Long-Term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife

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Objective: Cannabis use is increasing among midlife and older adults. This study tested the hypotheses that long-term cannabis use is associated with cognitive deficits and smaller hippocampal volume in midlife, which is important because midlife cognitive deficits and smaller hippocampal volume are risk factors for dementia.

Methods: Participants are members of a representative cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972–1973 and followed to age 45, with 94% retention. Cannabis use and dependence were assessed at ages 18, 21, 26, 32, 38, and 45. IQ was assessed at ages 7, 9, 11, and 45. Specific neuropsychological functions and hippocampal volume were assessed at age 45.

Results: Long-term cannabis users showed IQ decline from childhood to midlife (mean=−5.5 IQ points), poorer learning and processing speed relative to their childhood IQ, and informant-reported memory and attention problems. These deficits were specific to long-term cannabis users because they were either not present or were smaller among long-term tobacco users, long-term alcohol users, midlife recreational cannabis users, and cannabis quitters. Cognitive deficits among long-term cannabis users could not be explained by persistent tobacco, alcohol, or other illicit drug use, childhood socioeconomic status, low childhood self-control, or family history of substance dependence. Long-term cannabis users showed smaller hippocampal volume, but smaller hippocampal volume did not statistically mediate cannabis-related cognitive deficits.

Conclusions: Long-term cannabis users showed cognitive deficits and smaller hippocampal volume in midlife. Research is needed to ascertain whether long-term cannabis users show elevated rates of dementia in later life.

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In case-control studies, cannabis users exhibit subtle cognitive deficits and structural brain differences (1, 2). These findings come largely from studies of adolescents and young adults (3, 4). It is unclear whether the subtle cognitive and brain differences observed in young cannabis users might be larger in midlife and older adult cannabis users with longer histories of use (5). This issue is timely because cannabis use is increasing among baby boomers (born 1946–1964), a group who used cannabis at historically high rates as young adults (6) and who now use cannabis at historically high rates as midlife and older adults (7). This issue is important because mild cognitive deficits and greater hippocampal atrophy in midlife are risk factors for later dementia (8, 9).

We identified four longitudinal studies and seven cross-sectional studies that reported on cannabis users in midlife or older adulthood (3, 10–19) (see Table S1 in the online supplement). Limitations include use of crude or retrospective measures of cannabis exposure and a lack of neuroimaging data. Further, the studies did not address four questions of policy significance. First, are all midlife and older adult cannabis users at risk? Older adults in the United States are increasingly using cannabis (7), but only 10%−15% of users are cannabis dependent (20). Distinguishing problem and non–problem users is important, because non–problem users may not differ from nonusers. Second, are cognitive deficits and brain differences among cannabis users minor compared with those observed for alcohol or tobacco users, as some proponents of cannabis legalization claim (21)? Third, do differences among cannabis users persist after cessation? If so, these differences could increase risk for dementia. Fourth, do brain differences among long-term cannabis users underlie cognitive deficits? Brain differences, if observed, are inconsistently related to cognitive deficits in adolescent and young adult cannabis users. Research is needed in midlife and older adult cannabis users.

We addressed these questions by assessing cannabis use, cognitive function, and hippocampal volume in a population-representative cohort followed prospectively from birth to

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TABLE 1. Sociodemographic characteristics and substance use for the full Dunedin cohort, long-term cannabis users, and five informative comparison groups[a]

Characteristic	Full Cohort (N=938)		Long-Term Cannabis Users (N=86)		Cannabis Nonusers (N=202)		Long-term Tobacco Users (N=75)		Long-term Alcohol Users (N=57)		Midlife Recreational Cannabis Users (N=65)		Cannabis Quitters (N=60)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Male	474	50.5	55	64.0	82	40.6	30	40.0	32	56.1	38	58.5	37	61.7
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Childhood SES	3.78	1.13	3.42	1.08	3.92	1.17	3.23	0.97	3.80	1.18	3.86	1.24	3.57	1.20
Childhood low self-control	−0.02	0.96	0.34	1.08	−0.19	0.88	0.43	1.19	−0.01	0.92	−0.06	1.00	0.16	1.06
Family history of substance dependence	0.15	0.17	0.21	0.21	0.10	0.13	0.20	0.18	0.14	0.15	0.13	0.14	0.19	0.18
Substance use at age 45														
Cannabis frequency (days in past year)	25.70	82.90	257.07	117.84	0.00	0.00	0.11[b]	0.48	0.32[c]	1.18	4.88	8.24	0.00	0.00
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Weekly cannabis use	89	9.6	85	98.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Regular cannabis use[d]	56	6.1	55	64.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Daily tobacco use	199	21.6	54	63.5	0	0.0	75	100.0	10	17.5	13	20.0	20	33.3
Weekly alcohol use	856	92.6	76	88.4	184	91.1	68	90.7	57	100.0	62	95.4	50	83.3
Cannabis dependence	19	2.1	19	22.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tobacco dependence	107	11.6	38	44.7	0	0.0	37	50.0	6	10.5	5	7.7	10	16.7
Alcohol dependence	104	11.3	17	19.8	0	0.0	7	9.3	30	52.6	11	16.9	10	16.7
Illicit drug dependence	31	3.4	13	15.1	0	0.0	3	4.0	1	1.8	2	3.1	3	5.0
Amphetamine use[e]	29	3.1	16	18.6	0	0.0	1	1.3	0	0.0	2	3.1	3	5.0
Sedative use[e]	13	1.4	7	8.1	1	0.5	1	1.3	0	0.0	0	0.0	1	1.7
Cocaine use[e]	15	1.6	3	3.5	0	0.0	0	0.0	2	3.5	3	4.6	2	3.3
Opioid use[e]	15	1.6	8	9.3	0	0.0	2	2.7	0	0.0	1	1.5	0	0.0
PCP use[e]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hallucinogen use[e]	19	2.1	10	11.6	0	0.0	0	0.0	1	1.8	2	3.1	1	1.7
Inhalant use[e]	1	0.1	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other drugs[e]	7	0.8	3	3.5	0	0.0	0	0.0	2	3.5	1	1.5	0	0.0
Methadone maintenance	10	1.1	5	5.8	0	0.0	1	1.3	0	0.0	0	0.0	2	3.3

[a] PCP=phencyclidine; SES=socioeconomic status.
[b] Only four long-term tobacco users reported past-year cannabis use, with maximum use of 3 days.
[c] Only six long-term alcohol users reported past-year cannabis use, with maximum use of 7 days.
[d] Regular use ≥4 days per week.
[e] Used at least six times in the past year.

age 45. We compared long-term cannabis users against five groups: 1) lifelong cannabis nonusers (to replicate the control group most often reported in the case-control literature); 2) midlife recreational cannabis users (to ascertain whether cognitive deficits and structural brain differences are apparent in non–problem users—the majority of cannabis users); 3) long-term tobacco users and 4) long-term alcohol users (to serve as benchmark comparisons for any cannabis findings and to help disentangle potential cannabis effects from tobacco and alcohol effects); and 5) cannabis quitters (to ascertain whether differences are apparent after cessation).

We also conducted tests of dose-response associations using continuously measured persistence of cannabis use, and we rigorously adjusted for numerous confounders derived from multiple longitudinal waves and data sources. Robust dose-response associations would be expected if associations were causal. Finally, we tested whether associations between continuously measured persistence of cannabis use and cognitive deficits were mediated by hippocampal volume differences, a hypothesis that is fairly ubiquitous in the literature (22–24). We focused on the hippocampus because it has a high density of cannabinoid receptors, is instrumental for learning and memory (one of the most consistently impaired cognitive domains in cannabis users), and has been shown through meta-analysis to be the brain region that most consistently emerges as smaller in cannabis users relative to comparison subjects (2).

METHODS

Participants

Participants are members of the Dunedin Longitudinal Study, a representative birth cohort (N=1,037; 91% of eligible births; 52% male) born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible based on residence in the province and who participated in the first assessment at age 3. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island (25). As adults, the cohort's members match the New Zealand National Health and Nutrition Survey on key health

TABLE 2. Child IQ, adult IQ, and IQ change: comparison of long-term cannabis users and five informative subgroups in the Dunedin cohort[a]

			Comparison Group														
	Long-Term Cannabis Users (N=84)		1. Cannabis Nonusers (N=196)		2. Long-term Tobacco Users (N=75)		3. Long-term Alcohol Users (N=57)		4. Midlife Recreational Cannabis Users (N=65)		5. Cannabis Quitters (N=59)		Difference Between Long-Term Cannabis Users and Comparison Groups				
													LT vs. 1	LT vs. 2	LT vs. 3	LT vs. 4	LT vs. 5
IQ	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	p	p	p	p	p
Child IQ	99.3	96.4, 102.2	101.4	99.4, 103.4	93.0	89.8, 96.2	99.3	96.1, 102.5	105.1	102.0, 108.3	97.6	93.7, 101.5	0.14	**0.01**	0.99	**0.006**	0.48
Adult IQ	93.8	90.6, 97.0	102.1	99.9, 104.2	91.5	88.2, 94.7	98.8	95.8, 101.8	101.6	98.1, 105.2	94.3	90.6, 98.0	**<0.001**	0.44	**0.03**	**0.001**	0.85
Δ IQ	−5.5	−7.4, −3.6	0.70	−0.67, 2.0	−1.5	−3.8, 0.75	−0.50	−2.8, 1.8	−3.5	−5.8, −1.2	−3.3	−6.7, 0.01	**<0.001**	**0.02**	**<0.001**	0.17	0.24
Δ ES IQ	−0.37	−0.57, −0.18	0.25	0.12, 0.39	0.03	−0.20, 0.26	0.13	−0.10, 0.37	−0.17	−0.40, 0.06	−0.15	−0.49, 0.18	—	—	—	—	—

[a] Statistical tests of group comparisons are adjusted for sex, but means are unadjusted. Δ IQ=change in IQ (adult IQ minus child IQ); Δ ES IQ= effect size for IQ change (IQ change scores were standardized on the full sample [mean=0, SD=1]); LT=long-term cannabis users. Boldface for p values indicates a statistically significant difference ($p<0.05$) compared with long-term cannabis users. Dashes for Δ ES IQ indicate that the results are the same as the results for Δ IQ.

indicators (e.g., body mass index, smoking, physical activity, physician visits) (25) and the New Zealand Census of citizens the same age on educational attainment (26). The cohort is primarily white (93%), which matches South Island demographics. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and, most recently (completed April 2019), 45 years. Participants gave written informed consent. Study protocols were approved by the New Zealand Health and Disability Ethics Committee.

Measures

Measures are briefly described here, and details are provided in Table S2 in the online supplement.

Long-term cannabis users and five comparison groups. At ages 18, 21, 26, 32, 38, and 45, study members were interviewed about their substance use using the Diagnostic Interview Schedule (27, 28), and past-year substance use dependencies were assessed following DSM criteria (29, 30). This information was used to identify long-term cannabis users and five comparison groups (see Figure S1 in the online supplement).

Long-term cannabis users (N=86; 64% male) used cannabis weekly or more frequently in the past year at age 45, or were dependent on cannabis at age 45, and also used cannabis weekly or more frequently at one or more previous assessment waves. Of these, 31.4% used cannabis before age 18, 89.5% used regularly (≥4 days per week) at one or more waves (mean=3.4 waves, SD=1.4), and 72% met criteria for cannabis dependence at one or more waves. Frequency of use among long-term cannabis users at age 45 was a median of 300 days in the past year, with 64% using ≥4 days per week.

Lifelong cannabis nonusers (N=202; 41% male) never used cannabis, never had a diagnosis of any substance use disorder, and never used tobacco daily.

Long-term tobacco users (N=75; 40% male) smoked tobacco daily at age 45 and also smoked daily at one or more previous waves; were mostly free from cannabis at age 45 (Table 1); and had no history of weekly cannabis use or dependence.

Long-term alcohol users (N=57, 56% male) were weekly drinkers at age 45; had a diagnosis of alcohol dependence at two or more waves; were mostly free from cannabis at age 45 (Table 1); and had no history of weekly cannabis use or dependence.

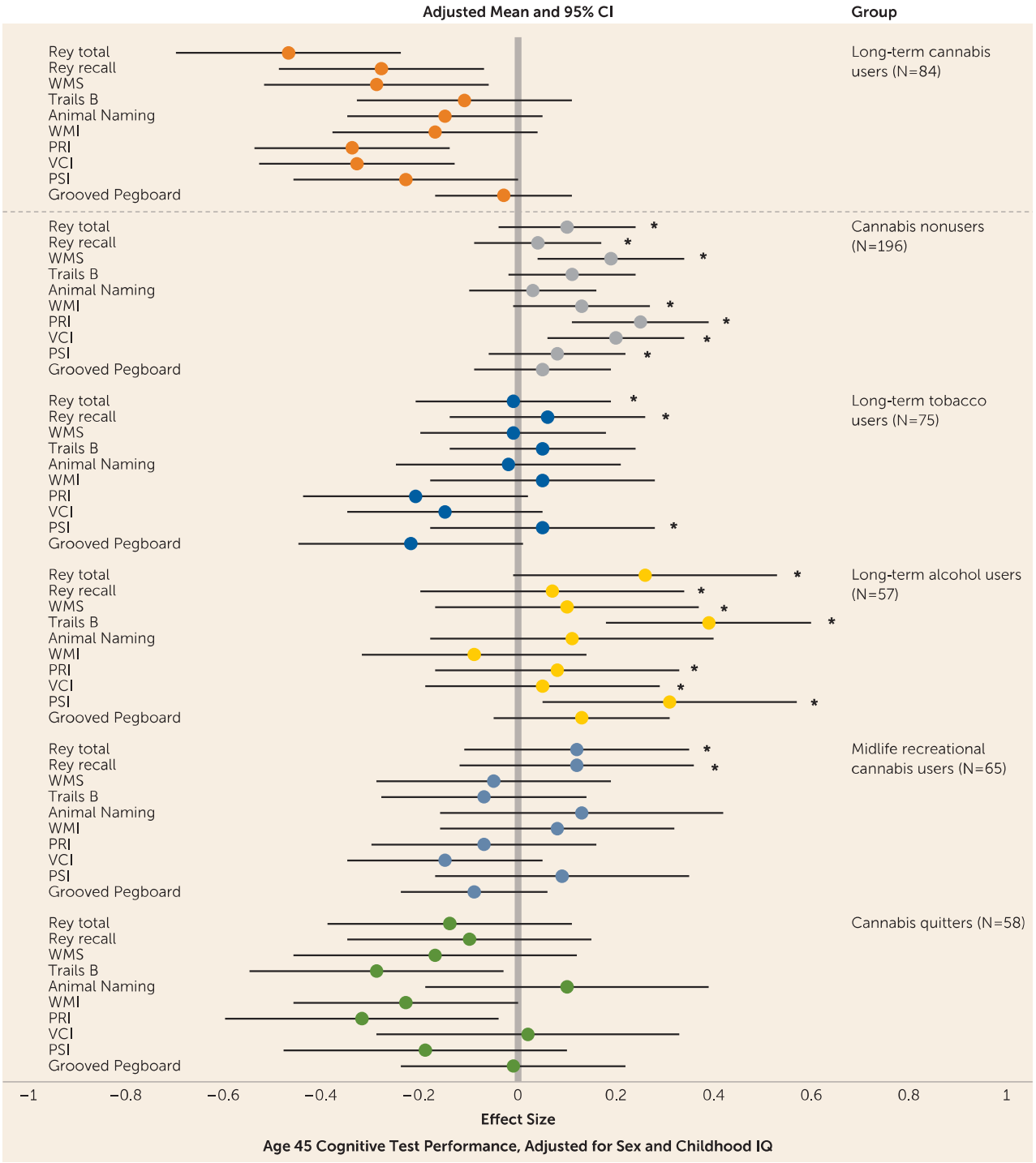
Midlife recreational cannabis users (N=65; 59% male) used cannabis between 6 and 51 days per year (i.e., used more than a few times but less than weekly) in midlife (age 32, 38, or 45), and had no history of weekly cannabis use or dependence.

Cannabis quitters (N=60; 62% male) did not use cannabis at age 45 but previously either were diagnosed with cannabis dependence or used regularly (≥4 days per week).

Persistence of cannabis dependence and persistence of regular cannabis use. Persistence of cannabis dependence comprised those who 1) never used cannabis (N=262), 2) used but were never diagnosed (N=498), 3) were diagnosed at one wave (N=85), 4) were diagnosed two waves (N=39), 5) were diagnosed three waves (N=32), and 6) were diagnosed at ≥4 waves (N=16). Persistence of regular cannabis use (i.e., ≥4 days per week) comprised those who never used cannabis (N=262), 2) used but never regularly (N=518), 3) used regularly at one wave (N=57), 4) two waves (N=32), 5) three waves (N=33), and 6) ≥4 waves (N=30). Agreement between the two exposures was high but not perfect (weighted kappa=0.75), because many regular users did not develop dependence (20). Persistence of tobacco dependence, alcohol dependence, and other illicit drug dependence were similarly defined (see Table S2 in the online supplement).

Cognitive tests. Intelligence was assessed at ages 7, 9, and 11 years, before the onset of cannabis use, and again in adulthood at age 45. We report comparison of the Wechsler Intelligence Scale for Children–Revised (31), averaged across ages 7–11, and the Wechsler Adult Intelligence Scale–IV (WAIS-IV) at age 45 (32). We also report performance on

FIGURE 1. Long-term cannabis use and neuropsychological functions in the Dunedin cohort[a]



[a] The figure shows a comparison of long-term cannabis users with five informative subgroups on age 45 test performance across specific neuropsychological domains. Mean scores on age 45 neuropsychological tests were adjusted for sex and childhood IQ and standardized on the full cohort (mean=0, SD=1). Average normative performance is indicated by the reference line at the representative cohort mean of 0. Estimates below zero indicate poorer than average test performance. Asterisks indicate mean scores that were statistically significantly better ($p<0.05$) as compared with long-term cannabis users, after adjustment for sex and childhood IQ. PRI=perceptual reasoning index; PSI=processing speed index; Rey recall and Rey total=Rey Auditory Verbal Learning Test delayed recall score (memory) and total score (learning); VCI=verbal comprehension index; WMI=working memory index; WMS=Wechsler Memory Scale, months backward test.

TABLE 3. Dose-response associations between persistence of cannabis dependence or persistence of regular cannabis use from ages 18 to 45 and IQ change from childhood to adulthood in the Dunedin cohort

						Statistical Tests[b]								
						Model 1			Model 2			Model 3		
Mean Standardized IQ Change[a]						β	95% CI	p	β	95% CI	p	β	95% CI	p
Persistence of cannabis dependence														
Never used (N=255)	Used but never diagnosed (N=496)	1 diagnosis (N=83)	2 diagnoses (N=39)	3 diagnoses (N=32)	≥4 diagnoses (N=15)									
0.21	−0.02	−0.18	−0.17	−0.40	−0.66	**−0.16**	**−0.23, −0.10**	**<0.001**	**−0.09**	**−0.18, −0.01**	**0.02**	**−0.10**	**−0.18, −0.01**	**0.02**
Persistence of regular cannabis use														
Never used (N=255)	Used but never regularly (N=516)	Used regularly 1× (N=55)	Used regularly 2× (N=32)	Used regularly 3× (N=33)	Used regularly ≥4× (N=29)									
0.21	−0.01	−0.26	−0.29	−0.27	−0.52	**−0.16**	**−0.23, −0.10**	**<0.001**	**−0.10**	**−0.18, −0.02**	**0.01**	**−0.10**	**−0.18, −0.03**	**0.01**

[a] Means represent unadjusted IQ change scores (adult IQ minus child IQ) that were standardized on the full sample prior to analysis (mean=0, SD=1).
[b] Model 1 was adjusted for sex; model 2 was additionally adjusted for persistent dependence on tobacco, alcohol, and other illicit drugs; and model 3 was additionally adjusted for low childhood socioeconomic status, low childhood self-control, and family history of substance dependence. Beta coefficients represent standardized estimates. Boldface indicates statistically significant estimates ($p<0.05$).

the WAIS-IV working memory index, perceptual reasoning index, verbal comprehension index, and processing speed index. At age 45, additional neuropsychological tests were administered: the Rey Auditory Verbal Learning Test (33), the Months Backward Test from the Wechsler Memory Scale–III (34), the Trail Making Test (35), the Animal Naming Test (36), and the Grooved Pegboard Test (33). All testing occurred in the morning.

Informant-reported memory and attention problems. At age 45, participants nominated people "who knew them well" as informants for the study. Informants completed mailed questionnaire checklists, which included items on whether the participant had problems with memory (e.g., forgets to do errands, return calls, pay bills) and attention (e.g., is easily distracted, gets sidetracked easily) over the past year.

Hippocampal volume. Structural MRI was carried out at age 45 for 875 study members (93% of age 45 participants). T_1-weighted and fluid-attenuated inversion recovery images were processed with FreeSurfer, version 6.0. Mean hippocampal gray matter volume was extracted using the automatic segmentation (*aseg*) step. Accuracy of subcortical segmentation was confirmed by visual inspection of the *aseg* labels overlaid on the volumes. Mean volumes within 12 hippocampal subfields were estimated with FreeSurfer's hippocampal subfields module. We report on bilateral total hippocampal volume and 12 subfield volumes (37) because the hippocampus is composed of anatomically and functionally distinct subfields, and examining them could provide a more nuanced understanding of potential cannabis effects on this structure.

Covariates. We selected covariates based on theory and documented associations with cannabis use, cognitive functioning, and brain volume: sex, persistent tobacco dependence, persistent alcohol dependence, persistent other illicit drug dependence, childhood socioeconomic status, low childhood self-control, and family substance dependence history (see Table S2 in the online supplement).

Statistical Analysis

We used t tests to compare long-term cannabis users with the five comparison groups. We used ordinary least squares regression to test dose-response associations between persistence of cannabis use (continuously measured) and outcomes, with associations adjusted for sex (model 1); sex and persistent alcohol, tobacco, and other illicit drug dependence (model 2); and these covariates plus childhood socioeconomic status, low childhood self-control, and family substance dependence history (model 3). We used path analysis to test mediation (i.e., whether the association between persistence of cannabis use and cognitive deficits arises indirectly through hippocampal volume). Mediation analyses were conducted in MPlus using maximum likelihood estimation and bootstrapped standard errors. Analyses were preregistered (https://sites.duke.edu/moffittcaspiprojects/files/2021/07/Meier_2020.pdf).

RESULTS

Of 997 cohort members still alive at age 45 years, 938 (94.1%) were assessed at age 45. Age 45 participants did not differ significantly from other participants on childhood socioeconomic status, childhood self-control, or childhood IQ (see Figure S2 in the online supplement). Table 1

summarizes the sociodemographic and substance use characteristics of the age 45 cohort, long-term cannabis users, and the five comparison groups.

Cannabis and Cognitive Functioning

Long-term cannabis users and the five comparison groups. Relative to the normative IQ of 100, long-term cannabis users had average IQ as children (mean=99.3) but below-average IQ as adults (mean=93.8). Their mean 5.5-point childhood-to-adulthood IQ decline was significantly larger than that observed among lifelong cannabis nonusers (mean=0.70), long-term tobacco users (mean=−1.5), and long-term alcohol users (mean=−0.50) (Table 2). Long-term cannabis users' IQ decline was not significantly larger than midlife recreational cannabis users' (mean=−3.5) or cannabis quitters' (mean=−3.3).

To ascertain whether long-term cannabis users showed deficits in specific neuropsychological functions, we examined age 45 test performance, with estimates adjusted for sex and childhood IQ (Figure 1; see also Table S3 in the online supplement). Long-term cannabis users performed significantly worse than lifelong nonusers on most tests; worse than long-term tobacco users on tests of learning and memory (Rey total and delayed recall) and processing speed; worse than long-term alcohol users on tests of learning and memory (Rey total and recall), executive function (Wechsler Memory Scale, Trails B), perceptual reasoning index, verbal comprehension index, and processing speed; and worse than midlife recreational cannabis users on tests of learning and memory. Long-term cannabis users did not perform significantly worse than cannabis quitters on any test.

Dose-response associations. Participants who used cannabis more persistently showed greater IQ decline than less persistent users, even after adjustment for persistent use of other substances, childhood socioeconomic status, low childhood self-control, and family substance dependence history (Table 3).

For specific neuropsychological functions, participants who used cannabis more persistently performed worse on most age 45 tests than less persistent users after adjusting for sex and childhood IQ (Table 4, model 1). Associations were attenuated after adjustment for persistent use of other substances (Table 4, model 2) and, to a lesser extent, after additional adjustment for childhood covariates (Table 4, model 3). However, even after adjustment for all covariates, more persistent cannabis users performed worse than less persistent users on tests of learning (Rey total), processing speed, and, to a lesser extent, verbal memory (Rey recall) and perceptual reasoning (Table 4, model 3).

Associations between persistence of cannabis use and cognitive functioning could not be explained by recent cannabis use (see Table S4 in the online supplement).

Cannabis and Informant-Reported Cognitive Problems

Long-term cannabis users and the five comparison groups. Long-term cannabis users showed significantly more informant-reported memory and attention problems at age 45 than all groups except long-term tobacco users and cannabis quitters (Table 5).

Dose-response associations. Participants who used cannabis more persistently had more memory and attention problems than less persistent users, according to informants, even after covariate adjustment (Table 6).

Cannabis and Hippocampal Volume

Long-term cannabis users and the five comparison groups. Long-term cannabis users showed significantly smaller volumes than cannabis nonusers in the left and right total hippocampus and five of 12 subfields (tail, hippocampal amygdala transition area, CA1, molecular layer, dentate gyrus), and significantly smaller volumes than midlife recreational cannabis users in the left and right hippocampus and three of 12 subfields (tail, CA1, and molecular layer) (Figure 2; see also Table S5 in the online supplement). Long-term cannabis users generally did not show significantly smaller volumes in left and right total hippocampus or hippocampal subfields than long-term tobacco users, long-term alcohol users, or cannabis quitters.

Dose-response associations. Participants who used cannabis more persistently had smaller volumes than less persistent users in the left and right hippocampus and numerous hippocampal subfields, after adjusting for sex. Most associations were nonsignificant after additional covariate adjustment (see Table S6 in the online supplement). Adjusting for total brain volume slightly attenuated associations (see Table S7 in the online supplement).

Test of Hippocampal Volume as a Mediator of Associations Between Persistence of Cannabis Use and Cognitive Deficits

Persistence of cannabis use was associated with cognitive deficits and, to a lesser extent, smaller hippocampal volume. Larger hippocampal volume was related to better cognitive test performance (see Table S8 in the online supplement). However, smaller hippocampal volume did not statistically mediate associations between persistence of cannabis use and cognitive deficits (see Table S9 in the online supplement).

Robustness to Unmeasured Confounding

To ascertain the robustness of associations to unmeasured confounding, we computed E-values for dose-response associations that were statistically significant after covariate adjustment (see Table S10 in the online supplement) (38). E-values were used to estimate how large a relative risk ratio would need to be between an unmeasured confounder and both persistence of cannabis use and outcomes to fully account for observed associations. E-values ranged from 1.33 to 1.56, which represent the risk

TABLE 4. Dose-response associations between persistence of cannabis dependence or persistence of regular cannabis use from ages 18 to 45 and neuropsychological test performance at age 45 in the Dunedin cohort[a]

Test	Mean Standardized Neuropsychological Test Scores[b]					
Persistence of cannabis dependence						
	Never used (N=261)	Used but never diagnosed (N=498)	1 diagnosis (N=85)	2 diagnoses (N=39)	3 diagnoses (N=32)	≥4 diagnoses (N=16)
Rey total	0.10	0.11	−0.37	−0.53	−0.46	−0.72
Rey recall	0.09	0.08	−0.36	−0.55	−0.26	−0.32
WMS	0.15	0.05	−0.48	−0.06	−0.41	−0.71
Trails B	0.07	0.05	−0.32	−0.20	−0.05	−0.43
Animal Naming	−0.01	0.02	−0.01	0.01	−0.12	−0.12
WMI	0.02	0.05	−0.23	−0.11	−0.08	−0.24
PRI	0.03	0.07	−0.29	−0.27	−0.13	−0.28
VCI	−0.02	0.06	−0.21	0.17	−0.43	−0.04
PSI	0.04	0.11	−0.35	−0.39	−0.38	−0.60
Grooved Pegboard	−0.01	0.07	−0.10	−0.41	−0.23	−0.15
Persistence of regular cannabis use						
	Never used (N=261)	Used but never regularly (N=518)	Regularly used 1× (N=57)	Regularly used 2× (N=32)	Regularly used 3× (N=33)	Regularly used ≥4× (N=30)
Rey total	0.10	0.11	−0.30	−0.72	−0.79	−0.55
Rey recall	0.09	0.09	−0.25	−0.67	−0.64	−0.39
WMS	0.15	0.04	−0.26	−0.55	−0.45	−0.45
Trails B	0.07	0.03	−0.10	−0.14	−0.32	−0.39
Animal Naming	−0.01	0.05	0.02	−0.41	−0.18	−0.25
WMI	0.02	0.04	−0.04	−0.27	−0.18	−0.22
PRI	0.03	0.07	−0.03	−0.39	−0.42	−0.55
VCI	−0.02	0.07	0.16	−0.39	−0.59	−0.31
PSI	0.04	0.09	−0.16	−0.64	−0.40	−0.57
Grooved Pegboard	−0.01	0.07	−0.21	−0.23	−0.21	−0.32

[a] PRI=perceptual reasoning index; PSI=processing speed index; Rey recall and Rey total=Rey Auditory Verbal Learning Test delayed recall score (memory) and total score (learning); VCI=verbal comprehension index; WMI=working memory index; WMS=Wechsler Memory Scale, months backward test.
[b] Means represent unadjusted test scores that were standardized (mean=0, SD=1) on the full sample prior to analyses. Lower scores indicate poorer test performance.
[c] Model 1 was adjusted for sex and childhood IQ; model 2 was additionally adjusted for persistent dependence on tobacco, alcohol, and other illicit drugs; and model 3 was additionally adjusted for low childhood socioeconomic status, low childhood self-control, and family history of substance dependence. Beta coefficients represent standardized estimates. Boldface indicates statistically significant estimates ($p<0.05$).

ratios needed for unmeasured confounders after adjustment for measured confounders.

DISCUSSION

This prospective study followed a population-representative birth cohort for 45 years, generating a unique evidence base for evaluating whether long-term cannabis users show cognitive deficits and smaller hippocampal volume in midlife. The longitudinal design enabled a comparison of a person's midlife cognitive abilities to their childhood cognitive abilities before cannabis initiation. The study also enabled a test of the role of hippocampal gray matter volume in mediating associations between long-term cannabis use and cognitive deficits. Six findings stand out.

First, long-term cannabis users exhibited IQ decline and poorer learning and processing speed in midlife relative to their childhood IQ. People who knew them well described them as having memory and attention problems. These associations were not explained by prospectively assessed persistent tobacco, alcohol, and other illicit drug dependence or by childhood socioeconomic status, low childhood self-control, and family substance dependence history. Associations were also not explained by recent cannabis use. Findings were consistent across two cannabis exposures (persistence of cannabis dependence, persistence of regular use) and in tests comparing long-term cannabis users to five comparison groups (cannabis nonusers, tobacco users, alcohol users, recreational cannabis users, and cannabis quitters). (Table S11 in the online supplement summarizes findings across tests of

Statistical Tests[c]								
Model 1			Model 2			Model 3		
β	95% CI	p	β	95% CI	p	β	95% CI	p
−0.14	**−0.19, −0.08**	**<0.001**	**−0.12**	**−0.19, −0.05**	**<0.001**	**−0.11**	**−0.18, −0.04**	**0.002**
−0.08	**−0.13, −0.02**	**0.01**	−0.05	−0.12, 0.02	0.18	−0.05	−0.12, 0.03	0.23
−0.13	**−0.19, −0.07**	**<0.001**	**−0.08**	**−0.15, −0.01**	**0.05**	−0.07	−0.14, 0.01	0.09
−0.07	**−0.12, −0.01**	**0.02**	−0.06	−0.13, 0.01	0.11	−0.06	−0.13, 0.01	0.11
0.00	−0.06, 0.06	0.99	−0.01	−0.08, 0.08	0.98	0.00	−0.08, 0.08	0.99
−0.08	**−0.14, −0.03**	**0.002**	−0.05	−0.12, 0.02	0.13	−0.05	−0.11, 0.02	0.17
−0.11	**−0.16, −0.06**	**<0.001**	−0.05	−0.11, 0.02	0.16	−0.04	−0.11, 0.02	0.19
−0.07	**−0.12, −0.02**	**0.007**	0.00	−0.06, 0.06	0.97	0.00	−0.06, 0.06	0.93
−0.11	**−0.17 −0.06**	**<0.001**	**−0.10**	**−0.17, −0.03**	**0.006**	**−0.10**	**−0.17, −0.03**	**0.006**
−0.05	−0.10, 0.01	0.11	−0.01	−0.08, 0.06	0.85	0.00	−0.07, 0.07	0.91
−0.15	**−0.21, −0.10**	**<0.001**	**−0.14**	**−0.21, −0.08**	**<0.001**	**−0.13**	**−0.20, −0.06**	**<0.001**
−0.10	**−0.16, −0.04**	**<0.001**	**−0.09**	**−0.16, −0.02**	**0.01**	**−0.09**	**−0.16, −0.01**	**0.02**
−0.11	**−0.18, −0.05**	**<0.001**	−0.06	−0.13, 0.01	0.11	−0.05	−0.12, 0.02	0.18
−0.05	−0.11, 0.01	0.07	−0.04	−0.11, 0.03	0.29	−0.03	−0.10, 0.03	0.33
−0.03	−0.10, 0.03	0.30	−0.05	−0.13, 0.02	0.17	−0.05	−0.13, 0.02	0.18
−0.06	**−0.11, −0.01**	**0.03**	−0.02	−0.09, 0.04	0.50	−0.02	−0.08, 0.05	0.64
−0.13	**−0.18, −0.08**	**<0.001**	**−0.07**	**−0.13, −0.02**	**0.009**	**−0.07**	**−0.12, −0.01**	**0.01**
−0.09	**−0.14, −0.05**	**<0.001**	−0.05	−0.11, 0.01	0.10	−0.04	−0.10, 0.01	0.13
−0.11	**−0.16, −0.05**	**<0.001**	**−0.09**	**−0.15, −0.02**	**0.01**	**−0.09**	**−0.15, −0.02**	**0.01**
−0.05	−0.10, 0.01	0.12	−0.01	−0.08, 0.06	0.81	0.00	−0.07, 0.06	0.91

dose-response associations and group comparisons.) This suggests that cannabis-related IQ decline, poorer learning and processing speed, and informant-reported memory and attention problems are not artifacts of analytic approach or of measured confounders, but rather are more likely to be consequences of long-term use. Cognitive childhood-to-adulthood changes such as those we observed have been shown to predict steeper cognitive decline from ages 70 to 82, and to do so better than adult cognitive level (39).

Second, long-term cannabis users showed significantly larger IQ decline, poorer learning and memory, and poorer processing speed than long-term tobacco or alcohol users. Thus, some cognitive deficits were more pronounced for long-term cannabis users than for long-term tobacco or alcohol users, contrary to some claims (21, 40).

Third, cognitive functioning among midlife recreational cannabis users was similar to representative cohort norms. This suggests that infrequent, non–problem recreational cannabis use in midlife is unlikely to compromise cognitive functioning. Our results highlight the importance of not conflating long-term and recreational cannabis users in future studies.

Fourth, cannabis quitters showed subtle cognitive deficits that may explain inconsistent findings on the benefits of cessation (11, 14, 41–45).

Fifth, long-term cannabis users showed smaller bilateral volume in total hippocampus and five of 12 structurally and functionally distinct subregions compared with nonusers, consistent with case-control studies (2).

Sixth, although persistence of cannabis use showed dose-response associations with cognitive deficits and, to a lesser extent, smaller hippocampal volume in the representative sample, smaller hippocampal volume did not statistically mediate associations between persistence of cannabis use and cognitive deficits. Smaller hippocampal volume has been suggested as a possible mediator of cannabis-related cognitive deficits (24), because the hippocampus is rich in type 1 cannabinoid (CB1) receptors and is involved in learning and memory. However, smaller hippocampal volume may be a reductionistic explanation for cannabis-related cognitive deficits. For example, in addition to the hippocampus, other

TABLE 5. Comparison of long-term cannabis users and five informative subgroups on informant-reported memory and attention problems at age 45 in the Dunedin cohort[a]

			Comparison Group										Difference Between Long-Term Cannabis Users and Comparison Groups				
	Long-term Cannabis Users (N=74)		1. Cannabis Nonusers (N=199)		2. Long-term Tobacco Users (N=69)		3. Long-term Alcohol Users (N=56)		4. Midlife Recreational Cannabis Users (N=74)		5. Cannabis Quitters (N=54)		LT vs. 1	LT vs. 2	LT vs. 3	LT vs. 4	LT vs. 5
Measure	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	p	p	p	p	p
Memory	0.53	0.20, 0.86	−0.19	−0.31, −0.08	0.19	−0.13, 0.51	0.05	−0.16, 0.26	0.03	−0.20, 0.26	0.18	−0.11, 0.47	**<0.001**	0.21	**0.03**	**0.02**	0.15
Attention	0.56	0.24, 0.89	−0.10	−0.23, 0.04	0.11	−0.14, 0.37	−0.16	−0.32, 0.00	0.00	−0.24, 0.23	0.23	−0.10, 0.57	**<0.001**	0.06	**<0.001**	**0.005**	0.18

[a] Means represent unadjusted informant-reported memory and attention scores that were standardized on the full sample (mean=0, SD=1) prior to analyses. Higher scores indicate worse memory and attention problems. Statistical tests of group comparisons are adjusted for sex. Boldface for p values indicates a statistically significant difference (p<0.05) compared with long-term cannabis users. LT=long-term cannabis users.

TABLE 6. Dose-response associations between persistence of cannabis dependence or persistence of regular cannabis use from ages 18 to 45 and informant-reported memory and attention problems at age 45 in the Dunedin cohort

							Statistical Tests[b]								
							Model 1			Model 2			Model 3		
Domain	Mean Standardized Informant-Reported Memory and Attention Scores[a]						β	95% CI	p	β	95% CI	p	β	95% CI	p
Persistence of cannabis dependence															
	Never used (N=249)	Used but never diagnosed (N=487)	1 diagnosis (N=73)	2 diagnoses (N=31)	3 diagnoses (N=28)	≥4 diagnoses (N=14)									
Memory	−0.16	−0.07	0.35	0.70	0.88	−0.02	**0.20**	**0.13, 0.27**	**<0.001**	**0.12**	**0.03, 0.20**	**0.007**	**0.11**	**0.02, 0.19**	**0.01**
Attention	−0.13	−0.09	0.36	0.85	0.69	0.21	**0.20**	**0.13, 0.27**	**<0.001**	**0.16**	**0.07, 0.24**	**<0.001**	**0.15**	**0.07, 0.23**	**<0.001**
Persistence of regular cannabis use															
	Never used (N=249)	Used but never regularly (N=503)	Regularly used 1× (N=48)	Regularly used 2× (N=30)	Regularly used 3× (N=29)	Regularly used ≥4× (N=23)									
Memory	−0.16	−0.05	0.32	0.73	0.41	0.70	**0.21**	**0.14, 0.28**	**<0.001**	**0.13**	**0.05, 0.21**	**0.002**	**0.12**	**0.04, 0.20**	**0.005**
Attention	−0.13	−0.06	0.30	0.67	0.48	0.60	**0.19**	**0.12, 0.26**	**<0.001**	**0.13**	**0.05, 0.21**	**0.002**	**0.11**	**0.03, 0.19**	**0.006**

[a] Means represent unadjusted informant-reported memory and attention scores that were standardized (mean=0, SD=1) on the full sample prior to analyses. Higher scores indicate worse memory and attention problems.

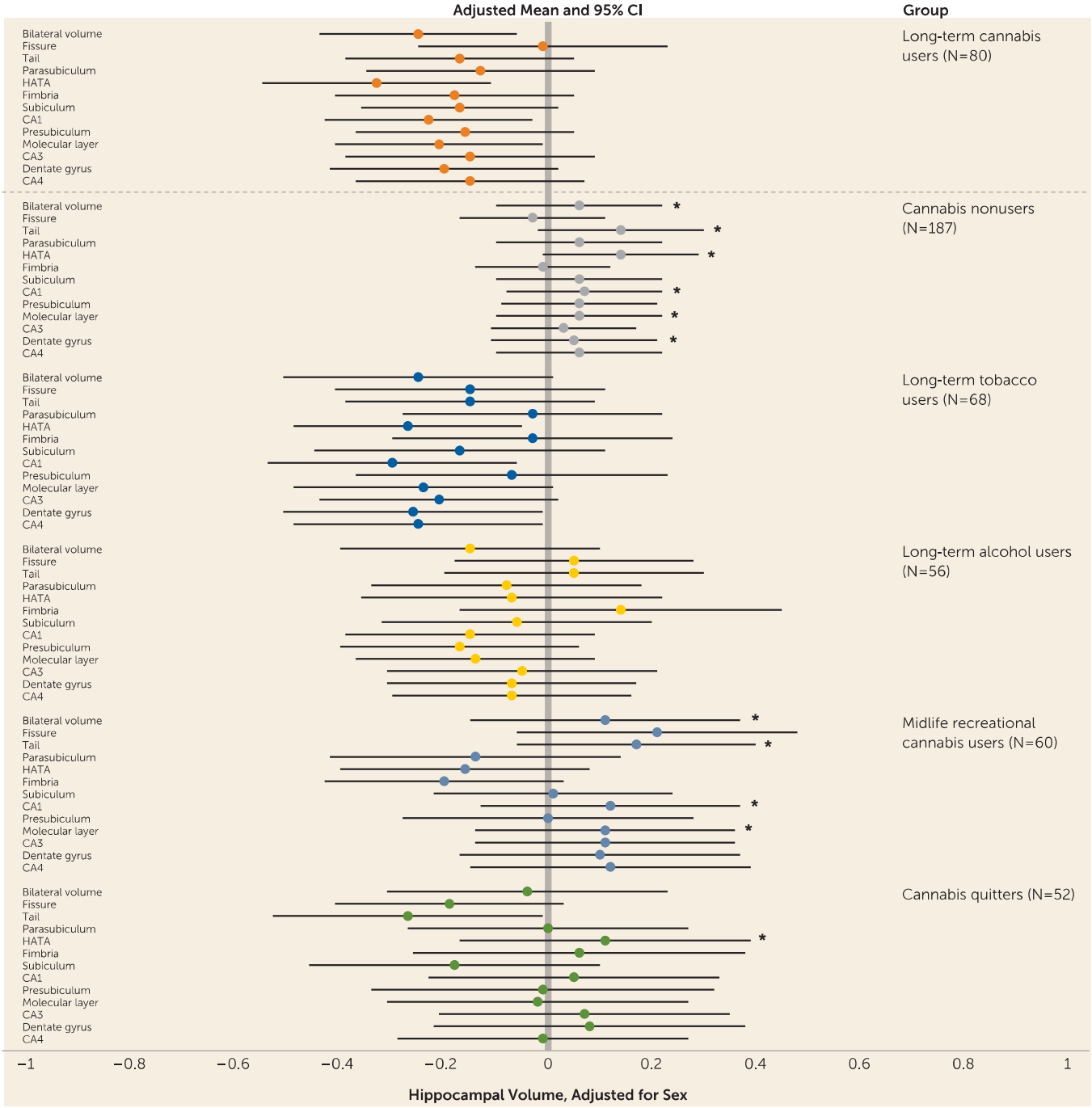
[b] Model 1 was adjusted for sex; model 2 was additionally adjusted for persistent dependence on tobacco, alcohol, and other illicit drugs; and model 3 was additionally adjusted for low childhood socioeconomic status, low childhood self-control, and family history of substance dependence. Beta coefficients represent standardized estimates. Boldface indicates statistically significant estimates (p<0.05).

CB1-rich brain regions, including those involved in reward and motivation, may play a role (2). Further, neurobiological mechanisms likely extend beyond gray matter volume differences to include differences in structural and functional connectivity (46). Finally, social mechanisms could also play a role.

Our findings conflict with those of some studies (including one by us) that compared the cognitive functioning of twins who were discordant for cannabis use and found little evidence of cannabis-related cognitive deficits (47–50). Discordant twin comparisons represent a compelling approach to controlling for shared genetics and family background. However, a limitation is that the size of the differences between twins in cannabis use and in cognitive functioning is much smaller than between unrelated individuals. Hence, it is unclear whether associations that are attenuated in twin-difference comparisons, relative to comparisons between unrelated individuals, are an indication of true confounding or are an artifact of reduced statistical power.

In the present study, we tackled confounding by incorporating the most notable confounding variables identified in the literature, including childhood socioeconomic status, low self-control, low childhood IQ, family substance dependence history, and persistent dependence on other substances, using unusually strong measures derived from multiple waves and data sources. These obvious confounders,

FIGURE 2. Long-term cannabis use and hippocampal volumes in the Dunedin cohort[a]



[a] The figure shows a comparison of long-term cannabis users with five informative subgroups on age 45 hippocampal volumes. Mean age 45 hippocampal volumes were adjusted for sex and standardized on the full cohort (mean=0, SD=1). Average normative volume is indicated by the reference line at the representative cohort mean of 0. Estimates below zero indicate smaller than average volume. Asterisks indicate mean volumes that were statistically significantly larger ($p<0.05$) as compared with long-term cannabis users, after adjustment for sex. CA1, CA3, CA4=cornu ammonis 1, 3, 4; HATA=hippocampal-amygdala transition area.

considered together, could not account for many of the observed associations. We also reported E-values, with larger E-values indicating that considerable unmeasured confounding would be needed to explain associations. E-values ranged from 1.33 to 1.56. These E-values represent the risk ratios needed after adjustment for measured confounders, raising the bar for unmeasured confounding to play a role.

This study has several limitations. First, cannabis use was self-reported. Underreporting for fear of admitting to illegal drug use is unlikely because participants were interviewed repeatedly over a lifetime and learned to trust the confidentiality guarantee. Second, some group sizes were small, raising concerns about low statistical power. These concerns were minimized through powerful tests of dose-response

associations and through transparent reporting of effect sizes in a representative cohort. Third, long-term cannabis users also use tobacco, alcohol, and other illicit drugs. Disentangling cannabis effects from other substances is challenging. We did not limit analyses to cannabis-only users because they are unrepresentative of cannabis users (51). Instead, we used two complementary approaches: 1) we reported no midlife cognitive deficits for long-term tobacco and alcohol users, groups who showed polysubstance use, like long-term cannabis users, but were free from cannabis, and 2) we controlled for persistent dependence on tobacco, alcohol, and other illicit drugs in analyses of dose-response associations and found that a number of associations were robust to covariate control. Collectively, the findings suggest that use of other substances cannot fully account for the cognitive deficits observed in long-term cannabis users.

Fourth, we focused on hippocampal volume as a key MRI outcome based on theory and previous research (2). We are preparing a separate report with results of exploratory analyses of associations between long-term cannabis use and comprehensive MRI measures of global and regional gray and white matter. Fifth, the results are based on a single birth cohort who began using cannabis in the 1980s or 1990s. The concentration of THC, the psychoactive constituent of cannabis, has risen in recent years (52). Therefore, if THC exposure underlies associations, we may have underestimated effect sizes in contemporary users. Finally, observational studies cannot conclusively demonstrate causality.

This study has notable implications. First, long-term cannabis use is robustly associated with cognitive deficits in midlife. These may be consequential given that mild cognitive deficits in midlife are a risk factor for dementia (8). The deficits we observed are comparable to midlife cognitive deficits of individuals who developed dementia in the Atherosclerosis Risk in Communities Study (8). Older adults who developed dementia showed midlife cognitive deficits that ranged from 0.32 to 0.53 standard deviations below the cohort mean on tests of memory, processing speed, and word fluency. Second, research is needed to ascertain whether long-term cannabis users show elevated rates of dementia in later life. This is important given the huge burden of dementia, and it is timely given the confluence of two trends: the growth of the aging population, and the record high rates of cannabis use among today's older adults.

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Examination Questions for Long-Term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife

1. **Which of the following characterizes the child IQ of long-term cannabis users?**
   A. Long-term cannabis users had below-average childhood IQ relative to a normative IQ of 100.
   B. Long-term cannabis users had average childhood IQ relative to a normative IQ of 100.
   C. Long-term cannabis users had above-average childhood IQ relative to a normative IQ of 100.
   D. Long-term cannabis users' childhood IQ was not reported.
2. **In tests of dose-response associations between persistence of cannabis use from age 18 to 45 and age-45 neuropsychological test performance, dose-response associations were found for which of the following neuropsychological functions, after adjustment for all covariates?**
   A. Learning and memory
   B. Learning, memory, and processing speed
   C. Learning, memory, processing speed, and perceptual reasoning
   D. Only learning
3. **Did smaller hippocampal volume statistically mediate associations between persistence of cannabis use and cognitive deficits?**
   A. No
   B. Yes
   C. Yes, for a subset of neuropsychological functions
   D. Statistical mediation was not tested