In adjusted and unadjusted analyses, study members with more persistent cannabis dependence showed greater IQ decline, and IQ decline was concentrated among adolescent-onset (before age 18) persistent cannabis users. Dose-response

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			exposure was defined as the total number of study waves out of five (ages 18, 21, 26, 32, 38) at which a study member met criteria for cannabis dependence. Study members were grouped according to their number of dependence diagnoses: (i) those who never used cannabis at any study wave and thus could not have become dependent, (ii) those who used cannabis at least once at one or more study waves but never diagnosed, (iii) those who diagnosed at one wave, (iv) those who diagnosed	speed, perceptual reasoning, and verbal comprehension; age-38 informant reports of attention and memory problems.	drug, or alcohol dependence), and schizophrenia.	associations were also observed between persistence of cannabis dependence and age-38 performance on tests of executive functions, memory, learning, processing speed, perceptual reasoning, and verbal comprehension, after adjusting for childhood IQ, as well as age-38 informant-reported attention and memory problems. IQ decline was apparent in the subset of adolescent-onset persistent cannabis users who had quit or reduced their use by age 38.

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			at two waves, and (v) those who diagnosed at three or more waves.			
Dregan & Gulliford et al., 2012[4]	Longitudinal study (National Child Development Study) of 17,415 people born in the United Kingdom in March of 1958 and followed up at ages 7, 11, 16, 23, 33, 42, 46, and 50 years.	Of the N=11,419 taking part in the study at age 42 years (75% of eligible target population), the analytic sample included N=8,992 participants who reported on illicit drug use at age 42 years (1999-2000) and took part in the survey at age 50 years (2008-09).	Self-reported current or past cannabis use at age 42 years. Exposures were ever use and past-year use.	Cognitive outcomes were assessed at age 50. Immediate and delayed memory were assessed with a verbal memory task, and scores on these tasks were combined into a single memory index. Executive function was assessed with an animal naming task, a letter cancellation task, and a random letter task, and scores on these tasks were	Sex, race/ethnicity, social class, highest educational level, partnership status, tobacco smoking status, alcohol use, exercise, body mass index, depression, low self-efficacy, life dissatisfaction, poor physical health, long-standing illness. All covariates except life dissatisfaction were categorical.	Current cannabis use at age 42 was not associated with cognitive test performance at age 50, but past cannabis use was associated with better memory, executive functioning, and overall cognitive functioning, after adjusting for covariates.

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				combined into a single executive function index. Overall cognitive functioning was derived by combining the memory index and executive function index.		
Thayer et al., 2019[5]	Cross-sectional, case-control study of older adult current cannabis users who used at least weekly in the past year and never users. Participants were recruited from the Boulder-Denver metro area in Colorado.	N=28 users (mean age =69.8) and N=28 non-users (mean age 66.8 years) for MRI outcomes. N=28 users and N=10 non-users for cognitive outcomes. Cannabis users were heterogenous with regard to history of regular use (mean =23.6, SD=19.89 years of regular cannabis use). Most cannabis users did not meet criteria for cannabis use disorder (mean=0.79,	Cannabis users vs. non-users.	Overall brain structure and cortical and subcortical gray matter. NIH Toolbox Cognition Battery: 7 tests assessing attention, episodic memory, working memory, vocabulary knowledge, oral reading skill, executive function, and processing	Age; depression symptoms; intracranial volume; and alcohol use were included as covariates in some analyses. (Groups were not different on intracranial volume, sex, years of education, alcohol use, or anxiety symptoms).	Users and non-users did not differ in total volume of CSF, gray matter, or white matter in voxel-based (VBM) or surface-based morphometry (SBM). In subcortical regions (brainstem, accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus), a few differences between users and non-users emerged in VBM, even after adjusting for age and depression differences (i.e., users showed greater VBM volume in left putamen,

Study	Design	Analysis Sample	Exposure	Outcome	Covariates	Finding
		SD=1.17 cannabis dependence symptoms). Exclusion criteria: >20 tobacco pack-years; uncontrolled diabetes, or insulin use; uncontrolled hypertension; history of antipsychotic medication use or serious mental illness; history of alcohol or other substance use disorder other than cannabis use disorder; magnetic resonance imaging (MRI) contraindications.		speed; and total composite score.		and in right putamen and left pallidum, though only associations for left putamen survived FDR correction, and were generally were not observed in SBM). In terms of whole brain, users and non-users did not differ in VBM after FDR correction. In SBM, users showed greater cortical volume in left lingual cortex and rostral middle frontal cortex, but group differences in cortical thickness were not apparent after FDR correction. Groups did not differ on cognitive test performance. Cognitive test scores were not statistically significantly correlated with volumes for left putamen, lingual cortex, or rostral middle cortex.
Burggren et al, 2018[6]	Cross-sectional case-control study of older adults with a history of early life cannabis use	N=24 former heavy cannabis users (mean age=65.4; SD=7.2) and N=26	Former cannabis users vs. never users.	Composite scores for tests of memory	Sex, age, estimated premorbid intellectual	There were no statistically significant differences between former cannabis users

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	and older adult comparison individuals who never used cannabis or any other illicit substance. Participants were recruited from the community in Los Angeles, California.	non-users (mean age=67.7, SD=7.1). Users had an average age of onset of cannabis use of 17.7 years (SD=4.2); lifetime cannabis use of 11.3 years (SD=13.0); and length of abstinence of 29.9 (SD=6.0) years. Exclusion criteria: history of neurological or psychiatric disorder, engagement in psychological treatment in previous 6 months, current/past psychotic disorder; history of uncontrolled hypertension or cardiovascular disease, head trauma, other major systemic disease affecting brain function, use of medications that could affect		encoding, delayed memory, processing speed, and executive function. MRI to assess cortical thickness of hippocampal subregions: CA1, CA2, CA3, dentate gyrus, subiculum, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and fusiform gyrus.	functioning, cigarette use, alcohol use, education, total intracranial volume.	and comparison individuals on any composite cognitive measure. Former cannabis users showed thinner cortex in subfields CA1; combined CA2, CA3, and dentate gyrus; and thinner hippocampus averaged across all subregions. Composite cognitive measures were not associated with cortical thickness in any subregion.

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		psychometric testing.				
Lyons et al., 2004[7]	Discordant twin study. Fifty-four male monozygotic twin pairs discordant for regular cannabis use selected from the Vietnam Era Twin Registry – a study of male-male twin pairs born between 1939-1957 in which both members served in the military during the Vietnam War era.	N=54 male twin pairs discordant for regular (i.e., weekly) cannabis use (mean age at time of cognitive testing=46.3 [SD=3.1]).Selection criteria: one twin used cannabis at least weekly for 1 year, while the co-twin never used more than 5 times; the cannabis-using twin did not use cannabis at least 1 month prior to telephone interview; neither twin used any other illicit drug on a weekly or greater basis; neither twin had ever experienced alcohol withdrawal. Several twin pairs were excluded because one twin had used cannabis within the preceding 12 months, one twin	Twins discordant for history of regular (i.e., weekly) cannabis use, with no use in the past year.	General intelligence, executive functioning, attention, memory, and motor function were assessed in 1995-96.	None.	Across cognitive domains, cannabis users performed statistically significantly ($p<.05$) worse than their non-using co-twin in terms of general intelligence and performed worse on the block design subtest of the test of general intelligence, the long-delay free recall, and non-dominant hand Finger Tapping. Total days of cannabis use was generally not related to cognitive test performance.

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		had experienced a stroke, and one twin had AIDS and a history of psychosis. The mean number of days of cannabis use was 916 (SD=1201). The mean duration of regular cannabis use was 5.8 years (SD-5.3). The mean age of last regular cannabis use was 27.1 (SD=6.0).				
Pope et al., 2003[8]	Case-control study of long-term cannabis users and comparison individuals ages 30-55 assessed between calendar years 1997-2001. Participants were recruited in Belmont, Massachusetts.	69 early-onset cannabis users (mean age=36); 53 late-onset users (mean age=44); 87 comparison individuals (mean age=40). Early-onset was defined as cannabis use before age 17. Exclusion criteria: use of any other illicit drug more than 100 times; lifetime alcohol dependence; current use of psychotropic medication; history	Three groups of participants were recruited: current users, former users, and comparison individuals. Current users: current daily users who had smoked cannabis at least 5000 times; former users=cannabis users who had smoked at least 5000 times but who had smoked fewer than 12	Participants underwent neuropsychological testing after a 28-day period of monitored abstinence from cannabis. Ten neuropsychological tests assessed verbal and visuospatial memory, attention, and executive functions.	Age, sex, ethnicity, and family of origin attributes (education, income, family history of psychiatric disorder). Some analyses additionally included estimated premorbid verbal IQ, lifetime duration of cannabis use,	In covariate adjusted and p-value corrected analyses, late-onset users did not differ from comparison individuals on any of the ten cognitive tests, but early-onset users performed worse than comparison individuals on tests of verbal IQ, verbal memory, and verbal fluency. After additionally adjusting for verbal IQ, there were no differences between early-onset cannabis users and

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		of head injury with loss of consciousness; medical or neurological condition that might affect cognitive function; current psychiatric disorder other than social or simple phobia.	times in the past 3 months; comparison individuals who had tried cannabis but had used no more than 50 times in their lives and no more than once in the past year. For analyses, cannabis users were pooled and subdivided based on age of onset (before age 17 vs. age 17+).	Participants also completed a test of verbal IQ prior to the 28-day abstinence period.	and measures of attention deficit hyperactivity disorder and conduct disorder as covariates.	comparison individuals.
Solowij et al., 2002[9]	Case-control study of cannabis users seeking cannabis treatment and non-users conducted from 1997-2000 in the United States.	Long-term cannabis users (N=51; mean age = 42.1, SD=5.2); shorter-term cannabis users (n=51; mean age=28.7, SD=5.5); non-users (n=33, mean age=34.8, SD=11.1). Exclusion criteria were serious illness or injury that might have affected the brain, any psychotic disorder, dependence on any	Long-term cannabis users used for a median of 27.4 days in the past month at study entry, and an average of 23.9 years (SD=4.1). Shorter-term cannabis users used for a median of 28.3 days in the past month at study entry, and for an average of 10.2	Participants were asked to abstain from cannabis for 12 hours before cognitive testing. Nine tests assessed premorbid IQ, speed of verbal information processing, verbal learning and memory,	Premorbid IQ and age were included as covariates when correlated with test performance. Analysis of covariance was repeated on a subsample of pure cannabis users with no history of other drug use or recent cannabis	Long-term cannabis users performed worse than shorter-term cannabis users and non-users on tests of verbal learning and memory and on a test of attention/working memory. Shorter-term users did not differ from non-users except on a time estimation task. Results were generally similar in analyses limited to the subsample of pure cannabis users and the

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		other drug or alcohol, and poor command of English language.	years (SD=3.8). Nearly all cannabis users (98%) met criteria for cannabis dependence.	attention, inhibition, working memory, cognitive flexibility, problem solving.	use prior to cognitive testing. (Tobacco and alcohol use were minimal, and 93% of the sample used other drugs less than once a month or not at all.)	subsample with no recent use. Duration of cannabis use was associated with performance on a number of tests.
Pope et al., 2001[10]	Case-control study of long-term cannabis users and comparison individuals ages 30-55. Participants were recruited in Belmont, Massachusetts.	63 current cannabis users (mean age=36); 45 former cannabis users (mean age=41); 72 comparison individuals (mean age=39.5). Exclusion criteria were: use of any other illicit drugs more than 100 times; history of alcohol abuse or dependence; history of psychiatric disorder other than simple or social phobia; history of head injury with loss of consciousness requiring	Current users: current daily users who had smoked cannabis at least 5000 times; former users=cannabis users who had smoked at least 5000 times but who had smoked fewer than 12 times in the past 3 months; comparison individuals=individuals who had tried cannabis but had used no more than 50 times in their lives and no	Cognitive tests were administered at days 0, 1, 7, and 28 of monitored cannabis abstinence. At day 0: vocabulary subtest of Wechsler Adult Intelligence Scale-Revised. At days 0, 1, 7, and 28: computerized continuous performance test, auditory continuous	Sex, age, ethnicity, parents' education, parents' household income, family history of psychiatric disorder. Some analyses additionally included estimated premorbid verbal IQ and measures of attention deficit hyperactivity disorder and conduct	Of the 4 cognitive tests administered at each of the four assessment days, there were no differences between current users and comparison individuals on the two continuous performance tests on any of the four assessment days, but current users performed worse than comparison individuals on memory tests at days 0, 1, and 7 and generally not at day 28. In contrast, former users did not differ from comparison individuals on any of the four tests at any of the four days. On tests administered at day 28,

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		hospitalization; current use of psychoactive medication; medical, psychiatric or neurological condition that might affect cognitive function.	more than once in the past year.	performance test, verbal learning and memory. On days 0, 7, 28: visuospatial memory. On day 28: 6 additional measures of attention and executive function and verbal and visuospatial memory.	disorder as covariates.	there were no differences between current users and comparison individuals and no differences between former users and comparison individuals. In addition, baseline THCCOOH-creatinine ratios for current users were associated with poorer learning and memory test performance at day 1, even after adjustment for verbal IQ.
Fletcher et al. 1996[11]	Study of two cohorts of long-term cannabis users and non-users in Costa Rica. One cohort was recruited in 1973 and the other was recruited in 1990.	For the older cohort: Users were initially eligible in 1973 if they used cannabis 3 times weekly for 10 years. Users were matched to non-users on age, sex, occupation, education, marital status, and alcohol and tobacco use. Exclusion criteria were history or evidence of psychiatric or neurological	Comparison of cannabis users vs. non-users. At the time of cognitive testing, the older cohort had used cannabis for an average of 34 years, with a median of 5.2 cannabis cigarettes per day, 2-7 times weekly. The younger cohort had used cannabis for an	Participants were asked to abstain from cannabis for 72 hours prior to the cognitive assessment. Four memory tests: selective reminding task, free recall paradigm, sorting task to assess free recall and	None.	Older cannabis users encoded words at a slower rate and recalled words at a slower rate than older non-users. Older cannabis users performed worse than older non-users on measures of selective and divided attention. No differences were observed between younger cannabis users and non-users.

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		disorders or a history of habitual use of drugs other than cannabis or alcohol; history of treatment for alcohol abuse, evidence of alcohol dementia or delirium tremens. Of the original 1973 cohort (41 non-users and 41 users), 30 non-users and 17 users were included in the analytic sample. They did not differ from the original cohort in terms of medical status, alcohol and tobacco use, chronicity of cannabis use, and sociocultural variables. For the younger cohort: Users were eligible if they used cannabis at least twice weekly for 5 years but no longer than 12 years. The younger cohort included 37	average of 8 years, with a median of 3.8 cannabis cigarettes per day, 2-7 times weekly.	control processes in short-term memory, episodic memory. Eight attention tasks evaluated preparedness, selection, and allocation components of attention.		

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		cannabis users and 49 non-users.				
Note. Studies with an asterisk are considered methodologically strong due to their prospective, repeated assessment of cannabis use over many years; sample size; and covariate adjustment. Studies of midlife and older adult medical cannabis users were not included.						

Table S2. Description of measures.		
Variable	**Description**	**N**
Exposures		
Long-term cannabis users and 5 informative comparative groups	Groups were defined based on past-year diagnostic interviews for cannabis, tobacco, alcohol, and other illicit drug dependence, as well as self-reported frequency of substance use as described in the methods section. Past-year cannabis, tobacco, and alcohol dependencies were assessed with the with the Diagnostic Interview Schedule (DIS)[12,13] following criteria for the Diagnostic and Statistical Manual of Mental Disorders [14,15] at each assessment age from age 18-45. Past-year dependence on illicit drugs other than cannabis was assessed using the DIS at each assessment age from age 26 to 45. Study members self-reported the number of days (0-365) they used cannabis, the number of cigarettes smoked per day, and the number of days they used alcohol in the past year at each assessment from age 18-45. Study members reported the number of days they used other drugs in the past year from age 26-45.	Long-term cannabis users: N=86. Lifelong cannabis non-users: N=202. Long-term tobacco users: N=75. Long-term alcohol users: N=57. Midlife recreational cannabis users: N=65. Cannabis quitters: N=60.
Persistence of cannabis use	*Persistence of cannabis dependence* was defined based on past-year diagnostic interview for cannabis dependence and self-reported number of days of cannabis use at each assessment age from age 18-45 years. *Persistence of regular cannabis use* was defined based on past-year self-reported number of days of cannabis use at each assessment age from age 18-45 years.	*Persistence of cannabis dependence* comprised those who (i) never used cannabis (n=262), (ii) used but never diagnosed (n=498), (iii) diagnosed at one wave (n=85), (iv) diagnosed at two waves (n=39), (v) diagnosed at three waves (n=32), and (vi) diagnosed at four or more waves (n=16). *Persistence of regular cannabis use* (i.e., 4+ days per week) comprised those who never used cannabis (n=262), (ii) used but never regularly (n=518), (iii) used regularly at one wave (n=57), (iv) used regularly at two waves (n=32), (v) used regularly at three waves

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		(n=33), and (vi) used regularly at four or more waves (n=30).
Outcomes		
Age-45 Intellectual Functioning		
Wechsler Adult Intelligence Scale-IV	The Wechsler Adult Intelligence Scale –IV (WAIS-IV)[16] was administered to study members individually according to standard protocol at age 45 years. Psychometrists were blind to the study member's earlier performance. Ten subtests were administered: Information, Similarities, Vocabulary, Arithmetic, Digit Symbol Coding, Block Design, Picture Completion, Digit Span, Symbol Search, Matrix Reasoning. Full scale IQ was derived from the ten subtests using the method recommended in the test manual.	932
Working Memory Index	Derived from the arithmetic and digit span subtests of the Wechsler Adult Intelligence Scale.	932
Perceptual Reasoning Index	Derived from the block design, picture completion, and matrix reasoning subtests of the Wechsler Adult Intelligence Scale.	931
Verbal Comprehension Index	Derived from the information, similarities, and vocabulary subtests of the Wechsler Adult Intelligence Scale.	930
Processing Speed Index	Derived from the digit symbol coding and symbol search subtests of the Wechsler Adult Intelligence Scale.	932
Age-45 Neuropsychological Tests		
Rey Auditory Verbal Learning Test	This is a test of verbal learning and memory administered at age 45 years.[17] The test involves a five-trial presentation of a 15-word list and a one-time presentation of an interference list. Four trials of the 15-word list were administered due to time constraints. Words are recalled immediately after each trial and later after a 25-30 minute delay. Total recall (learning): the total	932

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	number of words (0-60) recalled over four trials (the sum of words recalled across trials 1-4). Delayed recall (memory): The total number of words (0-15) recalled after a 25-30 minute delay.	
Wechsler Memory Scale – Months Backward test	The Wechsler Memory Scale (WMS-III) Months Backward test was administered individually according to standard protocol at age 45 years.[18] This is a test of attention and tracking. It requires reciting the months of the year in backwards order, starting with December. Responses were scored according to the instructions in the WMS-III manual. Scores ranged from 1 (poor performance) to 5 (good performance) and reflect both accuracy and speed.	930
Trail Making Test – B	This is a test of scanning and tracking, divided attention, and mental flexibility administered at age 45 years.[19] The test involves drawing lines to connect consecutively numbered and lettered circles, alternating between numbers and letters. Scores represent the time, in seconds, to complete the test.	931
Animal Naming Test	This is a test of verbal fluency administered at age 45 years.[20] Scores represent the maximum number of animals named in one minute.	898
Grooved Pegboard Test	This is a test of motor dexterity administered at age 45 years.[17] The test requires rotation and insertion of pegs with keys at one end into 25 holes. Scores represent the time, in seconds, to complete the test.	931
Age-45 Informant-Reported Memory and Attention Problems	Informant reports of study members' neuropsychological functioning were obtained at age 45 years. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study member	883

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Variable	**Description**	**N**
	had problems with their memory and attention over the past year. The *informant-reported memory problems* scale consisted of three items: “has problems with memory,” “misplaces wallet, keys, eyeglasses, paperwork,” and “forgets to do errands, return calls, pay bills” (internal consistency reliability=0.70). The *informant-reported attention problems* scale consisted of four items: “is easily distracted, gets sidetracked easily,” “can’t concentrate, mind wanders,” “tunes out instead of focusing,” and “has difficulty organizing tasks that have many steps” (internal consistency reliability=0.84).	
Age-45 Structural Magnetic Resonance Imaging	Each participant was scanned using a MAGNETOM Skyra (Siemens Healthcare GmbH) 3T scanner equipped with a 64-channel head/neck coil at the Pacific Radiology Group imaging center in Dunedin, New Zealand. High resolution T1-weighted images were obtained using an MP-RAGE sequence with the following parameters: TR = 2400 ms; TE = 1.98 ms; 208 sagittal slices; flip angle, 9°; FOV, 224 mm; matrix =256×256; slice thickness = 0.9 mm with no gap (voxel size 0.9×0.875×0.875 mm); and total scan time = 6 min and 52 s. 3D fluid-attenuated inversion recovery (FLAIR) images were obtained with the following parameters: TR = 8000 ms; TE = 399 ms; 160 sagittal slices; FOV = 240 mm; matrix = 232×256; slice thickness = 1.2 mm (voxel size 0.9×0.9×1.2 mm); and total scan time = 5 min and 38 Data from 4 study members were excluded due to major incidental findings or previous head injuries (e.g., large tumors or extensive damage to the brain) and 10 due to	861

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	incomplete or insufficient quality data (9 FLAIR or field map scans and 1 poor surface mapping). This resulted in brain-imaging data from 861 study members, who represented the original cohort (Supplemental Figure 1). Test re-retest reliability for bilateral hippocampal volume was excellent: ICC (intraclass correlation coefficient)=0.98.	
Covariates		
Childhood IQ	The Wechsler Intelligence Scale for Children – Revised (WISC–R)[21] was administered to study members at ages 7, 9, and 11 years, and scores were averaged across these assessments. The test was individually administered on each occasion according to standard protocol. Psychometrists were blind to the children's performance on previous administrations of the WISC–R. The WISC-R consists of 10 core subtests. Eight core subtests were administered (information, similarities, vocabulary, arithmetic, digit symbol coding, block design, picture completion, object assembly). Two core subtests (comprehension and picture arrangement) were omitted due to time constraints.[22] Full scale IQ was derived from the eight subtests using the method recommended in the test manual.	927
Childhood SES	The socioeconomic status of Study members' parents was measured with the Elley-Irving scale,[23] the forerunner of the NZSEI-06, which assigned occupations into 1 of 6 SES groups (from 1 = unskilled laborer to 6 = professional). The higher of either parents' occupation was averaged spanning the period from Study members' birth to age 15 (1972-1987).	933
Low childhood self-control	Assessed using a multi-occasion/multi-informant strategy,	938

Table S2. Description of measures.		
Variable	**Description**	**N**
	across ages 3-11 years. Nine measures of childhood self-control in the composite include observational ratings of children's lack of control, parent and teacher reports of impulsive aggression, and parent, teacher, and self-reports of hyperactivity, lack of persistence, inattention, and impulsivity.[24]	
Family history of substance dependence	Family histories were collected from study members (when they were age 30-33 years) and from their parents. Family psychiatric history data were collected about each study member's biological parents, grandparents, and siblings. Each participant's family history of substance use disorder was calculated as the % of family members with a positive history of disorder, taking into account genetic relatedness.[25]	928
Persistence of Alcohol Dependence	At each of the 6 assessment waves (ages 18, 21, 26, 32, 38, and 45 years), past-year alcohol dependence was assessed with the Diagnostic Interview Schedule [12,13] following criteria for the Diagnostic and Statistical Manual of Mental Disorders.[14,15]	Persistence of alcohol dependence comprised study members who (i) never used alcohol (n=52), (ii) drank alcohol at least weekly at one or more assessment waves but were never diagnosed with alcohol dependence (n= 533), (iii) were diagnosed at one wave (n= 181), (iv) were diagnosed at two waves (n= 83), (v) were diagnosed at three waves (n=49), and (vi) were diagnosed at four or more waves (n=32).
Persistence of Tobacco Dependence	At each of the 6 assessment waves (ages 18, 21, 26, 32, 38, and 45 years), past-year tobacco dependence was assessed with the Diagnostic Interview Schedule [12,13] following criteria for the Diagnostic and Statistical Manual of Mental Disorders.[14,15]	Persistence of tobacco dependence comprised study members who (i) never smoked tobacco (n=451), (ii) smoked tobacco daily at one or more assessment waves but were never diagnosed with tobacco dependence (n= 131), (iii) were diagnosed at one wave (n= 109), (iv) were diagnosed at two waves (n= 91), (v) were

Table S2. Description of measures.		
Variable	**Description**	**N**
		diagnosed at three waves (n=63), and (vi) were diagnosed at four or more waves (n=89).
Persistent Illicit Drug Dependence	Past-year dependence on illicit drugs other than cannabis was assessed from ages 26-45 years with the Diagnostic Interview Schedule [12,13] following criteria for the Diagnostic and Statistical Manual of Mental Disorders.[14,15]	Persistent illicit drug dependence comprised study members who met criteria for dependence on illicit drugs besides cannabis at 2 or more study waves (n=32) vs. all others (n=906).

Table S3. Specific neuropsychological functions: Group comparisons. Performance across neuropsychological domains in adulthood (age 45 years) for long-term cannabis users and 5 comparison groups. (This table corresponds to Figure 1 in the main text.)

	Long-term Cannabis Users (N=84)		Comparison Group 1: Cannabis Non-Users (N=196)		Comparison Group 2: Long-term Tobacco Users (N=75)		Comparison Group 3: Long-term Alcohol Users (N=57)		Comparison Group 4: Midlife Recreational Cannabis Users (N=65)		Comparison Group 5: Cannabis Quitters (N=58)		Statistical Tests of Difference Between Long-term Cannabis Users and Comparison Groups				
													LT vs 1	LT vs 2	LT vs 3	LT vs 4	LT vs 5
Age-45 Tests	M	95% CI	M	95% CI	M	95% CI	M	95% CI	M	95% CI	M	95% CI	p	P	p	p	p
Learning/ Memory																	
Rey Total	-0.47	-0.70, -0.24	0.10	-0.04, 0.24	-0.01	-0.21, 0.20	0.26	-0.01, 0.52	0.12	-0.11, 0.35	-0.14	-0.39, 0.11	**<.001**	**.003**	**<.001**	**.002**	.06
Rey Recall	-0.28	-0.49, -0.08	0.04	-0.09, 0.18	0.06	-0.14, 0.27	0.07	-0.20, 0.34	0.12	-0.12, 0.36	-0.10	-0.35, 0.15	**.01**	**.03**	**.04**	**.03**	.24
Executive Function																	
WMS	-0.29	-0.52, -0.06	0.19	0.04, 0.33	-0.01	-0.20, 0.19	0.10	-0.17, 0.36	-0.05	-0.29, 0.20	-0.17	-0.46, 0.12	**<.001**	.09	**.03**	.16	.53
Trails B	-0.11	-0.33, 0.12	0.11	-0.02, 0.24	0.05	-0.14, 0.24	0.39	0.18, 0.60	-0.07	-0.28, 0.14	-0.29	-0.55, -0.02	.22	.26	**.003**	.79	.34
Animal Naming	-0.15	-0.35, 0.06	0.03	-0.10, 0.17	-0.02	-0.25, 0.20	0.11	-0.18, 0.40	0.13	-0.16, 0.41	0.10	-0.19, 0.39	.16	.35	.14	.20	.17
WMI	-0.17	-0.38, 0.04	0.13	-0.01, 0.27	0.05	-0.18, 0.27	-0.09	-0.32, 0.14	0.08	-0.16, 0.32	-0.23	-0.46, 0.00	**.02**	.22	.62	.15	.65
Perceptual Reasoning																	
PRI	-0.33	-0.54, -0.13	0.25	0.11, 0.39	-0.21	-0.44, 0.01	0.08	-0.17, 0.33	-0.07	-0.30, 0.16	-0.32	-0.60, -0.03	**<.001**	.46	**.006**	.06	.95
Verbal Comprehension																	
VCI	-0.33	-0.53, -0.12	0.20	0.06, 0.34	-0.15	-0.35, 0.05	0.05	-0.19, 0.29	-0.15	-0.35, 0.05	0.02	-0.29, 0.33	**<.001**	.20	**.02**	.35	.06
Processing Speed																	
PSI	-0.23	-0.46, 0.00	0.08	-0.06, 0.22	0.05	-0.18, 0.29	0.31	0.05, 0.56	0.09	-0.17, 0.35	-0.19	-0.48, 0.09	**.02**	**.03**	**.001**	.10	.80
Motor Function																	
Grooved Pegboard	-0.03	-0.17, 0.12	0.05	-0.09, 0.18	-0.22	-0.45, 0.02	0.13	-0.05, 0.31	-0.09	-0.24, 0.06	-0.01	-0.24, 0.21	.70	.16	.15	.74	.97

Note. Means represent test scores that were adjusted for sex and child IQ and standardized on the full sample (M=0, SD=1). Lower scores indicate poorer than average test performance. Bolded p-values indicate a statistically significant (p<.05) difference compared with long-term cannabis users. LT=Long-term cannabis users. WMI=Working Memory Index. WMS=Wechsler Memory Scale Months Backwards. Rey Total=Rey Auditory Verbal Learning Test total score (learning). Rey Recall= Rey Auditory Verbal Learning Test delayed recall (memory). PRI=Perceptual Reasoning Index. VCI=Verbal Comprehension Index. PSI= Processing Speed Index.

Table S4. Dose-response associations between persistence of cannabis use and cognitive functioning, before and after adjustment for recent cannabis use. Recent cannabis use could not explain associations between persistence of cannabis use and cognitive deficits.

Panel A. Exposure: Persistence of Cannabis Dependence						
	Model 1: Adjusted for sex and childhood IQ[a]			Model 2: +Adjustment for past 24-hour cannabis use		
Cognitive Test	β	95% CI	p	β	95% CI	p
IQ Change	**-0.16**	**-0.23, -0.10**	**<.001**	**-0.15**	**-0.22, -0.08**	**<.001**
Rey Total	**-0.14**	**-0.19, -0.08**	**<.001**	**-0.12**	**-0.18, -0.06**	**<.001**
Rey Recall	**-0.08**	**-0.13, -0.02**	**.01**	**-0.07**	**-0.14, -0.01**	**.02**
WMS	**-0.13**	**-0.19, -0.07**	**<.001**	**-0.13**	**-0.19, -0.06**	**<.001**
Trails B	**-0.07**	**-0.12, -0.01**	**.02**	**-0.08**	**-0.14, -0.02**	**.01**
Animal Naming	0.00	-0.06, 0.06	.99	0.00	-0.07, 0.06	.92
WMI	**-0.08**	**-0.14, -0.03**	**.002**	**-0.09**	**-0.15, -0.04**	**.001**
PRI	**-0.11**	**-0.16, -0.06**	**<.001**	**-0.10**	**-0.15, -0.04**	**<.001**
VCI	**-0.07**	**-0.12, -0.02**	**.007**	**-0.06**	**-0.11, 0.00**	**.04**
PSI	**-0.11**	**-0.17 -0.06**	**<.001**	**-0.10**	**-0.16, -0.04**	**.001**
Grooved Pegboard	-0.05	-0.10, 0.01	.11	-0.06	-0.12, 0.00	.06

Panel B. Exposure: Persistence of Regular Cannabis Use						
	Model 1: Adjusted for sex and childhood IQ[a]			Model 2: +Adjustment for past 24-hour cannabis use		
Cognitive Test	β	95% CI	p	β	95% CI	p
IQ Change	**-0.16**	**-0.23, -0.10**	**<.001**	**-0.16**	**-0.23, -0.08**	**<.001**
Rey Total	**-0.15**	**-0.21, -0.10**	**<.001**	**-0.14**	**-0.20, -0.08**	**<.001**
Rey Recall	**-0.10**	**-0.16, -0.04**	**<.001**	**-0.10**	**-0.17, -0.04**	**.002**
WMS	**-0.11**	**-0.18, -0.05**	**<.001**	**-0.12**	**-0.19, -0.05**	**<.001**
Trails B	-0.05	-0.11, 0.01	.07	**-0.07**	**-0.14, -0.01**	**.02**
Animal Naming	-0.03	-0.10, 0.03	.30	-0.04	-0.11, 0.03	.24
WMI	**-0.06**	**-0.11, -0.01**	**.03**	**-0.07**	**-0.13, -0.01**	**.02**
PRI	**-0.13**	**-0.18, -0.08**	**<.001**	**-0.13**	**-0.18, -0.07**	**<.001**
VCI	**-0.09**	**-0.14, -0.05**	**<.001**	**-0.08**	**-0.14, -0.03**	**.002**
PSI	**-0.11**	**-0.16, -0.05**	**<.001**	**-0.10**	**-0.16, -0.04**	**.002**
Grooved Pegboard	-0.05	-0.10, 0.01	.12	-0.06	-0.12, 0.00	.05

Note. Estimates are standardized regression coefficients from ordinary least squares regressions of IQ change/age-45 cognitive test performance on persistence of cannabis use. Statistically significant estimates ($p<.05$) are bolded. a. Estimates for IQ change (adult IQ minus childhood IQ) were adjusted for sex but not adjusted for childhood IQ.

Table S5. Hippocampal Volume: Group comparisons. Comparison of long-term cannabis users and 5 informative subgroups on age-45 hippocampal volume. (This table corresponds to Figure 2 in the main text, but shows raw, as opposed to sex-adjusted and standardized, hippocampal volume.)

	Long-term Cannabis Users (N=80)		Comparison Group 1: Cannabis Non-Users (N=187)		Comparison Group 2: Long-term Tobacco Users (N=68)		Comparison Group 3: Long-term Alcohol Users (N=56)		Comparison Group 4: Midlife Recreational Cannabis Users (N=60)		Comparison Group 5: Cannabis Quitters (N=52)		Statistical Tests of Difference Between Long-term Cannabis Users and Comparison Groups				
													LT vs 1	LT vs 2	LT vs 3	LT vs 4	LT vs 5
Hippocampal Volume	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	p	p	p	p	p
Bilateral Volume	4291.5	42.5	4309.3	34.1	4179.0	52.2	4284.2	51.2	4392.6	57.1	4349.3	58.7	**.02**	.90	.57	**.02**	.20
Fissure	265.8	5.5	257.7	3.3	251.3	5.7	265.0	5.1	272.8	6.2	256.4	5.0	.97	.39	.75	.22	.29
Tail	1095.2	14.6	1116.7	11.1	1075.1	16.6	1116.0	17.4	1134.5	17.1	1077.6	19.0	**.03**	.82	.24	**.04**	.54
Parasubiculum	137.9	2.4	137.5	1.7	135.2	2.5	137.1	2.9	136.4	3.0	139.6	2.8	.11	.83	.83	.92	.51
HATA	131.2	2.1	136.2	1.3	128.9	2.0	134.3	2.6	133.2	2.1	138.0	2.4	**<.001**	.56	.12	.28	**.02**
Fimbria	154.8	3.3	153.1	2.0	151.7	3.8	160.3	4.3	152.4	3.1	159.8	4.4	.09	.33	.09	.88	.21
Subiculum	904.6	9.3	904.3	7.8	881.2	13.0	904.8	12.0	913.8	11.4	900.3	13.4	.06	.93	.52	.22	.97
CA1	1394.3	17.1	1404.5	12.4	1345.6	17.9	1391.4	17.9	1433.9	21.6	1428.7	23.0	**.02**	.57	.68	**.03**	.10
Presubiculum	619.7	7.2	619.1	5.7	608.4	10.4	612.6	8.6	625.8	10.3	626.8	11.5	.09	.75	.88	.36	.43
Molecular Layer	1202.9	12.0	1206.1	9.5	1170.7	14.6	1199.2	13.2	1229.6	16.5	1219.0	18.0	**.04**	.74	.70	**.03**	.24
CA3	475.7	7.3	475.5	4.4	460.3	6.5	476.6	7.5	487.1	8.4	486.0	8.4	.16	.72	.55	.10	.22
Dentate gyrus	630.3	7.0	631.2	5.0	611.7	7.5	632.0	7.3	643.1	8.9	643.6	9.4	**.05**	.69	.43	.06	.11
CA4	544.5	6.3	544.3	4.4	526.9	6.4	544.0	6.4	554.7	8.0	549.8	8.2	.10	.48	.63	.09	.40

Note. Statistical tests are adjusted for sex but means are unadjusted. Bolded p-values indicate a statistically significant difference (p<.05) compared with long-term cannabis users. LT=Long-term cannabis users.

Table S6. Hippocampal volume: Dose-response associations. Dose-response associations between persistence of cannabis use from age 18-45 and age-45 hippocampal volume.

Panel A. Exposure: Persistence of Cannabis Dependence

	Means for Hippocampal Volume as a Function of Persistence of Cannabis Dependence[a]						Statistical Tests: Model 1: Adjusted for sex			Model 2: +Adjustment for other substance use[b]			Model 3: + Adjustment for childhood SES, low childhood self-control, and family history of substance dependence[c]		
Exposure: Persistence of Cannabis Dependence	Never Used (n=242)	Used but never diagnosed (n=463)	1 diagnosis (n=77)	2 diagnoses (n=33)	3 diagnoses (n=29)	4+ diagnoses (n=16)	β	95% CI	p	β	95% CI	p	β	95% CI	p
Volume															
Bilateral	0.07	0.00	-0.05	-0.17	-0.05	-0.51	**-0.08**	**-0.14, -0.02**	**.01**	-0.07	-0.15, 0.01	.07	-0.06	-0.14, 0.01	.11
Fissure	0.05	0.00	-0.03	0.05	0.05	-0.58	-0.05	-0.11, 0.02	.17	**-0.12**	**-0.20, -0.04**	**.004**	**-0.12**	**-0.20, -0.04**	**.005**
Tail	0.10	0.03	-0.31	-0.16	-0.01	-0.57	**-0.11**	**-0.17, -0.04**	**.001**	**-0.11**	**-0.19, -0.03**	**.01**	**-0.10**	**-0.19, -0.02**	**.01**
Parasubiculum	0.06	0.00	-0.13	-0.13	0.01	-0.02	-0.04	-0.11, 0.02	.18	-0.04	-0.12, 0.04	.29	-0.04	-0.12, 0.04	.27
HATA	0.13	-0.04	0.08	-0.19	-0.12	-0.44	**-0.08**	**-0.15, -0.02**	**.01**	-0.01	-0.09, 0.07	.82	0.00	-0.08, 0.08	.92
Fimbria	0.01	0.01	-0.05	0.12	-0.22	-0.07	-0.02	-0.08, 0.04	.50	0.00	-0.08, 0.08	.96	0.00	-0.08, 0.08	.97
Subiculum	0.04	0.03	-0.18	-0.14	0.06	-0.33	-0.05	-0.11, 0.01	.09	-0.05	-0.13, 0.02	.17	-0.05	-0.12, 0.03	.23
CA1	0.09	-0.03	0.00	-0.12	0.00	-0.32	-0.06	-0.12, 0.01	.07	-0.04	-0.11, 0.04	.37	-0.03	-0.10, 0.05	.48
Presubiculum	0.05	0.02	-0.14	-0.11	-0.07	-0.28	-0.06	-0.12, 0.00	.06	-0.05	-0.13, 0.03	.20	-0.04	-0.12, 0.03	.26
Molecular Layer	0.07	0.00	-0.09	-0.12	0.00	-0.33	**-0.06**	**-0.12, -0.01**	**.05**	-0.05	-0.13, 0.02	.18	-0.04	-0.12, 0.03	.27
CA3	0.07	-0.03	-0.01	0.05	0.01	-0.21	-0.03	-0.09, 0.03	.30	-0.04	-0.12, 0.05	.39	-0.03	-0.11, 0.05	.49
Dentate gyrus	0.07	-0.01	-0.08	-0.02	-0.02	-0.25	-0.05	-0.11, 0.01	.10	-0.04	-0.12, 0.03	.28	-0.03	-0.11, 0.04	.38
CA4	0.08	-0.01	-0.11	-0.01	-0.02	-0.15	-0.05	-0.11, 0.01	.13	-0.04	-0.12, 0.04	.29	-0.03	-0.11, 0.04	.39

Panel B. Exposure: Persistence of Regular Cannabis Use

	Means for Hippocampal Volume as a Function of Persistence of Regular Cannabis Use[a]						Statistical Tests: Model 1: Adjusted for sex			Model 2: +Adjustment for other substance use[b]			Model 3: + Adjustment for childhood SES, low childhood self-control, and family history of substance dependence[c]		
Exposure: Persistence of Regular Cannabis Use	Never used (n=242)	Used but never regularly (n=481)	Regularly used 1x (n=47)	Regularly used 2x (n=31)	Regularly used 3x (n=31)	Regularly used 4⁺x (n=28)	β	95% CI	p	β	95% CI	p	β	95% CI	p
Volume															
Bilateral	0.07	0.02	-0.12	-0.27	-0.27	-0.19	**-0.09**	**-0.15, -0.03**	**.004**	**-0.08**	**-0.15, -0.01**	**.03**	-0.07	-0.14, 0.01	.08
Fissure	0.05	0.00	-0.19	0.09	-0.03	-0.07	-0.03	-0.09, 0.04	.53	-0.07	-0.14, 0.02	.12	-0.06	-0.14, 0.02	.14
Tail	0.10	0.02	-0.22	-0.26	-0.19	-0.27	**-0.10**	**-0.17, -0.04**	**.003**	**-0.10**	**-0.18, -0.02**	**.01**	**-0.09**	**-0.17, -0.02**	**.02**
Parasubiculum	0.06	0.01	-0.13	-0.23	-0.18	-0.03	-0.06	-0.12, 0.00	.06	-0.07	-0.14, 0.01	.08	-0.07	-0.14, 0.01	.09
HATA	0.13	-0.01	-0.02	-0.24	-0.34	-0.24	**-0.10**	**-0.17, -0.04**	**.001**	-0.05	-0.13, 0.03	.22	-0.04	-0.12, 0.04	.32
Fimbria	0.01	0.05	-0.09	-0.42	-0.03	-0.23	-0.06	-0.12, 0.00	.06	-0.05	-0.13, 0.02	.16	-0.05	-0.12, 0.03	.24
Subiculum	0.05	0.03	-0.16	-0.30	-0.14	-0.20	**-0.07**	**-0.13, -0.01**	**.02**	**-0.08**	**-0.15, -0.01**	**.04**	-0.07	-0.14, 0.01	.08
CA1	0.09	0.00	-0.04	-0.10	-0.36	-0.16	**-0.08**	**-0.15, -0.02**	**.008**	**-0.08**	**-0.15, -0.01**	**.05**	-0.06	-0.13, 0.01	.11
Presubiculum	0.05	0.03	-0.01	-0.30	-0.25	-0.25	**-0.08**	**-0.14, -0.02**	**.007**	**-0.09**	**-0.16, -0.02**	**.02**	**-0.08**	**-0.15, -0.01**	**.03**
Molecular Layer	0.07	0.01	-0.08	-0.20	-0.27	-0.20	**-0.08**	**-0.15, -0.02**	**.006**	**-0.09**	**-0.16, -0.01**	**.02**	-0.07	-0.14, 0.00	.06
CA3	0.07	-0.01	-0.08	-0.02	-0.11	-0.08	-0.04	-0.11, 0.02	.20	-0.04	-0.12, 0.03	.26	-0.03	-0.11, 0.05	.47
Dentate gyrus	0.07	0.00	-0.09	-0.13	-0.18	-0.14	**-0.07**	**-0.13, -0.01**	**.04**	-0.06	-0.14, 0.01	.11	-0.04	-0.12, 0.03	.25
CA4	0.08	-0.01	-0.12	-0.06	-0.16	-0.08	-0.05	-0.12, 0.01	.09	-0.05	-0.13, 0.03	.19	-0.03	-0.11, 0.04	.39

Note. a. Means were standardized (M=0, SD=1) on the full sample prior to analyses and adjusted for sex. b. Statistical tests were adjusted for sex and persistent tobacco, alcohol, and other illicit drug dependence. c. Statistical tests were adjusted for sex; persistent tobacco, alcohol, and other illicit drug dependence; childhood SES; low childhood self-control; and family history of substance dependence. Beta coefficients represent standardized estimates. Bolded estimates are statistically significant ($p<.05$).

Table S7. Hippocampal volume: Dose-response associations, with covariate adjustment for total brain volume. Dose-response associations between persistence of cannabis use from age 18-45 and age-45 hippocampal volume.

Panel A. Exposure: Persistence of Cannabis Dependence

	Means for Hippocampal Volume as a Function of Persistence of Cannabis Dependence[a]						Statistical Tests: Model 1: Adjusted for sex			Statistical Tests: Model 2: +Adjustment for total brain volume			Statistical Tests: Model 3: + Adjustment for childhood SES, low childhood self-control, family history of substance dependence, and other substance use		
Exposure: Persistence of Cannabis Dependence	Never Used (n=242)	Used but never diagnosed (n=463)	1 diagnosis (n=77)	2 diagnoses (n=33)	3 diagnoses (n=29)	4+ diagnoses (n=16)	β	95% CI	p	β	95% CI	p	β	95% CI	p
Volume															
Bilateral	0.07	0.00	-0.05	-0.17	-0.05	-0.51	**-0.08**	**-0.14, -0.02**	**.01**	-0.04	-0.09, 0.01	.13	-0.05	-0.12, 0.01	.11
Fissure	0.05	0.00	-0.03	0.05	0.05	-0.58	-0.05	-0.11, 0.02	.17	-0.03	-0.10, 0.03	.35	**-0.11**	**-0.19, -0.03**	**.005**
Tail	0.10	0.03	-0.31	-0.16	-0.01	-0.57	**-0.11**	**-0.17, -0.04**	**.001**	**-0.08**	**-0.14, -0.02**	**.01**	**-0.10**	**-0.17, -0.02**	**.01**
Parasubiculum	0.06	0.00	-0.13	-0.13	0.01	-0.02	-0.04	-0.11, 0.02	.18	-0.01	-0.07, 0.05	.67	-0.04	-0.11, 0.04	.33
HATA	0.13	-0.04	0.08	-0.19	-0.12	-0.44	**-0.08**	**-0.15, -0.02**	**.01**	-0.05	-0.10, 0.01	.11	0.00	-0.07, 0.08	.90
Fimbria	0.01	0.01	-0.05	0.12	-0.22	-0.07	-0.02	-0.08, 0.04	.50	0.00	-0.06, 0.06	.97	0.01	-0.07, 0.08	.85
Subiculum	0.04	0.03	-0.18	-0.14	0.06	-0.33	-0.05	-0.11, 0.01	.09	-0.02	-0.07, 0.04	.55	-0.04	-0.11, 0.03	.27
CA1	0.09	-0.03	0.00	-0.12	0.00	-0.32	-0.06	-0.12, 0.01	.07	-0.02	-0.07, 0.04	.50	-0.02	-0.09, 0.05	.59
Presubiculum	0.05	0.02	-0.14	-0.11	-0.07	-0.28	-0.06	-0.12, 0.00	.06	-0.02	-0.08, 0.03	.42	-0.03	-0.10, 0.03	.31
Molecular Layer	0.07	0.00	-0.09	-0.12	0.00	-0.33	**-0.06**	**-0.12, -0.01**	**.05**	-0.02	-0.07, 0.03	.46	-0.03	-0.10, 0.03	.31
CA3	0.07	-0.03	-0.01	0.05	0.01	-0.21	-0.03	-0.09, 0.03	.30	0.00	-0.06, 0.06	.96	-0.02	-0.09, 0.05	.59
Dentate gyrus	0.07	-0.01	-0.08	-0.02	-0.02	-0.25	-0.05	-0.11, 0.01	.10	-0.01	-0.06, 0.04	.69	-0.02	-0.09, 0.04	.46
CA4	0.08	-0.01	-0.11	-0.01	-0.02	-0.15	-0.05	-0.11, 0.01	.13	-0.01	-0.06, 0.05	.74	-0.02	-0.09, 0.04	.47

Panel B. Exposure: Persistence of Regular Cannabis Use

	Means for Hippocampal Volume as a Function of Persistence of Regular Cannabis Use[a]						Statistical Tests: Model 1: Adjusted for sex			Statistical Tests: Model 2: +Adjustment for total brain volume			Statistical Tests: Model 3: + Adjustment for childhood SES, low childhood self-control, family history of substance dependence, and other substance use		
Exposure: Persistence of Regular Cannabis Use	Never used (n=242)	Used but never regularly (n=481)	Regularly used 1x (n=47)	Regularly used 2x (n=31)	Regularly used 3x (n=31)	Regularly used 4+x (n=28)	β	95% CI	p	β	95% CI	p	β	95% CI	p
Volume															
Bilateral	0.07	0.02	-0.12	-0.27	-0.27	-0.19	**-0.09**	**-0.15, -0.03**	**.004**	-0.03	-0.08, 0.02	.23	-0.03	-0.09, 0.03	.35
Fissure	0.05	0.00	-0.19	0.09	-0.03	-0.07	-0.03	-0.09, 0.04	.53	0.00	-0.06, 0.06	.99	-0.05	-0.12, 0.03	.25
Tail	0.10	0.02	-0.22	-0.26	-0.19	-0.27	**-0.10**	**-0.17, -0.04**	**.003**	-0.06	-0.12, 0.01	.06	-0.07	-0.14, 0.01	.07
Parasubiculum	0.06	0.01	-0.13	-0.23	-0.18	-0.03	-0.06	-0.12, 0.00	.06	-0.02	-0.07, 0.04	.60	-0.04	-0.11, 0.03	.28
HATA	0.13	-0.01	-0.02	-0.24	-0.34	-0.24	**-0.10**	**-0.17, -0.04**	**.001**	-0.05	-0.11, 0.00	.07	-0.01	-0.08, 0.06	.85
Fimbria	0.01	0.05	-0.09	-0.42	-0.03	-0.23	-0.06	-0.12, 0.00	.06	-0.03	-0.09, 0.03	.39	-0.03	-0.10, 0.05	.49
Subiculum	0.05	0.03	-0.16	-0.30	-0.14	-0.20	**-0.07**	**-0.13, -0.01**	**.02**	-0.02	-0.07, 0.04	.50	-0.03	-0.10, 0.03	.33
CA1	0.09	0.00	-0.04	-0.10	-0.36	-0.16	**-0.08**	**-0.15, -0.02**	**.008**	-0.03	-0.08, 0.03	.31	-0.03	-0.09, 0.04	.44
Presubiculum	0.05	0.03	-0.01	-0.30	-0.25	-0.25	**-0.08**	**-0.14, -0.02**	**.007**	-0.03	-0.08, 0.02	.26	-0.05	-0.11, 0.02	.16
Molecular Layer	0.07	0.01	-0.08	-0.20	-0.27	-0.20	**-0.08**	**-0.15, -0.02**	**.006**	-0.02	-0.07, 0.03	.36	-0.03	-0.09, 0.03	.31
CA3	0.07	-0.01	-0.08	-0.02	-0.11	-0.08	-0.04	-0.11, 0.02	.20	0.00	-0.05, 0.06	.87	0.00	-0.07, 0.07	.99

Dentate gyrus	0.07	0.00	-0.09	-0.13	-0.18	-0.14	**-0.07**	**-0.13, -0.01**	**.04**	-0.01	-0.06, 0.05	.83	-0.01	-0.07, 0.06	.82
CA4	0.08	-0.01	-0.12	-0.06	-0.16	-0.08	-0.05	-0.12, 0.01	.09	0.00	-0.05, 0.06	.94	0.00	-0.06, 0.07	.97

Note. a. Means were standardized (M=0, SD=1) on the full sample prior to analyses and adjusted for sex. Beta coefficients represent standardized estimates. Bolded estimates are statistically significant (p<.05). Model 3 adjusts for sex; total brain volume; persistent tobacco, alcohol, and other illicit drug dependence; childhood SES; low childhood self-control; and family history of substance dependence

Table S8. Associations between age-45 hippocampal volume and cognitive test performance.

Hippocampal Volume/Neuropsychological Test	β	95% CI	P
Bilateral Volume			
IQ	**0.21**	**0.13, 0.28**	**<.001**
Rey Total	**0.09**	**0.02, 0.16**	**.02**
Rey Recall	0.03	-0.04, 0.10	.42
WMS	**0.08**	**0.01, 0.15**	**.03**
Trails B	**0.11**	**0.03, 0.18**	**.005**
Animal Naming	**0.09**	**0.02, 0.17**	**.02**
WMI	**0.18**	**0.10, 0.25**	**<.001**
PRI	**0.17**	**0.09, 0.24**	**<.001**
VCI	**0.20**	**0.13, 0.28**	**<.001**
PSI	**0.09**	**0.01, 0.16**	**.02**
Grooved Pegboard	0.06	-0.01, 0.12	.09
Fissure			
IQ	-0.04	-0.11, 0.03	.30
Rey Total	-0.03	-0.10, 0.04	.39
Rey Recall	-0.01	-0.08, 0.06	.81
WMS	0.00	-0.07, 0.07	.94
Trails B	-0.04	-0.11, 0.03	.22
Animal Naming	0.04	-0.03, 0.11	.28
WMI	-0.03	-0.10, 0.04	.45
PRI	-0.04	-0.12, 0.03	.22
VCI	-0.02	-0.09, 0.05	.62
PSI	-0.02	-0.09, 0.05	.56
Grooved Pegboard	**-0.07**	**-0.13, -0.01**	**.03**
Tail			
IQ	**0.11**	**0.04, 0.18**	**.002**
Rey Total	0.06	0.00, 0.13	.06
Rey Recall	0.05	-0.01, 0.12	.13
WMS	0.05	-0.02, 0.11	.19
Trails B	0.04	-0.03, 0.11	.26
Animal Naming	0.07	0.00, 0.14	.06
WMI	**0.08**	**0.01, 0.15**	**.02**
PRI	**0.12**	**0.06, 0.19**	**<.001**
VCI	**0.10**	**0.04, 0.17**	**.003**
PSI	0.03	-0.03, 0.10	.33
Grooved Pegboard	0.02	-0.04, 0.08	.55
Parasubiculum			
IQ	**0.13**	**0.06, 0.20**	**<.001**
Rey Total	**0.08**	**0.01, 0.15**	**.03**
Rey Recall	0.06	-0.01, 0.13	.09
WMS	0.03	-0.04, 0.10	.36
Trails B	0.06	-0.02, 0.13	.13
Animal Naming	**0.09**	**0.01, 0.16**	**.02**
WMI	**0.10**	**0.03, 0.17**	**.008**
PRI	**0.12**	**0.05, 0.19**	**.001**
VCI	**0.12**	**0.05, 0.19**	**<.001**
PSI	0.06	0.00, 0.13	.07
Grooved Pegboard	0.03	-0.03, 0.10	.28
HATA			
IQ	**0.17**	**0.10, 0.23**	**<.001**
Rey Total	**0.08**	**0.01, 0.15**	**.02**
Rey Recall	0.05	-0.02, 0.12	.14
WMS	0.03	-0.04, 0.10	.47
Trails B	**0.11**	**0.04, 0.18**	**.002**
Animal Naming	0.05	-0.02, 0.12	.15
WMI	**0.14**	**0.07, 0.21**	**<.001**

Table S8. Associations between age-45 hippocampal volume and cognitive test performance.

Hippocampal Volume/Neuropsychological Test	β	95% CI	P
PRI	**0.15**	**0.09, 0.23**	**<.001**
VCI	**0.14**	**0.07, 0.21**	**<.001**
PSI	0.07	0.00, 0.13	.06
Grooved Pegboard	0.06	0.00, 0.12	.06
Fimbria			
IQ	0.04	-0.03, 0.11	.27
Rey Total	0.03	-0.04, 0.10	.42
Rey Recall	0.00	-0.07, 0.07	.92
WMS	-0.02	-0.10, 0.05	.51
Trails B	0.00	-0.07, 0.07	.97
Animal Naming	0.01	-0.06, 0.09	.70
WMI	0.02	-0.05, 0.09	.62
PRI	0.05	-0.02, 0.13	.15
VCI	0.05	-0.02, 0.12	.19
PSI	-0.01	-0.08, 0.06	.69
Grooved Pegboard	0.04	-0.02, 0.11	.20
Subiculum			
IQ	**0.15**	**0.08, 0.22**	**<.001**
Rey Total	**0.08**	**0.00, 0.15**	**.04**
Rey Recall	0.06	-0.01, 0.13	.10
WMS	0.06	-0.02, 0.13	.13
Trails B	0.05	-0.03, 0.12	.21
Animal Naming	**0.09**	**0.02, 0.17**	**.01**
WMI	**0.11**	**0.03, 0.18**	**.005**
PRI	**0.15**	**0.07, 0.22**	**<.001**
VCI	**0.16**	**0.09, 0.24**	**<.001**
PSI	0.04	-0.03, 0.11	.25
Grooved Pegboard	0.04	-0.02, 0.11	.20
CA1			
IQ	**0.18**	**0.10, 0.25**	**<.001**
Rey Total	**0.08**	**0.01, 0.15**	**.02**
Rey Recall	0.03	-0.04, 0.10	.38
WMS	0.06	-0.01, 0.14	.08
Trails B	**0.11**	**0.04, 0.18**	**.003**
Animal Naming	0.07	0.00, 0.14	.06
WMI	**0.16**	**0.09, 0.23**	**<.001**
PRI	**0.13**	**0.06, 0.21**	**<.001**
VCI	**0.17**	**0.10, 0.25**	**<.001**
PSI	0.06	-0.01, 0.13	.08
Grooved Pegboard	0.05	-0.02, 0.11	.14
Presubiculum			
IQ	**0.11**	**0.03, 0.18**	**.004**
Rey Total	0.07	0.00, 0.14	.06
Rey Recall	0.06	-0.01, 0.13	.11
WMS	0.01	-0.06, 0.08	.77
Trails B	0.03	-0.04, 0.10	.44
Animal Naming	**0.10**	**0.03, 0.17**	**.009**
WMI	**0.07**	**0.01, 0.15**	**.05**
PRI	**0.10**	**0.03, 0.18**	**.006**
VCI	**0.11**	**0.04, 0.19**	**.002**
PSI	0.04	-0.03, 0.12	.21
Grooved Pegboard	0.05	-0.02, 0.11	.14
Molecular Layer			
IQ	**0.20**	**0.12, 0.27**	**<.001**
Rey Total	**0.09**	**0.02, 0.16**	**.01**
Rey Recall	0.04	-0.03, 0.11	.28

Table S8. Associations between age-45 hippocampal volume and cognitive test performance.

Hippocampal Volume/Neuropsychological Test	β	95% CI	P
WMS	**0.07**	**0.00, 0.15**	**.05**
Trails B	**0.12**	**0.04, 0.19**	**.002**
Animal Naming	**0.08**	**0.00, 0.15**	**.04**
WMI	**0.17**	**0.10, 0.24**	**<.001**
PRI	**0.16**	**0.08, 0.23**	**<.001**
VCI	**0.19**	**0.12, 0.26**	**<.001**
PSI	**0.08**	**0.01, 0.15**	**.03**
Grooved Pegboard	0.06	-0.01, 0.12	.08
CA3			
IQ	**0.18**	**0.11, 0.25**	**<.001**
Rey Total	**0.07**	**0.01, 0.14**	**.04**
Rey Recall	0.01	-0.06, 0.08	.83
WMS	**0.09**	**0.02, 0.16**	**.008**
Trails B	**0.13**	**0.06, 0.20**	**<.001**
Animal Naming	0.04	-0.03, 0.11	.31
WMI	**0.17**	**0.10, 0.24**	**<.001**
PRI	**0.14**	**0.06, 0.21**	**<.001**
VCI	**0.16**	**0.09, 0.23**	**<.001**
PSI	**0.09**	**0.02, 0.15**	**.01**
Grooved Pegboard	0.03	-0.03, 0.09	.36
Dentate gyrus			
IQ	**0.21**	**0.13, 0.28**	**<.001**
Rey Total	**0.11**	**0.04, 0.18**	**.002**
Rey Recall	0.05	-0.02, 0.12	.18
WMS	**0.08**	**0.01, 0.15**	**.03**
Trails B	**0.14**	**0.07, 0.21**	**<.001**
Animal Naming	0.07	0.00, 0.14	.07
WMI	**0.18**	**0.11, 0.25**	**<.001**
PRI	**0.16**	**0.08, 0.23**	**<.001**
VCI	**0.20**	**0.12, 0.27**	**<.001**
PSI	**0.09**	**0.02, 0.16**	**.02**
Grooved Pegboard	0.06	0.00, 0.13	.05
CA4			
IQ	**0.20**	**0.13, 0.27**	**<.001**
Rey Total	**0.11**	**0.04, 0.18**	**.003**
Rey Recall	0.05	-0.02, 0.12	.18
WMS	**0.09**	**0.02, 0.16**	**.01**
Trails B	**0.13**	**0.06, 0.20**	**<.001**
Animal Naming	0.06	-0.01, 0.14	.08
WMI	**0.18**	**0.11, 0.25**	**<.001**
PRI	**0.15**	**0.08, 0.22**	**<.001**
VCI	**0.19**	**0.12, 0.26**	**<.001**
PSI	**0.09**	**0.02, 0.16**	**.01**
Grooved Pegboard	0.06	-0.01, 0.12	.08

Note. Estimates are standardized regression coefficients from ordinary least squares regressions of age-45 neuropsychological tests on hippocampal volume. Coefficients are adjusted for sex. Statistically significant ($p<.05$) estimates are bolded. For all neuropsychological tests, higher scores reflect better performance. Rey Total=Rey Auditory Verbal Learning Test total score (learning). Rey Recall= Rey Auditory Verbal Learning Test delayed recall (memory). WMS=Wechsler Memory Scale Months Backwards test. WMI=Working Memory Index. PRI=Perceptual Reasoning Index. VCI=Verbal Comprehension Index. PSI= Processing Speed Index.

Table S9. Age-45 hippocampal volume does not mediate the association between persistence of cannabis use from age 18-45 and neuropsychological test performance at age 45 years.

	Exposure: Persistence of cannabis dependence			Exposure: Persistence of regular cannabis use		
Mediator/Outcome	Indirect Effect	95% CI	p	Indirect Effect	95 % CI	p
Bilateral Volume						
IQ	-0.001	-0.006, 0.003	.58	-0.001	-0.006, 0.004	.62
Rey Total	0.002	-0.004, 0.008	.46	0.003	-0.004, 0.010	.42
Rey Recall	0.005	-0.002, 0.012	.15	0.006	-0.002, 0.014	.13
WMS	0.002	-0.004, 0.008	.56	0.002	-0.005, 0.008	.58
Trails B	0.001	-0.004, 0.007	.60	0.002	-0.005, 0.008	.61
Animal Naming	0.001	-0.005, 0.007	.74	0.001	-0.005, 0.008	.67
WMI	-0.003	-0.008, 0.003	.31	-0.003	-0.010, 0.003	.29
PRI	-0.001	-0.006, 0.004	.79	-0.001	-0.006, 0.005	.85
VCI	-0.003	-0.008, 0.003	.34	-0.003	-0.008, 0.003	.38
PSI	0.003	-0.003, 0.010	.28	0.004	-0.003, 0.010	.28
Grooved Pegboard	0.001	-0.006, 0.009	.72	0.001	-0.007, 0.010	.73
Fissure						
IQ	0.002	-0.002, 0.005	.38	0.001	-0.002, 0.004	.63
Rey Total	0.001	-0.003, 0.005	.62	0.000	-0.003, 0.003	.79
Rey Recall	0.000	-0.003, 0.003	.93	0.000	-0.002, 0.003	.97
WMS	0.000	-0.003, 0.004	.98	0.000	-0.003, 0.003	.99
Trails B	0.002	-0.003, 0.006	.46	0.001	-0.003, 0.005	.68
Animal Naming	-0.002	-0.007, 0.003	.38	-0.001	-0.006, 0.003	.64
WMI	0.001	-0.003, 0.004	.64	0.000	-0.002, 0.003	.80
PRI	0.002	-0.002, 0.006	.36	0.001	-0.003, 0.005	.62
VCI	0.001	-0.002, 0.004	.64	0.000	-0.002, 0.003	.78
PSI	0.001	-0.003, 0.005	.70	0.000	-0.003, 0.003	.84
Grooved Pegboard	0.003	-0.003, 0.009	.32	0.001	-0.004, 0.007	.60
Tail						
IQ	-0.002	-0.007, 0.003	.37	-0.002	-0.007, 0.003	.39
Rey Total	0.000	-0.007, 0.006	.94	0.000	-0.006, 0.006	.95
Rey Recall	-0.001	-0.008, 0.006	.87	0.000	-0.007, 0.006	.91
WMS	0.001	-0.006, 0.008	.82	0.000	-0.003, 0.003	.95
Trails B	0.002	-0.004, 0.009	.53	0.002	-0.004, 0.008	.56
Animal Naming	-0.002	-0.009, 0.005	.56	-0.002	-0.008, 0.005	.62
WMI	-0.002	-0.008, 0.004	.54	-0.002	-0.008, 0.004	.49
PRI	-0.005	-0.012, 0.001	.12	-0.005	-0.011, 0.002	.14
VCI	-0.003	-0.009, 0.003	.37	-0.002	-0.008, 0.003	.42
PSI	0.003	-0.004, 0.010	.40	0.003	-0.004, 0.009	.44
Grooved Pegboard	0.002	-0.004, 0.008	.52	0.002	-0.004, 0.007	.56
Parasubiculum						
IQ	0.000	-0.003, 0.002	.80	0.000	-0.003, 0.003	.82
Rey Total	0.000	-0.003, 0.003	.94	0.000	-0.004, 0.003	.96
Rey Recall	0.000	-0.003. 0.003	.94	0.000	-0.004, 0.004	.97
WMS	0.001	-0.003, 0.004	.62	0.001	-0.003, 0.006	.54
Trails B	0.001	-0.002, 0.004	.61	0.001	-0.003, 0.006	.53
Animal Naming	-0.001	-0.005, 0.003	.62	-0.001	-0.006, 0.003	.55
WMI	0.000	-0.003, 0.003	.90	0.000	-0.004, 0.004	.88
PRI	-0.001	-0.003, 0.002	.67	-0.001	-0.004, 0.003	.65
VCI	-0.001	-0.003, 0.002	.70	-0.001	-0.004, 0.003	.70
PSI	0.000	-0.003, 0.003	.86	0.000	-0.004, 0.004	.82
Grooved Pegboard	0.001	-0.002, 0.003	.69	0.001	-0.003, 0.004	.60
HATA						
IQ	0.000	-0.004, 0.004	.90	0.000	-0.005, 0.005	.98
Rey Total	0.002	-0.004, 0.007	.51	0.003	-0.004, 0.009	.41
Rey Recall	0.002	-0.004, 0.008	.50	0.003	-0.004, 0.010	.41
WMS	0.006	-0.002, 0.013	.16	0.007	-0.002, 0.016	.12
Trails B	0.000	-0.006, 0.005	.88	-0.001	-0.007, 0.006	.87
Animal Naming	0.003	-0.004, 0.009	.40	0.004	-0.004, 0.011	.33

Table S9. Age-45 hippocampal volume does not mediate the association between persistence of cannabis use from age 18-45 and neuropsychological test performance at age 45 years.

	Exposure: Persistence of cannabis dependence			Exposure: Persistence of regular cannabis use		
Mediator/Outcome	Indirect Effect	95% CI	p	Indirect Effect	95 % CI	p
WMI	-0.001	-0.007, 0.004	.65	-0.002	-0.009, 0.005	.62
PRI	-0.002	-0.008, 0.003	.42	-0.003	-0.009, 0.004	.46
VCI	0.001	-0.004, 0.006	.68	0.002	-0.004, 0.008	.54
PSI	0.003	-0.002, 0.009	.25	0.004	-0.003, 0.011	.22
Grooved Pegboard	0.000	-0.006, 0.007	.95	0.000	-0.008, 0.008	.95
Fimbria						
IQ	0.001	-0.002, 0.003	.69	0.002	-0.002, 0.006	.36
Rey Total	0.000	-0.002, 0.003	.81	0.001	-0.003, 0.006	.54
Rey Recall	0.001	-0.003, 0.004	.66	0.003	-0.002, 0.007	.32
WMS	0.001	-0.003, 0.006	.59	0.004	-0.002, 0.010	.23
Trails B	0.001	-0.003, 0.005	.63	0.003	-0.002, 0.008	.30
Animal Naming	0.001	-0.003, 0.004	.75	0.002	-0.003, 0.007	.53
WMI	0.001	-0.003, 0.004	.68	0.002	-0.003, 0.007	.39
PRI	0.000	-0.002, 0.002	.96	0.000	-0.004, 0.004	.91
VCI	0.000	-0.002, 0.002	.86	0.001	-0.003, 0.005	.65
PSI	0.001	-0.003, 0.006	.60	0.004	-0.003, 0.010	.24
Grooved Pegboard	0.000	-0.004, 0.003	.85	-0.001	-0.006, 0.005	.77
Subiculum						
IQ	0.000	-0.003, 0.003	.96	0.000	-0.004, 0.004	.96
Rey Total	0.001	-0.003, 0.005	.71	0.001	-0.004, 0.007	.62
Rey Recall	0.001	-0.003, 0.005	.74	0.001	-0.004, 0.006	.66
WMS	0.001	-0.003, 0.005	.65	0.001	-0.004, 0.007	.61
Trails B	0.003	-0.002, 0.008	.28	0.004	-0.002, 0.010	.20
Animal Naming	-0.001	-0.005, 0.004	.74	-0.001	-0.006, 0.005	.76
WMI	0.000	-0.003, 0.004	.86	0.000	-0.004, 0.005	.86
PRI	-0.001	-0.005, 0.003	.52	-0.002	-0.007, 0.003	.53
VCI	-0.002	-0.006, 0.002	.35	-0.002	-0.007, 0.002	.31
PSI	0.003	-0.003, 0.009	.30	0.004	-0.002, 0.011	.21
Grooved Pegboard	0.001	-0.003, 0.005	.70	0.001	-0.004, 0.006	.68
CA1						
IQ	0.000	-0.003, 0.003	.84	0.000	-0.004, 0.004	.94
Rey Total	0.001	-0.004, 0.006	.63	0.002	-0.004, 0.009	.52
Rey Recall	0.003	-0.003, 0.009	.32	0.005	-0.003, 0.012	.21
WMS	0.001	-0.003, 0.006	.54	0.002	-0.004, 0.008	.48
Trails B	0.000	-0.004, 0.004	.94	0.000	-0.006, 0.005	.94
Animal Naming	0.003	-0.002, 0.008	.27	0.004	-0.002, 0.010	.18
WMI	-0.002	-0.007, 0.002	.35	-0.003	-0.009, 0.003	.27
PRI	0.000	-0.003, 0.004	.86	0.001	-0.004, 0.006	.73
VCI	-0.001	-0.005, 0.003	.55	-0.001	-0.006, 0.003	.61
PSI	0.003	-0.002, 0.008	.29	0.004	-0.002, 0.011	.19
Grooved Pegboard	0.001	-0.004, 0.006	.73	0.001	-0.006, 0.008	.71
Presubiculum						
IQ	0.002	-0.002, 0.006	.26	0.004	-0.001, 0.009	.16
Rey Total	0.001	-0.003, 0.005	.51	0.002	-0.003, 0.008	.41
Rey Recall	0.001	-0.003, 0.005	.67	0.002	-0.004, 0.007	.58
WMS	0.004	-0.002, 0.009	.19	0.005	-0.001, 0.012	.12
Trails B	0.004	-0.002, 0.010	.19	0.006	-0.001, 0.013	.11
Animal Naming	-0.001	-0.006, 0.004	.59	-0.002	-0.008, 0.005	.59
WMI	0.002	-0.002, 0.007	.33	0.003	-0.003, 0.009	.28
PRI	0.001	-0.003, 0.005	.62	0.002	-0.003, 0.007	.49
VCI	0.001	-0.003, 0.004	.74	0.001	-0.003, 0.006	.59
PSI	0.003	-0.003, 0.008	.31	0.004	-0.003, 0.011	.23
Grooved Pegboard	0.000	-0.004, 0.005	.87	0.001	-0.005, 0.006	.85
Molecular Layer						
IQ	-0.001	-0.004, 0.003	.74	-0.001	-0.005, 0.004	.82

Table S9. Age-45 hippocampal volume does not mediate the association between persistence of cannabis use from age 18-45 and neuropsychological test performance at age 45 years.

	Exposure: Persistence of cannabis dependence			Exposure: Persistence of regular cannabis use		
Mediator/Outcome	Indirect Effect	95% CI	p	Indirect Effect	95 % CI	p
Rey Total	0.001	-0.004, 0.006	.61	0.002	-0.004, 0.008	.51
Rey Recall	0.003	-0.002, 0.008	.28	0.005	-0.002, 0.012	.19
WMS	0.001	-0.003, 0.006	.57	0.002	-0.004, 0.008	.52
Trails B	0.000	-0.004, 0.004	.88	0.000	-0.005, 0.006	.86
Animal Naming	0.001	-0.003, 0.006	.56	0.002	-0.004, 0.009	.47
WMI	-0.002	-0.006, 0.002	.39	-0.003	-0.009, 0.003	.34
PRI	0.000	-0.004, 0.004	.94	0.000	-0.005, 0.005	.96
VCI	-0.001	-0.005, 0.003	.48	-0.002	-0.007, 0.003	.50
PSI	0.002	-0.003, 0.008	.36	0.004	-0.003, 0.010	.28
Grooved Pegboard	0.001	-0.005, 0.006	.77	0.001	-0.006, 0.009	.75
CA3						
IQ	-0.001	-0.005, 0.003	.59	-0.002	-0.005, 0.002	.45
Rey Total	0.000	-0.002, 0.003	.90	0.000	-0.003, 0.003	.85
Rey Recall	0.001	-0.003, 0.005	.58	0.002	-0.003, 0.007	.45
WMS	-0.001	-0.004, 0.003	.75	-0.001	-0.004, 0.003	.67
Trails B	-0.001	-0.004, 0.003	.63	-0.001	-0.005, 0.003	.52
Animal Naming	0.001	-0.003, 0.004	.64	0.001	-0.003, 0.005	.51
WMI	-0.002	-0.007, 0.004	.55	-0.002	-0.008, 0.003	.40
PRI	-0.001	-0.003, 0.002	.71	-0.001	-0.004, 0.003	.64
VCI	-0.001	-0.004, 0.002	.65	-0.001	-0.004, 0.002	.55
PSI	0.000	-0.002, 0.002	.95	0.000	-0.003, 0.003	.93
Grooved Pegboard	0.001	-0.003, 0.004	.71	0.001	-0.003, 0.005	.62
Dentate gyrus						
IQ	-0.001	-0.004, 0.002	.57	-0.001	-0.005, 0.003	.56
Rey Total	0.000	-0.004, 0.004	.96	0.000	-0.005, 0.005	.99
Rey Recall	0.002	-0.003, 0.006	.44	0.002	-0.003, 0.008	.38
WMS	0.001	-0.003, 0.004	.74	0.001	-0.004, 0.006	.70
Trails B	-0.001	-0.004, 0.003	.72	-0.001	-0.005, 0.004	.70
Animal Naming	0.001	-0.003, 0.006	.52	0.002	-0.003, 0.007	.44
WMI	-0.002	-0.007, 0.003	.38	-0.003	-0.008, 0.003	.31
PRI	0.000	-0.003, 0.003	.90	0.000	-0.004, 0.004	.95
VCI	-0.001	-0.005, 0.002	.48	-0.002	-0.006, 0.003	.45
PSI	0.001	-0.003, 0.006	.47	0.002	-0.003, 0.007	.40
Grooved Pegboard	0.000	-0.005, 0.005	.88	0.001	-0.006, 0.007	.87
CA4						
IQ	-0.001	-0.005, 0.002	.49	-0.001	-0.005, 0.002	.46
Rey Total	0.000	-0.004, 0.003	.92	0.000	-0.004, 0.004	.94
Rey Recall	0.001	-0.003, 0.005	.51	0.002	-0.003, 0.006	.48
WMS	0.000	-0.004, 0.003	.95	0.000	-0.004, 0.004	.94
Trails B	-0.001	-0.004, 0.003	.71	-0.001	-0.005, 0.003	.69
Animal Naming	0.001	-0.003, 0.005	.57	0.001	-0.003, 0.006	.51
WMI	-0.002	-0.007, 0.003	.37	-0.003	-0.008, 0.003	.32
PRI	0.000	-0.004, 0.003	.78	-0.001	-0.004, 0.003	.79
VCI	-0.001	-0.005, 0.002	.48	-0.002	-0.005, 0.002	.45
PSI	0.001	-0.003, 0.004	.59	0.001	-0.003, 0.005	.57
Grooved Pegboard	0.000	-0.004, 0.005	.85	0.001	-0.004, 0.005	.84

Note. Mediation tests were conducted in Mplus using maximum likelihood estimation and bootstrapped standard errors. Covariates included sex and child IQ. Estimates represent standardized indirect effects. Rey Total=Rey Auditory Verbal Learning Test total score (learning). Rey Recall= Rey Auditory Verbal Learning Test delayed recall (memory). WMS=Wechsler Memory Scale Months Backwards test. WMI=Working Memory Index. PRI=Perceptual Reasoning Index. VCI=Verbal Comprehension Index. PSI= Processing Speed Index.

Table S10. E-values for all dose-response associations that were statistically significant after adjusting for covariates.

Analysis	Exposure	Outcome	Regression coefficient for dose-response association	Standard Error of Regression Coefficient	E-value for point estimate (RR)	E-value for 95% CI
Dose-response for IQ (Table 3)	Persistence of cannabis dependence	IQ decline	-0.10	0.04	1.42	1.16
	Persistence of regular cannabis use	IQ decline	-0.10	0.04	1.42	1.16
Dose-response for Age-45 Neuropsychological Tests (Table 4)	Persistence of cannabis dependence	Rey total	-0.11	0.04	1.45	1.20
	Persistence of cannabis dependence	PSI	-0.10	0.04	1.42	1.16
	Persistence of regular cannabis use	Rey total	-0.13	0.03	1.50	1.33
	Persistence of regular cannabis use	Rey recall	-0.09	0.04	1.39	1.12
	Persistence of regular cannabis use	PRI	-0.07	0.03	1.33	1.11
	Persistence of regular cannabis use	PSI	-0.09	0.03	1.39	1.20
Dose-response for Age-45 Informant-reported Memory and Attention Problems (Table 6)	Persistence of cannabis dependence	Informant-reported memory problems	0.11	0.04	1.45	1.20
	Persistence of cannabis dependence	Informant-reported attention problems	0.15	0.04	1.56	1.34
	Persistence of regular cannabis use	Informant-reported memory problems	0.12	0.04	1.47	1.24

Table S10. E-values for all dose-response associations that were statistically significant after adjusting for covariates.

Analysis	Exposure	Outcome	Regression coefficient for dose-response association	Standard Error of Regression Coefficient	E-value for point estimate (RR)	E-value for 95% CI
	Persistence of regular cannabis use	Informant-reported attention problems	0.11	0.04	1.45	1.20
Dose-response for Age-45 Hippocampal Volume (Table S6)	Persistence of cannabis dependence	Fissure	-0.12	0.04	1.47	1.24
	Persistence of cannabis dependence	Tail	-0.10	0.04	1.42	1.16
	Persistence of regular cannabis use	Tail	-0.09	0.04	1.39	1.12
	Persistence of regular cannabis use	Pre-subiculum	-0.08	0.04	1.36	1.04

Note. RR=relative risk ratio. E-value for 95% CI represents the strength of the confounder (in terms of relative risk) that would be needed for observed associations between persistence of cannabis use and outcomes to have a confidence interval that included a null association. https://www.evalue-calculator.com/evalue/.

Table S11. Summary of results across tests of group comparisons and dose-response associations.

Outcome	Statistically significant difference: Long-term cannabis users vs. non-users?	Statistically significant dose-response after covariate adjustment: Exposure=persistence of cannabis dependence?	Statistically significant dose-response after covariate adjustment: Exposure=persistence of regular cannabis use?	Consistent association across two continuous exposures (persistence of cannabis dependence and persistence of regular cannabis use), after covariate adjustment?
Neuropsychological Test Performance				
IQ Change	Yes	Yes	Yes	Yes
Verbal Learning and Memory				
Rey Total (learning)	Yes	Yes	Yes	Yes
Rey Recall (memory)	Yes	No	Yes	No
Executive Function				
WMS	Yes	No	No	Yes
Trails B	No	No	No	Yes
Animal Naming	No	No	No	Yes
WMI	Yes	No	No	Yes
Perceptual reasoning				
PRI	Yes	No	Yes	No
Verbal Comprehension				
VCI	Yes	No	No	Yes
Processing Speed				
PSI	Yes	Yes	Yes	Yes
Motor Function				
Grooved Pegboard	No	No	No	Yes
Informant-Reported Memory Problems	Yes	Yes	Yes	Yes
Informant-Reported Attention Problems	Yes	Yes	Yes	Yes
Hippocampal Volume				
Bilateral Volume	Yes	No	No	Yes
Fissure	No	Yes	No	No
Tail	Yes	Yes	Yes	Yes
Parasubiculum	No	No	No	Yes
HATA	Yes	No	No	Yes
Fimbria	No	No	No	Yes
Subiculum	No	No	No	Yes

Table S11. Summary of results across tests of group comparisons and dose-response associations.

Outcome	Statistically significant difference: Long-term cannabis users vs. non-users?	Statistically significant dose-response after covariate adjustment: Exposure=persistence of cannabis dependence?	Statistically significant dose-response after covariate adjustment: Exposure=persistence of regular cannabis use?	Consistent association across two continuous exposures (persistence of cannabis dependence and persistence of regular cannabis use), after covariate adjustment?
CA1	Yes	No	No	Yes
Presubiculum	No	No	Yes	No
Molecular Layer	Yes	No	No	Yes
CA3	No	No	No	Yes
Dentate gyrus	Yes	No	No	Yes
CA4	No	No	No	Yes

Note. The first three columns show whether associations were statistically significant in tests of (i) long-term cannabis users vs. non-users, (ii) dose-response associations with persistence of cannabis dependence as the exposure, after controlling for covariates and (iii) dose-response associations with persistence of regular cannabis use as the exposure, after controlling for covariates. The first three columns are shaded light gray if findings were consistent across all three tests (either all three tests showed a statistically significant association, or all three tests showed a non-significant association). The last column shows if dose-response associations were consistent after controlling for covariates (either consistently statistically significant or consistently non-significant) across the two exposures (either persistence of cannabis dependence or persistence of regular cannabis use), and is shaded dark gray if associations were consistent.

Figure S1. Long-term cannabis users and 5 comparison groups. Long-term cannabis users: N=86. Lifelong cannabis non-users: N=202. Long-term tobacco users: N=75. Long-term alcohol users: N=57. Midlife recreational cannabis users: N=65. Cannabis quitters: N=60.

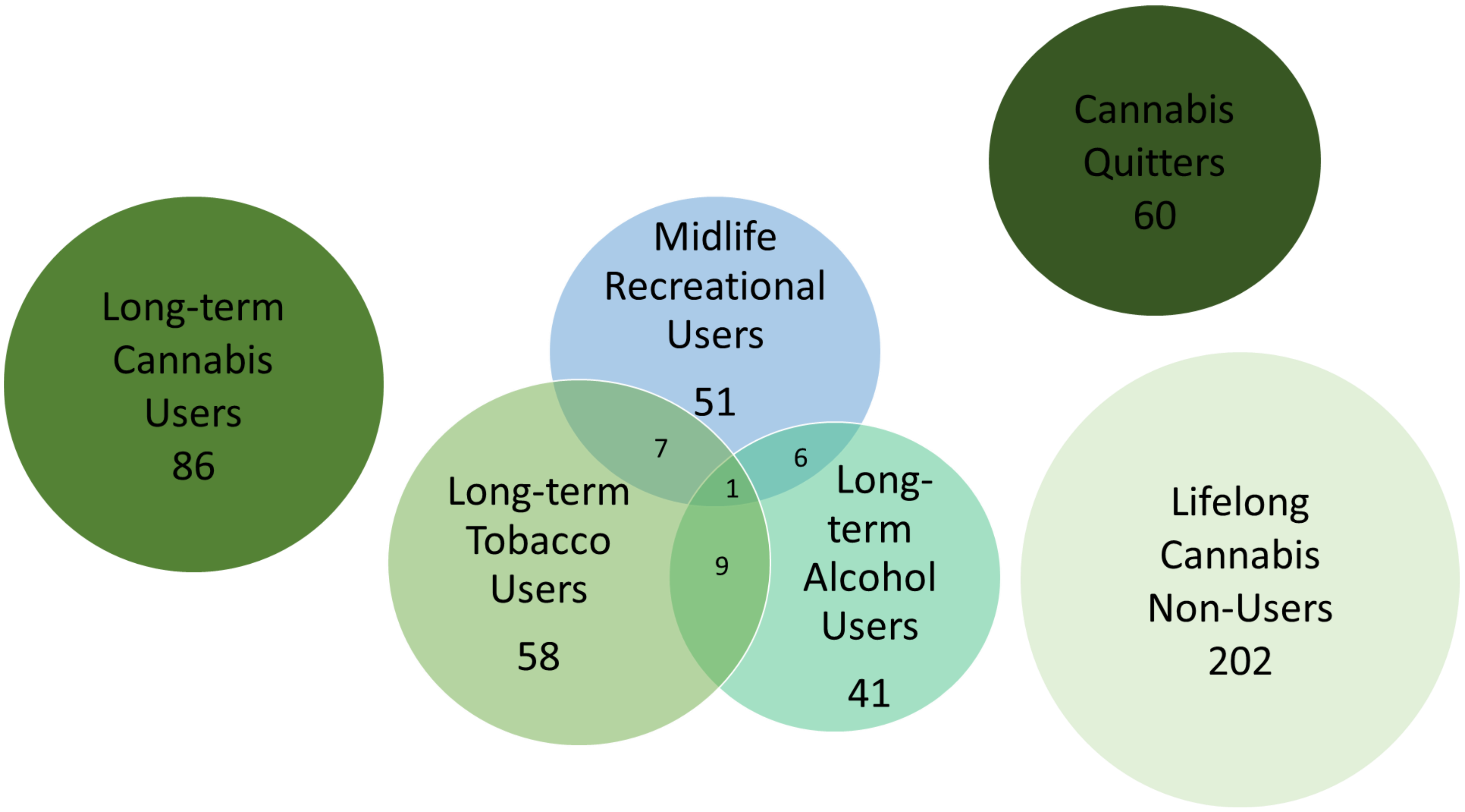
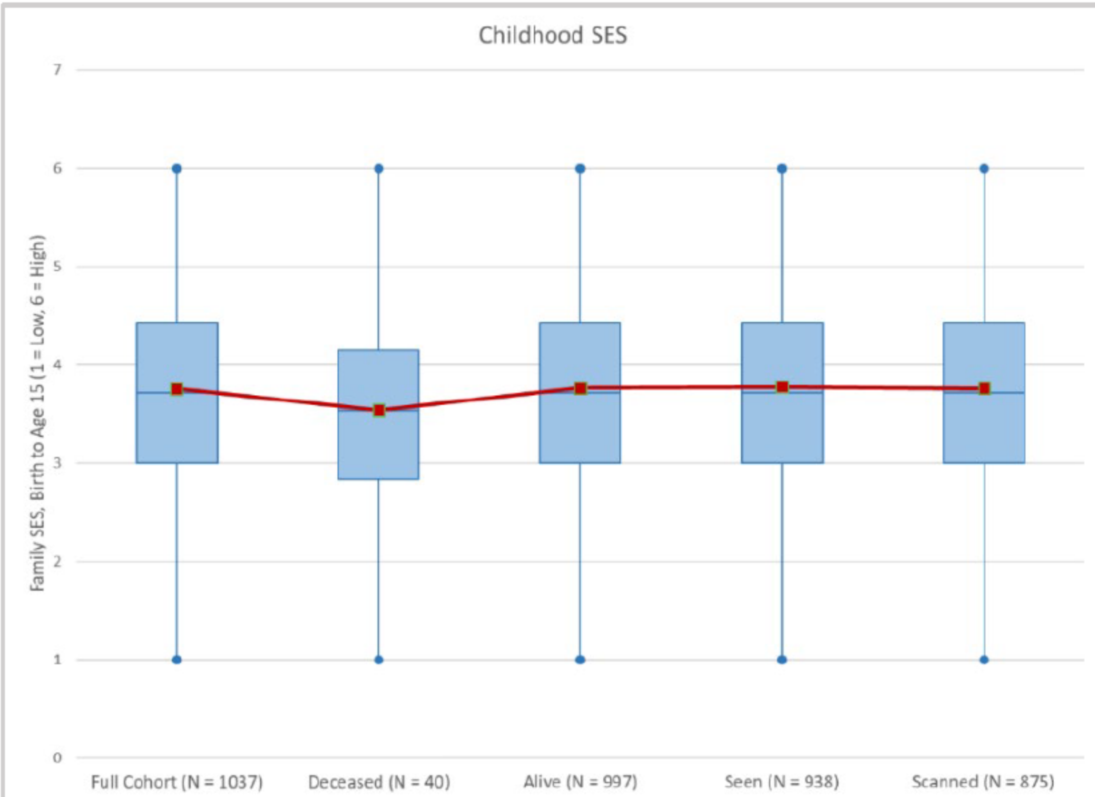


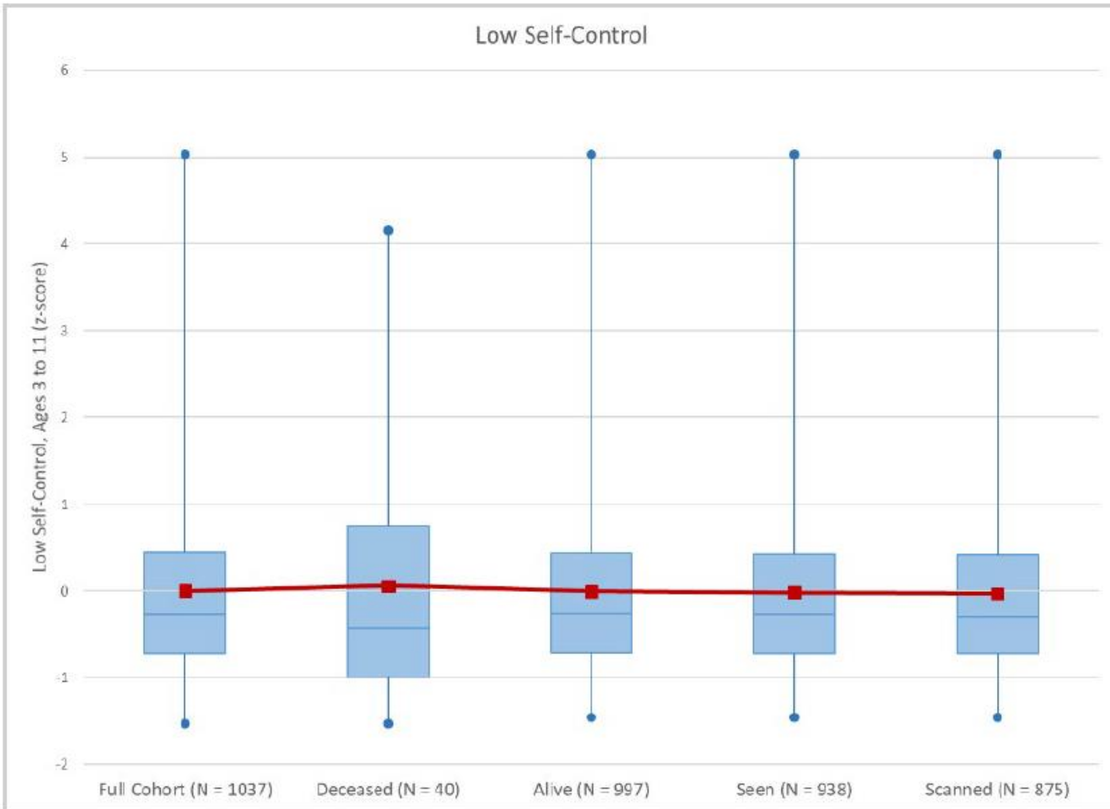
Figure S2. Attrition.

We conducted an attrition analysis using childhood socioeconomic status (SES), childhood low self-control, and childhood IQ (the Wechsler Intelligence Scale for Children–Revised (WISC–R)) to determine whether participants in the Phase-45 data collection were representative of the original cohort.

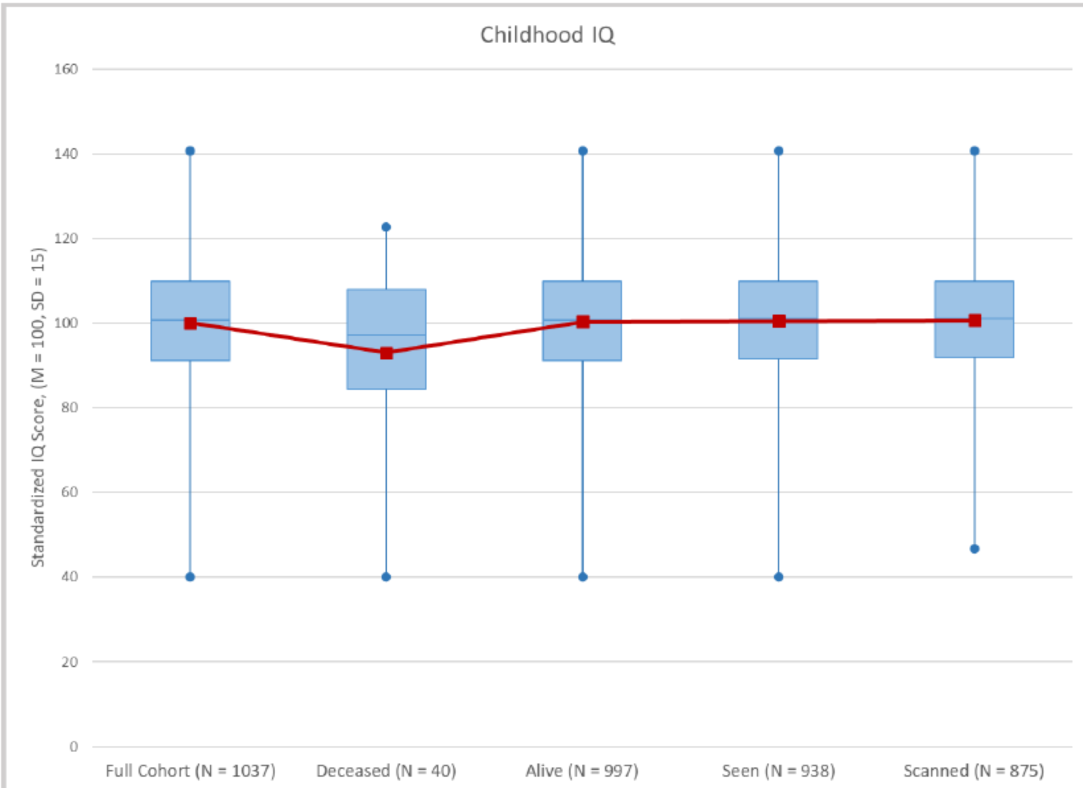
No significant differences were found between the full cohort, those deceased, those alive, those seen at Phase 45, or those scanned at Phase 45 on childhood SES.



No significant differences were found between the full cohort, those deceased, those alive, those seen at Phase 45, or those scanned at Phase 45 on childhood self-control problems.



No significant differences in childhood IQ were found between the full cohort, those still alive, those seen at Phase 45, or those scanned at Phase 45. Those who were deceased by the Phase-45 data collection had significantly lower childhood IQ's than those who were still alive (t=2.09, p=.04).



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