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Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults
A Systematic Review and Meta-analysis

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IMPORTANCE Substantial shifts in perception and policy regarding cannabis have recently occurred, with use of cannabis increasing while its perceived harm decreases. One possible risk of increased cannabis use is poorer cognitive functioning, especially in youth.

OBJECTIVE To provide the first quantitative synthesis of the literature examining cannabis and cognitive functioning in adolescents and young adults (with a mean age of 26 years and younger).

DATA SOURCES PubMed, PsycInfo, Academic Search Premier, Scopus, and bibliographies of relevant reviews were searched for peer-reviewed, English-language studies from the date the databases began through May 2017.

STUDY SELECTION Consensus criteria were used to determine study inclusion through abstract and manuscript review.

DATA EXTRACTION AND SYNTHESIS This study followed Meta-analysis of Observational Studies in Epidemiology guidelines. Effect size estimates were calculated using multivariate mixed-effects models for cognitive functioning outcomes classified into 10 domains.

MAIN OUTCOMES AND MEASURES Results from neurocognitive tests administered in cross-sectional studies were primary outcomes, and we examined the influence of a priori explanatory variables on variability in effect size.

RESULTS Sixty-nine studies of 2152 cannabis users (mean [SD] age, 20.6 [2.8] years; 1472 [68.4%] male) and 6575 comparison participants with minimal cannabis exposure were included (mean [SD] age, 20.8 [3.4]; 3669 [55.8%] male). Results indicated a small overall effect size (presented as mean *d*) for reduced cognitive functioning associated with frequent or heavy cannabis use (*d*, −0.25; 95% CI, −0.32 to −0.17; $P < .001$). The magnitude of effect sizes did not vary by sample age or age at cannabis use onset. However, studies requiring an abstinence period longer than 72 hours (15 studies; n = 928) had an overall effect size (*d*, −0.08; 95% CI, −0.22 to 0.07) that was not significantly different from 0 and smaller than studies with less stringent abstinence criteria (54 studies; n = 7799; *d*, −0.30; 95% CI, −0.37 to −0.22; $P = .01$).

CONCLUSIONS AND RELEVANCE Associations between cannabis use and cognitive functioning in cross-sectional studies of adolescents and young adults are small and may be of questionable clinical importance for most individuals. Furthermore, abstinence of longer than 72 hours diminishes cognitive deficits associated with cannabis use. Although other outcomes (eg, psychosis) were not examined in the included studies, results indicate that previous studies of cannabis in youth may have overstated the magnitude and persistence of cognitive deficits associated with use. Reported deficits may reflect residual effects from acute use or withdrawal. Future studies should examine individual differences in susceptibility to cannabis-associated cognitive dysfunction.

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Supplemental content

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Substantial shifts in the legality and public perceptions of cannabis have recently occurred in the United States. Cannabis use has increased, while the perception of its harms has decreased.[1,2] In view of these trends, it is of considerable public health importance to delineate potential risks of cannabis use. However, scientific debates about physical and mental health consequences of cannabis remain unresolved. A critical question concerns potential cognitive dysfunction associated with cannabis use during adolescence and early adulthood, when use typically begins and substantial neurodevelopment continues to occur. To address this question, we conducted a meta-analysis specifically examining studies of cognitive functioning in adolescent and young adult cannabis users.

Adolescence is a period of dynamic neurobiological and behavioral changes. Substantial increases in cognitive capacities, particularly in executive functioning,[3] occur alongside marked neurodevelopmental changes (eg, maturation of prefrontal networks) that continue into the mid-20s.[4,5] Because of this prolonged neurodevelopmental period and the potential involvement of the endocannabinoid system in such changes,[6,7] concerns have increased regarding use of cannabis during this putative critical period of brain development.[8,9]

While there is consensus that acute cannabis intoxication results in cognitive deficits, residual cognitive effects from cannabis (ie, ones that persist after acute intoxication) are still debated, particularly after a period of abstinence. Numerous studies in adolescents and young adults have reported associations between frequent or early-onset cannabis use and poorer cognitive performance in tasks requiring executive functioning, attention, and episodic memory.[10-14] However, findings are somewhat inconsistent,[15,16] with several explanatory and confounding variables contributing to variability; these include psychiatric and substance use comorbidities, frequency of cannabis use, and length of abstinence.[17-20]

Qualitative reviews of this literature have provided valuable insights, and most have concluded that adolescents and young adults are at heightened risk of cannabis-associated cognitive deficits, especially with early cannabis use.[8,15,21,22] However, qualitative reviews can be selective; they rely primarily on statistical significance, typically do not conduct analyses of potential bias, and cannot provide accurate estimates of the magnitude of associations or influence of important variables that might contribute to variability in findings. Meta-analysis is a powerful method for synthesizing results across existing literature and examining whether explanatory variables affect variability in outcomes. Meta-analysis also addresses inconsistences by standardizing outcomes and diminishing the effects of varying statistical power. To date, 3 meta-analyses of adult cannabis users exist,[23-25] reporting small negative associations between attention, learning, memory, and executive functioning and frequent or heavy cannabis use. Yet effects were almost undetectable in studies that require users to maintain a few days to weeks of abstinence prior to assessment.[23,24] However, a meta-analysis has not been conducted specifically in adolescents or young adults. In this study, we extend prior qualitative reviews by providing quantitative estimates of potential associations between heavy/frequent cannabis use and cognitive functioning in adolescents and young adults. We also examined potential associations between variability in effect sizes and a predetermined set of explanatory variables, including study design and subject characteristics proposed to influence cognition in cannabis-using youth.[15,21,22]

Key Points

Question Is frequent or heavy cannabis use associated with cognitive dysfunction in adolescents and young adults?

Findings This systematic review and meta-analysis of 69 cross-sectional studies of 2152 cannabis users and 6575 comparison participants showed a small but significant overall effect size for reduced cognitive functioning in adolescents and young adults who reported frequent cannabis use. However, studies requiring abstinence from cannabis for longer than 72 hours had a very small, nonsignificant effect size.

Meaning Although continued cannabis use may be associated with small reductions in cognitive functioning, results suggest that cognitive deficits are substantially diminished with abstinence.

Methods

Study Eligibility

We followed Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[26] We began by defining a priori meta-analysis study inclusion criteria as any study that (1) assessed human adolescents and/or young adults (with a mean age of 26 years or younger, to include potentially sensitive neurodevelopmental periods[22]); (2) identified heavy, frequent, and/or problematic cannabis use as the primary variable of interest; (3) did not solely identify cannabis as a comorbidity to another substance use or mental health disorder; (4) did not focus on acute effects; (5) included an appropriate comparison group; (6) reported at least 1 standardized neurocognitive test; (7) was written in English; and (8) provided sufficient data to calculate effect sizes. These criteria were intentionally designed to provide a comprehensive representation of existing research while also allowing the empirical examination of relationships between variability in study methods or study samples and effect sizes. (Details are presented in the eMethods in the Supplement.)

Only observational, cross-sectional studies were included. Reliable estimates for longitudinal studies were indeterminable; there were few such studies, with heterogeneity in length of follow-up and methods of reporting cognitive data, and we believed that inference would be imprecise and unreliable with this small number of heterogeneous studies. However, baseline data from longitudinal studies were used where available.

Search Strategies and Study Selection

Systematic literature searches were independently conducted by 2 of us (J.C.S. and S.T.S.) in PubMed, PsycINFO, Academic Search Premier, and Scopus, beginning on December 10, 2016, and continuing until final searches were completed on May 12,

2017. The publication date range for included studies was from the database start date to May 12, 2017. The eMethods in the Supplement include an example full electronic search for PubMed. All identified articles were independently reviewed by the same 2 authors and supplemented by searches of qualitative reviews.[8,15,21,22] Of the 2592 records initially retrieved, 363 full-text articles were assessed and 74 met inclusion criteria. After 5 studies with overlapping samples were removed, 69 studies were found to be eligible (**Figure 1**).

Data Extraction

Study information was independently extracted by 2 researchers (S.T.S. and J.D.J.), with discrepancies in coding resolved with by a third researcher (J.C.S.). Because certain cognitive domains may have different sensitivities to cannabis-associated effects,[15] raters classified tests into domains based on evidence of construct validity. These domains were attention, learning, delayed memory, speed of information processing, verbal/language, visuospatial, motor functioning, and executive functioning (eMethods in the Supplement).To examine specific subcomponents of executive functioning, this domain was separated into abstraction/shifting, updating/working memory, and inhibition subdomains based on a well-supported model of executive functioning.[27,28] See eTable 1 in the Supplement for tests in each cognitive domain.

Effect Size Calculation

We used the standardized mean difference statistic (*d*) as the measure of effect size, applied Hedges and Olkin correction for small sample bias,[29] and used the variance for each *d* to determine a weighting factor for the unbiased effect size. Measures where low scores indicated better performance were adjusted so that a negative *d* indicated worse performance in the cannabis group.

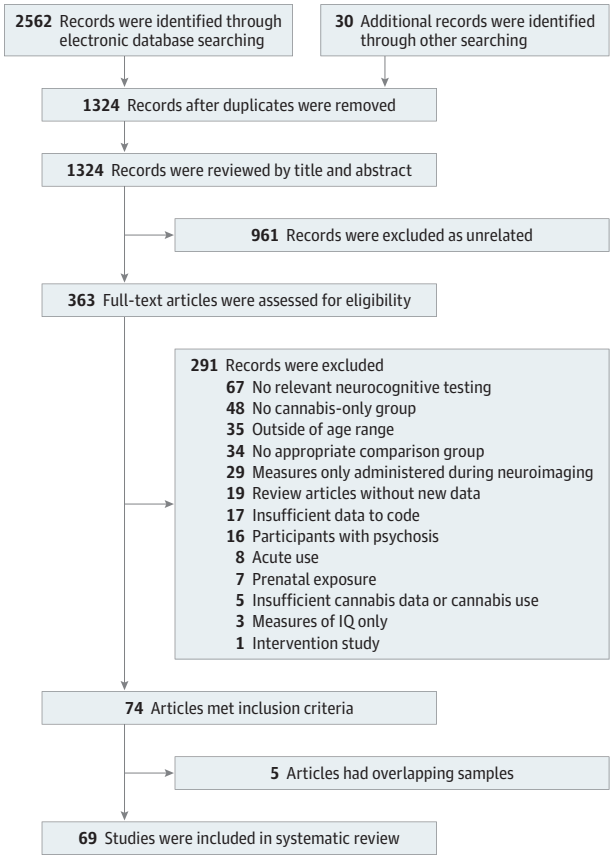
Funnel plot tests and exploratory analyses were conducted to examine potential small study bias including the method of Egger et al[30] to test for small study effects. Since no trim-and-fill method exists for multivariate mixed-effects meta-analysis, the Duval and Tweedie trim-and-fill method[31] for random-effects analyses provided an estimate of potentially missing effect sizes.

Statistical Analyses

Analyses were conducted using a mixed-effects multivariate model (eMethods in the Supplement).[32,33] Since most studies reported multiple cognitive measures, this method was chosen to allow for multiple outcomes per study. A multivariate model allows for multiple correlated within-study effect sizes, takes the hierarchical (clustered) data structure into account, and permits different cluster sizes (ie, effect sizes per study). A framework for such analyses is provided by Generalized Linear Latent and Mixed Models (GLLAMM) implemented in Stata version 13 (StataCorp),[34] which we have applied in prior meta-analyses.[35,36]

We defined a 2-level mixed-effects model; level 1 is represented by effect sizes within studies, and level 2 is represented by different studies. This model examines variability of effect sizes between studies (random factor) and associations between various explanatory variables (fixed factors) and effect sizes. Fixed-effects and random-effects parameters and their variances and covariance are estimated via adaptive quadrature, a robust and flexible numeric integration approach allowing heteroscedastic level 1 variances.[37]

Figure 1. Flowchart of Searches for Studies Included in the Meta-analysis



Results

Preliminary Analyses

There were 69 eligible studies (Figure 1; **Table**) with 8727 participants, including 2152 cannabis users and 6575 comparison participants who had minimal cannabis use. Studies were published between 1973 and 2017. We coded 384 effect sizes from 69 studies (mean (SD), 9.46 [5.32]; range, 1-17). Cannabis users in the studies had a mean (SD) age of 20.6 (2.8) years and were 68.1% male. Comparison participants had a mean (SD) age of 20.8 (3.4) years and were 55.8% male. Studies included were predominantly conducted in the United States, United Kingdom, Europe, and Australia. Cannabis users had a mean (SD) age at cannabis use initiation of 15.2 (1.5) years. The mean (SD) time of abstinence required by the studies was 152.7 (335.2) hours. Twenty-two studies (32%) reported either 0 hours of abstinence or no specificity in abstinence criteria, 32 studies (46%) reported between 1 and 72 hours of abstinence, and 15 studies (22%) reported greater than 72 hours of abstinence.

Table. Overview of the 69 Studies Included in the Meta-analysis[a]

Source	No. of Participants		Cognitive Domains Assessed	Age Range of Participants, y	Minimum Required Abstinence Period, h
	Cannabis User Group	Comparison Group			
Ashtari et al,[38] 2011	14	14	Learning, delayed memory	18-20	720
Becker et al,[39] 2014	35	35	Attention, learning, delayed memory, SIP, EF-U/WM, EF-A/S, V/L, motor	18-20	12
Brown et al,[40] 2010	32	33	Learning, delayed memory	≥18	48
Churchwell et al,[41] 2010	18	18	V/L	16-19	0
Cousijn et al,[42] 2013	17	26	EF-I	18-30	0
Cousijn et al,[42] 2013	10	26	EF-I	18-30	0
Croft et al,[43] 2001	18	31	Learning, delayed memory, SIP, EF-I, EF-U/WM, V/L, motor	≥18	48
Cuttler et al,[44] 2012	48	48	Learning, EF-U/WM	17-33	0
Cuyàs et al,[45] 2011	110	93	Delayed memory, learning, visuospatial, SIP, V/L	≥18	72
Dougherty et al,[10] 2013	45	48	Attention, EF-U/WM, EF-A/S, EF-I, learning	14-17	18
Ehrenreich et al,[14] 1999	48	49	Attention, EF-U/WM, EF-A/S	≥18	24
Ehrenreich et al,[14] 1999	51	49	Attention, EF-U/WM, EF-A/S	≥18	24
Epstein & Kumra,[46] 2014	29	53	Attention, EF-I	10-23	0
Filbey et al,[47] 2015	36	16	Learning, delayed memory	18-50	72
Filbey et al,[47] 2015	19	16	Learning, delayed memory	18-50	72
Flavel et al,[48] 2013	10	10	Motor	≥18	12
Fried et al,[17] 2005	35	59	Attention, learning, delayed memory, SIP, EF-U/WM, EF-A/S	17-21	2160
Fried et al,[17] 2005	35	59	Attention, learning, delayed memory, SIP, EF-U/WM, EF-A/S	17-21	0
Gonzalez et al,[49] 2012	65	65	EF-I, learning	17-24	24
Gouzoulis-Mayfrank et al,[50] 2000	28	28	Attention, learning, delayed memory, EF-U/WM, EF-A/S, EF-I, V/L	18-31	24
Grant et al,[51] 2012	16	214	Attention, EF-U/WM, EF-A/S, EF-I	18-29	0
Grant et al,[52] 1973	29	29	Learning, EF-A/S, SIP	≥18	0
Gruber et al,[13] 2012	19	28	Attention, learning, delayed memory, SIP, EF-U/WM, EF-A/S, EF-I, visuospatial, V/L	≥18	12
Gruber et al,[13] 2012	15	28	Attention, learning, delayed memory, SIP, EF-U/WM, EF-A/S, EF-I, visuospatial, V/L	≥18	12
Hadjiefthyvoulou et al,[53] 2011	12	18	Learning, delayed memory	≥18	24
Hanson et al,[54] 2010	19	21	Attention, EF-U/WM	15-19	504
Hanson et al,[55] 2014	24	34	Attention, EF-U/WM, EF-A/S, SIP, V/L	17-20	336
Harvey et al,[56] 2007	34	36	Attention, learning, delayed memory, EF-U/WM, EF-A/S, SIP	13-18	12
Hermann et al,[57] 2007	13	13	Attention, learning, delayed memory, EF-U/WM, EF-A/S	≥18	0
Herzig et al,[58] 2014	35	48	Delayed memory, EF-U/WM, EF-A/S	≥18	2
Hooper et al,[18] 2014	33	43	Attention, learning, delayed memory, EF-I, EF-A/S, EF-U/WM	12-17	720
Houck et al,[59] 2013	36	33	EF-U/WM	14-18	0
Jacobsen et al,[60] 2004	20	25	Attention	13-18	720
Jacobus et al,[61] 2014	24	30	Attention, learning, delayed memory, EF-I, EF-A/S, EF-U/WM, V/L, visuospatial, SIP, motor	15-18	672
Jacobus et al,[62] 2015	49	59	Attention, learning, delayed memory, EF-I, EF-A/S, EF-U/WM, V/L, visuospatial, SIP, motor	15-18	672
Lamers et al,[63] 2006	15	15	EF-I, EF-A/S, learning, delayed memory, SIP, visuospatial	21-42	0
Lane et al,[64] 2007	22	31	EF-A/S	14-18	0
Lisdahl & Price,[65] 2012	23	36	Attention, learning, delayed memory, EF-I, EF-A/S, V/L	18-28	168
de Sola Llopis[66] et al, 2008	23	34	Attention, EF-I, EF-A/S, learning, delayed memory, V/L, SIP	≥18	72
Mahmood et al,[67] 2010	65	65	Learning, delayed memory, visuospatial	15-19	552
Medina et al,[11] 2007	31	34	Attention, learning, delayed memory, EF-A/S, EF-U/WM, SIP, visuospatial, V/L	16-18	552

(continued)

Table. Overview of the 69 Studies Included in the Meta-analysis[a] (continued)

Source	No. of Participants		Cognitive Domains Assessed	Age Range of Participants, y	Minimum Required Abstinence Period, h
	Cannabis User Group	Comparison Group			
Messinis et al,[68] 2006	20	24	Attention, learning, delayed memory, EF-A/S, SIP, V/L	17-49	24
Morgan et al,[69] 2012	29	30	Attention, learning, delayed memory, V/L	18-50	0
Murphy et al,[70] 2011	13	12	EF-I	18-30	168
Nestor et al,[71] 2008	35	38	Learning, delayed memory	≥18	0
Price et al,[72] 2015	27	32	EF-I, EF-U/WM	18-25	168
Pujol et al,[73] 2014	28	29	Attention, learning, delayed memory	18-30	12
Quednow et al,[74] 2006	19	19	Attention, learning, delayed memory	≥18	72
Rochford et al,[75] 1977	26	25	Learning, visuospatial	≥18	0
Schwartz et al,[76] 1989	10	8	Learning, delayed memory	14-16	0
Schweinsburg et al,[77] 2005	15	19	Learning, delayed memory, EF-U/WM, EF-A/S, SIP, visuospatial	15-17	48
Schweinsburg et al,[78] 2010	13	18	EF-U/WM	15-18	48
Schweinsburg et al,[78] 2010	13	18	EF-U/WM	15-18	648
Scott et al,[16] 2017	227	3401	Attention, EF-U/WM, EF-A/S, learning, visuospatial	14-21	0
Skosnik et al,[79] 2008	14	10	EF-U/WM, SIP	18-35	24
Smith et al,[80] 2014	10	44	EF-U/WM	≥18	0
Smith et al,[81] 2015	10	44	Delayed memory	≥18	0
Solowij et al,[12] 2011	52	62	Attention, learning, delayed memory	16-20	12
Tait et al,[20] 2011	60	420	Learning, delayed memory, SIP, EF-U/WM	20-24	0
Tait et al,[20] 2011	60	420	Learning, delayed memory, SIP, EF-U/WM	20-24	0
Takagi et al,[82] 2011b	19	19	EF-I	13-24	24
Takagi et al,[83] 2011a	21	21	Attention, learning, delayed memory	13-24	24
Takagi et al,[84] 2014	19	19	EF-I	13-24	24
Tamm et al,[85] 2013	20	21	Learning, delayed memory, EF-I, EF-U/WM, EF-A/S	≥18	36
Varma et al,[86] 1988	26	26	SIP, visuospatial, learning, delayed memory	15-35	12
Verdejo-García et al,[87] 2013	86	58	EF-U/WM, EF-A/S, SIP	18-30	72
Vilar-López et al,[88] 2013	19	18	Attention, EF-I	12-25	24
Whitehurst et al,[89] 2015	17	13	EF-I, learning, delayed memory, SIP	≥18	0
Winward et al,[90] 2014	20	55	Learning, delayed memory, EF-U/WM, EF-A/S, SIP, visuospatial	16-18	672

Abbreviations: EF-A/S, Executive functioning–abstraction/shifting; EF-I, Executive functioning–inhibition; EF-U/WM, Executive functioning–updating/working memory; SIP, speed of information processing; V/L, Verbal/Language.

[a] eTable 2 in the Supplement contains a more complete overview of each study.

We first tested a model without explanatory variables,[35,36] revealing that the overall mean neurocognitive effect size was *d* was −0.247 (SE, 0.038; 95% CI, −0.32 to −0.17), and the between-study variance estimate was 0.070 (SE, 0.018; $P < .001$), indicating that variance between studies was significantly more than that explained by sampling error alone.

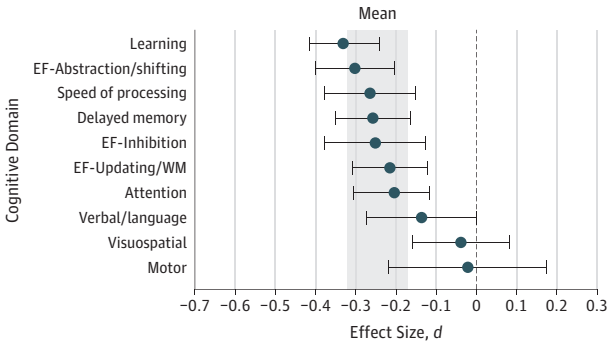
eFigure 1A in the Supplement displays a funnel plot of effect size estimates against their standard error. Visual inspection of this funnel plot revealed asymmetry, and the test of Egger et al[30] for small study effects revealed significant bias ($t = 4.70$; $P < .001$).

The Duval and Tweedie trim-and-fill method filled an additional 44 effect sizes and reduced the effect size by approximately 37.9% in random-effects analyses (from $d = -.206$; 95% CI, −0.24 to −0.16 to $d = -0.128$; 95% CI, −0.17 to −0.09; $P < .001$), although a significant effect size remained (eResults in the Supplement). However, the exact reduction in magnitude should be interpreted with caution.

Neurocognitive Domains

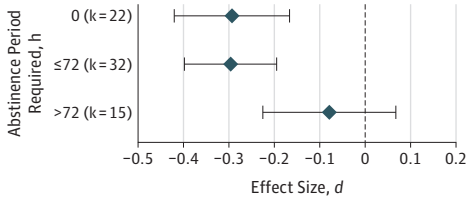
Figure 2 displays effect sizes by neurocognitive domain, which ranged from $d = -0.33$ to −0.02 (eResults in the Supplement). Effect sizes were significant in the domains of learning ($d = -0.33$; 95% CI, −0.42 to −0.24; $P < .001$), executive functioning-abstraction/shifting ($d = -0.30$; 95% CI, −0.40 to −0.20; $P < .001$), speed of information processing ($d = -0.26$; 95% CI, −0.38 to −0.15; $P < .001$), delayed memory ($d = -0.26$; 95% CI, −0.35 to −0.16; $P < .001$), executive functioning-inhibition ($d = -0.25$; 95% CI, −0.38 to −0.13; $P < .001$), executive functioning-updating/working memory (d = −.22; 95% CI, −0.31 to −0.12; $P < .001$), and attention ($d = -0.21$; 95% CI, −0.31 to −0.12; $P < .001$). Nonsignificant effect sizes were found in the domains of verbal/language ($d = -0.14$; 95% CI, −0.27 to 0.001; $P = .05$), visuospatial ($d = -0.04$; 95% CI, −0.16 to 0.08; $P = .53$), and motor functioning ($d = -0.02$; 95% CI, −0.22 to 0.18; $P = .83$). Significant differences in mean effect size estimates were found across neurocognitive domains ($\chi^2_9 = 41.14$;

Figure 2. Mean Weighted Effect Sizes for Each Neurocognitive Test Domain



The mean value shown is the grand mean effect size of 69 included studies; *d* is the standardized mean difference. The shaded area indicates the 95% CI around the mean, −0.247. EF indicates executive functioning; SIP, speed of information processing; WM, working memory. Blue circles indicate the domain effect size *d*; gray bands, the overall means; error bars, 95% CIs.

Figure 3. Mean Weighted Effect Sizes for Varying Abstinence Criteria



Subgroup analyses compared effect sizes (standardized mean difference *d*) from studies with abstinence periods longer than 72 hours to effect sizes from studies with abstinence lengths equal to or less than 72 hours. Data from all 3 groups are presented here to show that the subgroup of studies with unknown or 0 abstinence are not the primary contributor to reported subgroup differences. Blue diamonds indicate the domain effect size *d*; error bars, 95% CIs.

P < .001). However, there were no significant differences in effect size estimates between learning, delayed memory, attention, speed of information processing, or executive functioning domains after applying Bonferroni corrections.

Follow-up Analyses

Follow-up analyses were performed with several predetermined explanatory variables, including age at first cannabis use, sample sociodemographic characteristics, clinical characteristics (eg, depression), publication year, mean hours of abstinence, and length of required abstinence (longer than 72 hours vs 72 hours or less), given prior literature hypothesizing such moderating effects (hereafter, *k* indicates the number of studies corresponding to each variable).[15,21,22]

Subgroup analyses revealed no significant differences in effect sizes by the age category (adolescents or adults) of the sample population (eFigure 2 in the Supplement), early vs late cannabis use onset (ranging from 15 to 18 years old as defined by each individual study; studies were inconsistent in what age was considered early onset), whether studies matched groups by alcohol use, or period of publication (eFigure 3 in the Supplement). Further, mean age, mean age at first use, and between-groups difference in depression were not associated with variability in effect size estimates (eResults in the Supplement). However, studies with treatment-seeking samples (*k* = 12; n = 581; *d*, −0.43; 95% CI, −0.62 to −0.24) showed larger magnitude effect sizes (χ^2_1 = 4.32; uncorrected *P* = .04) compared with non-treatment-seeking samples (*k* = 56; n = 8146; *d*, −0.22; 95% CI, −0.29 to −0.14) in a test for subgroup differences.

At an uncorrected threshold for multiple comparisons, mean hours of reported abstinence (which were available for *k* = 28; n = 1661; β = 0.059; *P* = .04) in each study was associated with variability in effect sizes, such that longer abstinence periods were associated with reductions in effect size magnitude. Furthermore, as shown in **Figure 3**, studies requiring an abstinence period longer than 72 hours (*k* = 15; n = 928) had an overall effect size that was not significantly different from 0 (*d* = −0.08, 95% CI, −0.22 to 0.07; *P* = .29) and was significantly smaller than studies with less stringent abstinence criteria (*k* = 54; n = 7799; χ^2_1 = 6.36; *P* = .01).

Discussion

Prior reviews have concluded that frequent use of cannabis impairs cognitive functioning in several domains, with greater deficits associated with adolescent vs adult onset of use.[8,21,22,25] Our quantitative synthesis of data from 69 studies of adolescents and young adults revealed statistically significant but small cognitive effects associated with heavy/frequent cannabis use. These effects did not vary systematically by the age range studied or the age at which cannabis was initiated, although help-seeking samples in treatment evidenced slightly larger effects. Importantly, increasing abstinence was associated with smaller effect sizes, and studies that required an abstinence period from cannabis of longer than 72 hours had a very small, nonsignificant effect size. The magnitude of these deficits and their reduction by abstinence are consistent with prior meta-analyses conducted in adults with more chronic use patterns.[23,24] Taken together, our analyses suggest a detectable but limited association between cannabis use and cognitive functioning in adolescents and young adults; for a majority of individuals, such effects may be of questionable clinical significance, especially after sustained abstinence. These findings converge with a recent report from the National Academies of Sciences, Engineering, and Medicine,[91] which highlighted the multitude of confounders present in many studies and concluded that there is significant uncertainty about the presence of cannabis-associated cognitive deficits after sustained abstinence.

Findings Across Cognitive Domains

We found variability in effect sizes across cognitive domains, with the largest effects in learning and delayed memory, executive functioning, speed of processing, and attention. However, effect sizes in these domains were similar and within a relatively constricted range (mean *d*, −0.33 to −0.21). It is important to consider the practical implications of these effect size magnitudes. Although traditional conceptualizations of effect size magnitude do not necessarily correspond to clinical signifi-

cance, all effect sizes in this study were below one-third of a standard deviation. Thus our results do not support the conclusion that frequent cannabis use is associated with large or even medium magnitude deficits in memory, attention, or other aspects of cognitive functioning. Although it could be argued that neurocognitive testing lacks sensitivity to detect cognitive abnormalities in cannabis abusers, prior meta-analyses in substances such as alcohol,[92] methamphetamine,[35] benzodiazepines,[93,94] and cocaine[95] have shown medium to large effect sizes, arguing against a lack of sensitivity. Moreover, recent large-scale structural neuroimaging studies also report conflicting data on cannabis-associated alterations in adolescents and adults.[96-100]

Length of Abstinence and Reduction of Effect Sizes

A notable finding in this meta-analysis was that the length of abstinence was associated with variance in effect sizes across studies, albeit at thresholds uncorrected for multiple comparisons. Although accurate measurement of abstinence is challenging because only 14 studies reported monitored abstinence, a longer required length of abstinence was associated with smaller magnitude effect sizes. Similarly, increasing the reported (as opposed to required) length of abstinence was associated with decreased magnitude of effect sizes. Moreover, studies with abstinence periods longer than 72 hours had small, nonsignificant effect sizes that were significantly less than studies with shorter abstinence periods, suggesting that some effects observed in studies associating cannabis use with cognitive dysfunction may be due to residual effects of recent use or withdrawal, rather than persistent changes associated with chronic use.[23,101] Thus, small negative associations between continued cannabis use and cognitive functioning may diminish after sustained abstinence. However, these findings contrast with those from a large longitudinal study[102] and a recent systematic review in adolescents and adults.[25] Discrepancies with the latter may reflect differences in the age range covered, study selection, and methods of analysis.

Association of Age With Effect Sizes

Age did not influence cognitive effect size estimates. In fact, older samples had slightly larger (nonsignificant) effect sizes overall. Additionally, studies of early-onset cannabis users did not have significantly larger effects than studies examining late-onset users. Perhaps studies not specifically focusing on early-onset users nonetheless included substantial numbers of these individuals, because heavy cannabis users are more likely to initiate use at an early age. Taken together, these results do not support a heightened risk for poor cognitive outcomes in cannabis-using adolescents compared with adults, although such differences may emerge with adolescent onset and long-term frequent use, as previously reported.[102,103] Only longitudinal data can delineate whether initiation of cannabis use during adolescence vs adulthood results in greater risks for brain-behavior functioning.

Considerations for Interpretation

The magnitude of these effect sizes and potential implications of findings should be considered in the context of additional relevant factors. First, it is critical to highlight that all psychoactive substances are associated with risks of use, and cannabis is no exception. Importantly, the data reported here do not address associations between cannabis use and other significant physical and mental health outcomes, such as negative lung functioning outcomes, deleterious outcomes on motivation, or risk for psychosis, which have been reported as heightened with chronic or early use.[104-106]

A second consideration is that functional outcomes may ultimately be more important than measures of cognitive functioning, and some studies suggest particular risks of early, heavy use for academic and occupational outcomes.[107,108] However, findings regarding academic functioning have been inconsistent and may depend on other substance use or familial factors.[109,110] These associations are obviously complex and will require more specific prospective modeling.

Third, there is likely heterogeneity in who is at greatest risk of brain-behavior problems associated with frequent cannabis use. Studies show interparticipant variability in behavioral and brain response to cannabis,[111,112] which could contribute to individual differences in cognitive outcomes. Moreover, for certain individuals, small effects could be clinically meaningful because of individual differences influencing cognitive functioning (eg, socioeconomic status). On the other hand, most of the studies that were included predominantly enrolled frequent cannabis users or those with cannabis use disorders, and findings may not generalize to more occasional users or to those administered cannabinoids in medical settings.

Fourth, reported effect sizes may actually be overestimates, considering results from measures of bias. Smaller published studies often show larger effects than large studies, which can bias meta-analyses.[30] Several factors can lead to these effects,[113] including methodological differences or publication bias, in which statistically significant findings are more likely to be published.[114] We found potential small study effects in this literature, and a data augmentation method that imputes missing studies (accounting for potential bias) suggested that effect sizes might be inflated. Furthermore, though some studies used normative neurocognitive data that adjust for influential demographic factors, our analyses primarily used raw scores to calculate effect sizes. As such, results do not account for sociodemographic, psychiatric, or substance use confounders, which are common in case-control studies of cannabis[115,116]; effects may be further attenuated once such factors are accounted for.

Finally, we cannot make conclusions about the causal contribution of cannabis to alterations in cognitive functioning since results do not account for cognitive deficits that may have existed prior to cannabis use initiation. Adolescents at risk of substance use problems may display cognitive vulnerabilities,[17,117-120] which could partially contribute to cognitive findings described here, although they do not exclude the possibility of additional deficits. Furthermore, our data do not address associations between cannabis use and cognitive functioning over longer periods, although some included studies did examine chronic cannabis users and outcomes after protracted abstinence. Consideration of results from longitudinal studies offers conflicting evidence

regarding long-term trajectories of cognitive functioning in cannabis users, especially after abstinence. Strong evidence for cognitive dysfunction associated with adolescent-onset, long-term frequent cannabis use comes from a longitudinal study of the Dunedin cohort,[102] showing that individuals with adolescent-onset daily cannabis use who continued heavy use throughout adulthood showed declines in IQ and poorer cognitive functioning at age 38 years, even after adjusting for multiple relevant covariates. However, the sample size of this specific subgroup was small, which raises questions about generalizability. Further, other longitudinal studies argue against the strength or persistence of deficits over shorter periods,[17,20] especially in studies where abstinence was carefully monitored.[101] Two recent, large-scale studies also question the specificity of cannabis as a causal factor in predicting cognitive change after adjusting for confounding variables and familial factors.[118,121] The landmark Adolescent Brain Cognitive Development study (https://abcdstudy.org) will hopefully help resolve discrepancies and answer critical questions about consequences of cannabis use with longitudinal data on 10 000 children aged 9 to 10 years in the United States. Additionally, once the quantity of longitudinal research increases, additional research syntheses should be conducted to ascertain the long-term effects of cannabis.

Future Directions

Studies of the therapeutic potential of cannabinoids continue to progress, with evidence of efficacy for several conditions (eg, nausea with cancer treatment).[91] However, optimizing the risk/benefit profile of cannabinoids will require focused research into variables affecting outcomes. Studies would benefit from detailed characterization of cannabinoid content, as there may be divergent behavioral effects that depend on cannabinoid concentrations/ratios.[122-124] Optimizing cannabis therapeutics will also require a comprehensive understanding of patient factors that affect risks to facilitate patient selection. There is likely substantial variability in risk for cognitive and mental health problems associated with cannabis use, and research into such factors (eg, genomic profiles) will be crucial to avoid unnecessary cannabinoid-related adverse effects.

Limitations

A substantial limitation in this literature is the heterogeneity in measurement of cannabis use (eTable 2 in the Supplement). There is little consensus regarding what level of cannabis use is hazardous for cognitive or mental health outcomes. A continuous measure of cannabis use could be useful to this end, but it is likely to be unreliable except in studies of consistent, frequent users or studies with detailed microlongitudinal data collection, which is often unfeasible. Research is also limited by variation in how cannabis use data are collected. For example, studies report data that vary substantially across time (eg, past year, past month), frequency levels (eg, per week, per day), measurements of quantity (eg, grams, joints), and, potentially, across cannabinoid content. To advance knowledge and provide valuable public health information, the field needs to converge on standardized cannabis use metrics[125] or devise innovative ways of measuring cannabinoid levels[126] to examine cumulative and frequency effects.

Neuropsychological meta-analyses are hindered by variability in tests administered across a body of literature, creating challenges in assigning outcomes into specific cognitive domains. Although tests purport to measure specific cognitive functions, most tests involve multiple cognitive processes. Thus, cautious interpretation of effect size differences between domains is warranted. However, this limitation is diminished in our meta-analysis given the substantial overlap in effect size magnitudes. Furthermore, studies often report multiple neurocognitive outcomes and focus primarily on significant between-group differences as evidence of cognitive deficits. We attempted to mitigate this outcome selection bias by selecting measures based on construct validity and not statistical significance, and avoided selecting multiple indices from individual tests that measure similar constructs. Moreover, we used sophisticated analytic models to account for within-study correlations. Together, these methods reduce the problems of multiple comparisons evident in this literature.

Conclusions

In light of the changing perceptions of cannabis use and an evolving policy landscape surrounding cannabis, understanding the potential risks of cannabis use for mental health and brain functioning is of paramount importance. In the first quantitative synthesis of 69 studies examining frequent or heavy use of cannabis by adolescents and young adults, we found statistically significant but small negative effect sizes in cognitive functioning associated with cannabis. Inconsistent with conclusions from previous reviews, we found little evidence for more severe effects with cannabis use at earlier ages or specifically in adolescence. Moreover, the data suggest associations between length of abstinence and restored cognitive functioning, with greater abstinence associated with smaller group differences. Furthermore, we found very small, nonsignificant effect sizes in studies that required more than 72 hours of cannabis abstinence. Large-scale longitudinal studies are needed to examine the effects of sustained, heavy cannabis use and identify genetic factors, individual differences, and cannabis use parameters that may affect risk for brain-behavior dysfunction in individuals who use cannabis.

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